MEDICINAL CHEMISTRY-I

B. PHARM IV TH SEMESTER

UNIT-V (B)

Shailesh Pathak

NORCOTIC AND NON-NORCOTIC ANALGESIC :-

Analgesics are defined as drugs that selectively relieve pain by acting in the CNS or on peripheral pain mechanism without disturbing consciousness.

These are mainly divided into two types.

a) Narcotic analgesic

b) Non-norcotic analgesic

* Narcotic analgesics :- Narcotic analgesics are also known as opoid analgesic

They relieve severe pain by acting mainly on the CNS.

The oldest and the best narcotic analgesic are opium alkaloid.

The narcotic analgesics are potentially additive.

If intake of drug is stopped, very undesirable withdrawal effects like sever pain, sweating, salvation, Hyperventillation, restlessness and confusion are observed.

Classification :-

(1) Morphine and related drugs or Narcotic or opioid analgesic.
- Morphine sulphate
- Codeine
- Meperidine HCl
- Anileridine HCl
- Diphenoxylate HCl
- Loperamide HCl
- Fentanyl citrate *
- Methadone HCl *
- Propoxyphene HCl
- Pentazocine
- Levorphanol tartrate

(2) Narcotic antagonist.
- Nalorphine HCl
- Levallorphan tartrate
- Naloxone HCl.

(3) Anti inflammatory agent or Non opioid analg or NSAIDs / Non-narcotic or aspirin like analgesic.

SOAAPP-P

a) Non-Selective COX Inhibitor.
i) Salicylates - Sod. salicylate, Aspirin, Salol
ii) Oxicam - Tenoxicam, Piroxicam
iii) Aryl acetic acid - Indomethacin, Sulindac
iv) Propionic acid derivative → Naproxen, ~~Ibuprofen~~ Ibuprofen
v) Pyrazolone derivative - phenyl butazone, oxyphenbutazone
vi) Fenamate derivative - Mefanamic acid, Meclofenamic acid

b) Selective COX-II Inhibitor :-
- Celecoxib, Valdecoxib, Etoricoxib, Parecoxib.

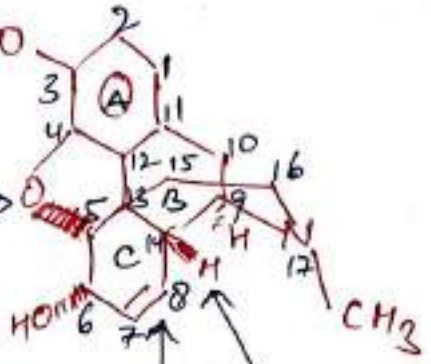
c) Preferential COX-II Inhibitor :-
- Nimesulid, Meloxicam, Nabumetone.

d) Analgesic and Antipyratic →
i) Paraaminophenol derivative - Paracetamol
ii) Pyrazolone derivative - Metamizole, Propiphenazone
iii) Benzoxazocine derivatives - Nefopam

*SAR of Morphine analogues :-

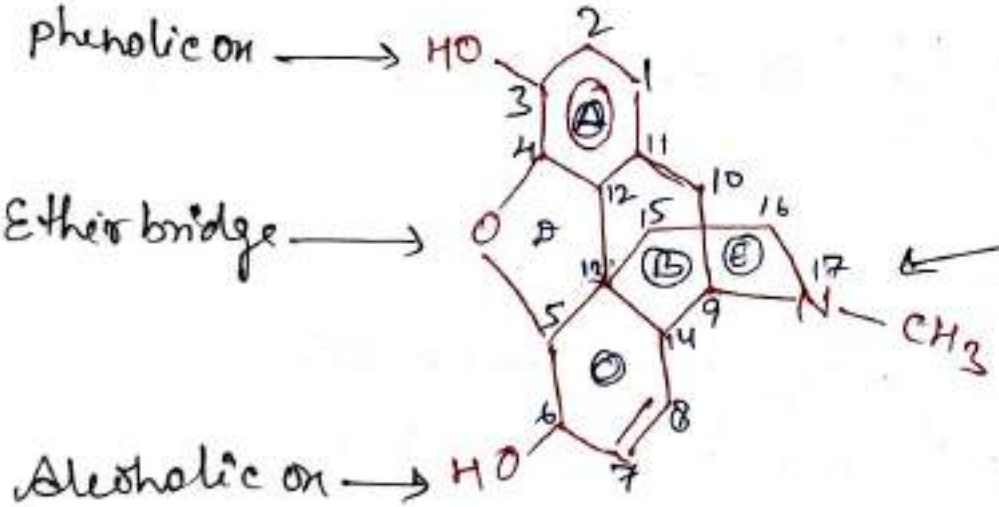
Removal of OH reduce activity

Removal Nse activity.



Introduction of OH Nse activity

Reduction Nse activity.



⇒ The ring A and the basic nitrogen are the two necessary components in every potent opoid receptor agonist.

⇒ The aromatic ring A and the tertiary nitrogen may be connected by an ethylene / propelin linkage

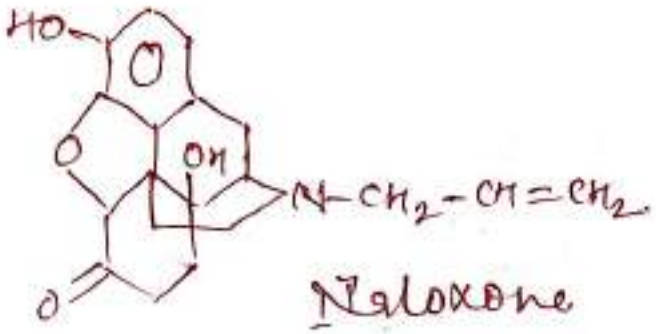
⇒

① Tertiary nitrogen atom :-

→ The substituent on nitrogen of morphine and morphine like structure is critical to degree and type of activity.

⇒ N-methyl substituents generally results in compound with good agonist properties.

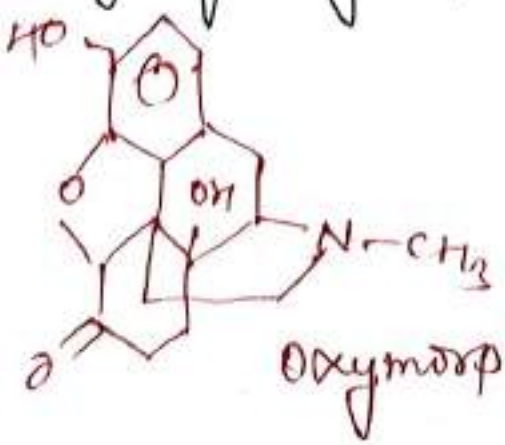
⇒ Increasing the size of the N-substituent results in antagonist eg. Naloxone



Naloxone

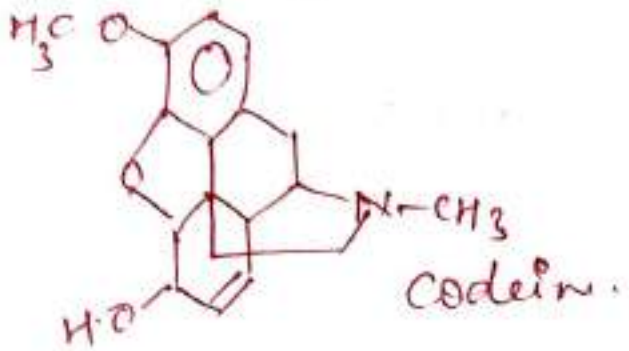
② Hydroxyl group :-

- Esterification of hydroxyl group leads to more active compound than morphine. eg. Heroin.
- Introduction of Hydroxyl group at 14th position lead to increase in activity eg. Oxymorphone.



