OPIOID ANALGESICS/ NARCOTIC AGENTS

B. Pharm IV semester
Medicinal Chemistry

Prepared By:
Neetu Sabarwal
Department of Pharmaceutical Chemistry
SOS Pharmaceutical Sciences Jiwaji University. Gwalior

INTRODUCTION

Analgesics are agents that relieve pain by acting centrally to elevate pain threshold without disturbing consciousness or altering other sensory modalities. Certain analgesics like aminopyrine and phenylbutazone also possess anti-inflammatory properties. Many drugs that are used to relieve pain are not analgesics; the general anaesthetics relieves pain by producing unconsciousness, local anaesthetics prevent pain by blocking peripheral nerve fibres, antispasmodics relieve pain by relaxing smooth muscles and the adrenal corticoids relieve pain associated with rheumatoid arthritis by anti-inflammatory action.

Analgesics are classified into two major categories:

1. **Opioid analgesics/narcotic analgesics (centrally acting).**
2. **Nonopioid analgesics/non-narcotic analgesics (peripherally acting).**

Opioid analgesics

Opioid analgesics are drugs that denote all naturally occurring, semisynthetic and synthetic drugs, which have a morphine like action, namely, relief from pain and depression of CNS associated with the drug dependence. Opioid drugs are not only used as analgesics, but also possess numerous other useful properties.

For example, morphine is used to induce sleep in the presence of pain, diarrhoea, suppress cough, and facilitate anaesthesia.

Non-Opioid Analgesics

I. Acetaminophen (paracetamol)
II. Anticonvulsants (including gabapentin and pregabalin)
III. Antidepressants (including amitriptyline and duloxetine)
IV. Aspirin (acetylsalicylic acid)
V. Other NSAIDs (including ibuprofen, diclofenac, naproxen and COX-2 inhibitors)

Introduction

- **Narcotic analgesics** are a class of medicines that are used to provide relief from moderate-to-severe acute or chronic pain.
- They may also be called opiates, opioid **analgesics** or **narcotics**.
- **Opioids** are substances that act on opioid receptors like mu, kappa and delta receptors to produce morphine-like effects.

History of opioids –

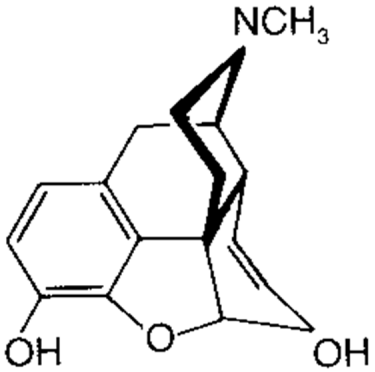
- First reference of opium by Theophrastus 3rd century BC.
- Arab physician used it for control of dysentry
- 1806, Frederich Serturner a pharmacist isolated by crystallization of pure substance in opium named Morphine after Morpheus – Greek god of dreams.
- middle of 19th century – use of pure alkaloids coincided with development of hypodermic syringe and hollow needle.

- They used in a civil war in U.S named as soldiers disease.
- C.R Alder Wright in 1874 – heroin
- Early 1970 – effect of Morphine, Heroin and other opioids as anti nociceptive and addictive agents were well described.
- Martin and Goldstein discovered receptors.

Papaver somniferum L.

- Opium
- morphine (1806)
- codeine
- papaverine

F. SERTÜRNER
(1783–1841)



Morphine

ENDOGENOUS OPIOID PEPTIDES –

- In 1973 researchers determined the existence of opiate binding sites in the brain through the use of radioligand-binding assays

- Have Morphin like actions & μ receptor binding activity
  - Endorphins,
    Encephalin
    Dynorphins &
    Nociceptin

share a common terminal amino acid sequence of five amino acids joined to MET/LEU

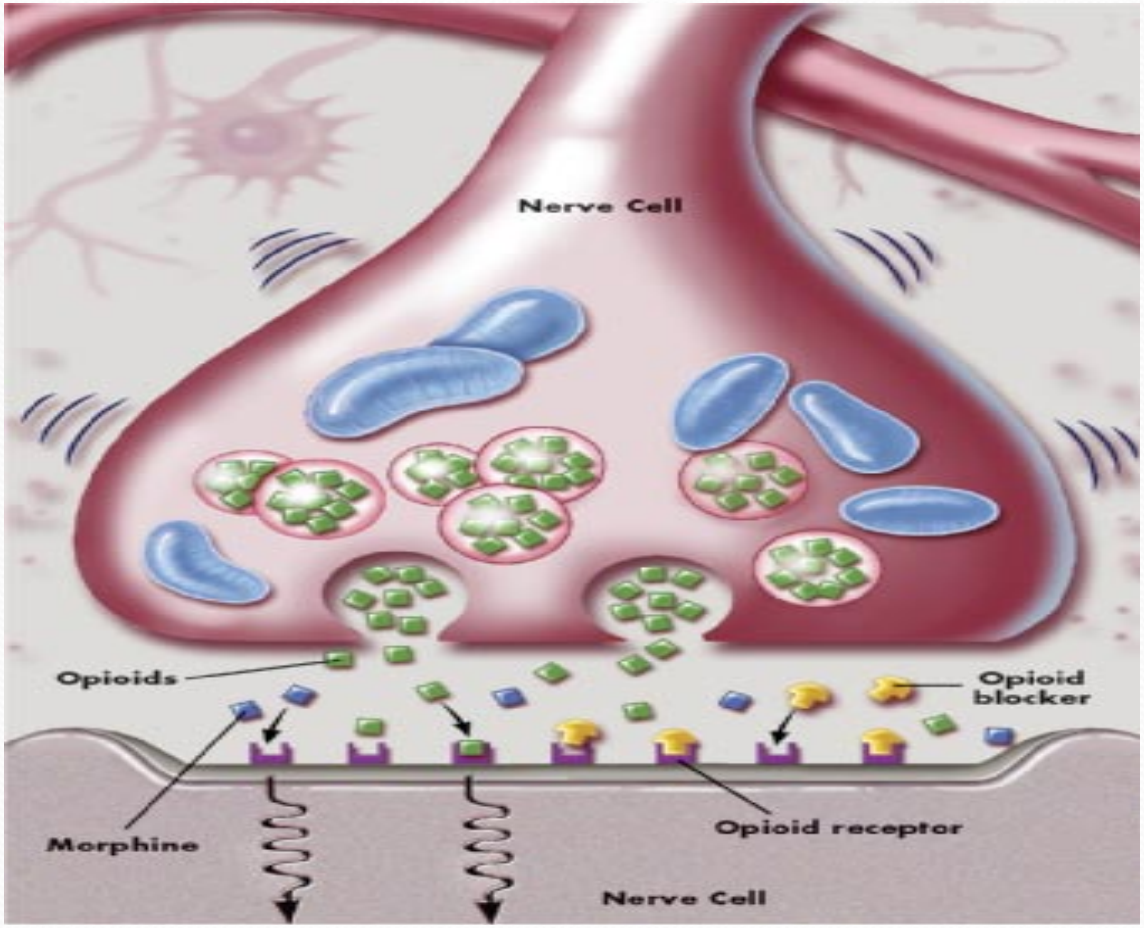
TYPES OF OPOID RECEPTORS

1. Mu (μ) receptors, are responsible for supra-spinal analgesia mediated by μ1 and spinal mediated by μ2. Respiratory depression and gastric motility reduction is mediated by μ2 subtypes. μ receptor produces euphoria, physical dependence, and miosis.

2. Kappa receptors, appear to mediate spinal analgesia through κ1 subtypes and supra-spinal analgesia through κ3 subtype. It produces respiratory depression, dysphoria, hallucination, miosis, sedation, and nicotinic effects.

3. δ receptors, Activation of δ receptors produces spinal analgesia, respiratory depression, affective behaviour, reinforcing actions, and reduced GI motility.

CNS Opioid receptors – mu, delta, kappa



Based on the chemical structure opium alkaloid are classified into two types:

Phenanthrene derivatives

- Morphine
- Codeine
- Thebaine

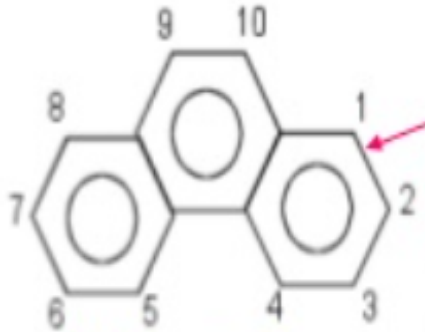
Benzoisoquinoline derivatives

Papaverine, Noscapine, Narcine

Opioids - Opium

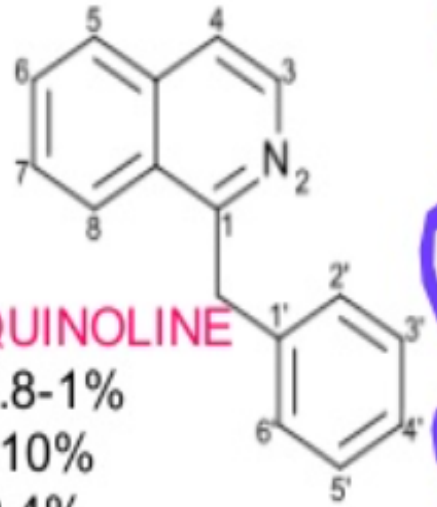
- A dark brown, resinous material obtained from poppy (*Papaver somniferum*) Capsules.

