Name of Unit	Drugs acting on central nervous system
Course/Subject Code	BP402T
Class	B. Pharm
Semester	IV
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Faculty	Baljeet kaur

Learning Outcome of Module -05

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students will learn about the Mechanism of Anaestheics, Opoid analgesics, anti-inflammatory drugs.	BP402.1
LO2	Drugs of each class	BP402.1
LO3	Uses and adverse effect of each class	BP402.2
LO4	Structure activity relationship.	BP402.3
LO5	Synthesis of drugs.	BP402.4

Content Table

Topic
• Introduction of Anaesthetics, opoid analgesics and anti-inflammatory drugs. • Classification • Drugs • SAR • Synthesis. • Important questions

General anaesthetics

Introduction

General Anaesthetics are known to be depressant drug that produces partial or total reversible loss of sense of pain, loss of consciousness.

➢This state of insensibility is known as Anaesthesia causes descending depression of the CNS, start from cerebral cortex to basal ganglia then to cerebellum and finally spinal cord.

General anaesthesia is essential to surgical practice, because it renders patient's analgesic, amnesic, and unconscious, while causing muscle relaxation and suppression of undesirable reflexes.

➢ No single drug is capable of achieving these effects both rapidly and safely. Rather, several different categories of drugs are utilized to produce optimal anaesthesia. Potent general anaesthetics are delivered via inhalation or intravenous injection.

➢ With the exception of nitrous oxide, modern inhaled anaesthetics are all volatile, halogenated hydrocarbons that derive from early research and clinical experience with diethyl ether and chloroform.

On the other hand, intravenous general anaesthetics consist of a number of chemically unrelated drug types that are commonly used for the rapid induction of anaesthesia.

Goal of Analgesia

To produceAnalgesia

Loss of reflex

Loss of conciousness

Skeletal muscle relaxation

Stages of Anesthesia

Stage 1. Analgesia Characterized by a mild depression of higher cortical neurons, this stage is suitable for surgical procedures that do not require significant neuromuscular

Stage2: Delirium

Especially in the reticular formation, as depression of inhibitory neurons in

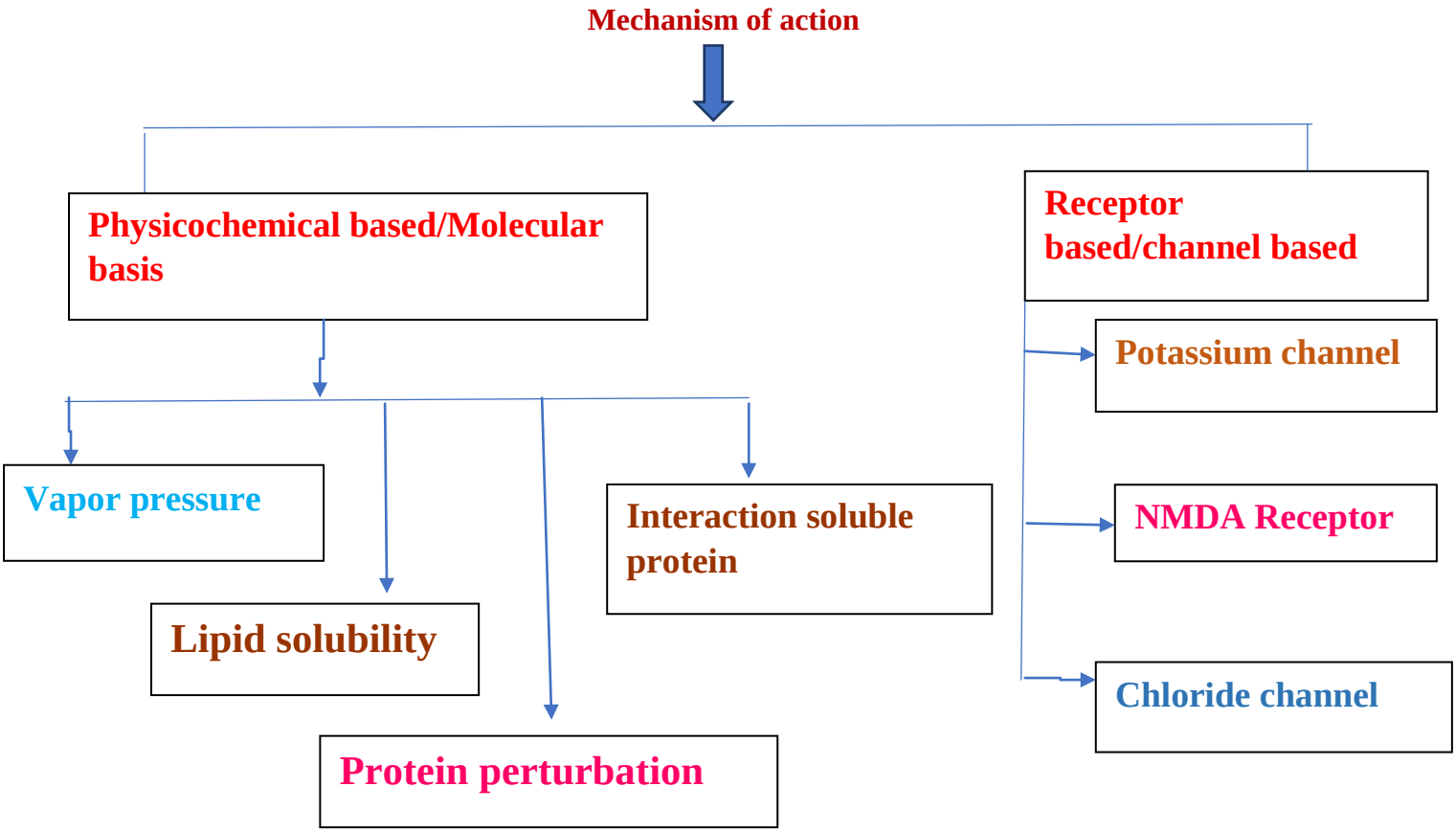
Stage 3. SurgicalAnaesthesia

This stage is divided in to four planes characterized by increasing CNS depression and includes • Loss of spinal reflexes • Decreased muscle reflexes • Paralysis of intercostals muscles • Loss of muscle tone Stage 3 is characterized by regular breathing, a loss of many reflexes, and moving eyeball movement

Stage 4 Respiratory Paralysis Characterized by respiratory and vasomotor paralysis, this stage represents an overdose or toxic level that should be avoided

Ideal characteristics of General Anaesthetics

1. Rapid and pleasant withdrawal from anaesthesia
2. Adequate relaxation of skeletal muscles
3. Potent enough to permit adequate oxygen supply in mixture
4. Wide margin of safety
5. Non-toxic
6. Rapid and pleasant induction of surgical anaesthesia
7. Absence of adverse effects
8. Non-flammable/non-explosive
9. Chemically compatible with aesthetic devices
10. Non-reactive



Classification

Inhalational anesthetics

- **Non halogenated hydrocarbons**
  - Ether
  - Vinyl ether
  - Cyclopropane
  - Nitrous oxide
  - Ethyl vinyl ether
- **Halogenated hydrocarbons**
  - Chloroform
  - Ethyl chloride
  - Halothane
  - Isoflurane
  - Sevoflurane
  - Enflurane
  - Methoxyflurane
  - Fluroxene

Intravenous anesthetics agents

- **Benzodiazepines**
  - Midazolam
- **Opioid Analgesics**
  - Morphine
  - Fentanyl
- **Barbiturates**
  - Thiopentone sodium
  - Thiamylal sodium
  - Methohexital sodium
- **Miscellaneous**
  - Etomidate
  - Ketamine
  - Propofol

Structure activity relationship

- An electron donating substituent in the ortho or para or both positions increase local anaesthetic potency.
- Groups such as:

  An amino (procaine and chloroprocaine)

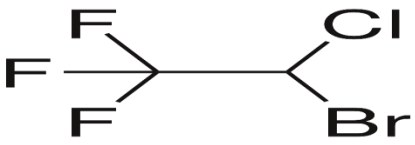
  An alkylamino(tetracaine)

  Contribute electron density to the aromatic ring by both resonance and inductive effects thereby enhancing local anaesthetic potency.

Drugs :

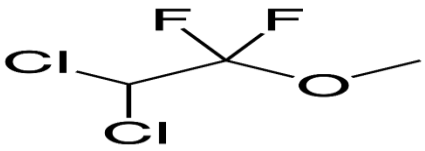
1. **Halothane**

IUPAC NAME:2-bromo,2-chloro,1,1,1-trifluoroethane



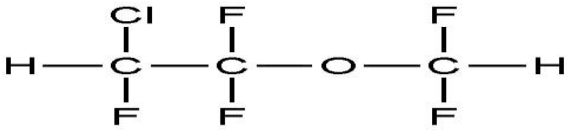
2. **Methoxyflurane**

IUPAC NAME:2,2-dichloro-1,1-difluoro-1-methoxyethane



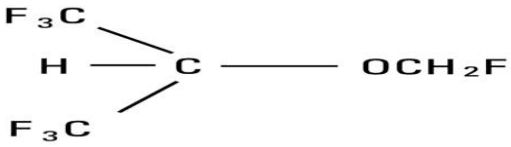
3. **Enflurane**

IUPAC NAME:2-chloro-1,1,2-trifluoroethyldifluoromethylether



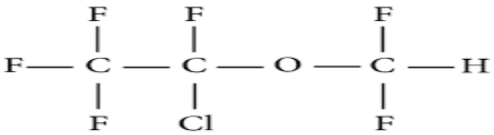
4. **Sevoflurane**

IUPAC NAME:1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy) propane



5. **Isoflurane**

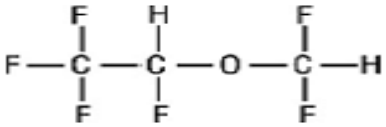
IUPAC NAME:2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane.



