NARCOTIC ANALGESICS

Opioid Analgesics

Opioid – refers broadly to all compounds related to the opium, a natural product derived from poppy.

Opiates – are drug derived from opium & includ the natural products morphine, codeine, and thebaine & many Semi-synthetic derivative

Narcotic – Greek word for "Stupor", any drug that induce sleep, naw it is associated with opoids

Drug Classification

① Natural Alkaloids
   - ⓐ Phenanthrene type – Morphine, Codeine
   - ⓑ Benzylisoquinoline type – Papaverine, Noscapine

② Semisynthetic – Buprenorphine, Oxycodone, hydromorphon, hydrocodon, Diacetylmorphine (Heroin)

③ Synthetic Derivative (Morphine derivative) – Ethylmorphine, Dimorphine, Dihydrocodeine, Oxymorphone

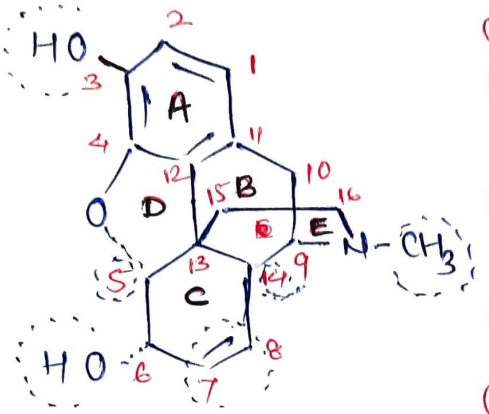
④ Synthetic Analogue
   - ⓐ Benzomorphan: Metazocine, Penazocine, Loperamide
   - ⓑ Methadone derivative – Methadone, Isomethadone, Pheadoxone
   - ⓒ Novel agonist-antagonist – Pentazocine
   - ⓓ 4-phenyl piperidine derivative – Fentanyl, Loperamide, Meperidine (pethidine), Diphenoxylate

Opioid Receptors - classified by WR Martin & Co-workers (1976)

Receptors	μ (μ_1 & μ_2)	κ ($\kappa_1, \kappa_2, \kappa_3$)	δ (δ_1 & δ_2)
Pathway	GiPCR - ↓ cAMP & Ca^{+2} - ↑ K^+ conduction	GiPCR ⊣	GiPCR ⊣
Agonist (Selective)	β-endorphine Morphine	Dynorphine A&B Ketocyclazocine Butorphanol	Met/Leu Enkephalin
Antagonist (Selective)	Nalorphine β-Funaltrexamine (irrivesible)	Norbinaltorphimine	
Location	Thalamus, laminae III & IV of Cortex, periaqueductal gray, spinal cord.	Hypothalamus, spinal & supra spinal regim	spinal regim (myenteric plexus
Features	Mainly Analgesia, Side effects = Res. depression, sedation, Euphoria, dependence.	Analgesia at spinal level, - Sedation, - dysphoria	Analgesia
Analgesia			
supra-spinal	+++ μ_1	+ K_3	−
spinal	++ μ_2	+ K_1	++
Periphery	++	++	−
Res. depres.	+++ μ_2	−	++
Miosis	++	+	−
Euphoria	+++	−	−
Dysphoria	−	+++	−
↓ GI motility	++ μ_2	+	++
sedation	++	++	−
Dependence	+++	−	++

SAR OF MORPHINE ANALOGUE

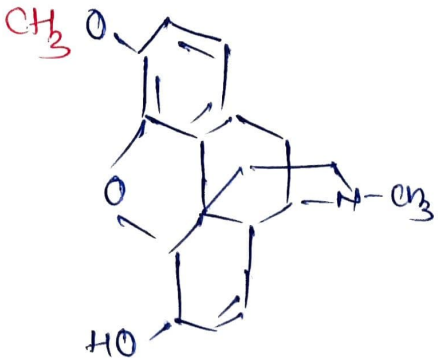
Morphine - air dry latex (opium) obtained by incision from capsule of poppy plant, (" Papaver somniferum)



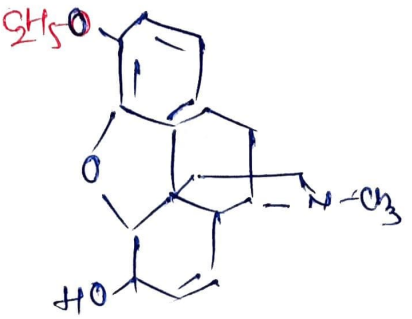
(A)- Benzene Ring
(B) - Cyclohexane (partially unsaturated)
(C) - partially unsaturated Cyclohexane
(D) Tetrahydrofuran ring
(E) Piperidine Ring