OPIUM



PHENANTHRENE

- Morphine 9-14%
- Codeine 0.5-2%
- Thebaine 0.2-1%



BENZYLISOQUINOLINE

- Papaverine 0.8-1%
- Noscapine 3-10%
- Narcine 0.2-0.4%

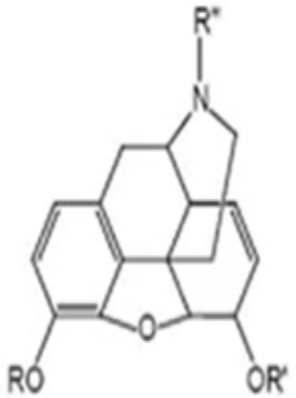
Classification

BASED ON SOURCE :

- **Natural opium alkaloids**- Morphine, Codeine
- **Semisynthetic**-Pholcodeine, Heroin
- **Synthetic-** Pethidine, Methadone, Fentanyl, Tramadol

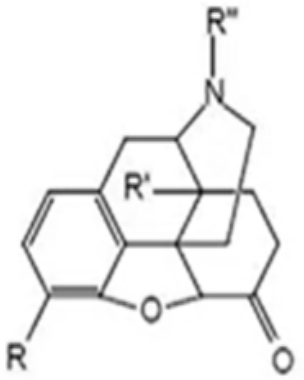
CLASSIFICATION

I. Morphine and its analogues



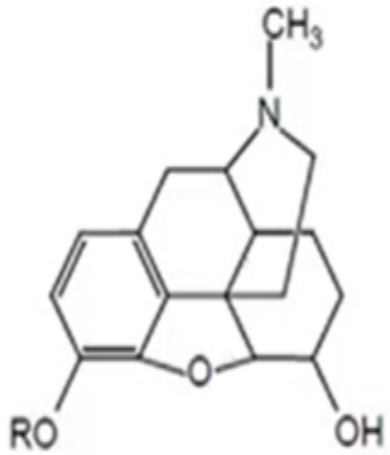
S. No.	Name	R	R'	R''
1	Morphine	–H	–H	$-CH_3$
2	Ethyl morphine	$-C_2H_5$	–H	$-CH_3$
3	Codeine	$-CH_3$	–H	$-CH_3$
4	Heroin	$-COCH_3$	$-COCH_3$	$-CH_3$
5	Nalorphine	–H	–H	$-CH_2-CH=CH_2$

a. Hydromorphone derivatives



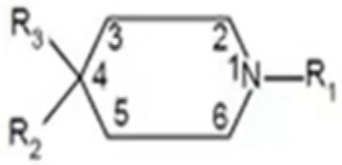
S. No.	Name	R	R′	R″
1	Hydromorphone	–OH	–H	$-CH_3$
2	Oxy morphone	–H	–OH	$-CH_3$
3	Hydrocodone	$-OCH_3$	–H	$-CH_3$
4	Oxycodone	$-OCH_3$	–OH	$-CH_3$

b. Dihydromorphine derivatives

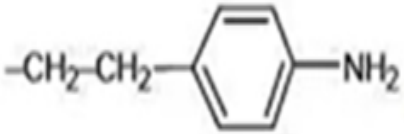
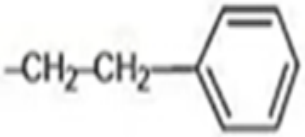
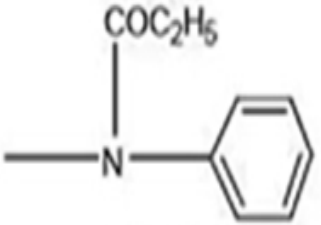
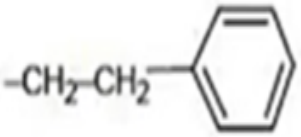
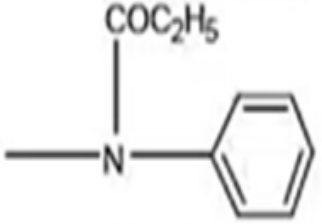
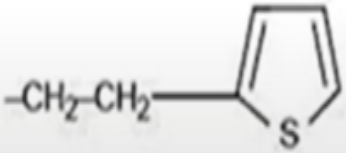
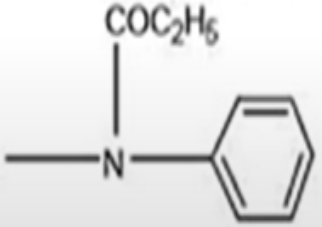


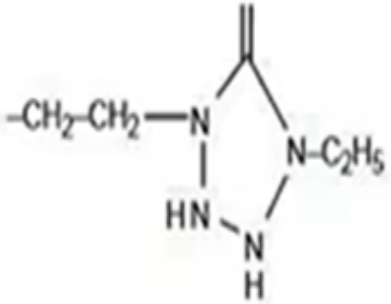
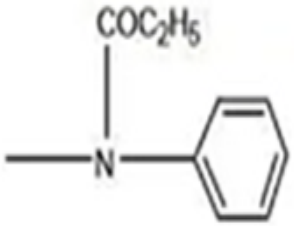
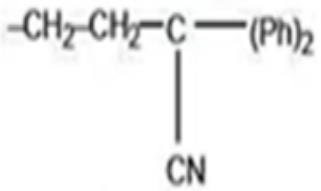
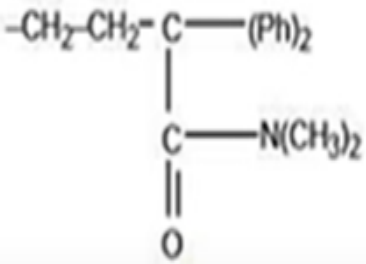
Name	R
Dihydromorphine	–H
Dihydrocodeine	CH_3

II. Meperidine analogues

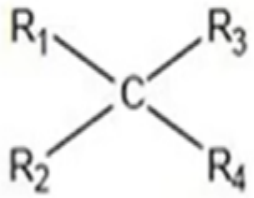


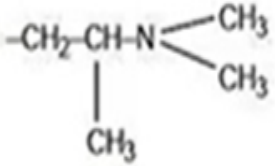
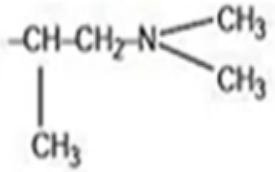
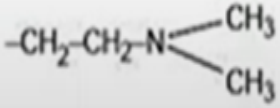
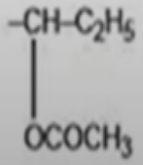
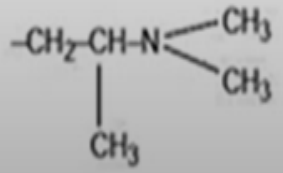
S. No.	Name	R_1	R_2	R_3
1.	Meperidine	$-CH_3$	$-C_6H_5$	$-COOC_2H_5$
2.	Bemidone	$-CH_3$	$-C_6H_4OH$	$-COOC_2H_5$
3.	Properidone	$-CH_3$	$-C_6H_5$	$-COCH(CH_3)_2$

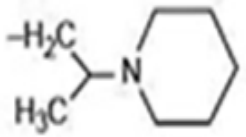
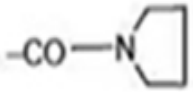
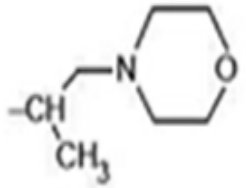
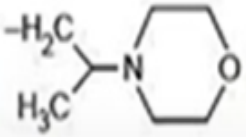
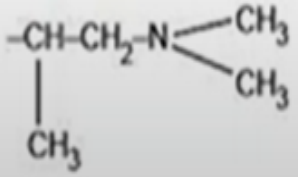
S. No.	Name	R_1	R_2	R_3
4.	Ketobemidone	$-CH_3$	$-C_6H_4OH$	$-COC_2H_5$
5.	Anileridine		$-C_6H_5$	$-COC_2H_5$
6.	Fentanyl		$-H$	
7.	Lofentanil		$-COOCH_3$	
8.	Sufentanil		$-CH_2OCH_3$	

S. No.	Name	R_1	R_2	R_3
9.	Alfentanil		$-CH_2OCH_3$	
10.	Diphenoxylate		$-C_6H_5$	$-COOC_2H_5$
11.	Lopramide		$-C_6H_4Cl$	$-OH$

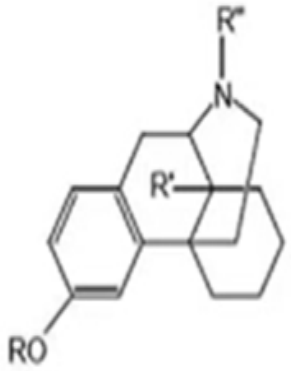
III. Methadone analogues



S.No	Drug	R_1	R_2	R_3	R_4
1.	Methadone	–Ph	–Ph	$-COC_2H_5$	
2.	Isomethadone	–Ph	–Ph	$-COC_2H_5$	
3.	Normethadone	–Ph	–Ph	$-COC_2H_5$	
4.	Alpha acetyl methadone	–Ph	–Ph		

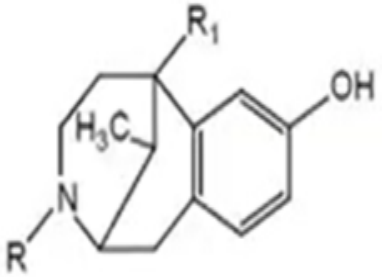
S.No	Drug	R_1	R_2	R_3	R_4
5.	Dipanone	–Ph	–Ph	$-COC_2H_5$	
6.	Dextromoramide	–Ph	–Ph		
7.	Phenadoxone	–Ph	–Ph	$-COC_2H_5$	
8.	Propoxyphen	–Ph	$-CH_2-C_6H_5$	$-COC_2H_5$	

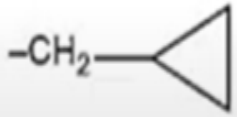
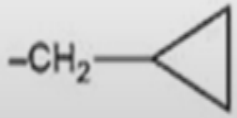
IV. Morphinan analogues



Name	R	R′	R″
(i) Levorphanol tartarate	–H	–H	$-CH_3$
(ii) Butorphanol tartarate	–H	–OH	$-H_2C$ 
(iii) Dextromethorphan	$-CH_3$	–H	$-CH_3$

