Organic Pharmaceutical Chemistry II

Analgesic

Lec. 10

Analgesic Agents

Analgesic drugs- : **may be defined as a drug bringing about insensibility to pain without loss of consciousness.**

Classification of Pain

physiological

(nociceptive)

Touching a hot object or getting a cut

the most common and is often caused by an injury to body organs or tissues. It is further categorized, according to the source of the pain, into cutaneous pains (skin and surface tissues), somatic pains (ligaments, tendons, bones, blood vessels), and visceral pains (body organs and internal cavities).

Inflammatory

Inflammatory pain can be initiated in a wide variety of ways, such as infection and tissue injury

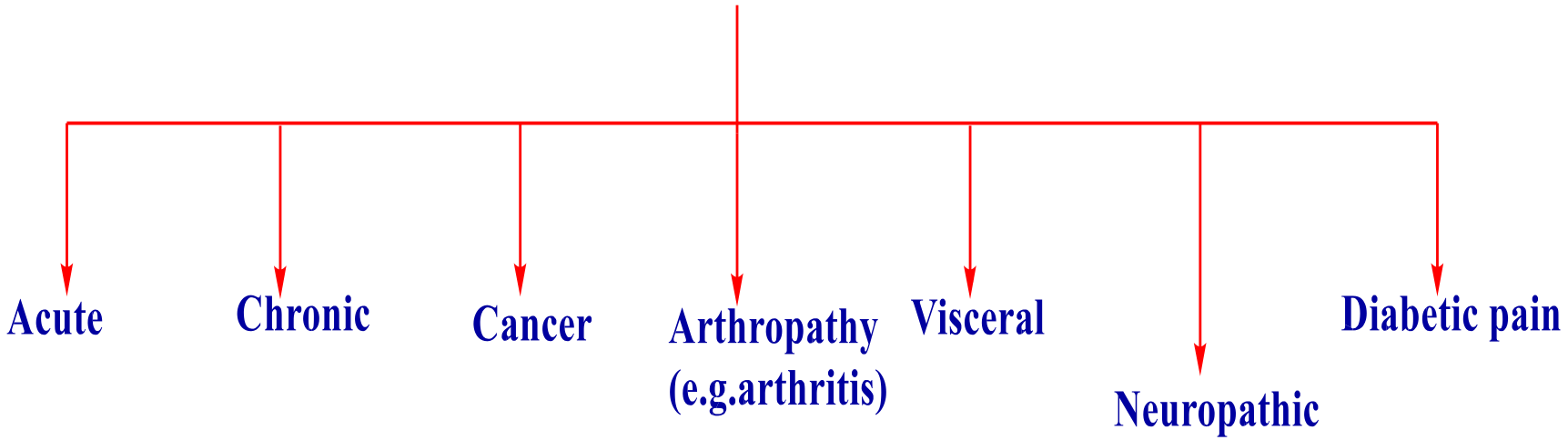
Inflammatory pain originates from an infection or inflammation as a result of the initial tissue or organ damage.

Neuropathic

Injury to the peripheral or central nervous system (CNS)

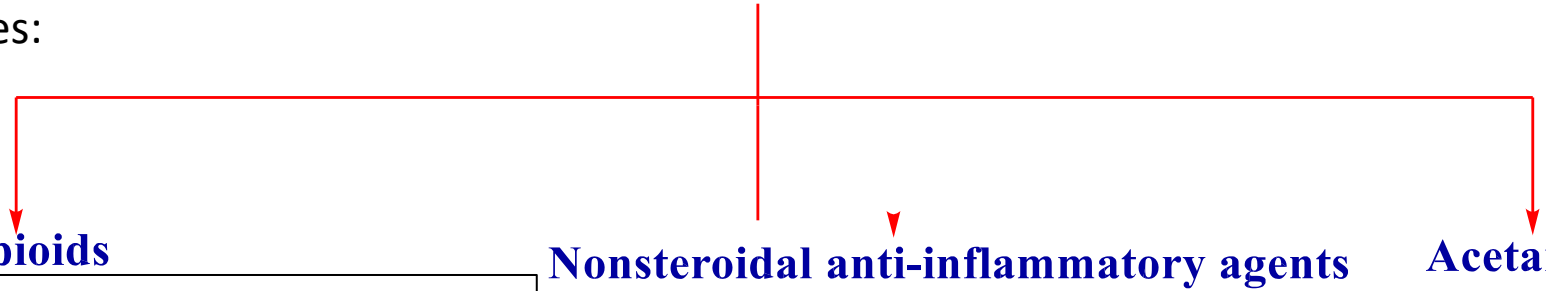
Neuropathic pain is a very complex, chronic pain, resulting from injury of the nervous systems. Neuropathic pain may originate from limb amputation, spinal surgery, viral infections such as shingles, or worsening of disease states associated with diabetes, acquired immunodeficiency syndrome (AIDS), or multiple sclerosis.