Isoflurane

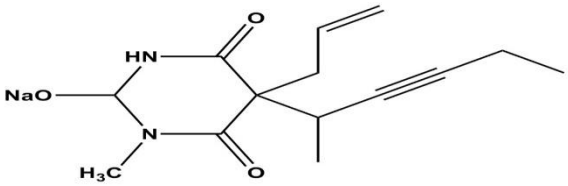
6. Desflurane

IUPAC NAME:2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane



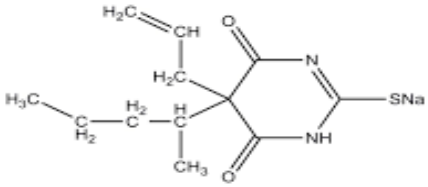
7. Methohexital sodium

IUPAC NAME: Sodium;5-hex-3yn-2-yl-1-methyl-2,6-dioxo-5-prop-2-enylpyrimidin-4- olate



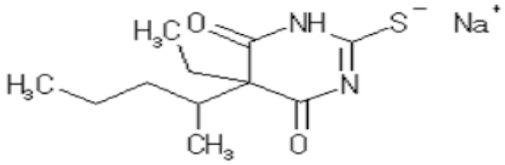
8. Thiamylal sodium

IUPAC NAME: Sodium;4,6-dioxo-5-pentan-2-yl-5-prop-2-enyl-1H-pyrimidine-2-thiolate



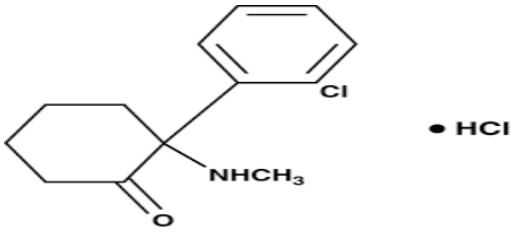
9. Thiopental sodium

IUPAC NAME: sodium;5-ethyl-4,6-dioxo-5-pentan-2-yl-1H-pyrimidine-2-thiolate



10. Ketamine hydrochloride

IUPAC NAME:2-(2-chlorophenyl)-2(methylamino)cyclohexane-1-one hydrochloride



Complications of Anaesthesia:

During anaesthesia

- Respiratory depression
- Salivation, respiratory secretions
- Cardiac arrhythmias
- Fall in BP
- Aspirations
- Laryngospasm
- Awareness
- Delirium and asphysia
- Fire and explosion

After anaesthesia

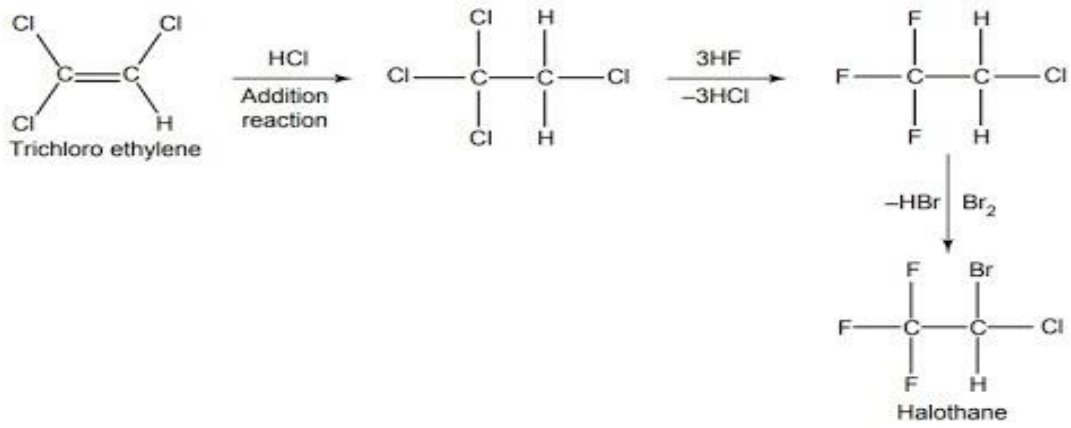
- Nausea and vomiting
- Persisting sedation
- Pneumonia
- Organ damage-liver, kidney
- Emergence delirium
- Cognitive defects

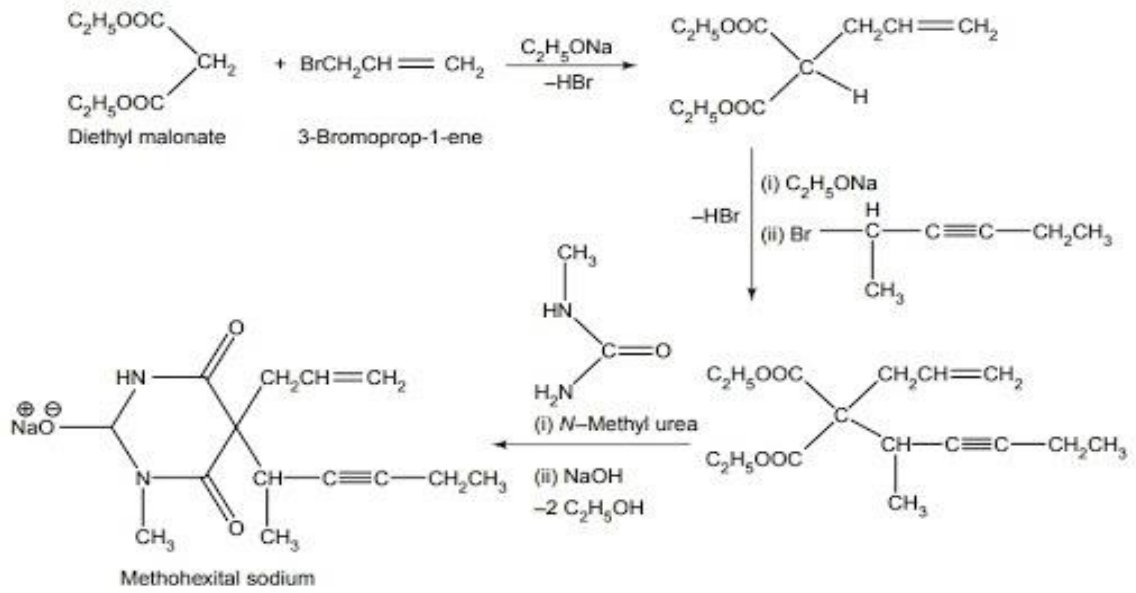
USES OF GENERAL ANAESTHETICS

1. For surgeries of head, neck and face.
2. Short procedures-dessing of burns.
3. For induction and maintenance of anaesthesia
4. Postoperative pain.
5. As an adjuvant to anaesthetics for effective analgesia.

Synthesis

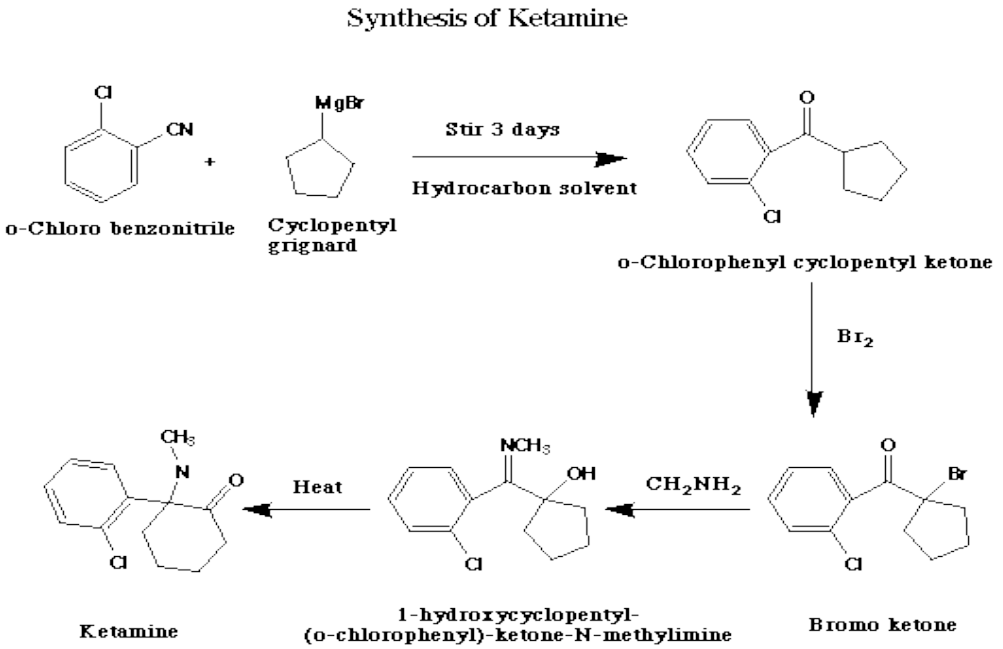
Synthesis of Halothane





Synthesis of Methohexital sodium

Synthesis of Ketamine hydrochloride



Narcotic and Non-Narcotic Analgesics

OPIOID ANALGESICS

Introduction

Pain is a designation for a spectrum of sensations of highly divergent character and intensity ranging from unpleasant to intolerable. Pain stimuli are detected by physiological receptors (sensors, nociceptors) least differentiated morphologically, viz., free nerve endings.

Pain sensation can be influenced or modified as follows: elimination of the cause of pain lowering of the sensitivity of nociceptors (antipyretic analgesics, local anesthetics) interrupting nociceptive conduction in sensory nerves (local anesthetics) suppression of **transmission of** nociceptive impulses in the spinal medulla (opioid) inhibition of **pain perception** (opioid, general anesthetics) alter in **emotional responses** to pain, i.e., pain behavior.

Analgesics

Analgesia may be defined as a state of relative insensitivity to pain, where the capacity to tolerate pain is increased without the loss of consciousness. The term “analgesic” is generally applied to the agents or action required to produce analgesia.