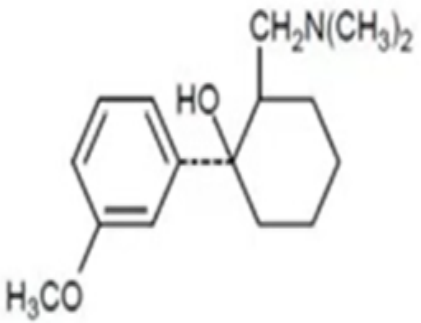
V. Morphan analogues or benzazocin derivatives



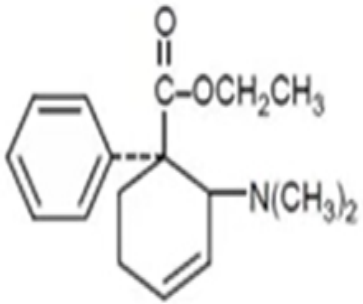
S.no	Name	R	R_1
1	Pentazocine	$-CH_2-CH=C(CH_3)_2$	$-CH_3$
2	Phenazocaine	$-CH_2-CH_2-C_6H_5$	$-CH_3$
3	Cyclazocine		$-CH_3$
4	Ketazocine		= O
5	Metazocine	$-CH_3$	$-CH_3$

VI. Miscellaneous

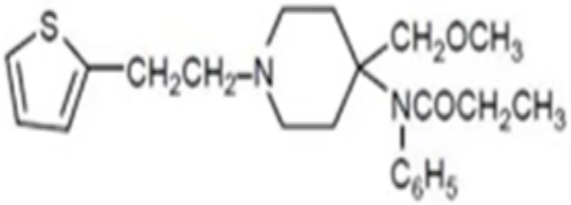
a. Tramadol



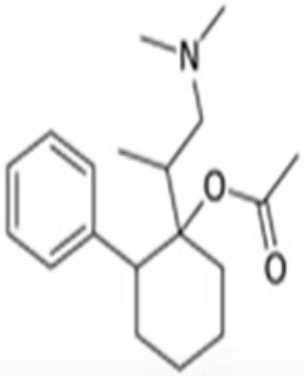
b. Tilidine



c. Sufentanil



d. Nexeridine

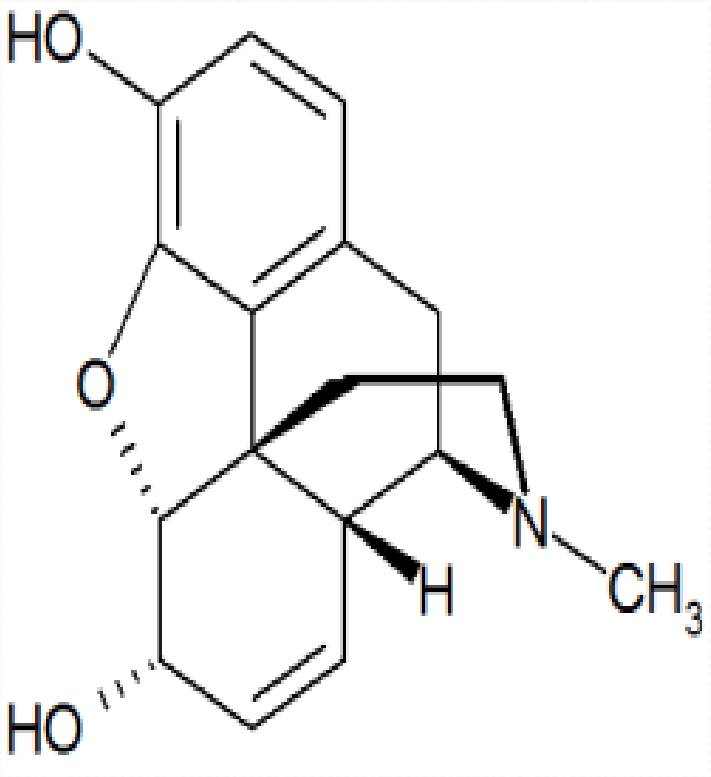


Based on RECEPTOR INTERACTIONS

- Pure agonists – Morphine, Methadone, Meperidine[Pethidine], Codiene.
- Partial agonists –Buprenorphine
- Mixed agonists-antagonists – Nalorphine, Pentazocine, Nalbuphine
- Pure antagonists – Naloxone, naltrexone.

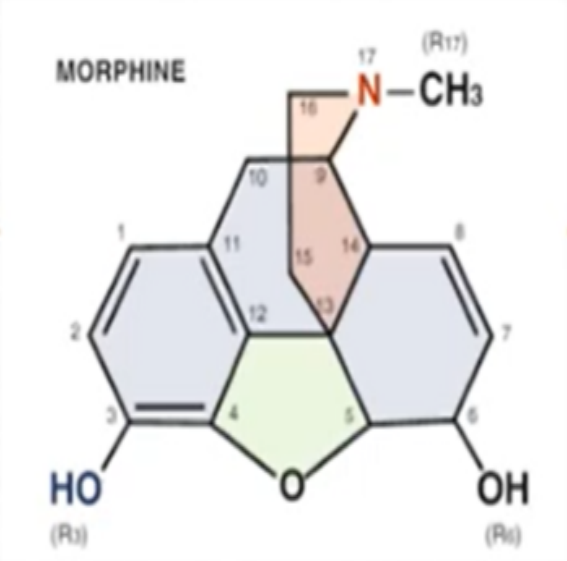
Structure of Opioids

- In order to examine important structural features of Opioid analgesics, which are all derived from the opiate structure, we will refer to the structure of morphine, the first identified alkaloid.



- The structure of morphine consists of five rings forming a T-shaped molecule.
- The important binding groups on morphine are the phenol, the aromatic ring, and the ionized amine. These groups are found in all Opioid analgesics.
- . “A free phenol group is crucial for analgesic activity (3).” The aromatic ring of the opiate also seems to be integral to its function as compounds that lack the aromatic ring show no analgesic activity. The ionized amine also plays an important role in its activity and is common in opioid structure. In experiments where the Nitrogen was replaced by a Carbon no analgesic activity was found. It interacts with certain analgesic receptors in its ionized form.

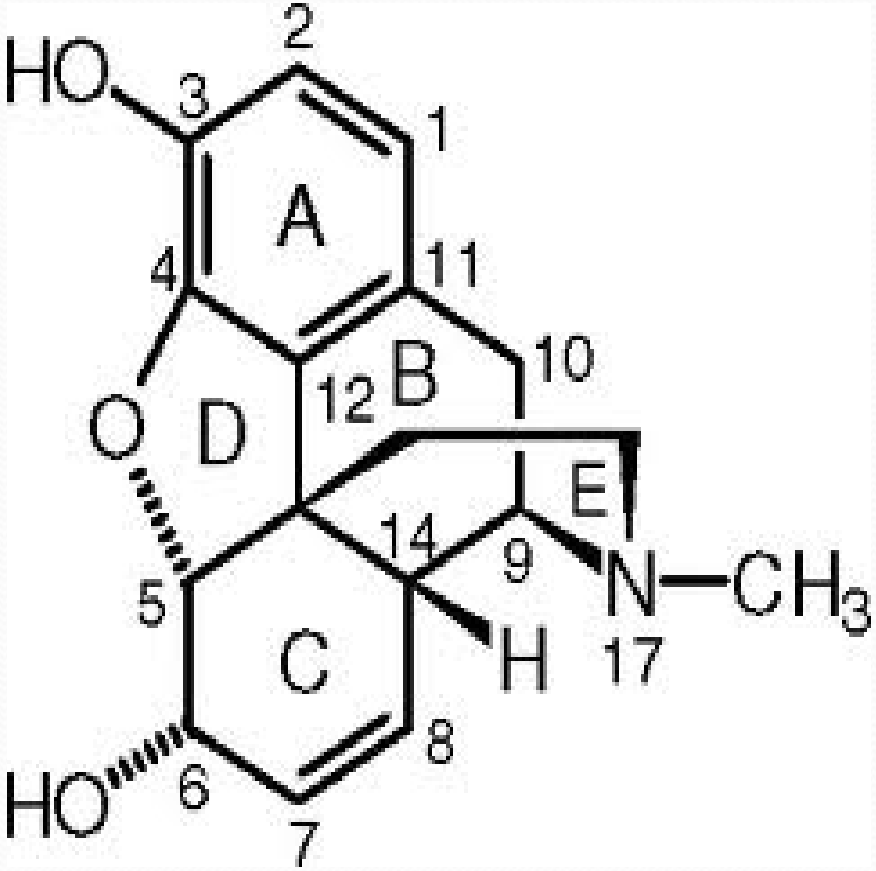
Structure of Morphine



- It is a phenanthrene ring derivative.
- Morphine have 5 chiral center at 5,6,9,13 & 14.
- The naturally occurring isomer of morphine is levo (-) rotatory.
- Morphenan is parent nucleus of morphine.