Within these classes of pain there are different levels of pain or categories of pain includes



Classes of pain-relieving drugs

Analgesics can be broadly categorized, according to their therapeutic use, into several drug classes:



Opioids

(or narcotic analgesics), which play a major role in the relief of acute pain and in the management of moderate to severe chronic pain

Nonsteroidal anti-inflammatory agents

Acetaminophen

the NSAIDs and acetaminophen, which are the most widely used analgesic drugs for relieving mild to moderate pain and reducing fever

The triptans (the antimigraine medications)

which are specifically designed and targeted for acute and abortive treatment of migraine and cluster headaches.

A new emerging class of analgesics

known as analgesic adjuvants that include tricyclic antidepressants such as amitriptyline, anticonvulsants such as gabapentin and pregabalin, and topical analgesics such as lidocaine patches that can be used to treat neuropathic pains.

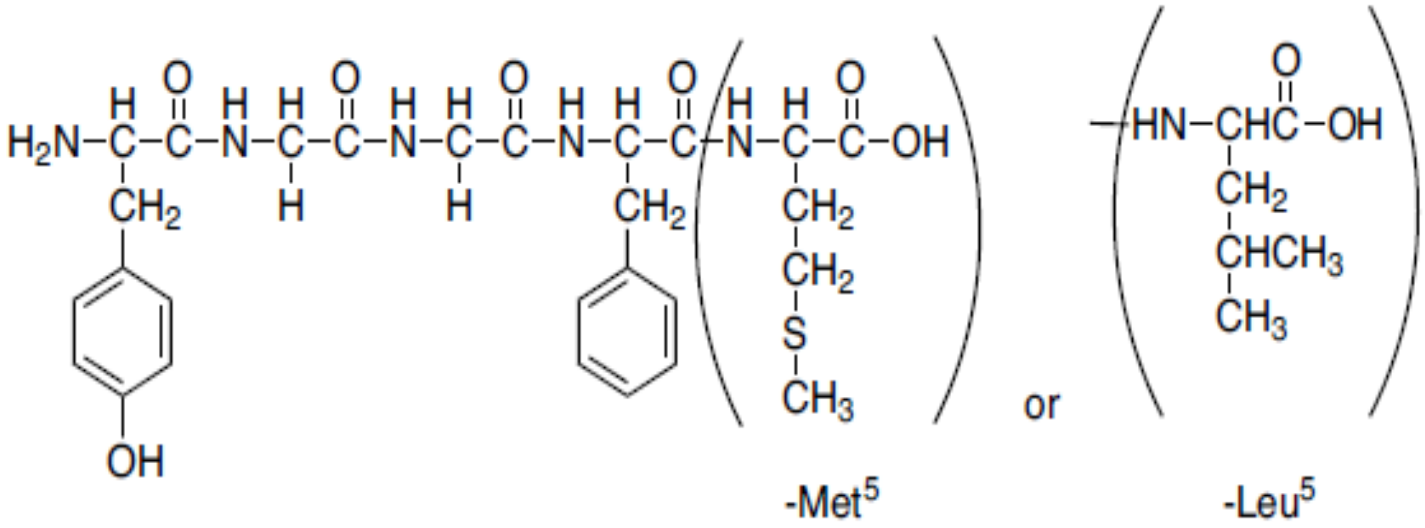
Acute and Chronic Pain

Pain may be acute or chronic. Acute pain is often severe but usually lasts only until the removal of the source that triggered the pain. Acute pain includes nociceptive, somatic, or visceral pain, postoperative and posttraumatic pain, burn pain, acute pain during childbirth, acute headache, etc.

Acute and postoperative pains are most often treated with the opioid analgesics. Chronic pain, on the other hand, is defined as a pain lasting longer than 6 months that persists even when the initial cause has been resolved through appropriate medical intervention. Chronic pain can be further divided into chronic malignant pain (e.g., cancer, human immunodeficiency virus [HIV]/AIDS, amyotrophic lateral sclerosis, multiple sclerosis, end-stage organ failure) and chronic nonmalignant pain (e.g., lower-back pain, chronic degenerative

arthritis, osteoarthritis (OA), rheumatoid arthritis (RA), migraine and chronic headache, and bond pain). Pain therapy in patients with chronic pain only provides transient pain relief but does not resolve the underlying pathological process. Chronic pain is also often associated with behavior and psychological components that make effective pain management quite subjective and difficult to resolve. Chronic pain is also the leading cause of disability among the elderly; the prevalence of pain may be as high as 80%.