Classification

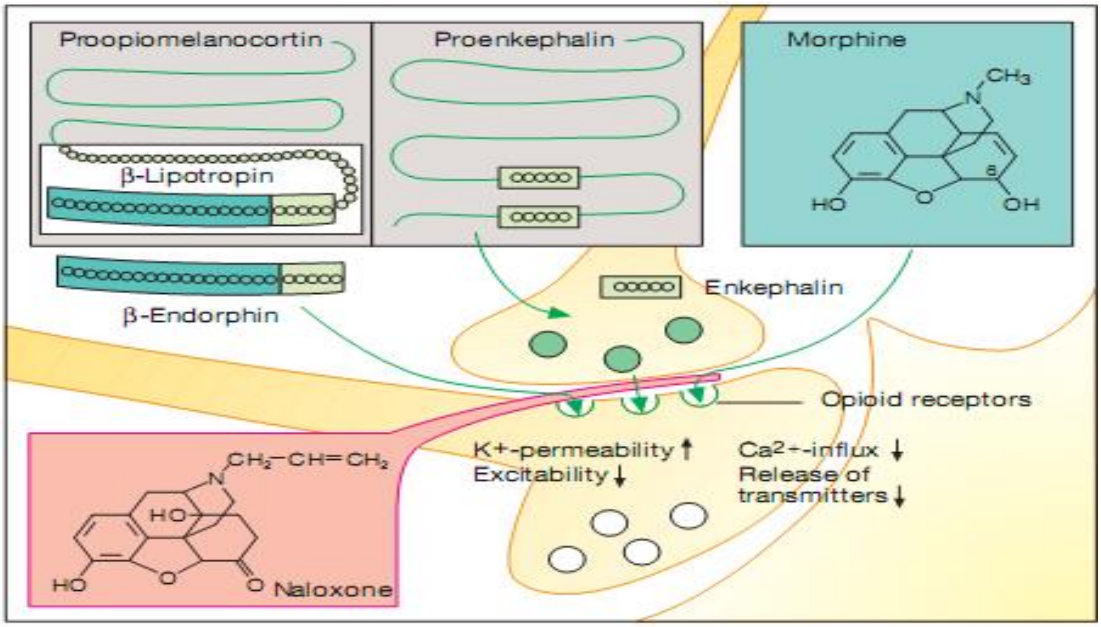
1.Narcotic analgesics (centrally acting drugs)

2. Non-narcotic analgesics (peripherally acting drugs)

Narcotics

- Narcotics are addictive drugs that reduce the user's perception of pain and induce euphoria (a feeling of exaggerated and unrealistic well-being). The English word narcotic is derived from the Greek narkotikos which means "numbing" or "deadening." Although the term can refer to any drug that deadens sensation or produces stupor, it is commonly applied to the opioids—that is, to all natural or synthetic drugs that act like morphine.Sertuner, in 1805, isolated and discovered the potent analgesic activity of Morphine, an alkaloid isolated from the juice of unripe seed capsules of the poppy plant, Papaver somniferum.

Mechanism of action



- Most neurons react to opioids with hyper polarization, reflecting an increase in K+ conductance. $Ca2^{+}$ influx into nerve terminals during excitation is decreased, leading to a decreased release of excitatory transmitters and decreased synaptic activity.
- Depending on the cell population affected; this synaptic inhibition translates into a depressant or excitant effect.

OPIOID ANALGESICS

MORPHINE AND RELATED OPIOIDS

MEPERIDINE AND CONGENER

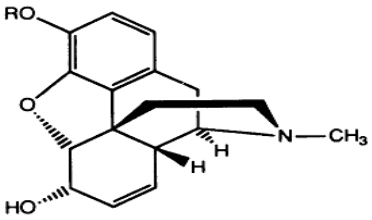
METHADONE AND CONGENER

OPIOID RECEPTOR ANTAGONIST AND PARTIAL ANTAGONIST

Structure Activity Relationship

THE PHENOLIC OH: -

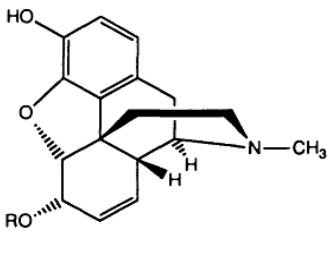
- Codeine is the methyl ether of morphine and is also present in opium. It is used for treating moderate pain, coughs, and diarrhea.
- By methylating the phenolic OH, the analgesic activity drops drastically and codeine is only 0.1 per cent as active as morphine. This drop-in activity is observed in other analogues containing a masked phenolic group. Clearly, a free phenolic group is crucial for analgesic activity.

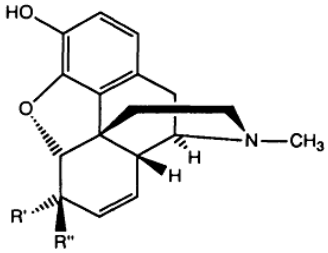


R = Me CODEINE
R = Et ETHYLMORPHINE
R = Acetyl 3-ACETYLMORPHINE
} Analgesic Activity ↓

THE 6-ALCOHOL

- The complete loss of the alcohol group does not decrease analgesic activity andhas the opposite effect. Again, it has to be emphasized that the testing of analgesics has generally been done in vivo and that there are many ways in which improved activity can be achieved.





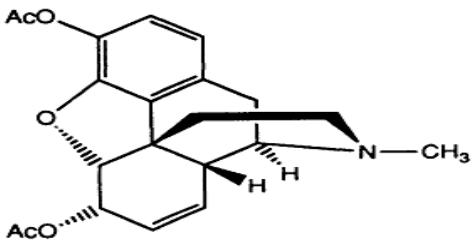
R		Analgesia wrt morphine
Me	Heterocodeine	5x
Et	6-Ethylmorphine	greater
Acetyl	6-Acetylmorphine	4x

R'	R"	Analgesia wrt morphine
H	OH	Increased
H	H	or
Ketone	Ketone	similar

Effect of loss of alcohol group on analgesic activity

In these examples, the improvement in activity is due to the pharmacodynamic properties of these drugs rather than their activity for the analgesic receptor.

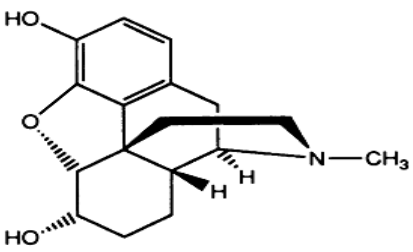
- They enter the brain more easily and accumulate at the receptor sites in greater concentrations; hence, the better analgesic activity.
- It is interesting to compare the activities of morphine, 6-acetylmorphine, and diamorphine (heroin). The most active (and the most dangerous) compound of the three is 6-acetylmorphine. It is four times more active than morphine.
- Heroin is also more active than morphine by a factor of two, but less active than 6- acetyl morphine. 6-Acetylmorphineis less polar than morphine and will enter the brain more quickly and in greater concentrations. The phenolic group is free and therefore it will interact immediately with the analgesic receptors.



- Heroin has two polar groups which are masked and is therefore the most efficient compound of the three to cross the blood-brain barrier.
- However, before it can act at the receptor, the acetyl group on the phenolic group has to be removed by esterases in the brain. Therefore, it is more powerful than morphine because it enters the brain more easily, but it is less powerful than 6-acetylmorphine because the dactyl group has to be removed before it can act.
- Heroin and 6-acetylmorphine are both more potent analgesics than morphine .Unfortunately, they also have greater side-effects and have severe tolerance and dependence characteristics. Heroin is still used to treat terminally ill patients, such as that dying of cancer, but 6-acetylmorphine is so dangerous that its synthesis is banned in many countries.
- To conclude, the hydroxyl group is not required for analgesic activity and its removal can be beneficial to analgesic activity.

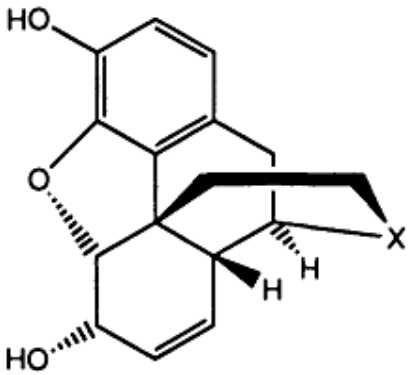
THE DOUBLE BOND AT 7-8

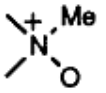
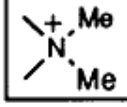
- Several analogues including dihydromorphine have shown that the double bond is not necessary for analgesic activity.



THE N-METHYL GROUP

- The N-oxide and the N-methyl quaternary salts of morphine are both inactive, which might suggest that the introduction of charge destroys analgesic activity.
- However, we have to remember that these experiments were done on animals and it is hardly surprising that no analgesia is observed, since a charged molecule has very little chance of crossing the blood-brain barrier.
- If these same compounds are injected directly into the brain, a totally different result is obtained and both these compounds are found to have similar analgesic activity to morphine. This fact, allied with the fact that neither compound can lose its charge, shows that the nitrogen atom of morphine is ionized when it binds to the receptor.



X		Analgesic Activity wrt morphine
NH	Normorphine	25%
	N-Oxide	0%
	Quaternary salt	0%

Effect of introduction of charge group on analgesic activity

- The replacement of the N-methyl group with a proton reduces activity but does not eliminate it. The secondary NH group is more polar than the tertiary N-methyl group and therefore ands it more difficult to cross the blood-brain barrier, leading to a dropin activity. The fact that significant activity is retained despite this shows that the methyl substituent is not essential to activity.

However, the nitrogen itself is crucial. If it is removed completely, all analgesicactivity is

lost. To conclude, the nitrogen atom is essential to analgesic activity and interacts with the analgesic receptor in the ionized form.

THE AROMATIC RING

- The aromatic ring is essential. Compounds lacking it show no analgesic activity.

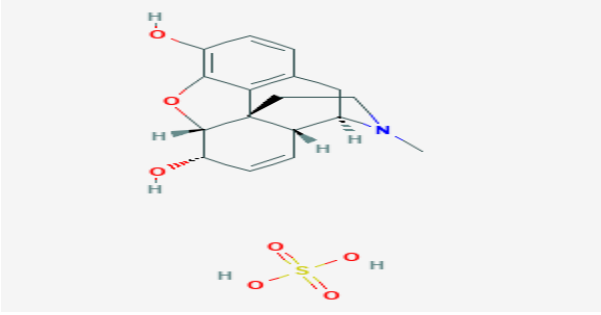
THE ETHER BRIDGE

- The ether bridge is not required for analgesic activity.