Morphine


MORPHINE
Sulfate Inj., USP


HO
2
3
1
A
4
11
10
12
B
O
D
E
14
9
N—CH3
5
C
H
17
8
HO
6
7

MORPHINE

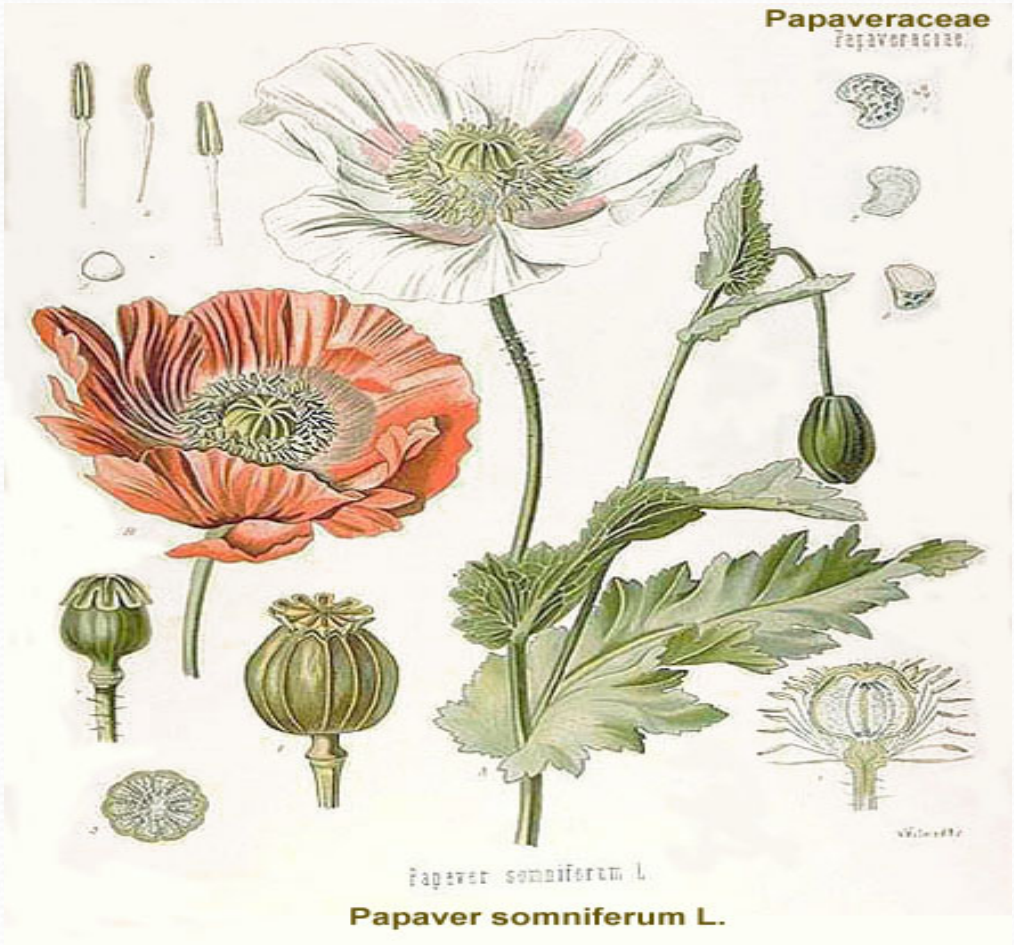
- *Morphine is the principal alkaloid in opium and still widely used. Therefore it is describe as prototype.*

***Biological Source:** It is obtained from the juice or latex from the unripe seed pods of the Papaver somniferum.*

Family : Papavaraceae

PAPAVER SOMNIFERUM

OPIUM POPPY SEED



General Mechanism of Action

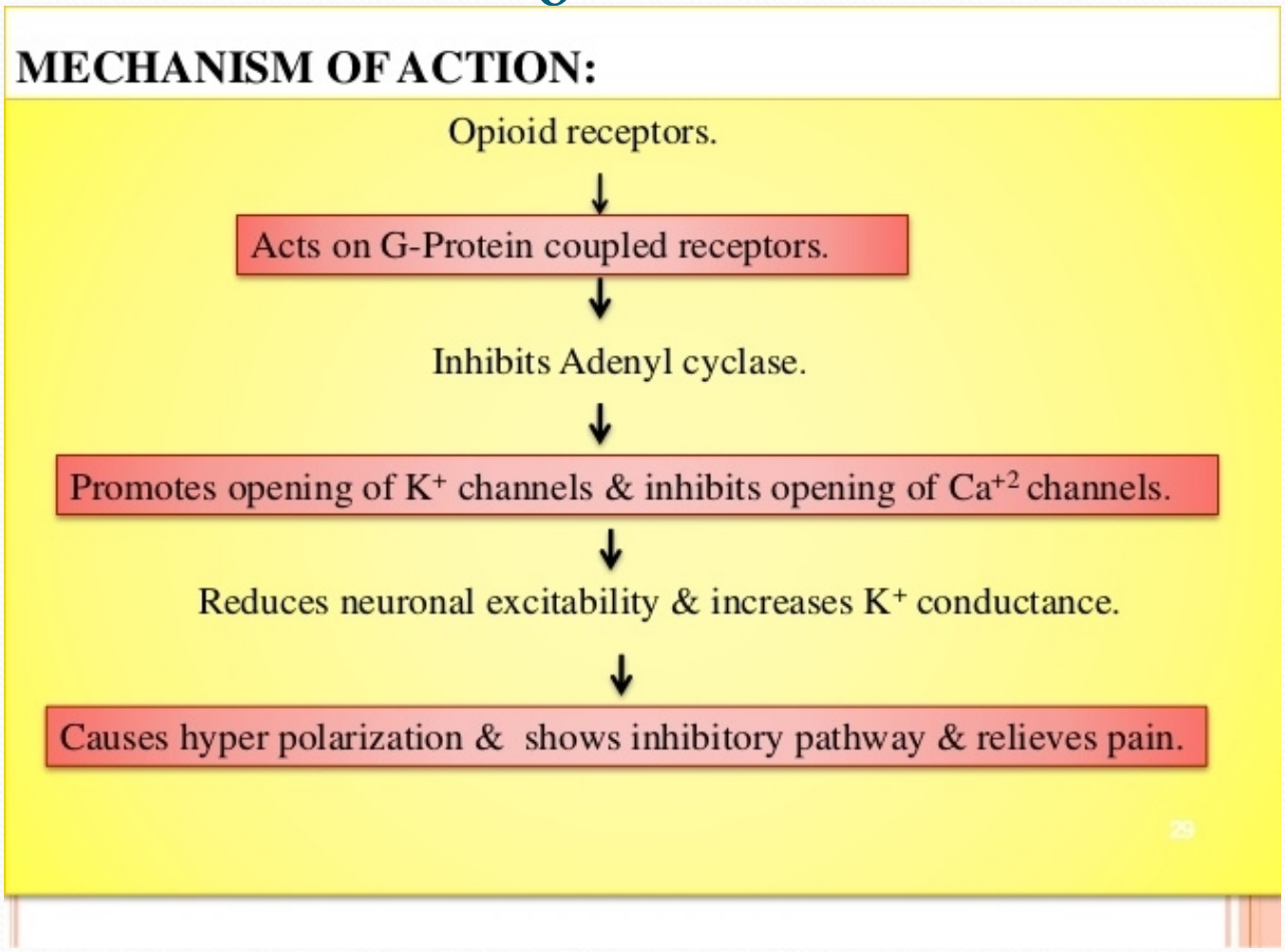
All opioid receptors μ, k, and δ are G protein coupled receptors situated on prejunctional neurons. They exert inhibitory modulations by decreasing the release of junctional transmitter (i.e. noradrenaline, dopamine, 5HT), and glutamate. Opioid receptors activation reduce intracellular cAMP formation and open K+ channels or suppress voltage gated N type Ca2+ channels. These results in hyper-polarization in synaptic junctions and decrease the neurotransmitter release.

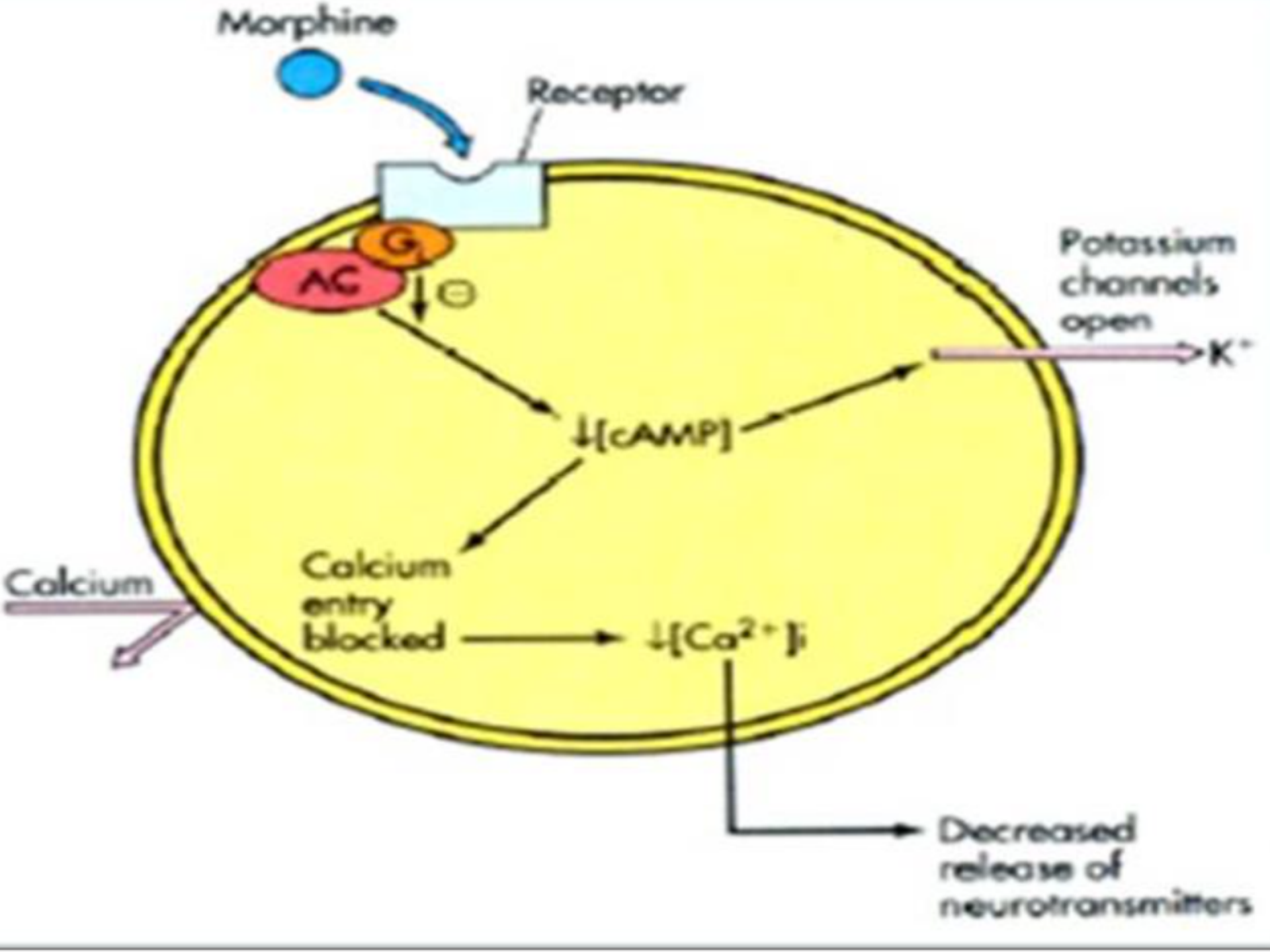
1. Mu (μ) receptors are responsible for supra-spinal analgesia mediated by μ1 and spinal mediated by μ2. Respiratory depression and gastric motility reduction is mediated by μ2 subtypes. μ receptor produces euphoria, physical dependence, and miosis.