Met-enkephalin = Tyr^1-Gly^2-Gly^3-Phe^4-Met^5(OH) Leu-enkephalin = Tyr^1-Gly^2-Gly^3-Phe^4-Leu^5(OH)



The first endogenous peptide was termed enkephalin, which was found to be a mixture of the two pentapeptides that only differ in their terminal amino acid.
Both methionine-enkephalin (Met-enkephalin) and leucine-enkephalin (Leu-enkephalin) were shown to inhibit the contraction of electrically stimulated guinea pig ileum (GPI) and mouse vas deferens (MVD). These two tests are still used as screening methods for opioid activity.

The central administration of enkephalins in rats produced short analgesic activity. The transient nature of the enkephalins' actions correlated with the rapid degradation of the enkephalin Tyr-Gly bond by aminopeptidases.

SARs of Enkephalins

TYR1(tyrosine)

The first amino acid of the pentapeptide shows a distinct preference for tyrosine. Most changes to this amino acid, either by substituting with other amino acids or masking the phenolic hydroxyl (OH) or amino function, produce an inactive or weakly active peptide.

GLY2

Replacing the naturally occurring L-Gly with various D-amino acids produces a peptide that is resistant to peptide cleavage by aminopeptidases. Replacement with D-Ser is the most effective replacement, and all L-amino acid analogs had low activities.

GLY3 (glycine)

Almost all changes to this amino acid result in a drop in potency, unless they are also accompanied by another change such as replacing the Gly2 with D-Ala2 as described above.

PHE4 (phenyl anlanine)

The aromatic nature of the fourth residue is required for high activity. When combined with the D-Ala2 replacement, the addition of an electron withdrawing, lipophilic substituent (e.g., NO2, Cl, and Br) in the para position of Phe4 greatly increases activity. Para substitutions with electron donating, hydrophilic functional groups (e.g., NH2 and OH) abolish activity.

MET5/LEU5

Position 5 appears to tolerate more residue changes than the other positions. Many amino acid substitutions at this position maintain activity (e.g., Ala, Gly, Phe, Pro). Even the loss of the fifth residue to yield the tetrapeptide Tyr1-Gly2-Gly3-Phe4 maintains weak activity in both the GPI and MVD assays. The protected peptide, Tyr1-D-Ala2-Gly3-MePhe4-Gly-ol5, known as DAMGO is highly selective for the μ-receptor. *DAGO. [D-Ala2.McPhe4.Glycol5] enkephalin; DADLE, [D-Ala2, D-Leu5]enkephalin.*

Endogenous Precursor Proteins

Pro-opimelanocortin ⟶ ACTH + β LPH ⟶ γ-LPH + β endorphin

Pro-enkephalin A^{263} ⟶ 4Met-enkephalin + Leu-enkephalin

Pro-enkephalin B^{256} ⟶ β neo-endorphin$^{175\text{-}183}$ + dynorphin$^{209\text{-}225}$ + Leu-enkephalin$^{228\text{-}232}$

Endogenous Opioid Peptide sequences

β Endorphin = Tyr-Gly-Gly-Phe-Met^{5}-Thr-Ser-Glu-Lys-Ser^{10}-Gln-Thr-Pro-Leu-Val^{15}-Thr-Leu-Phe-Lys-Asn^{20}-Ala-Ile-Ile-Lys-Asn^{25}-Ala-Tyr-Lys-Lys-Gly-Glu^{31} = δ and μ opioid receptor ligand

Endomorphin-1 = Tyr-Pro-Trp-Phe-NH_2 = μ receptor agonist

Endomorphin-2 = Tyr-Pro-Phe-Phe-NH_2 = μ receptor agonist

Dynorphin = Tyr-Gly-Gly-Phe-Leu^{5}-Arg-Arg-Ile-Arg-Pro^{10}-Lys-Leu-Lys^{13} = κ opioid selectivity

α-Neoendorphin = Tyr-Gly-Gly-Phe-Leu^{5}-Arg-Lys-Tyr-Pro-Lys^{10}

β-Neoendorphin = Tyr-Gly-Gly-Phe-Leu^{5}-Arg-Lys-Tyr-Pro^{9}

Nociceptin = Phe-Gly-Gly-Thr-Gly^{5}-Ala-Arg-Lys-Ser-Ala^{10}-Lys-Ala-Asn-Gln^{14} = orphanin receptor