1. Masking the phenolic 3-OH group by etherification to methyl ether (codeine) and ethyl ether (ethyl morphine) results in about one tenth the analgesic activity of morphine. The phenolic OH may augment through hydrogen bonding the binding of the opiate pharmacophore to its receptor binding site. The ethers are not easily hydrolyzed to OH group.
2. Esterification of 3-OH group gives compound more active than morphine
3. Blockade of the alcoholic 6-OH by acetylation on its conversion to carbonyl function, gives compounds several times more active. Inversion of 6-OH group and its removal altogether gave compound with enhanced analgesic potency.
4. Introduction of 14-OH substituent gave compounds several times more potent as analgesics as compared to parent drugs.
5. Replacement of N-CH3 by –N-C2H5 resulted in only a slight fall in analgesic response. More hydrophobic group such as propyl, pentyl, hexyl and phenylethyl gave an increase in activity. N –allyl morphine has powerful antagonist activity
6. Breaking of the ether bridge and opening of piperidine ring cause decrease in activity
7. Hydrogenation of the C7-C8 double bond produces compounds with equal or superior analgesic action
8. Substitution other than 3 position in the aromatic ring results in reduction of opioid actions.

Drugs

1. Morphine sulphate



Uses:

• Preservative-free Morphine Sulfate Injection is indicated for the management of pain where use of an opioid analgesic by PCA is appropriate.

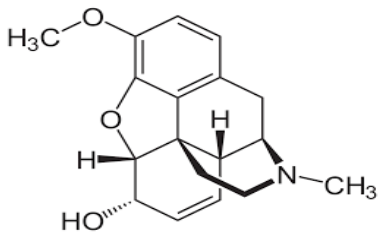
• It was developed for administration via a compatible Hospira infusion device

Adverse Effects:

• The most serious side effect is respiratory depression. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing

• The depression may be severe and could require intervention While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines.

2. Codeine



Uses:

• Codeine is used to treat mild to moderate pain and to relieve coughing.

• It is also used to treat diarrhea and diarrhea-predominant irritable bowel syndrome, although loperamide (which is available without a prescription for milder diarrhea), diphenoxylate, paregoric, or even laudanum is more frequently used to treat severe diarrhea.

• Weak evidence indicates that it is useful in cancer pain, but it is associated with increased side effects.

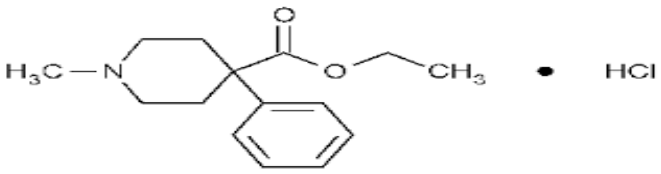
• The American Academy of Pediatrics does not recommend its use in children due to side effects. The FDA lists age under 12 years old as a contraindication to use.

Adverse effects:

• Common adverse effects associated with the use of codeine include drowsiness and constipation.

• Less common are itching, nausea, vomiting, dry mouth, miosis, orthostatic hypotension, urinary retention, euphoria, and dysphoria. • Rare adverse effects include anaphylaxis, seizure, acute pancreatitis, and respiratory depression.

3. Meperidine hydrochloride(Pethidine)



Uses:

• Pethidine is the most widely used opioid in labor and delivery but has fallen out of favor in some countries such as the United States in favor of other opioids, due to its potential drug interactions (especially with serotonergic) and its neurotoxin metabolite, norpethidine.

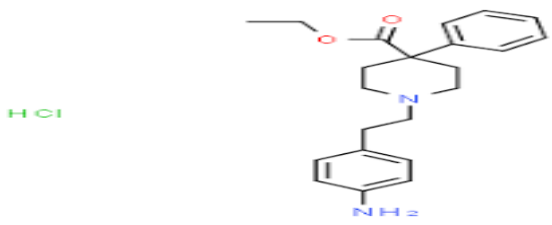
• It is still commonly used in the United Kingdom and New Zealand and was the preferred opioid in the United Kingdom for use during labor, but has been replaced largely by hydromorphone since the mid-2000s.

• Pethidine is the preferred painkiller for diverticulitis, because it decreases intestinal intraluminal pressure.

Adverse effects:

• The major hazards of Meperidine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest. • The most frequently observed adverse reactions included lightheadedness, dizziness, sedation, and nausea, vomiting, and sweating.

4. Anilerdine hydrochloride



Uses:

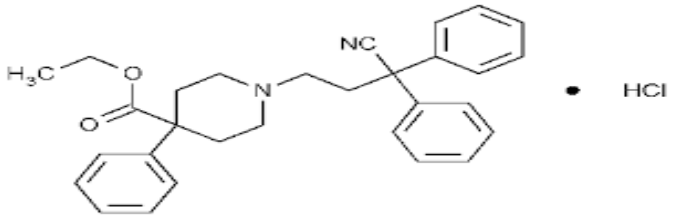
• Anilerdine is a synthetic opioid and strong analgesic medication. • It is a narcotic pain reliever used to treat moderate to severe pain.

• Narcotic analgesics act in the central nervous system (CNS) to relieve pain. Some of their side effects are also caused by actions in the CNS.

Adverse effects:

Anilerdine is absorbed by all routes of administration. • Symptoms of overexposure include dizziness, perspiration, a feeling of warmth, dry mouth, visual difficulty; itching, euphoria, restlessness, nervousness and excitement have been reported.

5. Diphenoxylate hydrochloride



Uses:

• This medication is used to treat diarrhea.

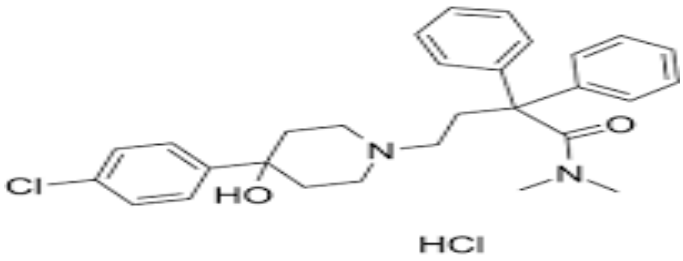
• It helps to decrease the number and frequency of bowel movements. It works by slowing the movement of the intestines.

• Diphenoxylate is similar to narcotic pain relievers, but it acts mainly to slow the gut.

Adverse effects:

• drowsiness, dizziness, feeling restless
• headache
• numbness in your hands or feet
• depression, not feeling well
• confusion, feelings of extreme happiness
• red or swollen gums
• dry mouth, nose, or throat;
• Nausea, vomiting, upset stomach, loss of appetite.

6. Loperamide hydrochloride



Uses:

• This medication is used to treat sudden diarrhea (including traveler's diarrhea).

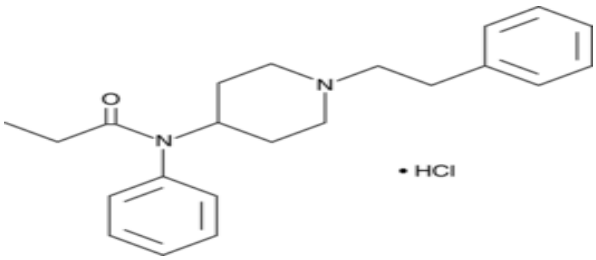
• It works by slowing down the movement of the gut.

• This decreases the number of bowel movements and makes the stool less watery. Loperamide is also used to reduce the amount of discharge in patients who have had an ileostomy.

Adverse effects:

• Dizziness.
• Drowsiness.
• Dry mouth.
• Vomiting.
• Constipation.
• Fatigue.
• Stomach pain, discomfort, or enlargement

7. Fentanyl citrate



Uses:

• Intravenous fentanyl is often used for anesthesia and to treat pain.

• To induce anesthesia, it is given with a sedative-hypnotic, like propofol or thiopental, and a muscle relaxant.

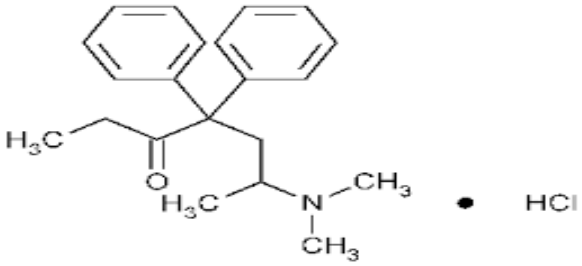
• To maintain anesthesia, inhaled anesthetics and additional fentanyl may be used. These are often given in 15-30minute intervals throughout procedures such as endoscopy, surgeries, and in emergency rooms.

Adverse effects:

• Fentanyl's most common side effects, which affect more than 10% of people, include diarrhea, nausea, constipation, dry mouth, somnolence, confusion, asthenia (weakness), sweating.

• Less frequently, in 3-10% of people, fentanyl can cause abdominal pain, headache, fatigue, anorexia and weight loss, dizziness, nervousness, hallucinations, anxiety, depression, flu-like symptoms, dyspepsia (indigestion), shortness of breath, hypoventilation, apnoea, and urinary retention. • Fentanyl use has also been associated with aphasia. Despite being a more potent analgesic, fentanyl tends to induce less nausea, as well as less histamine-mediated itching, than morphine.

8. Methadone hydrochloride



Uses:

• Methadone is used for the treatment of opioid use disorder.

• It may be used as a maintenance therapy or in shorter periods for detoxification to manage opioid withdrawal symptoms.

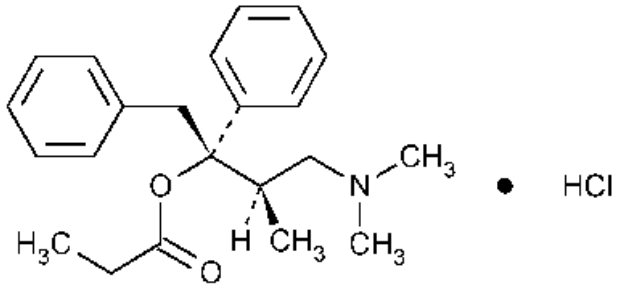
• A 2009 Cochrane review found methadone was effective in retaining people in treatment and in the reduction or cessation of heroin use as measured by self-report and urine/hair analysis but did not affect criminal activity or risk of death.

• Treatment of opioid-dependent persons with methadone follows one of two routes: maintenance or detoxification. Methadone maintenance therapy (MMT) usually takes place in outpatient settings.