Oxymorphone.

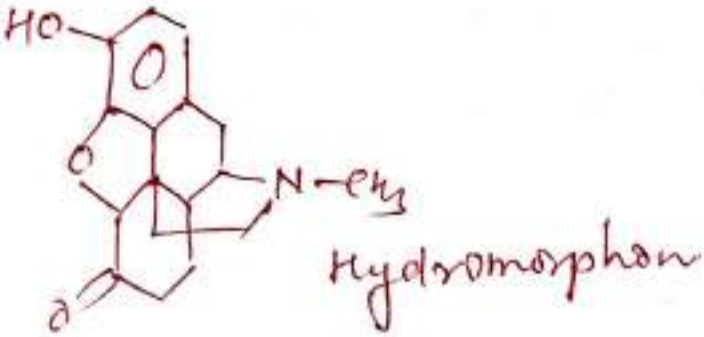
⇒ Masking the phenolic hydroxyl groups by etherification to methyl ether decrease the analgesic activity about 10 fold. eg. Codeine.



Codein.

③ Ring C –

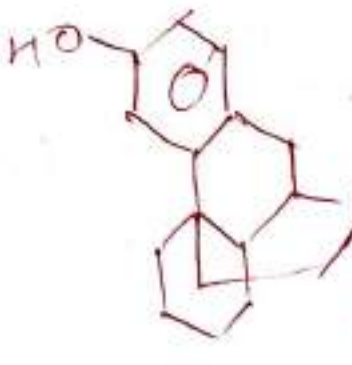
⇒ Change in the C-ring chemistry of morphine can lead to compounds with increased activity. eg- Hydromorphone is 8-10 times more potent than morphine



Hydromorphon

④ 4,5-epoxide bridge ⇒

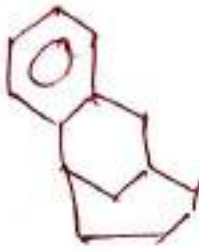
- Removal of 4,5-epoxide bridge in the morphine structure results in morphinans.
- Only levo isomer of morphinans possess opioid analgesic activity while dextro isomer have anti-tussive activity.
- Levorphanol is 8 times more potent than morphine.



Levorphanol.

⇒ Compound that lack both epoxide bridge and the C ring of morphine retain opoid analgesic activity.

Eg- Benzomorphans



Benzomorphan

*Mechanism of Action of Narcotic/Opioid agent:-

⇒ All opioid receptors are G-protein coupled receptors and inhibit adenylate cyclase.

⇒ They are also involved in

⇒ Post synaptic hyperpolarization (↑ K^+ efflux).

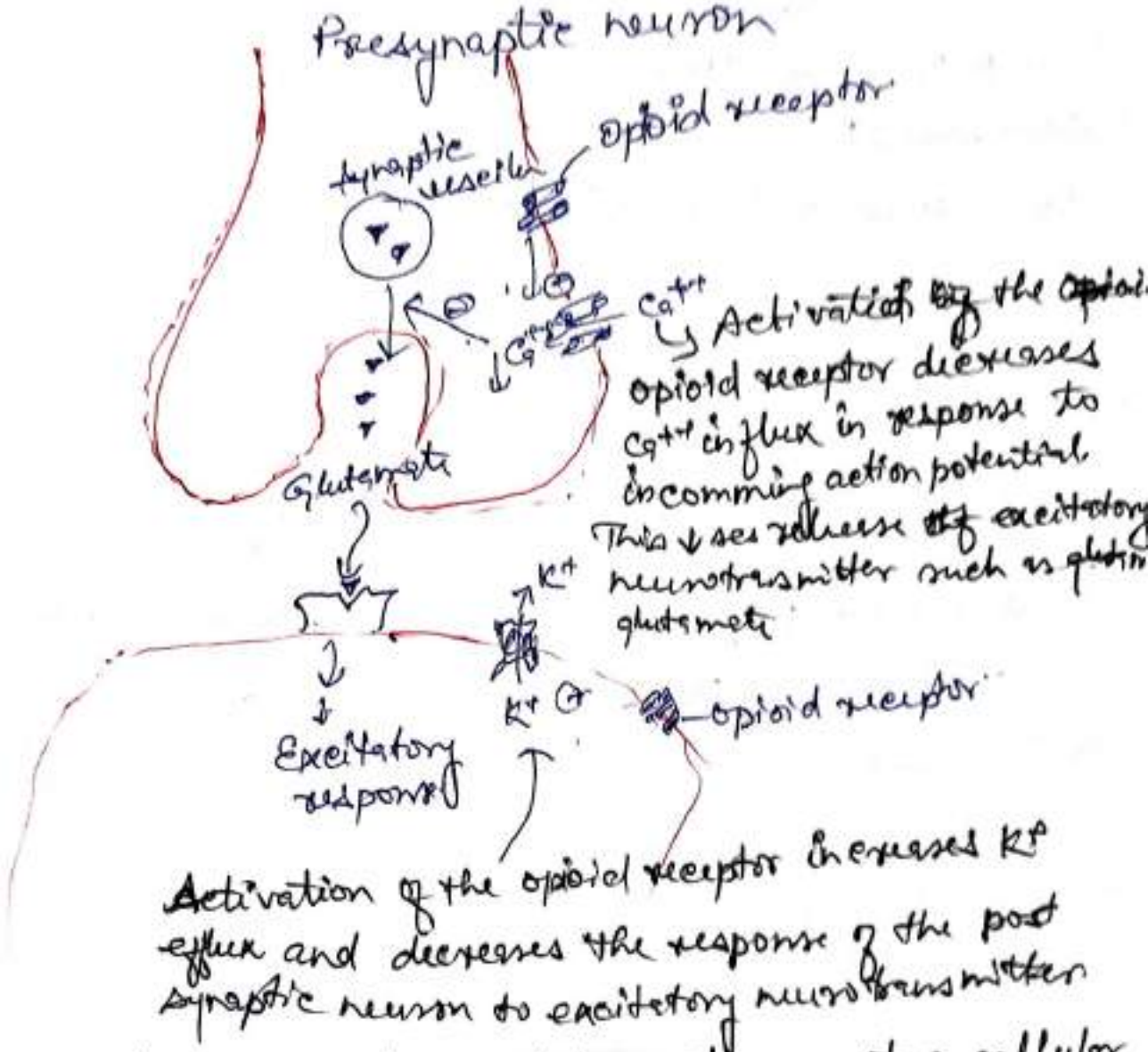
⇒ Reducing presynaptic Ca^{++} influx

thus inhibit neuronal activity

*Opioid receptor:- All opioid receptors are linked through G. protein to inhibition of adenylate cyclase. They also facilitate opening of K^+ channels (causing hyperpolarization) and inhibit opening of Ca^{++} channels (inhibit transmitter release)

* They are of 4 types.

i) μ receptor
ii) δ receptor
iii) κ receptor
iv) K receptor



⇒ Narcotic analgesics produce their actions at a cellular level by activating on opioid receptor.