Orphanin FQ = Phe-Gly-Gly-Phe-Thr^{5}-Gly-Ala-Arg-Lys-Ser^{10}-Ala-Arg-Lys-Leu-Ala-Asn-Gln^{17}

Exogenous Opioid Peptide sequences "Exorphins"

DADLE = Tyr-D-Ala-Gly-Phe-D-Leu = δ selective agonist

DPDPE = Tyr-D-Pen-Gly-Phe-D-Pen = δ selective agonist

DSLET = Tyr-D-Ser-Gly-Phe-Leu-Thr = δ selective agonist

Casomorphin (cow's milk μ opioid receptor agonist) = Tyr-Pro-Phe-Pro-Gly-Pro-Ile^{7}

Dermorphin (South American frog skin μ opioid receptor agonist) = Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser^{7}-NH_2

Gluten exorphins (multiple peptides from wheat having opioid agonist and antagonist activity)

Figure 24.2 ● Endogenous and exogenous opioid peptides.

The opioid receptor subtypes share extensive residue homology in their transmembrane (TM) domains with most of the variation found in the extracellular loops.

All of the opioid receptors belong to the G-protein–coupled receptor class and as such, they are composed of seven TM domains. When the receptor is activated, a portion of the G protein diffuses within the membrane and causes an inhibition of adenylate cyclase activity. The decreased enzyme activity results in a decrease in cyclic adenosine monophosphate (cAMP) formation, which regulates numerous cellular processes.
One process that is inhibited is the opening of voltagegated calcium influx channels on nociceptive C-fibers. This results in the hyperpolarazation of the nerve cell and decreased firing and release of pain neurotransmitters such as glutamate and substance P.

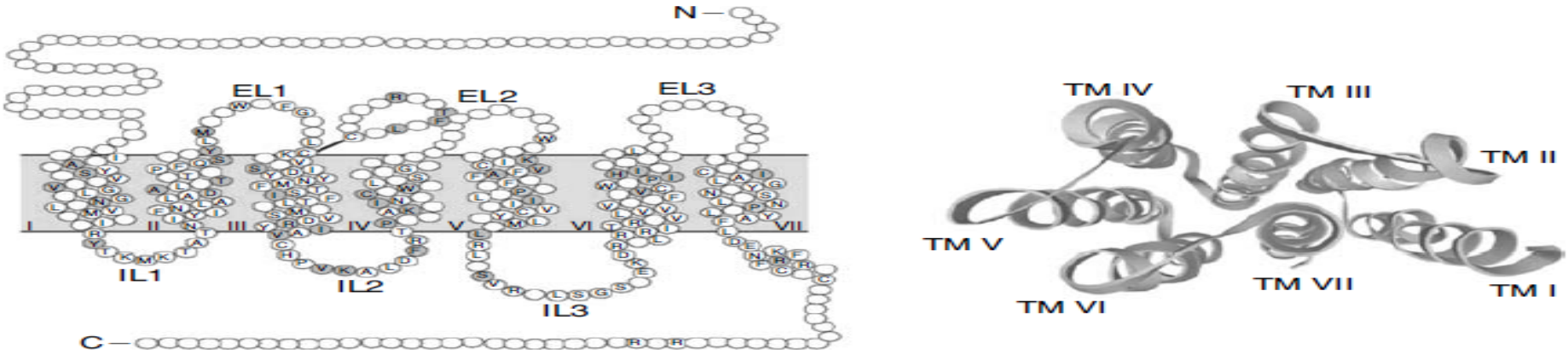


Figure 24.3 • Structure of opioid receptors. (*Left*) Serpentine model of the opioid receptor. Each transmembrane helix is labeled with a roman number. The white empty circles represent nonconserved amino acids among the MOP, DOP, KOP, and NOP receptors. White circles with a letter represent identical amino acids among all four opioid receptors. Violet circles represent further identity between the MOP-R, DOP-R, and KOP-R. Green circles highlight the highly conserved fingerprint residues of family A receptors, Asn I:18 in TM1, AspII:10 in TM2, CysIII:01 in TM3, TrpIV:10 in TM4, ProV:16 in TM5, ProVI:15 in TM6, and ProVII:17 TM7. Yellow circles depict the two conserved cystines in EL loops 1 and 2, likely forming a disulfide bridge. (IL, intracellular loop, and EL, extracellular loop.) (*Right*) Proposed arrangement of the seven transmembrane helices of opioid receptors as viewed from the top (extracellular side). The seven transmembrane helices are arranged sequentially in a counterclockwise manner. Each transmembrane helix is labeled with a roman number. (Reprinted with permission from the *Annual Review of Biochemistry*, Volume 73 © 2004 by Annual Reviews.)