2. Kappa receptors appear to mediate spinal analgesia through κ1 subtypes and supra-spinal analgesia through κ3 subtype. It produces respiratory depression, dysphoria, hallucination, miosis, sedation, and nicotinic effects.

3. Activation of δ receptors produces spinal analgesia, respiratory depression, affective behavior, reinforcing actions, and reduced GI motility.

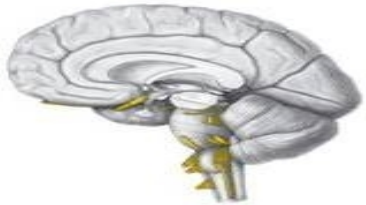
Mechanism of Action

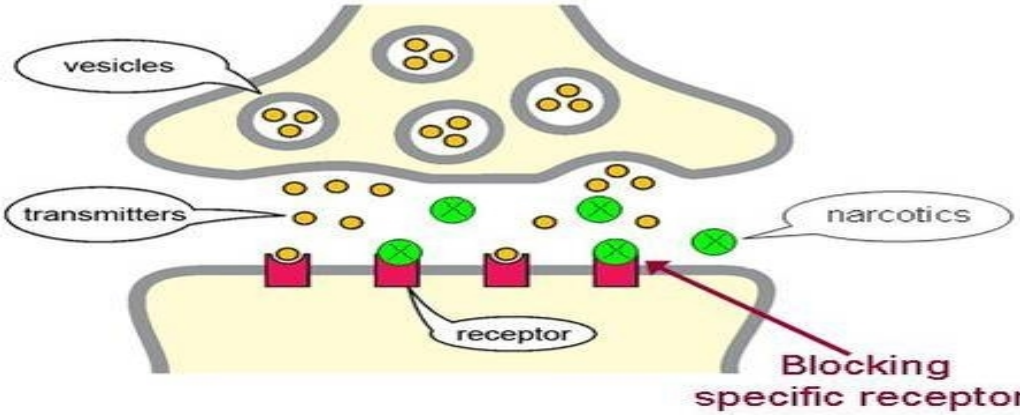



Morphine
Receptor
G
AC
⊖
Potassium channels open
K+
↓[cAMP]
Calcium
Calcium entry blocked
↓[Ca2+]i
Decreased release of neurotransmitters

Mode of action

- Effects located in the Central Nervous System
- Specific receptors in the brain for different narcotics lead to different side effects





Action on:

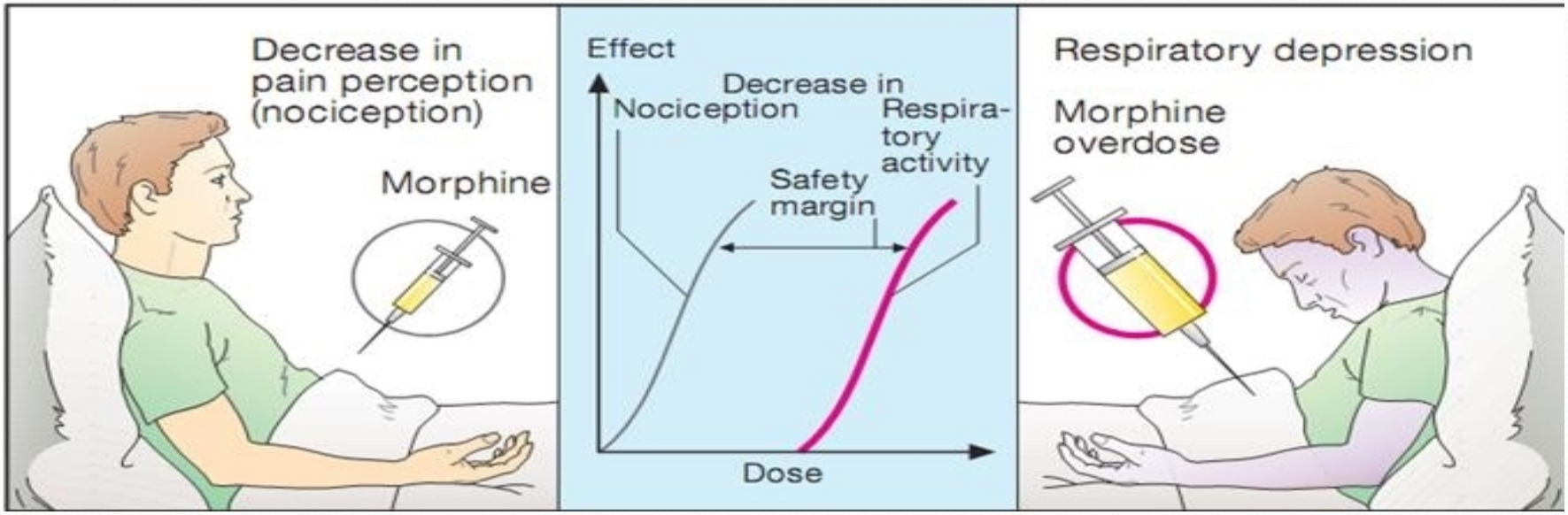
μ-receptor *(Endorphins)*
⇨ Analgesia Euphoria

κ-receptor *(Dynorphines)*
⇨ Analgesia Sedation

δ-receptor *(Enkephalins)*
⇨ Analgesia Dysphoria

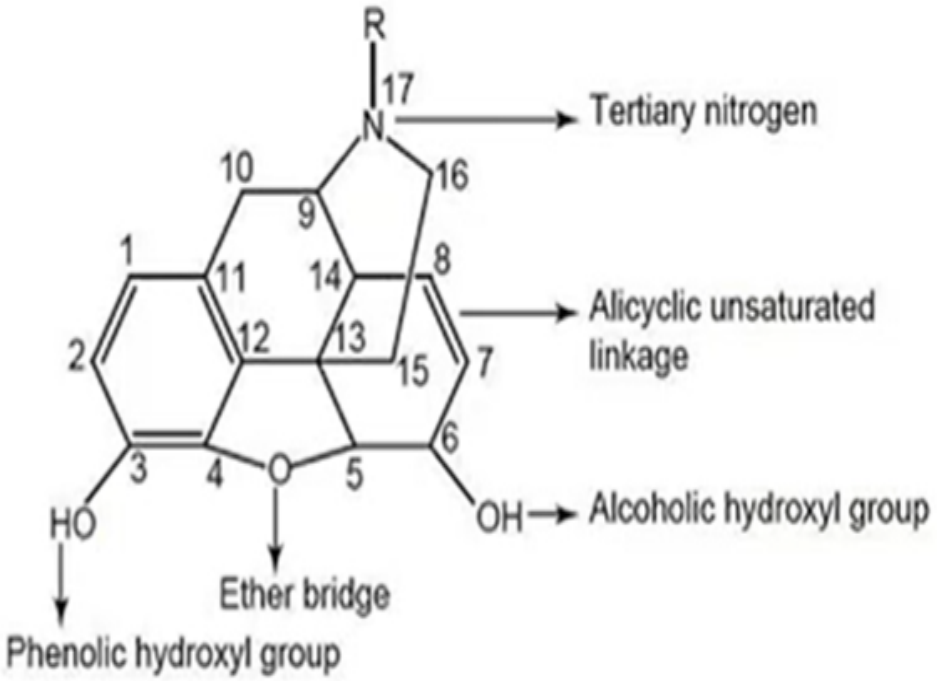
Müller-Esterl: Biochemie, 2004
© Spektrum Akademischer Verlag, Heidelberg

Sobotta: Atlas der Anatomie des Menschen
©Elsevier GmbH, Urban & Fischer Verlag München



SAR of Morphine Analogues

1. Modification of alicyclic ring
2. Modification of aromatic ring
3. Modification of 3^0 Nitrogen

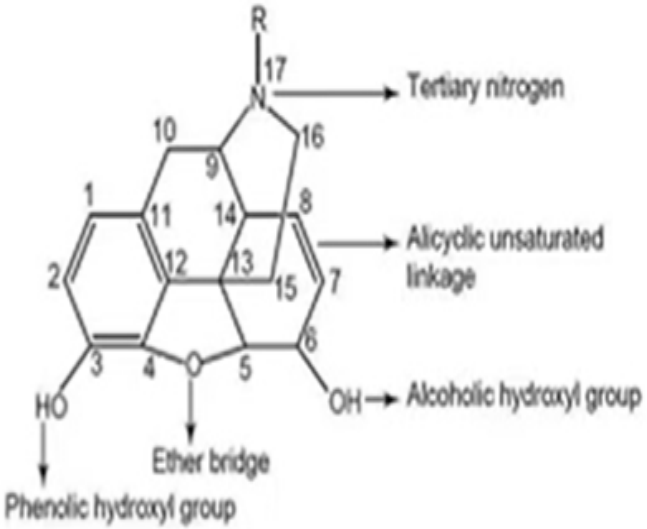


1. Modification on alicyclic ring

1. The alcoholic hydroxyl group at C-6 when methylated, esterified, oxydized, removed, or replaced by halogen analgesic activity as well as toxicity of the compound increased.
2. The reduction of C-6 keto group to C-6 β-hydroxyl in oxymorphone gives Nalbupine, it shows antagonistic action of μ receptors.
3. The saturation of the double bond at C-7 position gives more potent compound. Examples, Dihydro morphine and Dihydro codeine.
4. The 14 β-hydroxyl group generally enhances μ agonistic properties and decreases antitussive activity. However, activity varies with the overall substitution on the structure.
5. Bridging of C-6 and C-14 through ethylene linkage gives potent derivatives.
6. Reaction of thebaine with dienophile (i.e diel's alder reaction) results in 6, 14 endo etheno tetrahydro thebaine derivatives, which are commonly called ' oripavines'. Some oripavines are extremely potent μ agonist, for example, Etorphine and Buprenorphine are the best known. These derivatives are about thousand times more potent than morphine as μ agonist.