(1) At C_3 - -OH phenolic group
↳ Imp. for analgesic activity and binding to the receptor through H-bonding

(a) Methylation or ethylation - ↓ analgesic activity

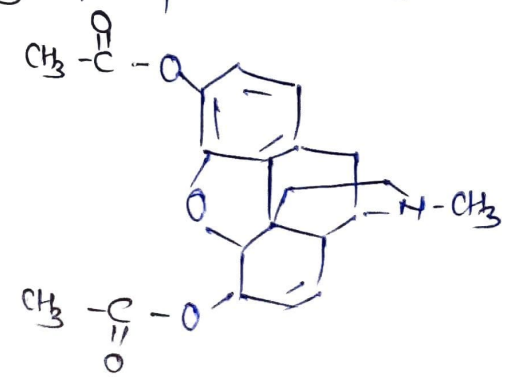


Codeine
1/10 than morphine



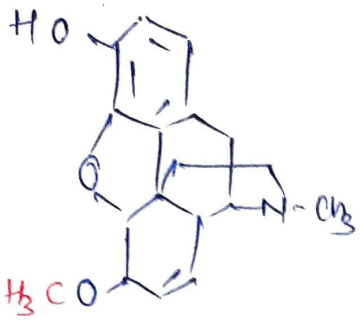
ethyl morphine
ethyl morphine < Codeine

(b) Acetylation at C_3 & C_6 - ↑ activity & addiction

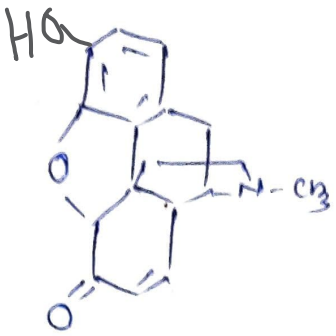


↳ Diamorphine
↳ Diacetyl morphine
↳ Heroin

② Modification of alcoholic C_6-OH group



Heterocodeine



Morphinone

\# Both are more active than Morphine

③ modification of (=) at C_7-C_8

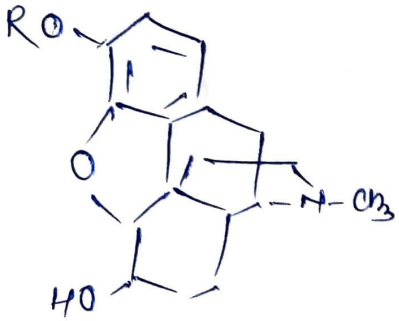
(=) at C_7-C_8 not essential for analgesic activity,

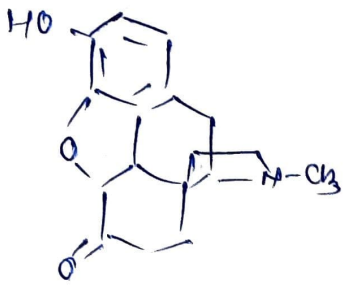
If = removed — ↓ duration
↑ activity

dihydro

R = H (Morphine)

R = CH_3 (dihydrocodeine)



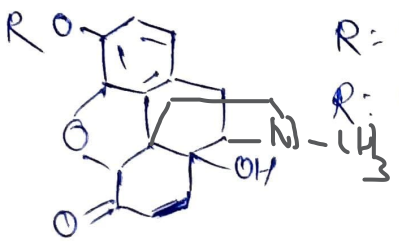


Dihydromorphinone

10 times more potent

④ Introduction to substituents at C_{14} & C_5

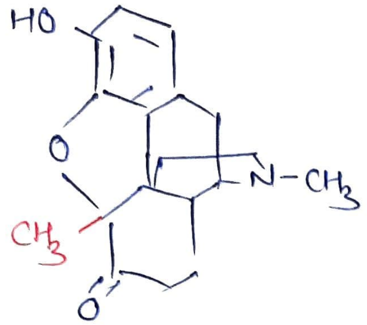
→ -OH introduce at C_{14} gives potent compound like oxymorphone and oxycodone



R = H (Oxymorphone)

R = CH_3 (Oxycodone)