OPIOID LIGAND BINDING SITE

As of yet, no definitive model of the ligand-binding site is available. The opioid-binding site for all four opioid receptors is believed to be an inner cavity formed by conserved residues on TM helices TM3, TM4, TM5, TM6, and TM7. Not all groups agree that the binding pocket is formed via TM domains; some evidence suggest that the amino terminus is an important determinant of ligand binding affinity as well.

The ligand specificity that each receptor shows may be a result of differences in the extracellular loops that form lids on the binding cavities or differences in amino acids within the binding cavity. Within the cavity, agonists are thought to bind toward the bottom of the cavity via interactions with a conserved Asp from TM3 and a His from TM6.

Molecular modeling calculations show that the phenolic OH of the Tyr1 opioid peptide, or the ring A OH of nonpeptide opioids, forms a hydrogen bond with the conserved His on TM6. The Tyr1-charged nitrogen, or the N of the nonpeptide agonist, forms an ionic bond with the conserved Asp of TM3.

Antagonist ligands are thought to bind deeper in the binding pocket but retain the ionic bond with the Asp of TM3. The bulky substituent on the charged nitrogen of antagonists is believed to insert itself between TM3 and TM6, preventing the shifts required for activation. Thus, antagonists prevent the necessary movement of TM3 and TM6 resulting in functional antagonism.

THE μ-RECEPTOR

Mu receptors are found primarily in the brainstem and medial thalamus. Endogenous peptides for theμ-receptor include endomorphin-1, endomorphin-2, and β-endorphin(Fig. 24.2). Exogenous agonists for the μ-receptor include drugs from the five structural classes discussed later in this chapter (4,5-epoxymorphinan, morphinan, benzomorphan, 4-phenyl/4-anilido piperidines, and the diphenylheptanes)

In general, agonists at the μ-receptor produce analgesia, respiratory depression, decreased gastrointestinal (GI) motility, euphoria, feeding, and the release of hormones.

Agonists are also responsible for the addictive effects of the opioid analgesics. Most clinically used opioid drugs bind to the μ-opioid receptor.

THE δ-RECEPTOR

Opioid peptides for the δ-receptor include the endogenous peptides described previously, Met and Leu enkephalin, as well as some synthetic peptides such as DADLE, DSLET, and DPDPE (see Fig. 24.2 for amino acid sequences). These peptides have high affinity for the receptor but low bioavailability and thus limited clinical usefulness.

THE *k*-RECEPTOR

Kappa receptors are primarily found in the limbic, brain stem, and spinal cord. The *k*-receptor shows less structural homology to the μ-receptor than the δ-receptor does. (Fig. 24.3)
Unlike the μ- and δ-receptors that bind the (enkephalin) peptide sequence Tyr-Gly-Gly-Phe-(Leu/Met), the *k*–receptor does not. The *k*-receptor shows a clear preference for binding peptides with an arginine in position 6 as seen in the dynorphin peptides (Fig. 24.2).

THE ORPHANIN RECEPTOR/FQ/NOP1 (nociceptin opioid peptide receptor)

The traditional opioid peptides do not elicit any biological effect at the orphanin receptor. An endogenous peptide for the orphanin receptor has been found and termed orphanin FQ or nociceptin (Fig. 24.2). This 17 amino acid peptide can reverse the analgesic effects of morphine thus is antiopioid in some situations. The carboxy-terminal half of the receptor may serve as the portion that excludes binding to the μ-, δ-, and k-opioid ligands.