2. Modification on phenyl ring

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



3. Modification of 3° nitrogen

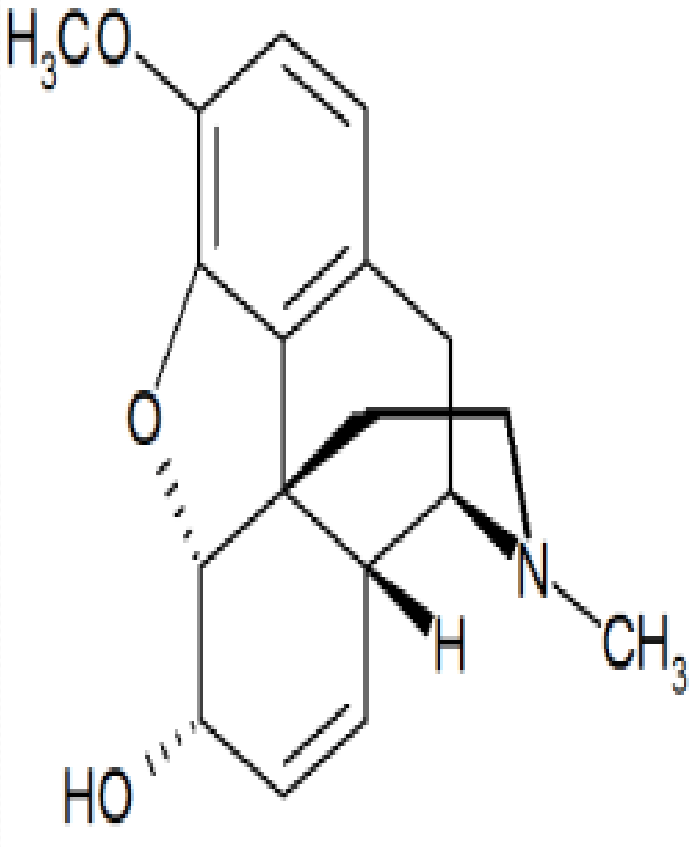
1. A tertiary amine is usually necessary for good opioid activity.
2. The size of the N substitution can dictate the compounds potency and its agonists and its reverse antagonistic property.
3. The *N*-methyl substitution is having good agonistic property, when increased the size of the substitution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

4. Epoxide Bridge

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

Codeine

- Codeine is also an alkaloid that is found in opium but to a far lesser extent than morphine.
- It differs structurally from morphine in that its phenol group is methylated. It is often referred to as methyl-morphine.



- Oxycodone and methadone are analogs of codeine
- Codeine itself has low binding affinity to all of the opioid receptors. Its analgesia producing effects come from its conversion to morphine.
- When codeine is administered about ten percent is converted to morphine by O-demethylation that occurs in the liver by an enzyme called cytochrome p450.
- Because of this Codeine is far less potent than morphine

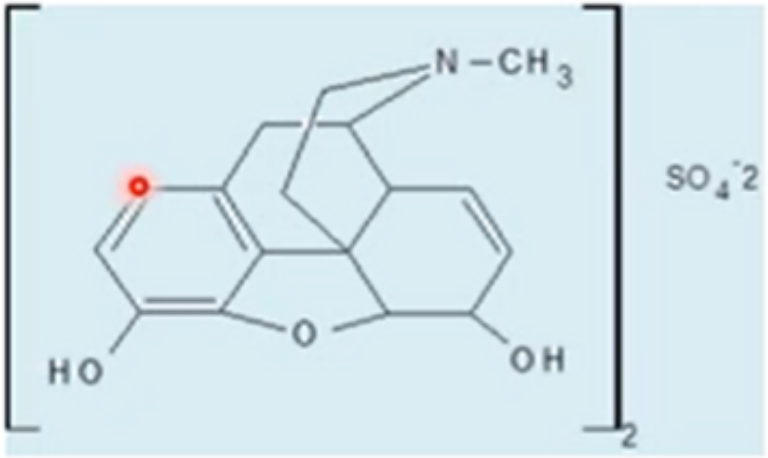
- Codeine is usually administered orally and it is much more effective orally than morphine (about 60%)
- Because of the side effect of respiratory depression and depressed cough, codeine is often found in cough medicines

Abuse of Codeine

- The use of Codeine as a recreational drug for its euphoric effects is spreading greatly.
- This abuse is mostly isolated to Texas
- Recreational users refer to codeine as “lean” and will mix the drug with alcohol or other drugs.

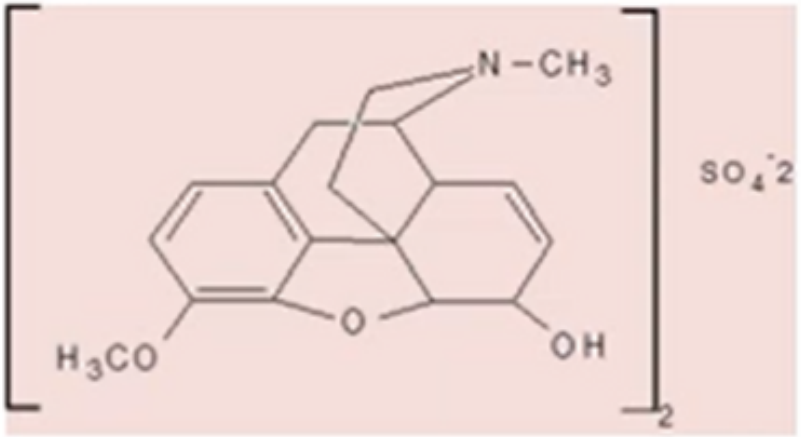
1. Morphine derivatives or 4,5-epoxy morphinans:

Morphine sulphate



- ✓ Ligand for μ-receptor.
- ✓ Naturally occurring active form of morphine is levorotatory enantiomer.

Codeine sulphate



- ✓ Pharmacological actions similar to morphine.
- ✓ It is an effective antitussive agent.
- ✓ In combination used to treat moderate pain.

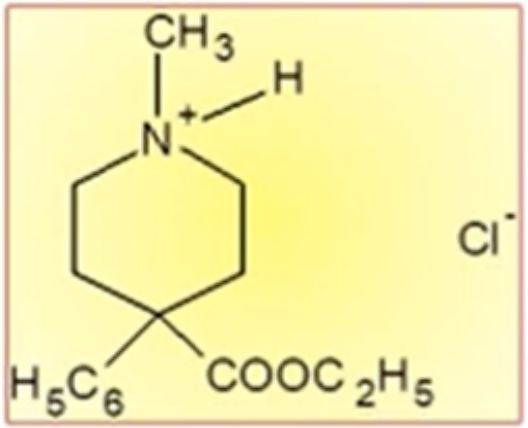
PETHIDINE(MEPERIDINE)

- It interacts with μ opioid receptor and its actions are blocked by naloxane.
- Analgesic activity is near to morphine and more than codeine.
- After i.m injection the onset of action is more rapid but duration is shorter.
- Does not effectively suppress cough.
- It is equally **sedative and euphoriant** has similar abuse potential.
- The degree of respiratory depression is same as that in morphine.

4. 4-phenyl piperidines

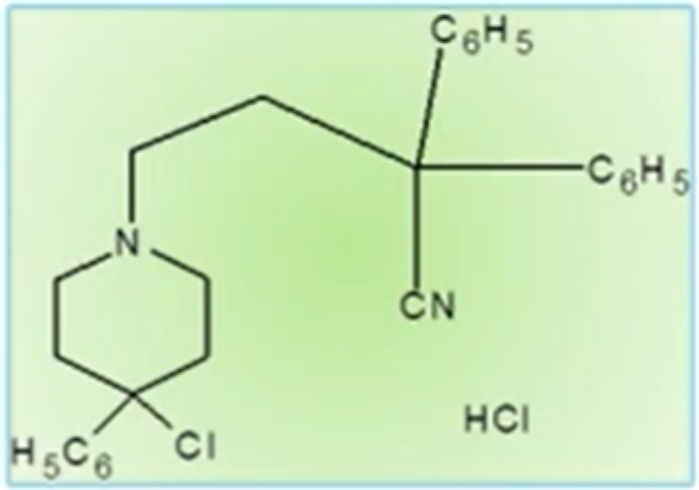
Eg:

Meperidine HCl



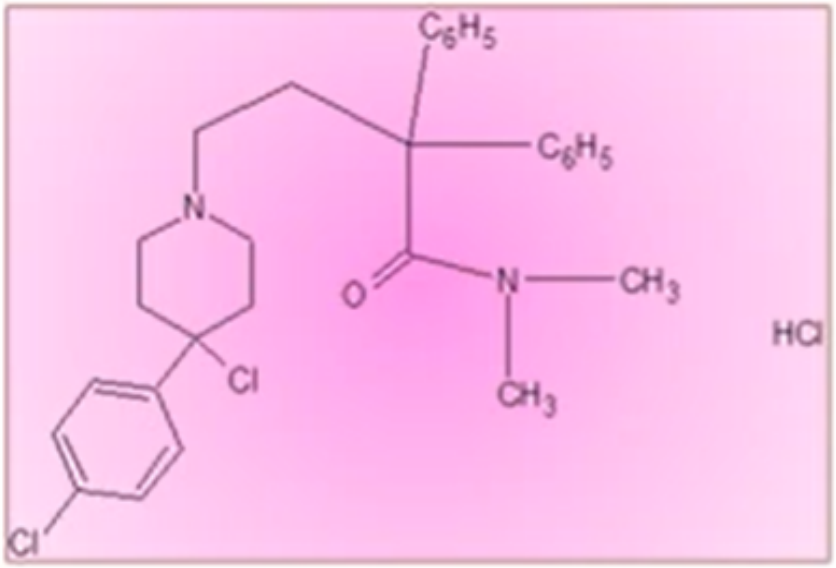
- ✓ Low potency when compared to morphine.
- ✓ It is a μ-receptor agonist.
- ✓ Normeperidine shows CNS side effects.