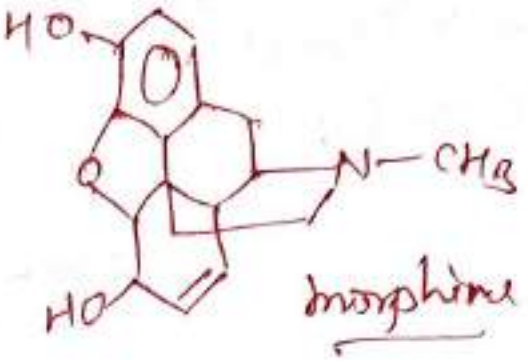
⇒ Eg- Morphine and its derivatives act as agonists of the mu and kappa opioid receptors.

⇒ These receptors are distributed throughout the CNS and also been found on peripheral afferent nerve terminals.

⇒ Opoid receptors are coupled with inhibitory G-proteins and their activation has no. of action like closing voltage sensitive Ca^{++} channels, stimulation of K^+ efflux leading to hyperpolarization which causes reduction in neuronal cell excitability

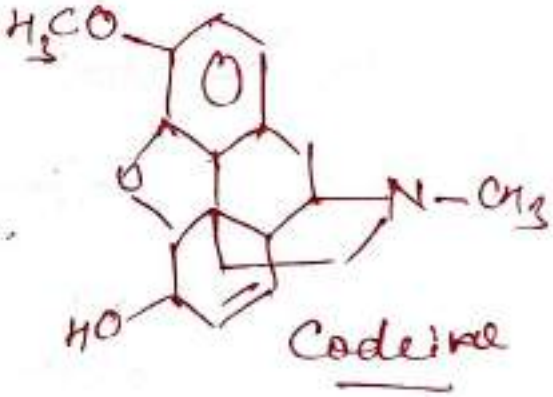
① Morphine analogues

(1) Morphine Sulphate :-



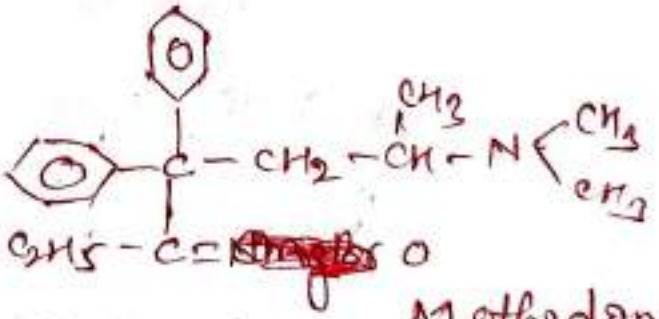
→ MI to relieve pain
- Pulmonary edema
- diarrhea
- Preanaesthetic medication

(2) Codeine :-



- Treat moderate pain and also reduce coughing
- Antitussive.

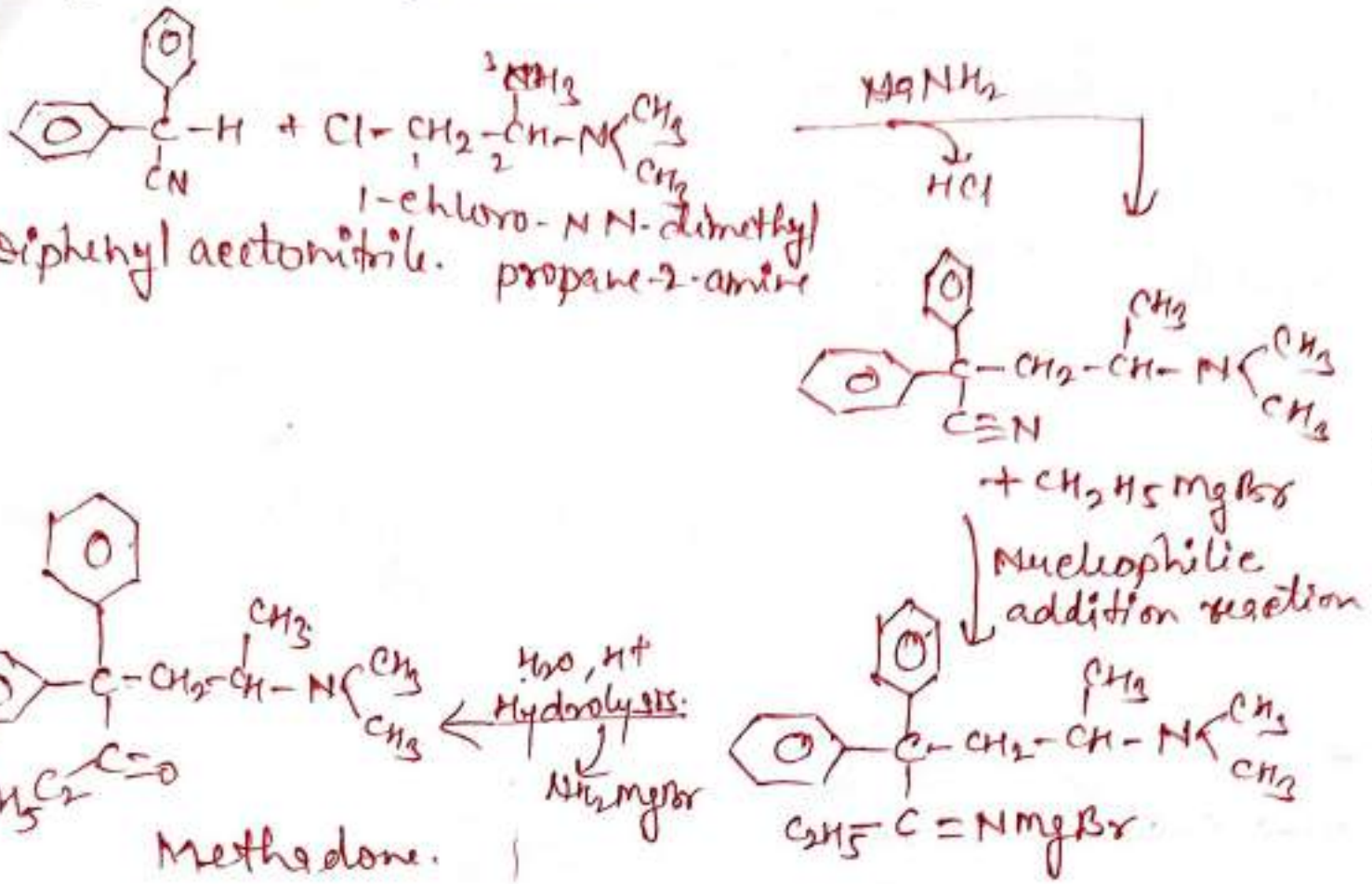
(3) Methadone :-



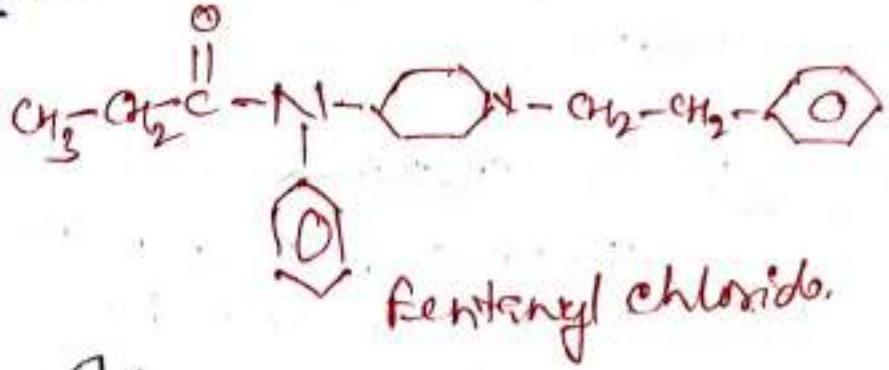
MOA ⇒ It addition to opioid receptor agonist activity methadone also act as antagonist of N-methyl-D-Aspartate (NMDA) receptor and it strongly inhibition serotonin and norepinephrine uptake.