Adverse effects:

• Sedation
• Diarrhea or constipation
• Flushing
• Perspiration and sweating
• Heat intolerance
• Dizziness or fainting
• Weakness

9. Propoxyphene Hydrochloride



Uses

• Propoxyphene is in a group of drugs called narcotic pain relievers.

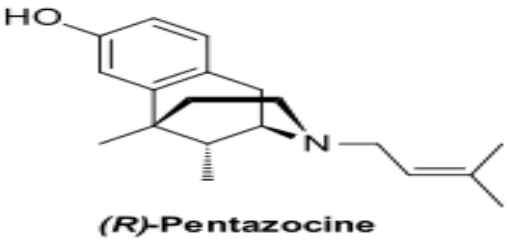
• Propoxyphene is used to relieve mild to moderate pain.

• Propoxyphene may also be used for purposes other than those listed in this medication guide.

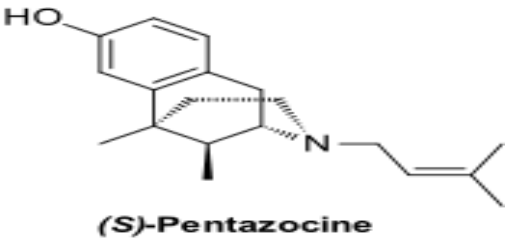
Adverse effects:

• lightheadedness
• drowsiness
• dizziness
• sleepiness
• constipation

10. Pentazocine



(R)-Pentazocine



(S)-Pentazocine

Uses:

• Pentazocine injection is used to relieve moderate to severe pain.

• It may also be used before surgery or with a general anesthetic (medicine that puts you to sleep).

• Pentazocine belongs to the group of medicines called narcotic analgesics (pain medicines). It acts on the central nervous system (CNS) to relieve pain.

Adverse effects:

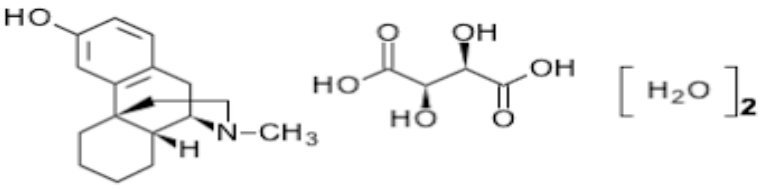
• noisy breathing, sighing, shallow breathing

• a light-headed feeling, like you might pass out

• severe constipation

• pain, burning, irritation, or skin changes where the injection was given.

11. Levorphanol tartarate



D00841

Uses:

• This medication is used to treat moderate to severe pain.

• Levorphanol is an opioid (narcotic) pain reliever.

• It acts on certain centers in the brain to give you pain relief.

Adverse effects:

• Nausea,

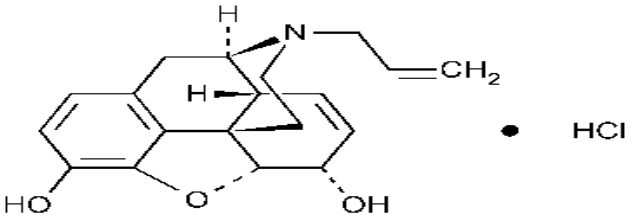
• vomiting, constipation, light headedness,

• dizziness, drowsiness, dry mouth,

• Flushing, or vision problems may occur.

• If any of these effects persist or worsen, tell your doctor or pharmacist promptly

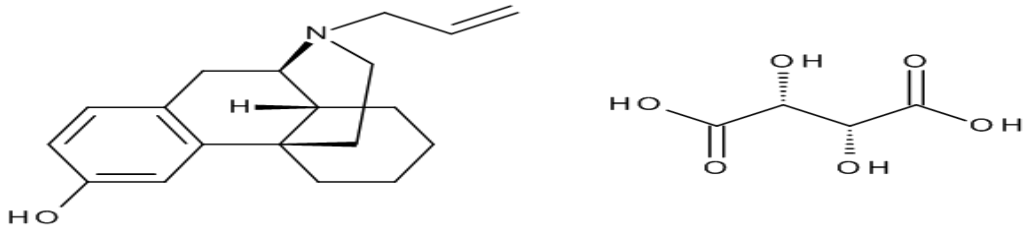
12. Nalorphine hydrochloride



Adverse effects:

Nalorphine produces side effects such as dysphoria, anxiety, confusion, and hallucinations, and for this reason, is no longer used medically.

13. Levallorphantartarate

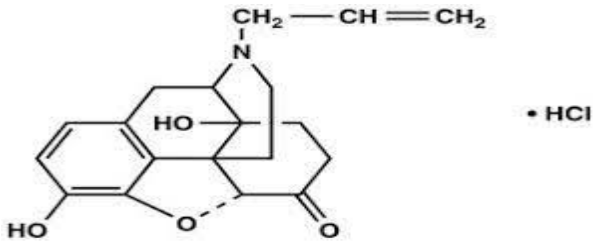


Uses: Levallorphan was formerly widely used in general anesthesia, mainly to reverse the respiratory depression produced by opioid analgesics and barbiturates used for induction of surgical anaesthesia whilst maintaining a degree of analgesia.

Adverse effects:

• Levallorphan can produce severe mental reactions at sufficient doses including hallucinations, dissociation, and other psychotomimetic effects, dysphoria, anxiety, confusion, dizziness, disorientation, derealization and feelings of drunkenness.

14. Naloxone hydrochloride:



Uses:

• It is an opioid antagonist used for the complete or partial reversal of opioid overdose, including respiratory depression.

• Narcan is also used for diagnosis of suspected or known acute opioid overdose and also for blood pressure support in septic shock.

• Narcan is available in generic form.

Adverse effects:

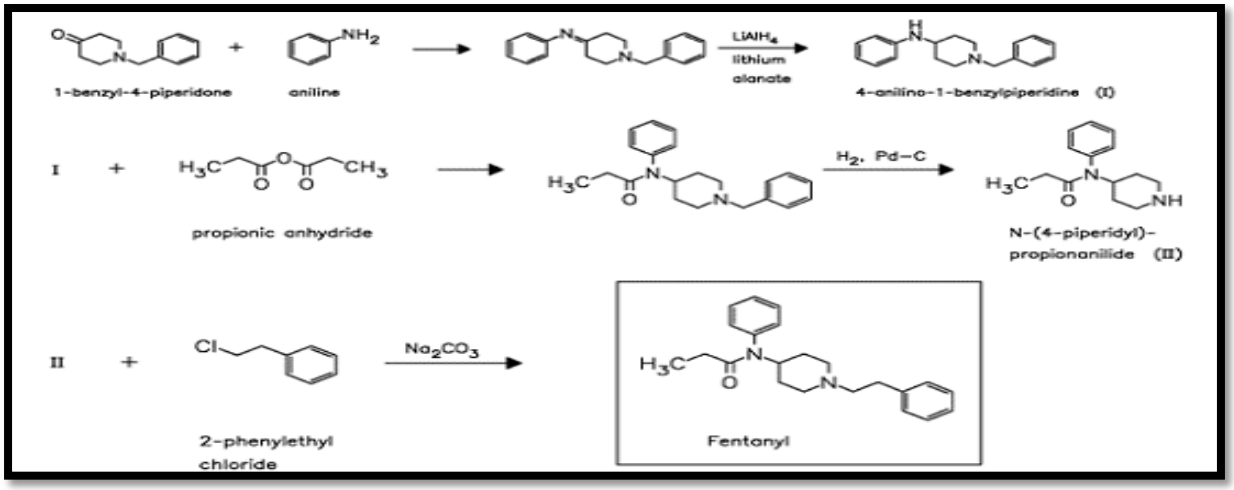
• nausea, vomiting, diarrhea, stomach pain;

• fever, sweating, body aches, weakness;

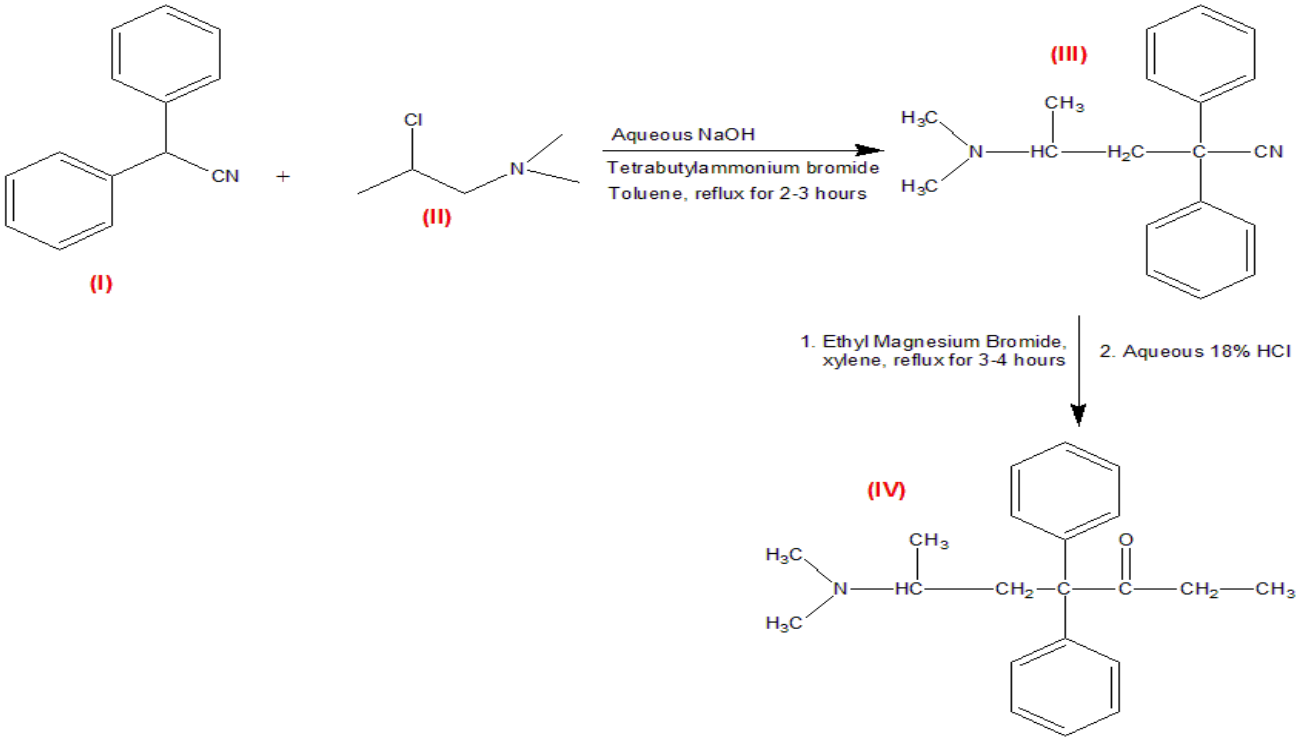
• tremors or shivering, fast heart rate, pounding heartbeats, increased blood pressure;

• Feeling nervous, restless, or irritable.