Diphenoxylate HCl



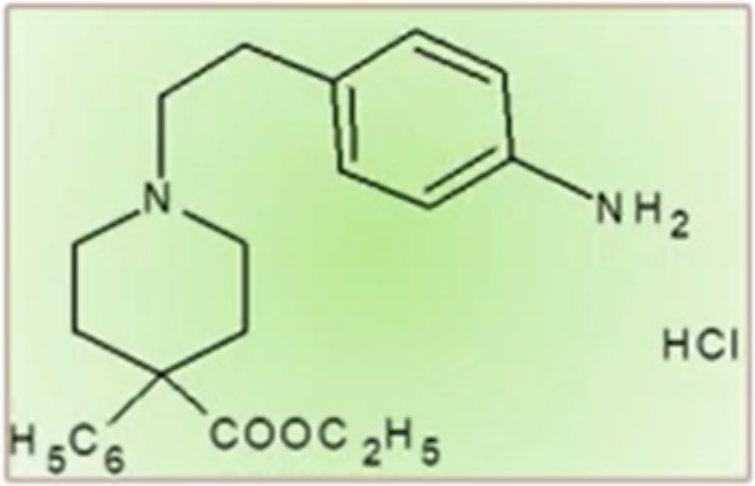
- ✓ Weak opioid agonist and is available combined with atropine for use as an antidiarrheal.

Loperamide HCl



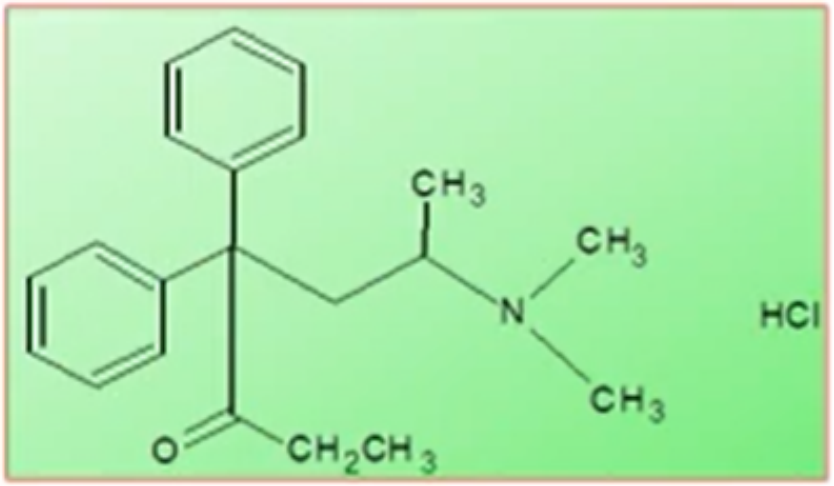
- ✓ It acts as an antidiarrheal by directly binding to opiate receptors in the gut wall.
- ✓ It inhibits Ach & PG release, decreasing peristalsis and fluid secretion and increase GI transit time.