Uses ⇒
Severe pain
drug addiction

(9) Synthesis of Methadone :-



(10) Fentanyl chloride :-



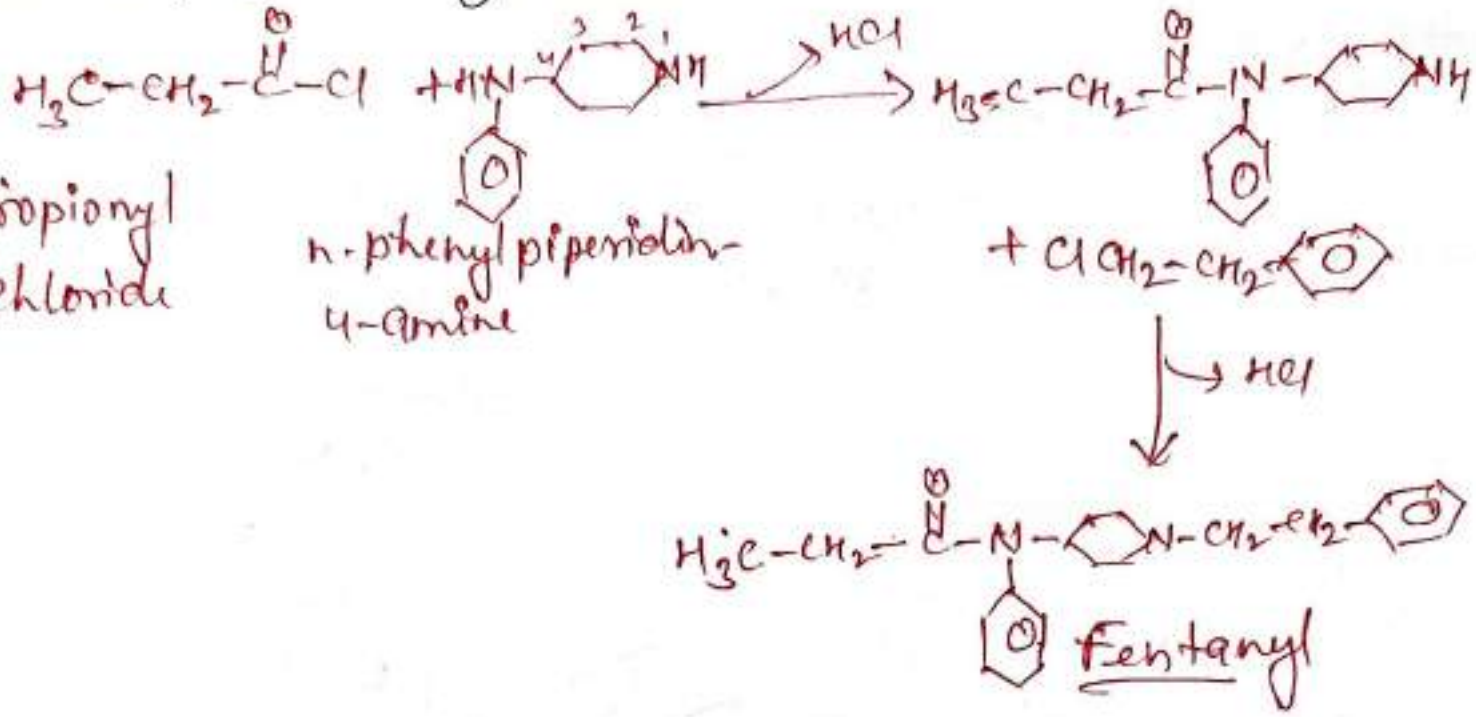
Fentanyl chloride.

MOA ⇒ Similar to morphine

Uses ⇒ It is uses both Independently and in combination with droperidol for preanaesthetic medication, post operational anaesthesia.

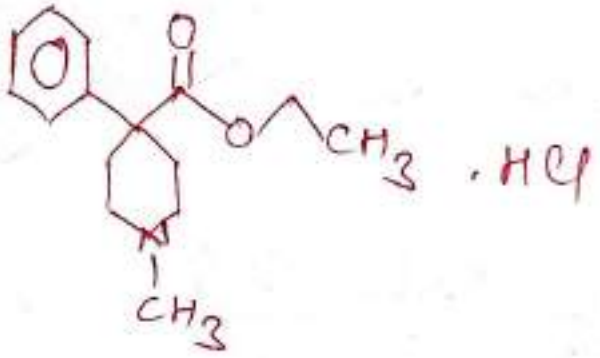
- In different form of neurosis (It is form of cell death in living being)

(4) ** Synthesis of Fentanyl :-



(5) Meperidine HCl ⇒

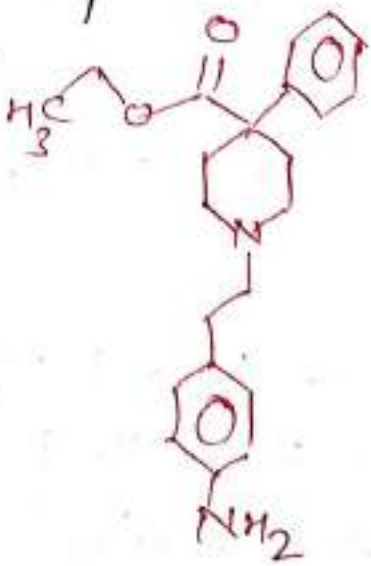
Also known as Pethidine



MOA ⇒ mu-opioid receptor.
Similar morphin

* Uses :⇒ In obstetrics
- To treat post operative pain
- Relieve moderate to severe pain

(6) Alfentanil HCl :-

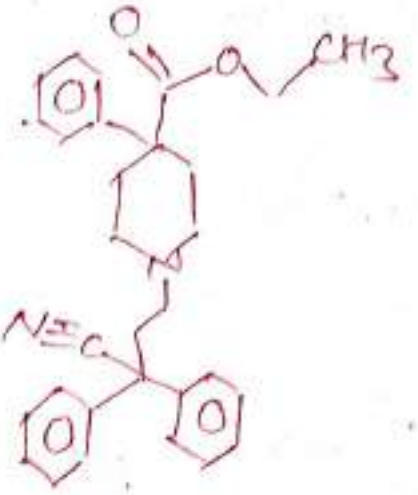


*Uses :- Same as meperidine HCl
⇒ Treat moderate to severe pain

MOA ⇒ Opioid receptor.
Similar morphin

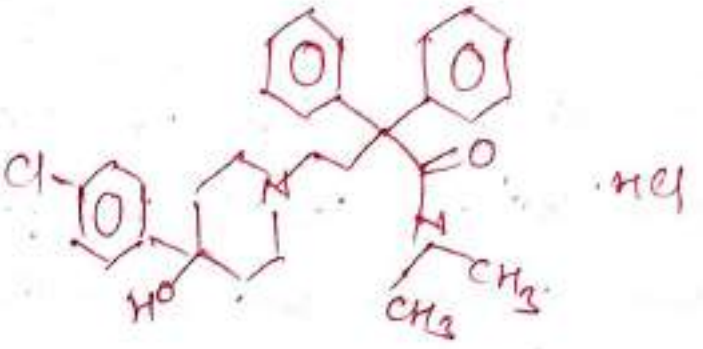
⇒

(7) Diphenoxylate HCl :-



⇒ It acts on opioid receptors in the GIT, thereby decreasing gastrointestinal motility and causing constipation or preventing diarrhoea.