↳ addition of $-CH_3$ at C_5 in dihydromorphinone gives drug which orally effective



Metopon

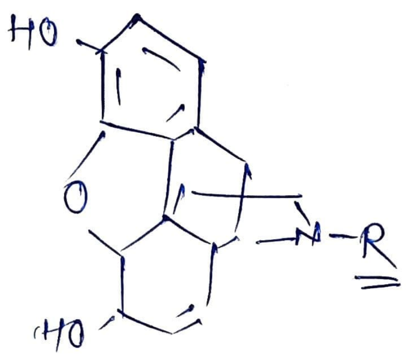
⑤ Modification of $N-CH_3$ group

ⓐ $-N-CH_3$ produce sufficient partition cofficient to drug.
If $-N-CH_3$ is replaced by $-N-H$, this decrease the activity
ex. N-nor morphine { -N-H

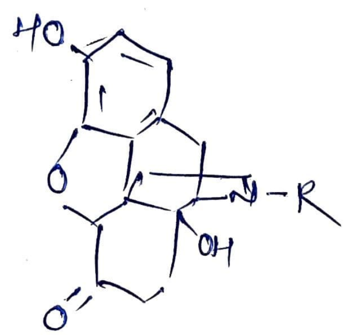
ⓑ Higher alkyl Substitution $N-C_2H_5$ → ↓ activity

ⓒ Aromatic Substituent N-⟨O⟩ → ↑ activity
ex. N-phenyl normorphine

ⓓ If $N-CH_3$ replaced by N-alkene, N-cycloalkylmethyl
It will produce Antagonistic activity



$R = -CH_2-CH=CH_2$
(Nalorphine)

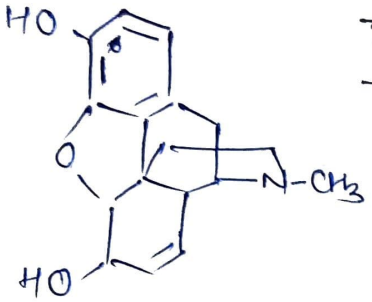


$R = -CH_2-CH=CH_2$ Naloxone
$R = -CH_2-$◁ Naltrexone

Med. Chemistry of Morphine & Related Drugs

Morphine, codeine, Meperidine, Anileridine, Diphenoxylate, Loperamide, Fentanyl*, Methadone*, Propoxyphene, Pentazocine, Levophenol

① Morphine Sulphate

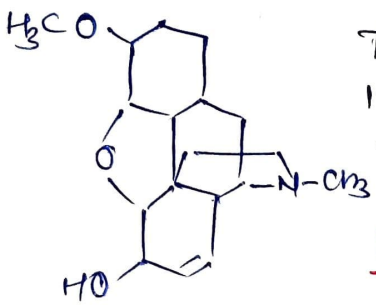


7,8-didehydro-4,5-epoxy-17-methyl morphinan-3,6 diol

MOA - (+) μ receptor → Analgesia, Euphoria, Respiratory depression, ↓ GI motility, & pupil constriction.

Uses -
- # Powerful analgesic and narcotic & used in management of pain (accidental, cancer, post operative)
- # ↓ Cough & relieving anxiety
- # Diarrhoea
- # also induce sleep (~~dec~~ in pain cond")

② Codeine



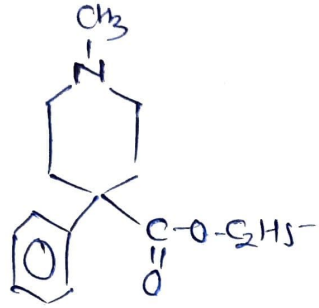
7,8-didehydro-4,5-epoxy-17-methyl-3-methoxy-morphinane-6α ol

MOA : (+) μR but lower affinity

Codeine —metabolism→ Morphine

Use- # Mild to moderate pain (single or along with pcm)
Treatment of cough
Treatment of Diarrhoea
#

③ Meperidine hydrochloride (~~Pet~~ Pethidine)