Synthesis of Fentanyl citrate



Methadone hydrochloride



Anti-inflammatory drugs

Inflammation

Inflammation can be defined as a defensive but exaggerated local tissue reaction in response to exogenous or endogenous injury. It is a complex phenomenon, comprising of biochemical as well as immunological factors. It is recognized by following symptoms: -

1) Redness
2) Heat
3) Pain
4) Loss of sensation

- Tissue damage initiates or activates the local release of various chemo tactic factors that provoke directly or indirectly the appearance of the mediators of pain and inflammation. These factors include:
    1) Amines
    2) Proteases
    3) Prostaglandins.
    4) Hageman factor
    - The non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs to treat the disorder caused due to inflammation
    - Inflammation is an attempt to dispose of microbes, toxins, or foreign material at the site to injury, to prevent their spread to other tissues, and to prepare the site for repair in an attempt to restore tissue homeostasis.

Mechanism of action of NSAIDS: Arachidonic acid is the main precursor for substrate cyclooxygenase (prostaglandin synthetase) leading to the production of prostaglandin F, D and E, prostacyclin and thromboxane. Arachidonic acid also acted upon by the enzyme lipoxygenase leading to the formation of 12- and 5-hydroxyeicosatetraenoic acid (HETE) and leukotrienes. The NSAIDS act by blocking the action of cyclooxygenase and thus inhibiting the synthesis of endogenous prostaglandins. There are two forms of cyclooxygenase termed as cyclooxygenase-I(COX-1) and cyclooxygenase-II (COX-2). Most of the nonsteroidal anti-inflammatory drugs inhibit activities of both cyclooxygenase-1 which is a constitutive enzyme found in most normal cells and tissue and cyclooxygenase-2 which is induced in setting of inflammation. Inhibition of COX-1 results in unwanted side effects particularly those leading to gastric ulcers, which results from decreased prostaglandin formation. This accounts for the markedly reduced gastric disturbances with the use of selective COX-2

inhibitors. Aspirin and NSAIDS do not inhibit formation of leukotrienes, which contributes to inflammation. Glucocorticoids which also have anti-inflammatory actions suppress expression of COX-2 and thus mediated prostaglandin synthesis. Being organic NSAIDS get easily absorbed by the gastrointestinal tract and are highly bound to plasma proteins

CLASSIFICATION OF NSAIDs

Salicylates

- Aspirin
- Salicylic acid and its salts
- Diflunisal

Propionoic acid derivatives

- Ibuprofen
- Naproxen
- Fenoprofen
- Ketoprofen
- Dexketoprofen
- Dexibuprofen

Acetic acid derivatives

- Indomethacin
- Tolmetin
- Sulindac
- Ketorolac

Enolic acid derivatives

- Piroxicam
- Meloxicam
- Tenoxicam
- Droxicam
- Phenylbutazone
- Lornoxicam

Anthranilic acid derivatives

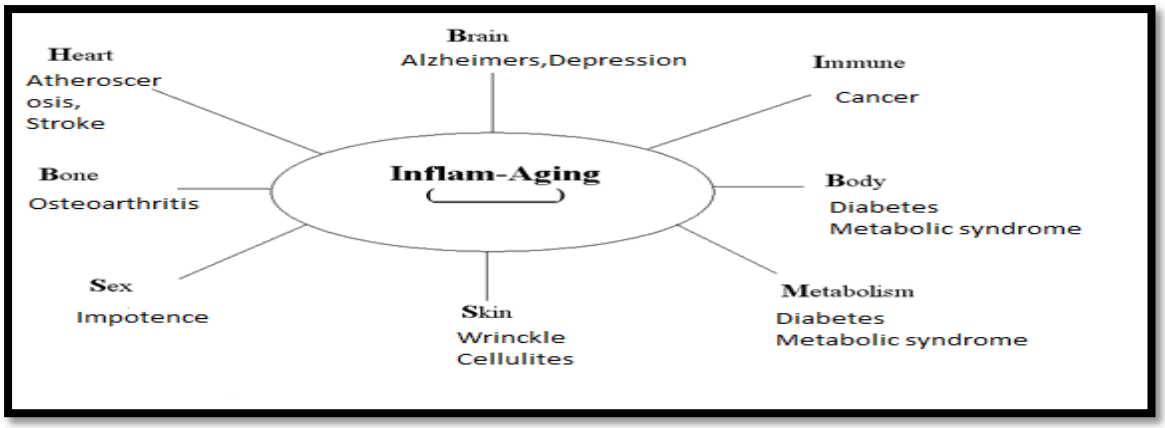
- Mefenamic acid
- Meclofenamic acid
- Flufenamic acid
- Tolfenamic acid

COX-2 inhibitors

- Celecoxib
- Rofecoxib
- Parecoxib
- Etoricoxib

Sulfonanilides

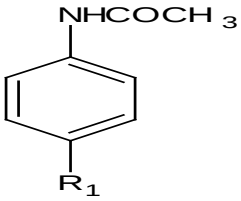
- Nimesulide



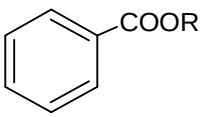
Causes of Inflammation

SALICYLIC ACID DERIVATIVES

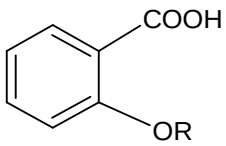
SAR: -



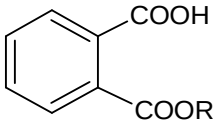
1. The drug most widely used to treat arthritis is salicylic acid. The simplest active anti-inflammatory compound is salicylic acid. The active moiety appears to be the salicylates anion. The carboxyl group is necessary for activity and the carboxyl group must be adjacent to it. Side effects of salicylates, particularly the GI effects, appear to be associated with the carboxylic acid functional group.
2. Reducing activity of this group (carboxylic acid group) by converting to an amide – Salicylamide maintains the analgesic action of salicylic acid derivative but eliminates the anti-inflammatory properties.
3. The derivative of salicylic acid is of two types – Type I & Type II (a & b)



Type I



Type II (a)

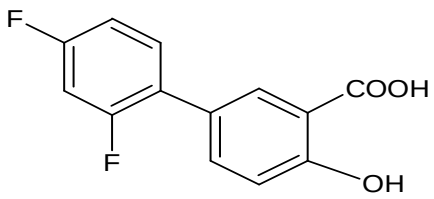


Type II (b)

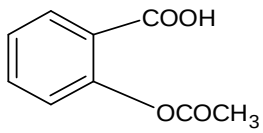
Type I – represents those that are formed by modifying the carboxyl groups e.g., Salts, ester or amide

Type II – (a & b) those that are derived by substitution on the hydroxyl group of salicylic acid.

4. Substitution on either the carboxyl (type I) or phenolic (type II a) hydroxyl groups may effect potency and toxicity. Benzoic acid itself has weak activity.
5. Placing the phenolic hydroxyl group Meta or Para to carboxyl group abolishes activity.
6. Substitution of halogen atoms on aromatic rig enhances potency and toxicity. E.g. 5-chloro salicylic acid.
7. 4-amino salicylic acid is at active substitution of amino group at position 4 abolishes activity.
8. Introduction of a methyl group (adjacent to the phenolic OH group) I aspirin and in salicylic acid produces 3-methyl aspirin acid 3-salicylic acid have slower metabolic excretion.
9. Substitution of aromatic ring at position 5 of salicylic acid increase anti- inflammatory activity. E.g., Diflunisal



10. **Aspirin acetyl salicylic acid**

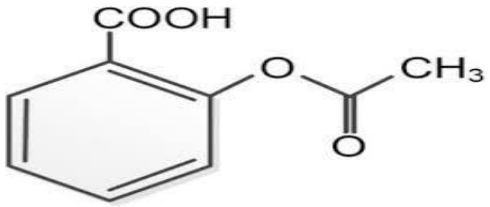


Type II (b) derivative of salicylic acid

Potent agent but has more adverse effect due to presence of o-acetyl group e.g., blood loss due to GIT hemorrhage. Diflunisal has fewer side effectthan aspirin.

The acute gastric irritancy of salicylates associated with its carboxylic acid group. It can be reduced by modification of the acidic characteristic of the carboxylic group of compounds. E.g., by esterification of carboxylic group.

1. **Aspirin**



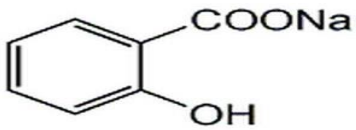
Therapeutic uses:

- Aspirin is used in the treatment of a number of conditions, including fever, pain, rheumatic fever, and inflammatory conditions, such as rheumatoid arthritis, pericarditis, and Kawasaki disease
- Lower doses of aspirin have also been shown to reduce the risk of death from a heart attack, or the risk of stroke in people who are at high risk or who have cardiovascular disease, but not in elderly people who are otherwise healthy.
- There is some evidence that aspirin is effective at preventing colorectal cancer, though the mechanisms of this effect are unclear.

Adverse Effects: -

- Aspirin should not be taken by people who are allergic to ibuprofen or naproxen, or who have salicylate intolerance or a more generalized drug intolerance to NSAIDs, and caution should be exercised in those with asthma or NSAID-precipitated bronchospasm.
- Owing to its effect on the stomach lining, manufacturers recommend people with peptic ulcers, mild diabetes, or gastritis seek medical advice before using aspirin.