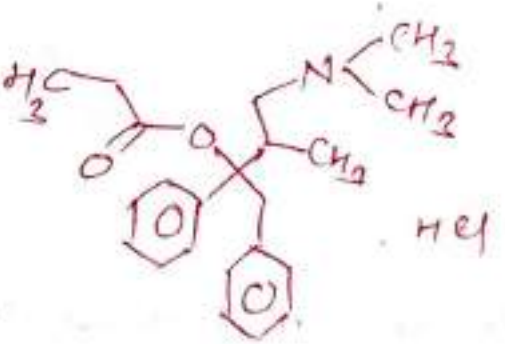
(8) Loperamide HCl ⇒



MOA ⇒ Act on μ receptor in the intestinal mucosa. Lead to ↓ the GI motility

To control acute & chronic diarrhoea. (Antidiarrheal activity)

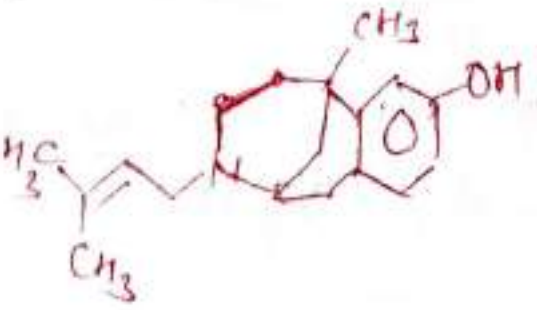
(9) Propoxyphene HCl :-



MOA ⇒ μ receptor
similar to morphine

Uses ⇒ for the relief of mild-to moderate pain

(10) Pentazocine :-

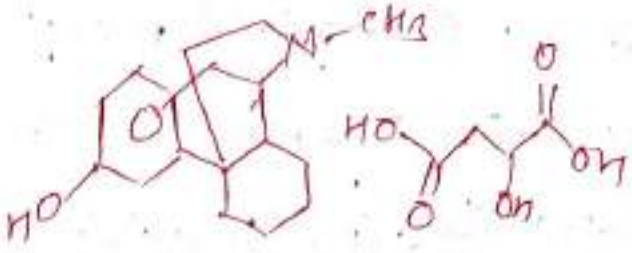


MOA ⇒ Activate κ-opioid receptors and blocking μ-opioid receptors

Uses ⇒ To treat cardiac asthma
- To treat chronic pain

(11) Levorphanol Tartarate :-

MOA →
Like morphine.

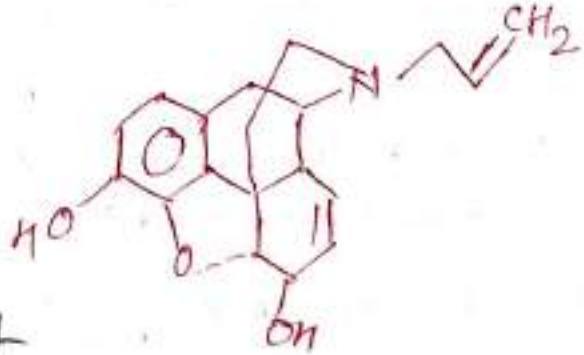


To treat severe pain.

*Narcotic Antagonist :-

The drugs which are competitive antagonists that bind to the opioid receptors with higher affinity than agonists but do not activate the receptors.
* These drugs effectively blocks the receptor, preventing the body from responding to opioids and endorphins

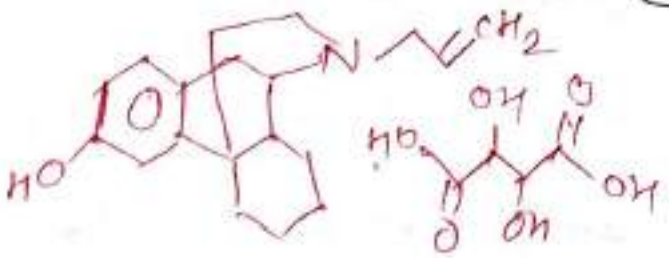
(1) Nalorphine HCl :-



MOA →
It is an antagonist at μ opioid receptors and an agonist and kappa opioid receptors.

Use → -Antidote to reverse opioid overdose & drug dependence

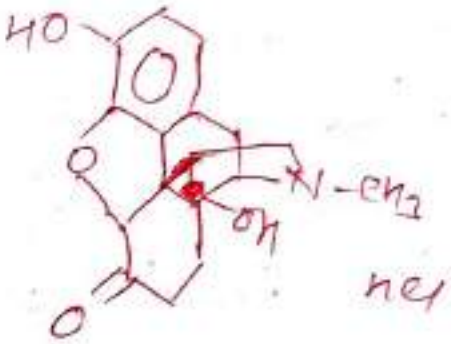
(2) Levalorphan Tartarate :-



MOA → block opioid receptor

Uses → Antidotes.

(3) Naloxone HCl →



MOA → block or reverses the effects of opioid medication; including drowsiness, slowed breathing or loss of consciousness.

Uses → Used to treat respiratory depressant effect of opioid overdose

ANTI-INFLAMMATORY AGENT :- Shailesh

* Non-Steroidal anti-Inflammatory Drugs (NSAIDs) *

⇒ NSAIDs are drug class that reduce pain, decrease fever, prevent blood clots and in higher dose ↓ inflammation

⇒ Side effect of NSAIDs - G.I ulcer, & bleed, attack and kidney disease

⇒ NSAIDs work by inhibiting the activity of cyclo-oxygenase enzymes (COX-1 and or COX-2).

⇒ In cell these enzymes are involved in the synthesis of key biological mediators, namely prostaglandins which are involved in inflammation and thromboxane's which are involved in blood clotting.

INFLAMMATION :- Inflammation is defined as the local response of living mammalian tissues to injury due to any agent. It is a body defence reaction in order to eliminate or limit the spread of ~~injurous~~ injurous agent as well as to remove the the consequent necrosed cells and tissue.