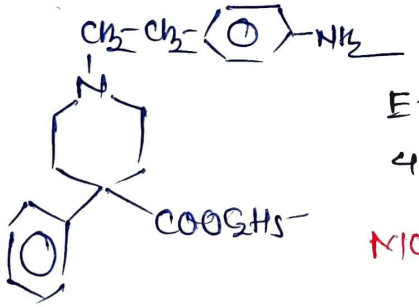


Ethyl-1-methyl-4-phenyl-piperidine-4-carboxylate

MOA - (+) μ R - Analgesic
(-) Na^+ channel - Local Anesthetic

Use- # Moderate to severe pain (Labour pain, post operative)
Cough & Diarrhoea

④ Anileridine hydrochloride

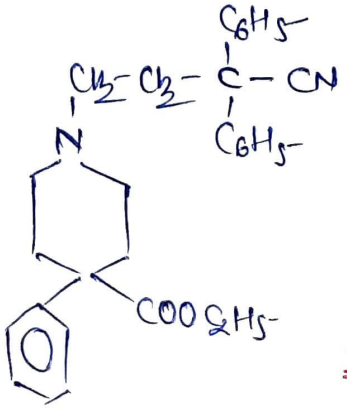


Ethyl-1-(2-(4-aminophenyl) ethyl)-4-phenyl-piperidine-4-carboxylate

MOA : + μR

Uses — ① pain management (more potent than pathidine)
② Some local anesthetics

⑤ Diphenoxylate hydrochloride

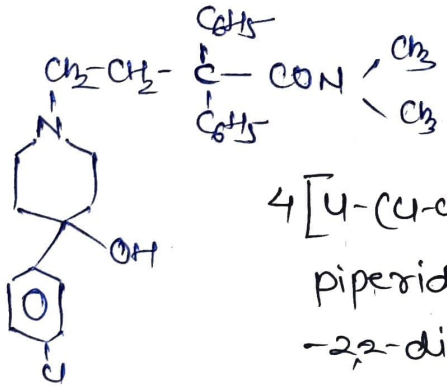


Ethyl-1-(3-cyano-3,3-diphenyl propyl) -4-phenyl-piperidine-4-carboxylate

MOA - Interacts with opioid receptor ~~not~~ in intestine. Little or no analgesic action

Uses - # Acute & Chronic Diarrhoea singly or combination with atropine

⑥ Loperamide hydrochloride

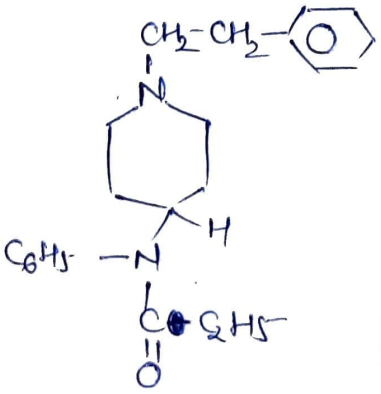


4[4-(4-chlorophenyl)-4-hydroxy-piperidinyl]-N,N-dimethyl-2,2-diphenyl-butyramide

MOA – opioid receptor at GI, ↓ GI motility

Use : Diarrhoea

⑦ Fentanyl Citrate*

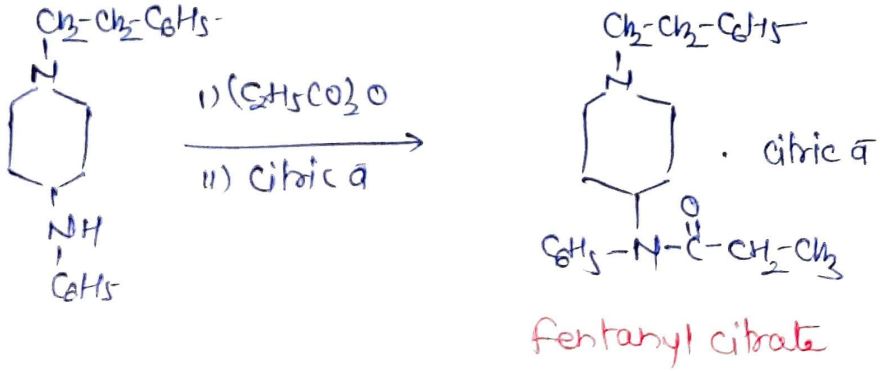


1-phenyl ethyl-4-propionyl anilino piperidine

N-phenyl-N-[1-(2phenylethyl) piperidin-4-yl] propanamide

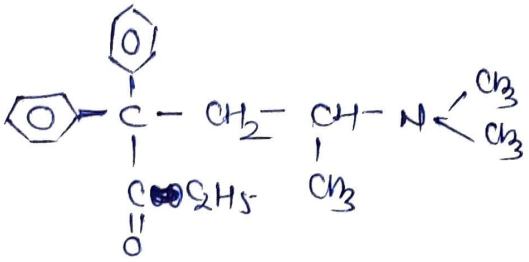
MOA – UR, highly lipophilic

Uses – # Analgesic, 80 times more potent than morphine
General anesthesia # ~~Neuropt~~
Neuroleptanalgesia