Opiate Receptors and effect of Agonist

Mu_1 (μ_1)	analgesia, euphoria
Mu_2 (μ_2)	constipation, respiratory depression
Kappa	spinal analgesia, dysphoria
Delta	unknown

Receptor Binding at Mu receptor

Agonist	Morphine-like effect (e.g., heroin, weak binding except for Fentanyl)
Partial Agonist	Weak morphine-like effects with strong receptor affinity (e.g., buprenorphine)
Antagonists	No effect in absence of an opiate or opiate dependence (e.g., naltrexone)

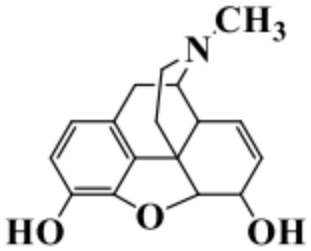
Effect of Common Opiates at Mu Receptor

• Heroin, morphine, methadone	Agonists
• Buprenorphine	Partial Agonist
• Naltrexone • Nalmefene	Antagonist

Opioid drugs

Two basic types of structures are recognized among the opium alkaloids include

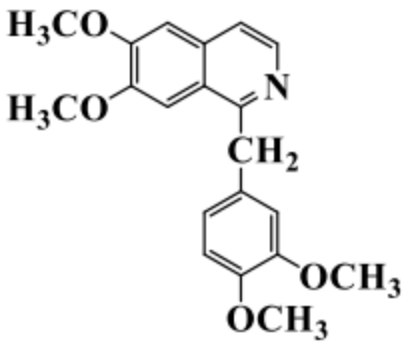
Phenanthrene (morphine)



acts principally on

CNS as a depressant and stimulant

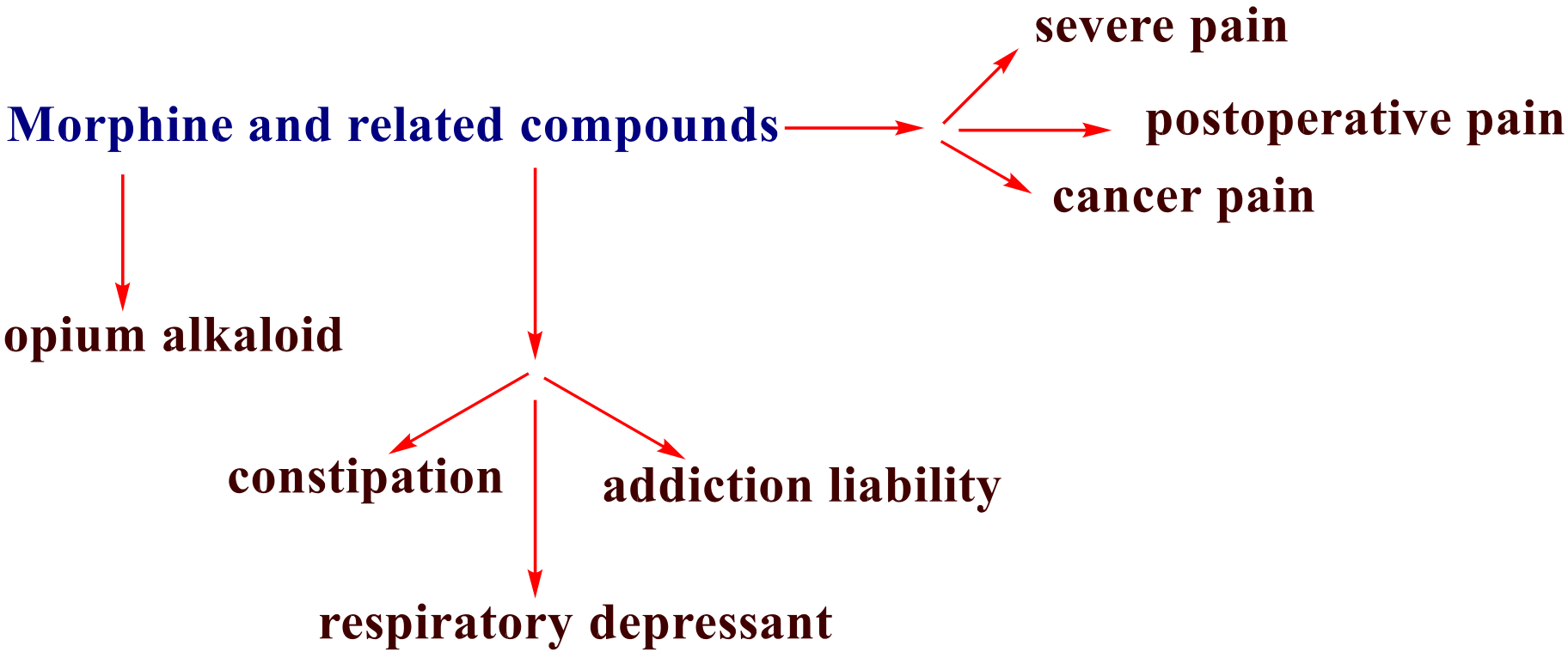
Benzylisoquinoline(papaverine)