- Sign of inflammation -

1. Rubor (redness)
2. Tumor (swelling)
3. Calor (heat)
4. Dolor (pain)
5. Functio laesa (loss of function)

* Classifications of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) :-

1. Non-selective COX-2 inhibitor :-

a) Salicylate :- Aspirin, Sod. salicylate.

b) Propionic acid derivatives :- Ibuprofen *
- Ketoprofen, naproxen

c) Acetic acid derivatives :- Diclofenac
- Aceclofenac
- Tolmetin

d) Fenamic acid derivatives :- Mefenamic acid *

e) Pyrrolo-pyrrole derivatives :- Ketorolac, Zomepirac

f) Oxicam derivatives :- Piroxicam
- Meloxicam

g) Indole derivatives :- Sulindac
- Indomethacin

h) Anthranilic acid derivatives → Meclofenamate.

i) Pyrazolone derivatives :- phenyl butazone, Antipyrine

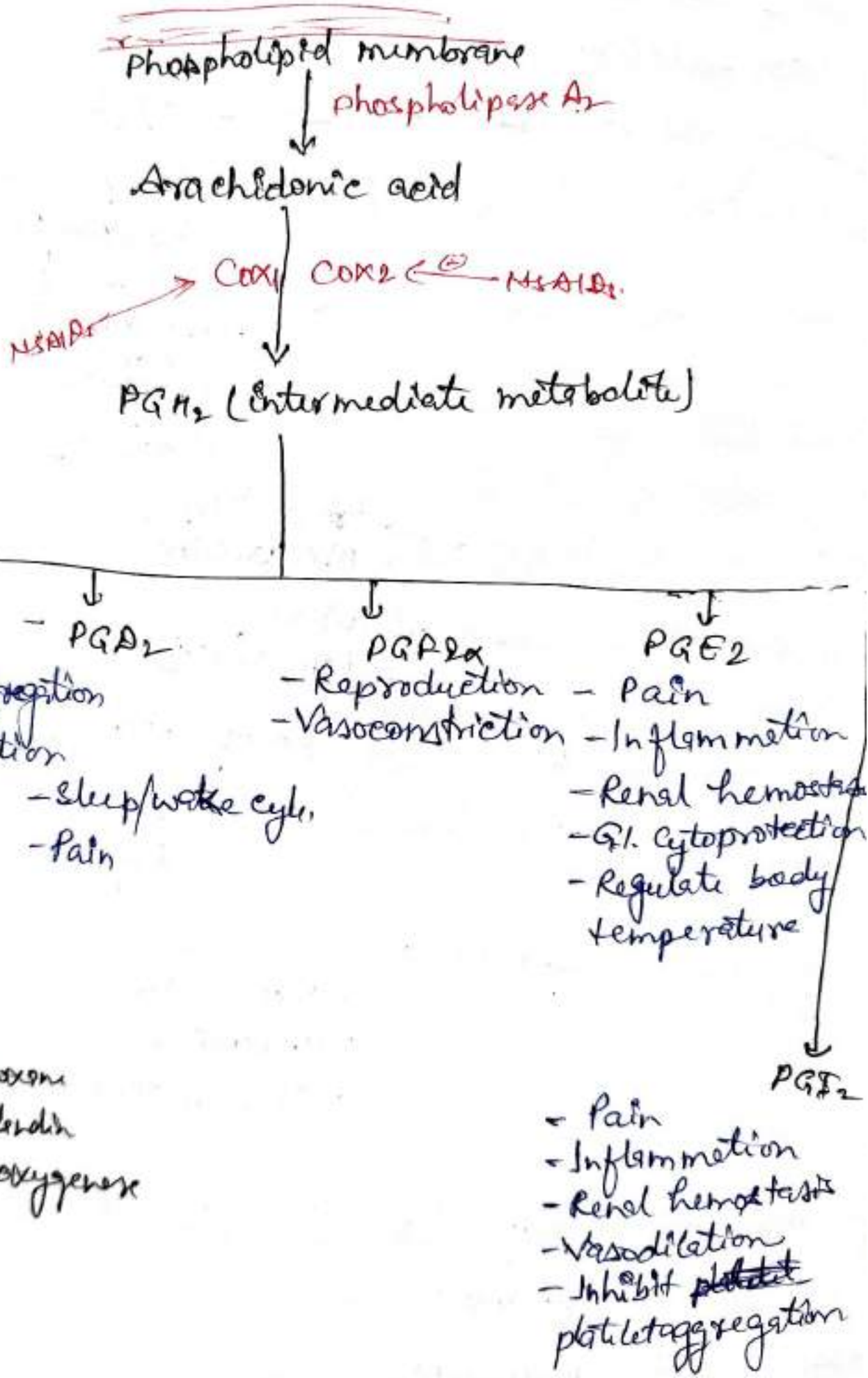
2. Selective COX-2 Inhibitors :- Celecoxib
- Rofecoxib

3) Preferential selective cox inhibitors :-
- Nimesulide
- meloxicam
- Nabumetone

4) Analgesic-antipyratic with poor anti-inflammatory effect - Paracetamol.

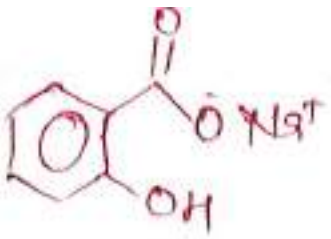
* Acetamides - Phenacetin
Non NSAIDs - Acetaminophen

* Mode of Action of NSAIDs :-



TX = Thromboxane
PG. Prostaglandin
Cox. cyclooxygenase

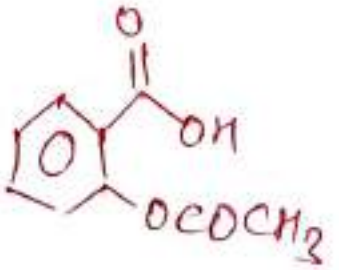
(1) Sodium Salicylate :-



MOA → Block synthesis of PG by inhibiting COX

Uses → - Relieve pain
- fever
- Treatment of gout

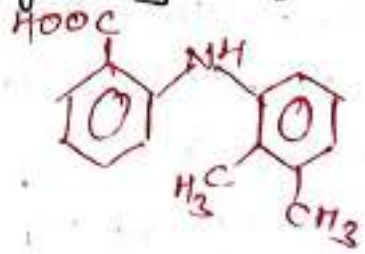
(2) Aspirin :-



MOA → Inhibit COX-1 & COX-2 and decrease the formation of PG and thromboxane.

Uses → Relief pain
- Rheumatoid arthritis - (auto immune disease, when immune system attacks the joint)
- Osteoarthritis - (break down cartilage in joint)