1. **Sodium Salicylate**



Therapeutic Uses: -

- It is used in medicine as an analgesic and antipyretic. Sodium salicylate also acts as nonsteroidal anti-inflammatory drug (NSAID) and induces apoptosis in cancer cells and also necrosis.
- It is also a potential replacement for aspirin for people sensitive to it.

- It may also be used as a phosphor for the detection of vacuum ultraviolet radiation and electrons.

Adverse Effects: -

• Heartburn.

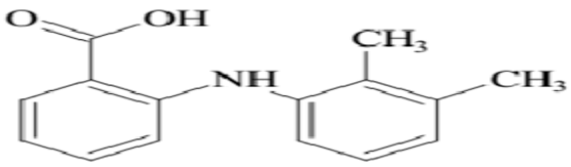
• Irritation of the Stomach or Intestines.

• Nausea.

• Stomach Cramps.

• Vomiting

2. Mefenamic acid



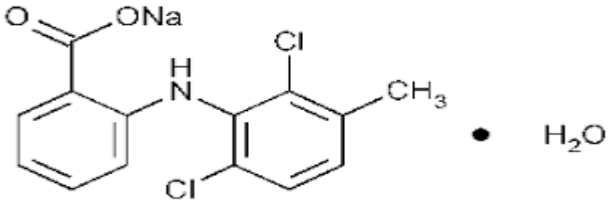
Therapeutic Uses

- Mefenamic acid is used to treat moderate pain and menstrual pain.
- There is evidence that supports the use of mefenamic acid for perimenstrual migraine headache prophylaxis, with treatment starting 2 days prior to the onset of flow or 1 day prior to the expected onset of the headache and continuing for the duration of menstruation.

Adverse Effects

- Headaches, nervousness, and vomiting.
- Serious side effects may include diarrhea, hematemesis (vomiting blood), hematuria (blood in urine), blurred vision, skin rash, itching and swelling, sore throat and fever.
- It has been associated with acute liver damage.

3. Meclofenamate Sodium



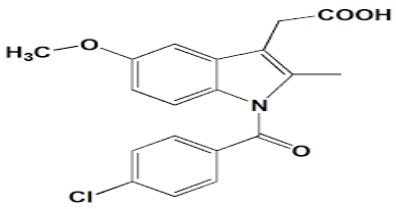
Therapeutic Uses

- Used for joint, muscular pain, arthritis and dysmenorrhea.
- It is a member of the anthranilic acid derivatives (or fenamate) class of NSAID drugs and was approved by the FDA in 1980.
- Like other members of the class, it is a COX inhibitor and prevents formation of prostaglandins.

Adverse Effects

• Nausea.
• Vomiting.
• Heartburn.
• Dizziness.
• Drowsiness.
• Diarrhea.

4. Indomethacin



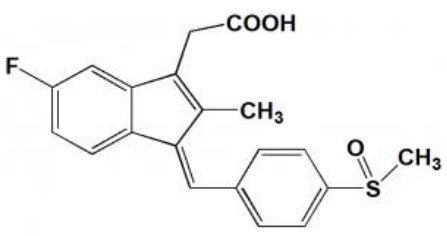
Therapeutic Uses

• rheumatoid arthritis
• ankylosing spondylitis
• osteoarthritis
• gouty arthritis

Adverse Effects

• Edema (swelling due to fluid retention)
• Hyperkalemia (high potassium levels)
• Hypernatremia (high sodium levels)
• Hypertension

5. Sulindac



Therapeutic Uses

• Like other NSAIDs, it is useful in the treatment of acute or chronic inflammatory conditions.

• This is thought to help maintain constant blood levels with reduced gastrointestinal side effects

Adverse Effects

• nausea, vomiting, stomach pain, indigestion, loss of appetite;

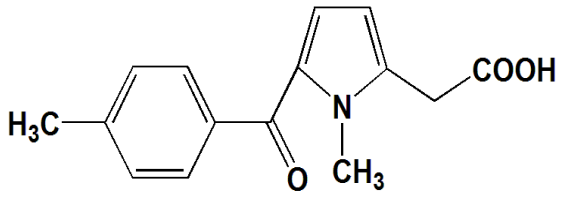
• Diarrhea, constipation.

• Headache, dizziness, nervousness.

• Itching, rash.

• Ringing in your ears

6.**Tolmetin**



Therapeutic uses

• Tolmetin is used alone or with other treatments to reduce pain, swelling, and joint stiffness from rheumatoid arthritis and osteoarthritis. • It is also used for juvenile rheumatoid arthritis.

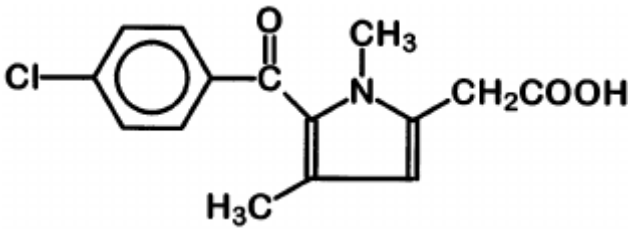
Adverse Effects

• Tolmetin can also increase the risk of gastrointestinal conditions such as perforation or bleeding, which is fatal.

• Antacids can be taken with Tolmetin to relieve stomachaches that often occur.

• Overdose can result in drowsiness, nausea, epigastric pain, and vomiting.

7. Zomepirac



Therapeutic Uses

• Zomepirac was indicated for the management of mild to severe pain.

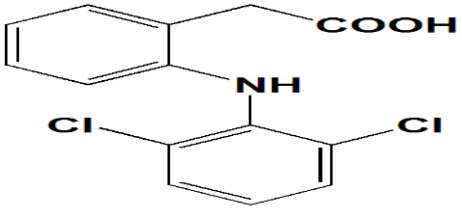
• Multiple clinical trials demonstrated zomepirac to be more effective than aspirin or codeine alone and to be as effective as analgesic combinations containing codeine or other opioids.

Adverse Effects

• Zomepirac is associated with an increased incidence of urogenital symptoms such as dysuria and pyuria.

• Because of tumorigenicity in rats, the drug is contraindicated in children, pregnant women, and nursing mothers.

8. Diclofenac



Therapeutic Uses

• Diclofenac is used to treat pain, inflammatory disorders, and dysmenorrhea.

Adverse Effects

• Indigestion, gas, stomach pain, nausea, vomiting.

• Diarrhea, constipation.

• Headache, dizziness, drowsiness.

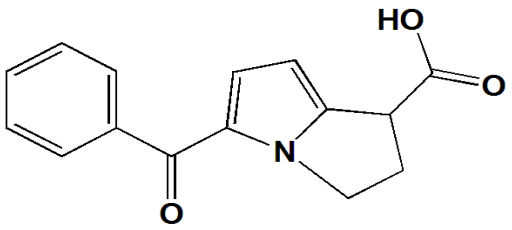
• Stuffy nose.

• Itching increased sweating.

• Increased blood pressure.

• Swelling or pain in your arms or legs.

9. Ketorolac



Therapeutic Uses:-

• Ketorolac is used for short-term management of moderate to severe pain.

• It is usually not prescribed for longer than five days, due to its potential to cause kidney damage.

• Ketorolac is effective when administered with paracetamol to control pain in newborns because it does not depress respiration as do opioids. • Ketorolac is also an adjuvant to opioids medications and improves pain relief.

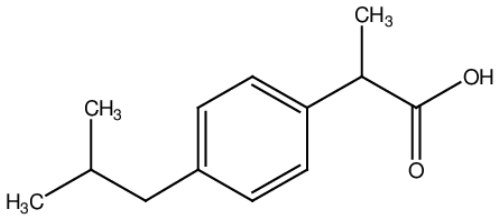
Adverse Effects: -

• Headache.

• Drowsiness.

• Indigestion.

10. Ibuprofen



Therapeutic Uses: -

• Ibuprofen is used primarily to treat fever (including post-vaccination fever), mild to moderate pain (including pain relief after surgery), painful menstruation, osteoarthritis, dental pain, headaches, and pain from kidney stones.

• About 60% of people respond to any NSAID; those who do not respond well to a particular one may respond to another.

• It is used for inflammatory diseases such as juvenile idiopathic arthritis and rheumatoid arthritis.

Adverse Effects: -

• upset stomach, mild heartburn, nausea, vomiting;

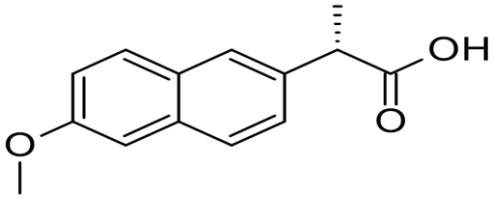
• bloating, gas, diarrhea, constipation;

• dizziness, headache, nervousness;

• decreased appetite;

• mild itching or rash;

11. Naproxen



Therapeutic Uses:-

• Naproxen's medical uses are related to its mechanism of action as an anti-inflammatory compound.

• Naproxen is used to treat a variety of inflammatory conditions and symptoms that are due to excessive inflammation, such as pain and fever (naproxen has fever-reducing, or antipyretic, properties in addition to its anti-inflammatory activity).

• Notably, not all medications that reduce fever are anti-inflammatory compounds (such as paracetamol).

Adverse Effects: -

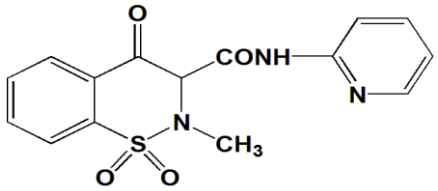
• indigestion, heartburn, stomach pain, nausea;

• headache, dizziness, drowsiness;

• bruising, itching, rash; • swelling

• ringing in your ears.

10. Piroxicam



Therapeutic Uses: -

• It is used in the treatment of rheumatoid and osteoarthritis, primary dysmenorrhea, postoperative pain; and act as an analgesic, especially where there is an inflammatory component.

• The European Medicines Agency issued a review of its use in 2007 and recommended that its use be limited to the treatment of chronic inflammatory conditions, as it is only in these circumstances that its risk-benefit ratio proves to be favorable.