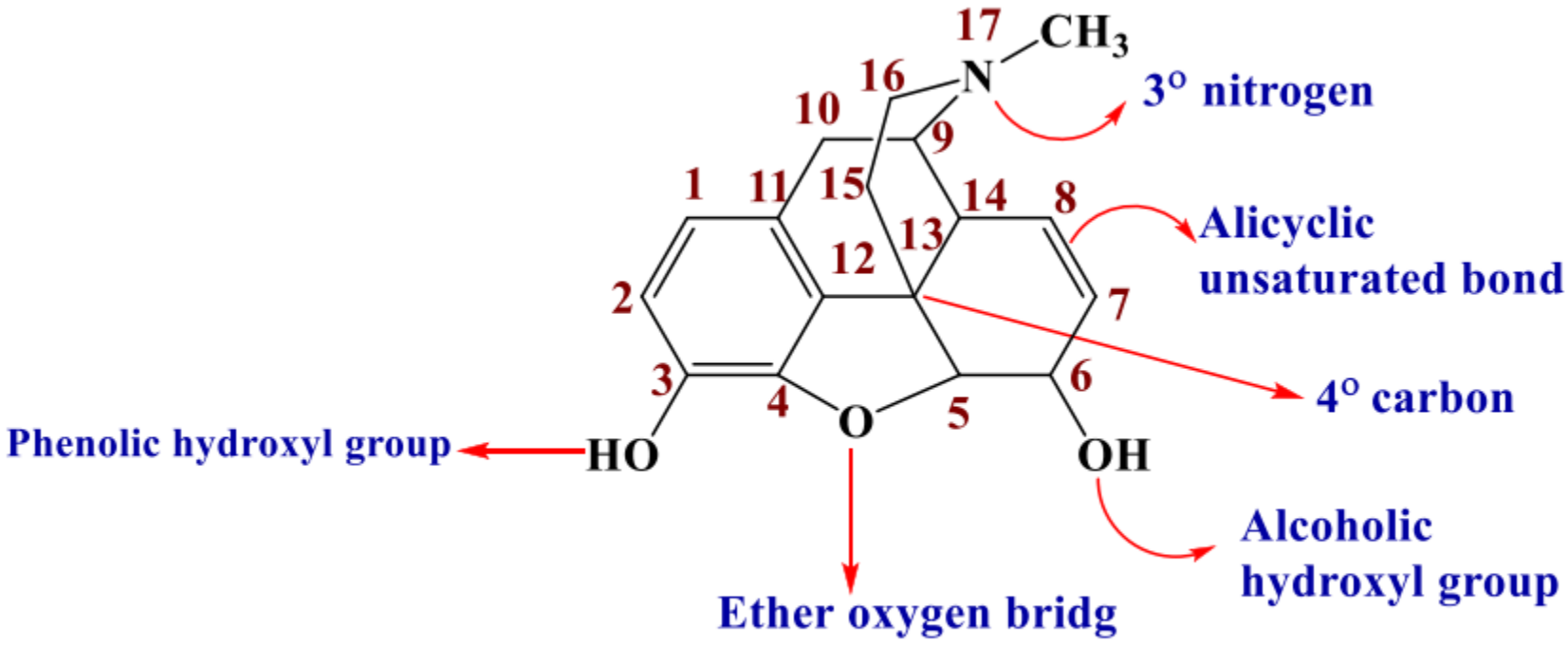
act on

smooth muscle
(has little effect on the nervous system)

1. **Morphine and related compounds:- there are compounds first obtained from opium alkaloid used for severe pain or postoperative pain and cancer pain. These drugs produce wide range of side effect like, constipation, respiratory depressant, and addiction liability.**



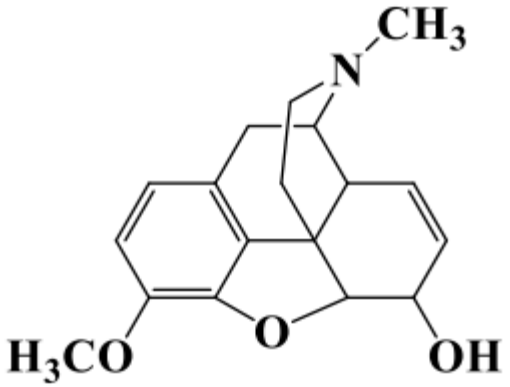
SAR of morphine



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

Early modification before 1929

1- Replacement of hydroxyl group at position 3 by methoxy(codeine) or ethoxy (ethylmorphine) groups , results in compound have good analgesic but less than morphine and act as cough depressant (antitussive effect).