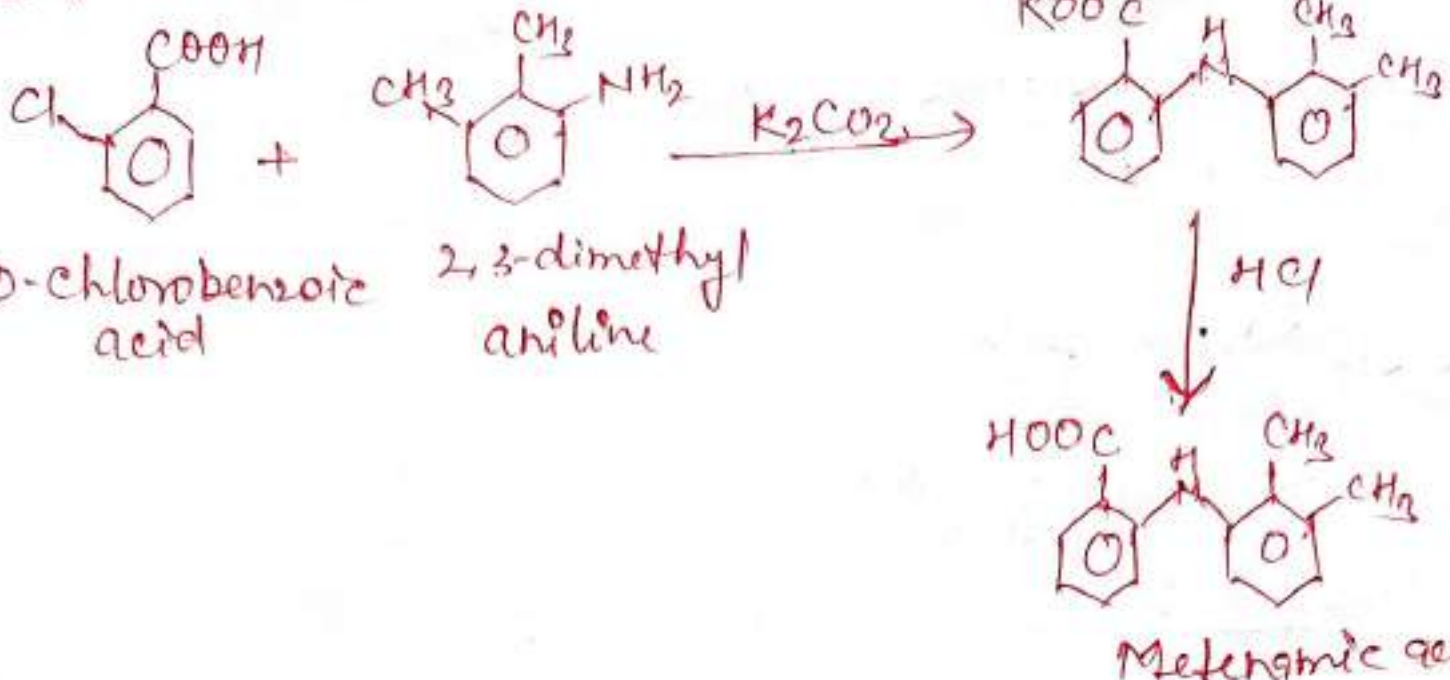
(3) Mefenamic acid :-



MOA → Inhibit COX1 & COX2

Uses → mild to moderate pain
- dysmenorrhea (painful menstrual periods).

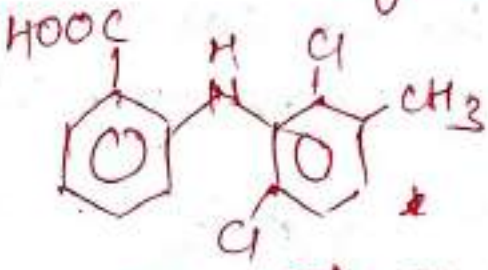
* Synthesis of Mefenamic acid :-



O-Chlorobenzoic acid + 2,3-dimethyl aniline

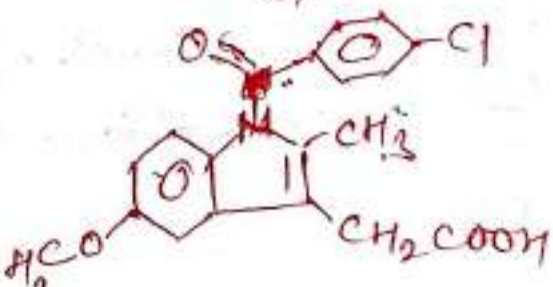
Mefenamic acid.

(4) Meclofenamate :-



MOA & uses as mefenamic acid.

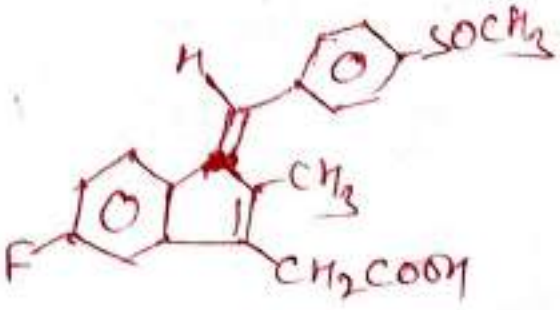
(5) Indomethecin :-



MOA → Inhibit COX-1 and COX-2
- Inhibit phospholipase A2 enzyme responsible for releasing arachidonic acid from phospholipid.

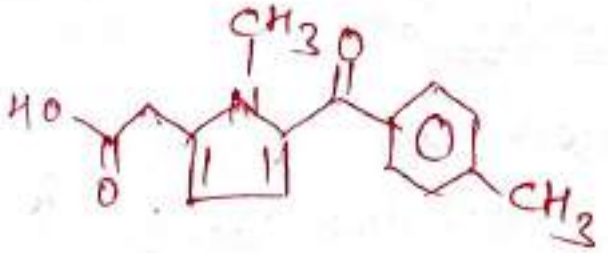
Uses →
- Rheumatoid arthritis
- Osteoarthritis
- Spondylitis (Inflamation of vertebral or spinal bone

(6) Sulindac :-



Same as Indomethecin

(7) Tolmetin :-

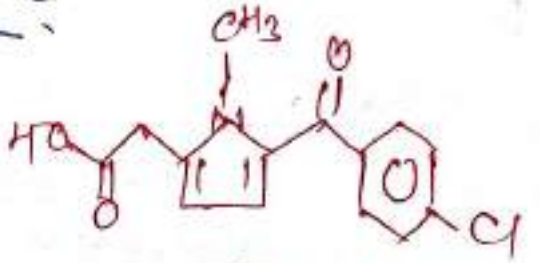


MOA: Inhibit PG Synthesis

Uses: · Rheumatoid arthritis
Osteoarthritis.
Spondylitis.

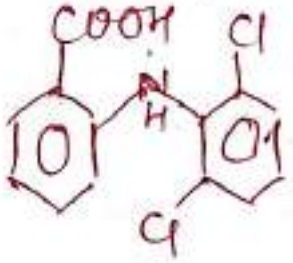
(8) Zomepirac ⇒ Zomepirac -

Same as tolmetin.



Zomepirac

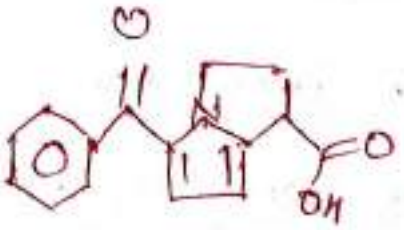
(9) Diclofenac :-



MOA ⇒ Inhibit COX-1 and COX-2

Uses ⇒ -Rheumatoid arthritis
-Osteoarthritis.

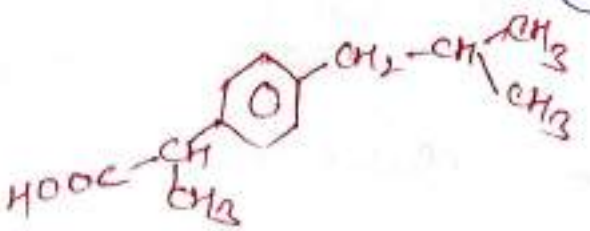
(10) Ketorolac :-



MOA ⇒ · Inhibit COX-1 & COX-2
Leads to inhibition of PG. synthesis.