Adverse Effects: -

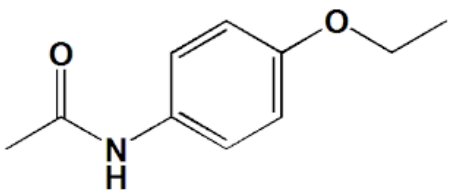
• abnormal liver function tests;

• urination problems;

• upset stomach, heartburn, loss of appetite, stomach pain, nausea, vomiting;

• gas, diarrhea, constipation.

11. Phenacetin



Therapeutic Uses: -

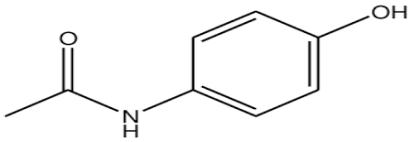
• Phenacetin has been used as a cutting agent to adulterate cocaine in the UK and Canada, due to the similar physical properties.

• Due to its low cost, phenacetin is used for research into the physical and refractive properties of crystals. It is an ideal compound for this type of research.

Adverse Effects: -

• In the United States, the Food and Drug Administration ordered the withdrawal of drugs containing phenacetin in November 1983, due to its carcinogenic and kidney-damaging properties.

12. Acetaminophen



Therapeutic Uses: -

• Acetaminophen is an analgesic used to temporarily relieve minor aches and pains due to headache, muscular aches, backache, minor pain of arthritis, the common cold, toothache, and premenstrual and menstrual cramps.

• Acetaminophen is also used to temporarily reduce fever.

Adverse Effects: -

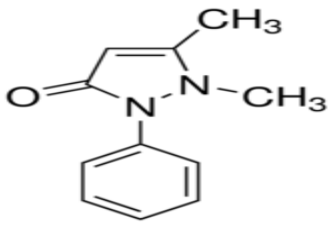
• Nausea, vomiting, loss of appetite, or severe stomach pain.

• Trouble passing urine or change in the amount of urine.

• Light-headedness, sweating, fainting, or weakness.

• Unusual bruising or bleeding.

13. Antipyrine



Therapeutic Uses: -

• Antipyrine and benzocaine is used to relieve ear pain and swelling caused by middle ear infections.

• It may be used along with antibiotics to treat an ear infection. It is also used to help remove a buildup of ear wax in the ear.

• Antipyrine and benzocaine are in a class of medications called analgesics.

Adverse Effects: -

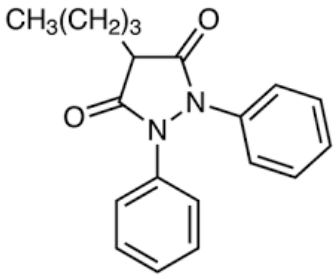
• Allergy to pyrazolones

• Nausea

• Agranulocytosis

• Hepatotoxicity

14. Phenylbutazone



Therapeutic Uses: -

• Phenylbutazone is a nonsteroidal anti-inflammatory drug (NSAID) effective in treating fever, pain, and inflammation in the body.

• As a group, NSAIDs are non-narcotic relievers of mild to moderate pain of many causes, including injury, menstrual cramps, arthritis and other musculoskeletal conditions.

Adverse Effects: -

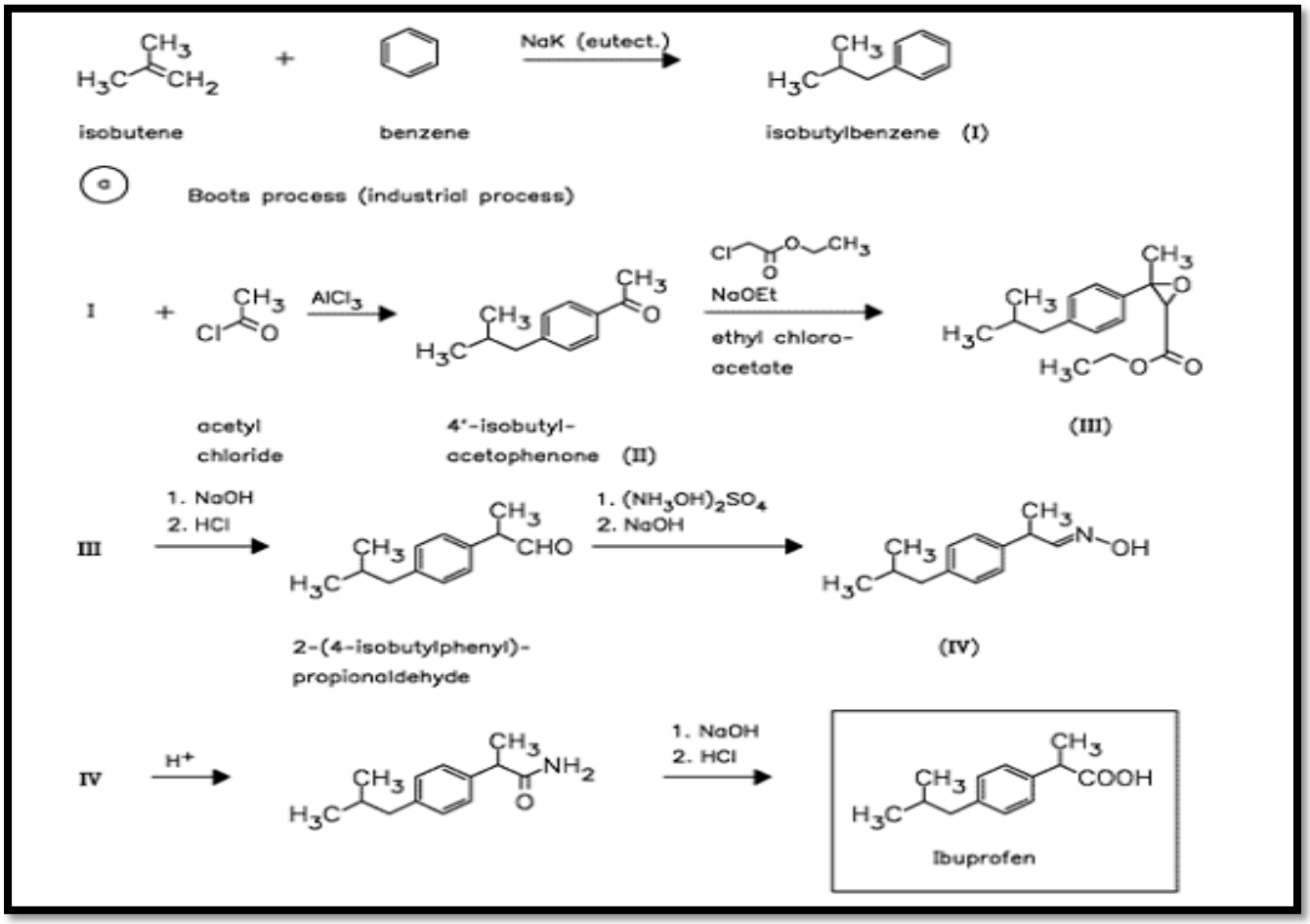
• Overdose or prolonged use can cause gastrointestinal ulcers, blood dyscrasia, kidney damage (primarily dose-dependent renal papillary necrosis), oral lesions if given by mouth, and internal hemorrhage.

• This is especially pronounced in young, ill, or stressed horses which are less able to metabolize the drug.

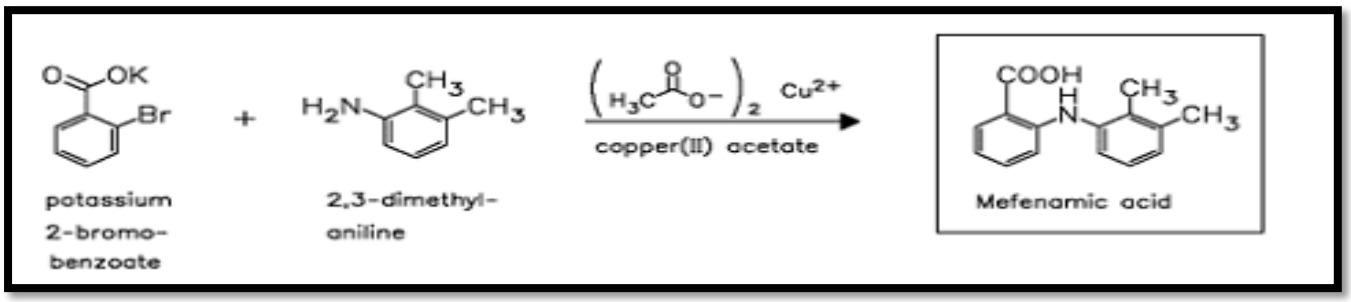
• Effects of gastrointestinal damage include edema of the legs and belly secondary to leakage of blood proteins into the intestines, resulting in decreased appetite, excessive thirst, weight loss, weakness, and in advanced stages, kidney failure and death.

Synthesis

IBUPROFEN



MEFENAMIC ACID



Long Questions:

1. Write a note on General anaesthetics.
2. What are the two types of anaesthetics? Give classification of general anaesthetic drugs.
3. Explain the drugs used as General anaesthetics.
4. Write a note on SAR of morphine analogues.
5. Write a note on opioid analgesics.
6. Explain the drugs used as narcotic analgesics.
7. Write a note on NSAIDS.
8. Write a note on Drugs used in treatment of Inflammation.
9. Write the synthesis of following drugs:
10. (A)Mefenamic acid (B)Ibuprofen
11. Write classification of NSAIDS and also explain their mechanism of action with structure activity relationship.

Short Questions:

1. Write a note on narcotic antagonists.
2. Write a note on following drugs:
    - Diphenoxylate hydrochloride
    - Pentazocine
    - Fentanyl citrate
3. What are narcotics and explain 5 drugs used as narcotic analgesics.
4. Write a note on SAR of general anaesthetics.
5. Explain briefly the mechanism of action of General anaesthetics.
6. Write synthesis of Ketamine hydrochloride and methohe
7. Write a short note on SAR of NSAIDS.
8. Explain briefly classification of NSAIDS.
9. Write anote on SAR of Opoid analgesics.