Anilerdine HCl

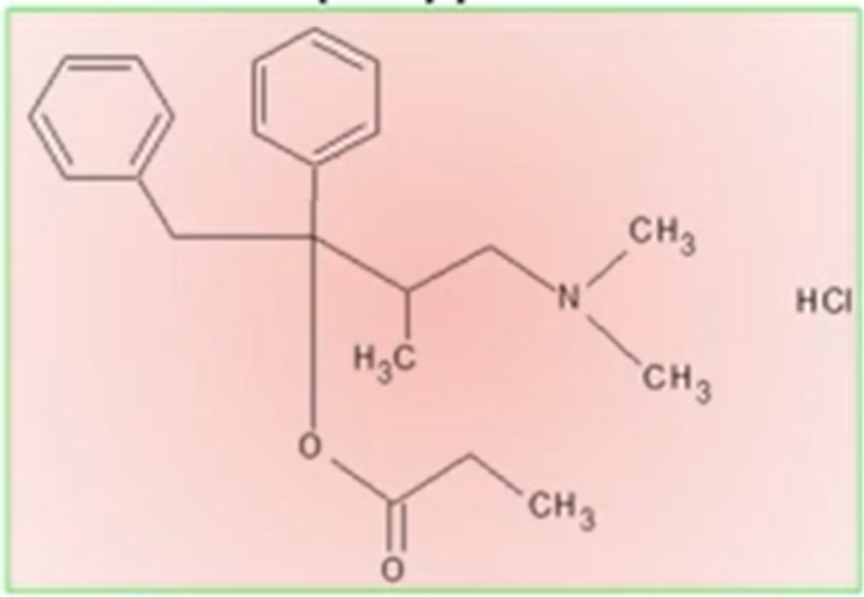


6. Diphenyl heptanes

Eg: Methadone HCl

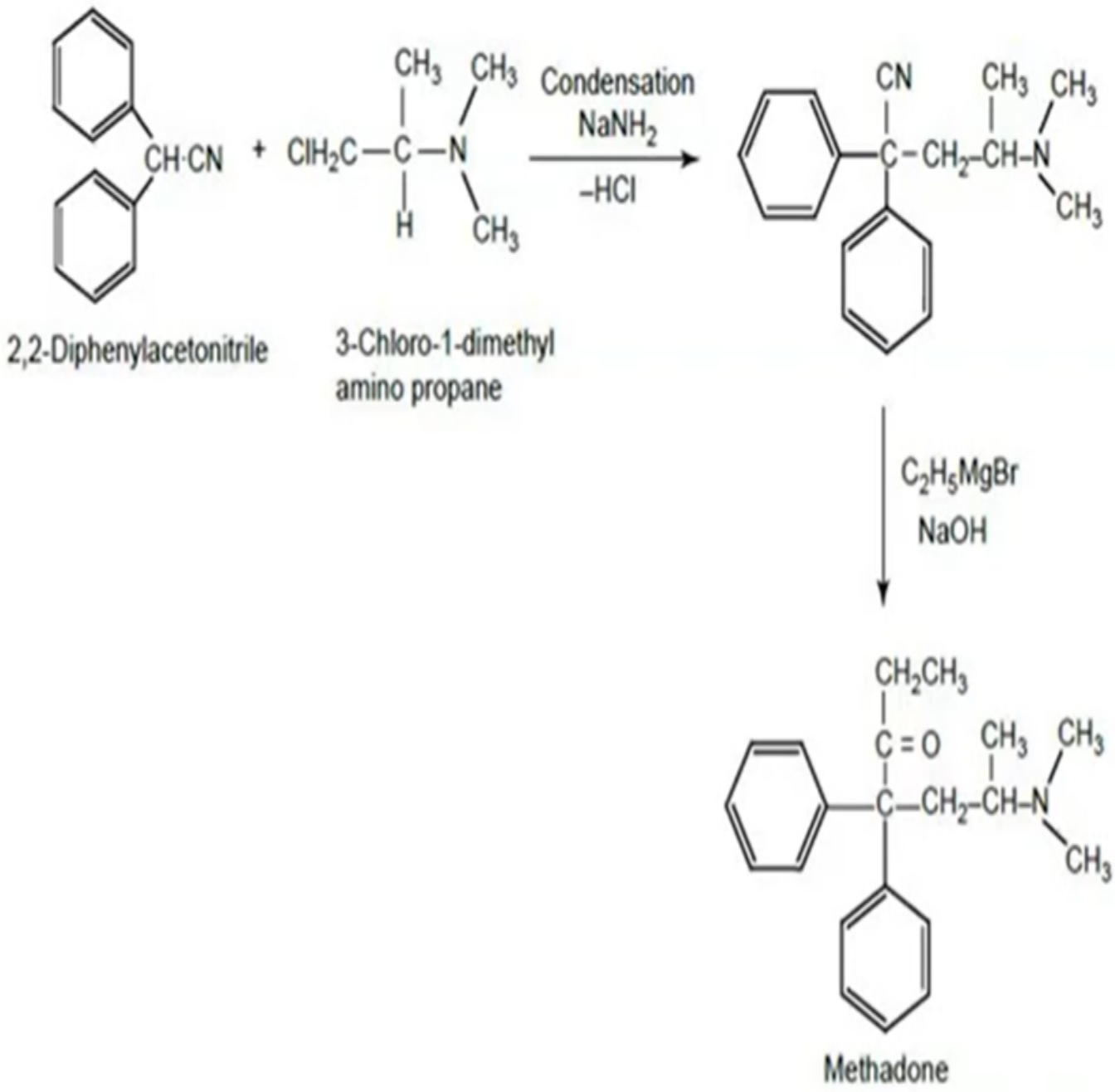


Propoxyphene HCl



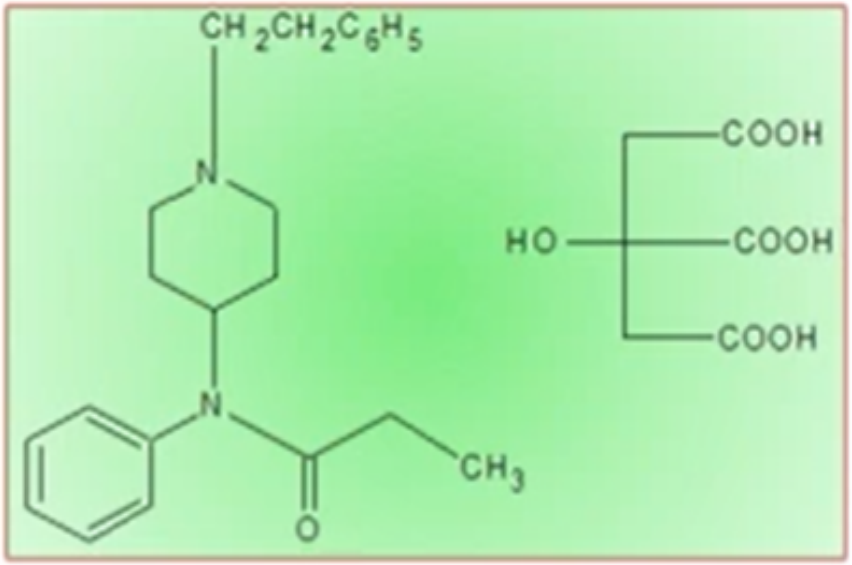
- ✓Synthetic opioid approved for analgesic therapy and for the maintenance and treatment of opioid addiction.
- ✓R-enantiomers 7-50 times more potent than S-enantiomer

Synthesis of Methadone



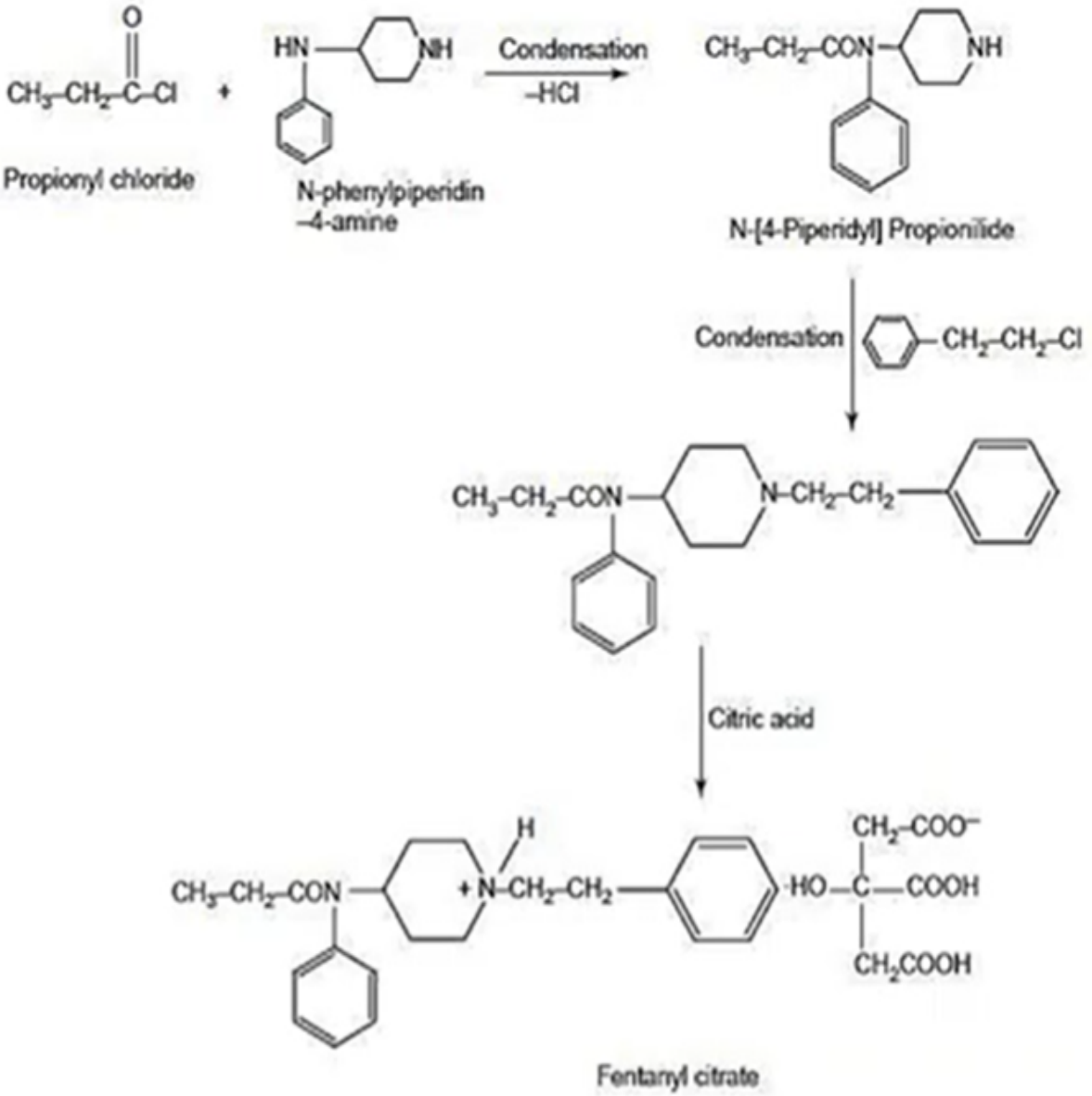
5. 4-Anilino piperidines

Eg: Fentanyl Citrate



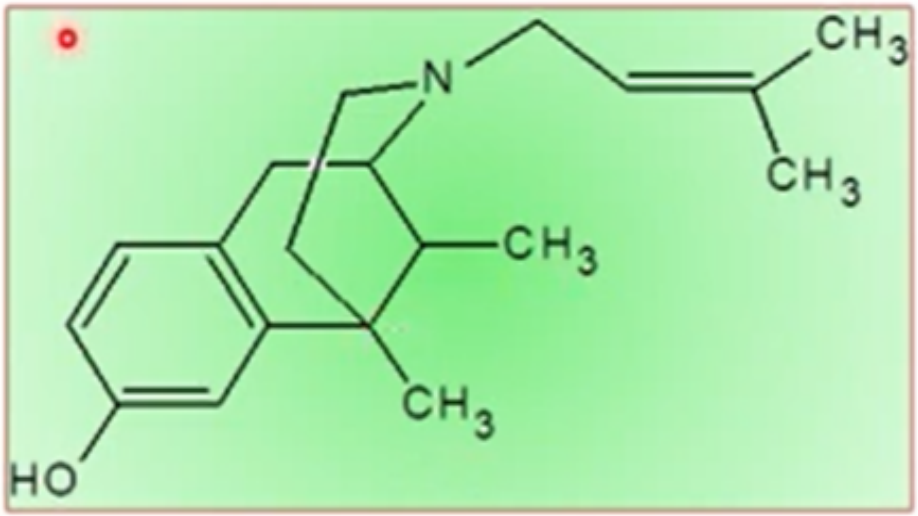
- ✓ Sedative and euphoria inducing analgesic with a potency approximately 50-100 fold than morphine because of lipophilicity.
- ✓ Duration of action is 30-60 minutes.
- ✓ Administered IV as adjuncts to anesthesia.
- ✓ Transmucosal, transdermal and nasal spray formulations of fentanyl are available to treat chronic pain including the pain of cancer.

Synthesis of Fentanyl citrate



3. Benzomorphans or Benzazocin derivatives

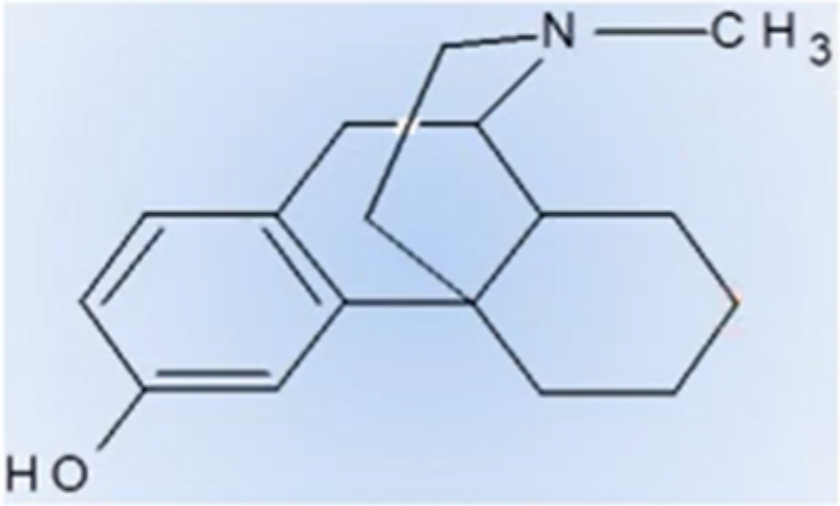
Eg: Pentazocine

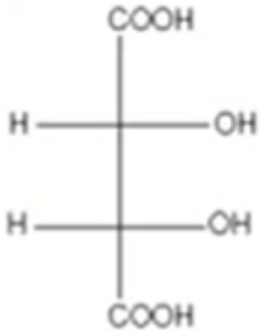


- ✓ The only benzomorphan in clinical use is pentazocine prepared as 2(R), 6(R), 11(R) enantiomer.
- ✓ It is a mixed agonist / antagonist at opioid receptors.
- ✓ At the μ-receptor it is a partial agonist and weak antagonist.

2. Morphinan derivatives :

✓ Eg: Levorphanol tartarate





✓Morphinan derivatives obtained by removing of 4,5-ether bridge, double bond and alcoholic hydroxyl group due to these changes leads to increased binding affinity to all opioid receptors.

✓Strong agonist activity at mu, kappa and delta receptors.

THANK YOU