Uses ⇒ Treat moderate to severe pain

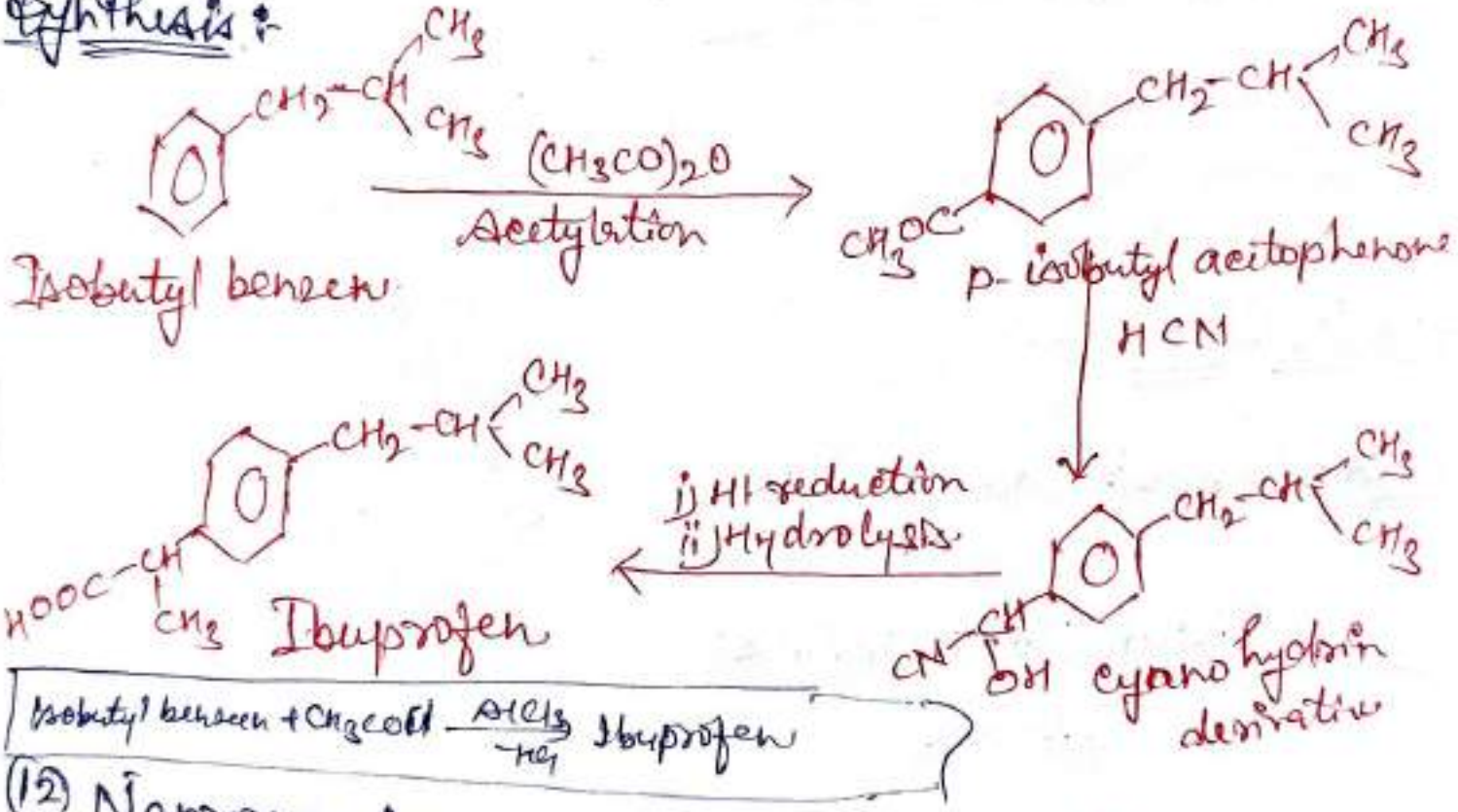
(11) Ibuprofen :-



MOA → Inhibit the activity of both COX-1 and COX-2

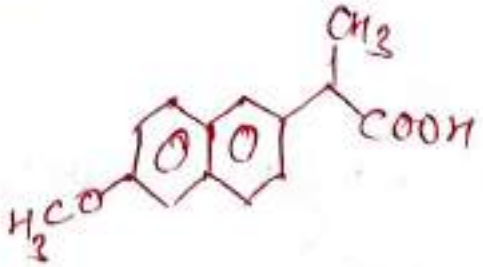
Uses → management of mild to moderate pain related to dysmenorrheal, headache, migraine, dental pain, spondylitis, osteoarthritis, Rheumatoid arthritis

Synthesis :-



Isobutyl benzene + CH_3COCl $\xrightarrow[HCl]{AlCl_3}$ Ibuprofen

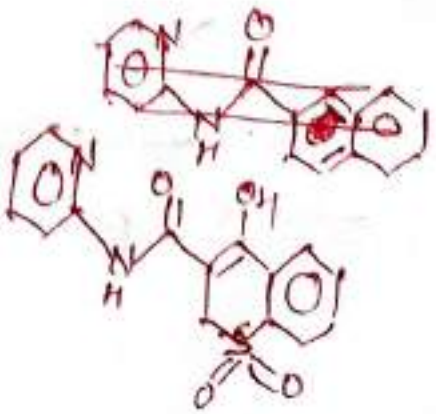
(12) Naproxen :-



MOA - Inhibit COX-1 & COX-2

Uses → RA, OA, spondylitis, gout, dysmenorrhoea.

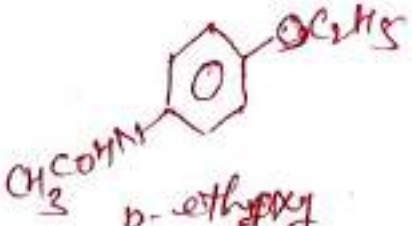
(13) Piroxicam :-



MOA → Inhibit COX-1

Uses → Arthritis.

(14) Phenacetin :-

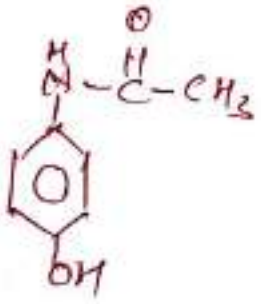


p-ethoxy acetanilide.

MOA - Phenacetin analgesic effects are due to its actions on the sensory tracts of the spinal cord.

Uses → Rheumatoid Arthritis (RA)
Ataxias.

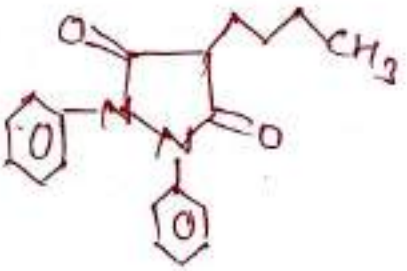
(15) Acetaminophen :- or Paracetamol



MOA → Weak inhibitor of PG synthesis of COX-1 and COX-2.

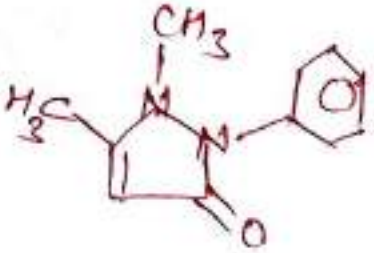
Uses → Analgesic & Antipyretic

(16) Phenylbutazone :-



MOA → Inactivation PG synthesis
Reduce production of PG

Uses → & pondylitis



(17) Antipyrine :-

MOA → Inhibit COX-1 & COX-2

Uses → Analgesic