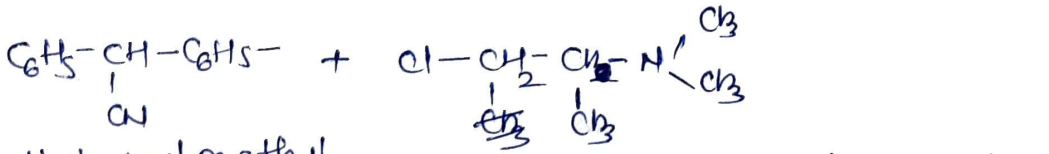
Fentanyl citrate

⑧ Methadone Hydrochloride



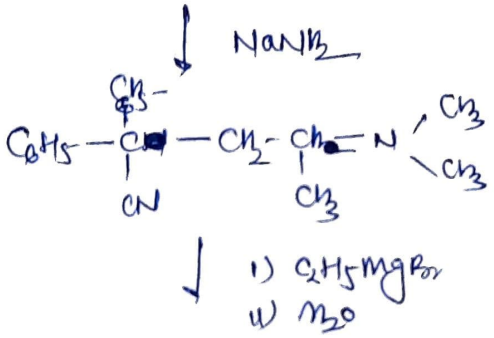
6-(dimethyl amino)-4,4-diphenyl-heptan-3-one

MOA - +ve R



diphenyl methyl cyanide

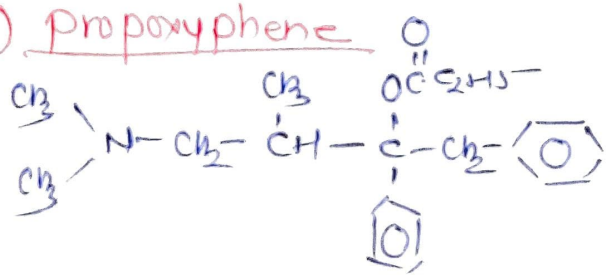
3-Chloro-2-dimethyl amino propane



Methadone

use # potent analgesic with less Sedation
manage drug addiction
depressant action on cough

⑨ Propoxyphene



~~1-benzyl-3~~

4-(dimethyl amino)-3-methyl-1,2-diphenyl-butan-2-ol] propanoate

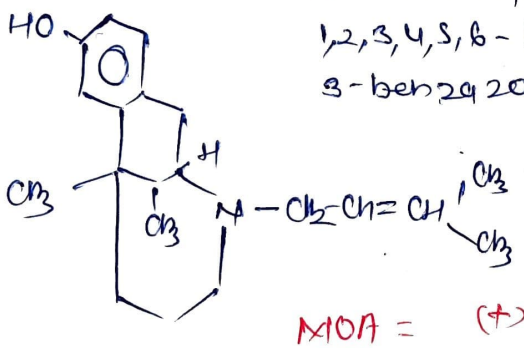
MOA - +ve R, antagonise Nicotinic acetylcholine receptor & weak 5HT reuptake inhibitor

Use - # Analgesic
dextro salt used to relieving the symptom of restless leg Syndrome (Strong urge to move one legs)
dextro salt → ↓ withdrawal symptoms in opioid addiction

levo form - antitussive action

10) Pentazocine

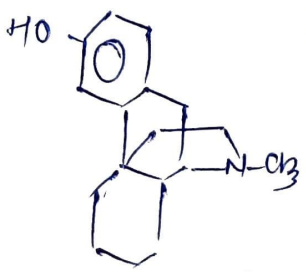
6,11-dimethyl-3-(3-methyl but-2-enyl) 1,2,3,4,5,6-hexa hydro-2,6-methano-3-benzazocin-8-ol



MOA = (+) κ R
partial Agonist μR

Uses - # Analgesic
↓ symptoms of mania with Bipolar disorder

(11) Levorphanol Tartarate



(-) 3-hydroxy-N-methyl-morphinan

MOA - μ, κ, δ R
SNRI

Use - # 20 times more analgesic than morphinane
dextro - antitussive
pain management