Codeine

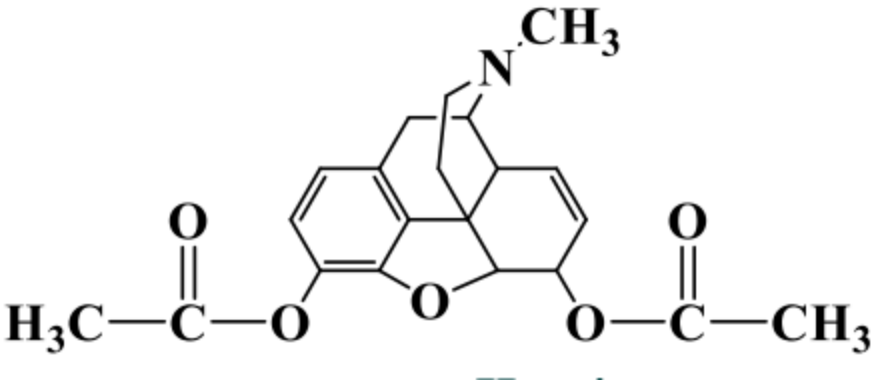
analgesic effect less than morphine

cough depressant(antitussive effect)

7,8-dehydro-4,5-epoxy- 3-methoxy-17-methyl morphinan-6-ol

2- Esterfication of the phenolic and/ or alcoholic hydroxyl groups give • compounds with greater activity than morphine but also with greater toxicity and addiction potential.

- **C6-OH to OAc ↑ activity**
- **C3 and C6-OH to OAc ↑activity**

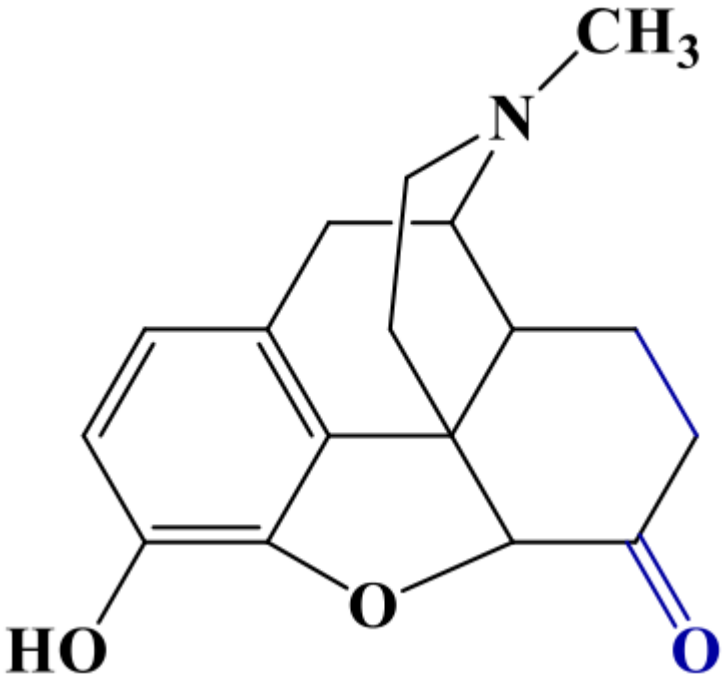


Heroin

7,8-dehydro-4,5-epoxy- 17-methyl-3,6-diacetyl morphinan

Addiction liability (dependence liability):- this term indicates the ability of a substance to induce true addictive tolerance and physical dependence and/or to suppress the morphine abstinence syndrome after withdrawal of morphine from addicts.

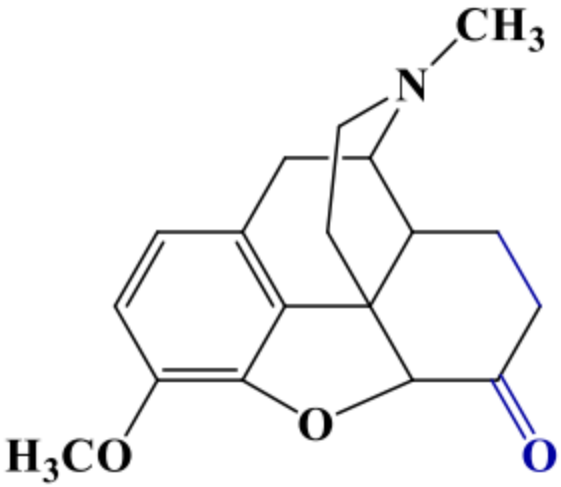
3- Reduction of 7,8-double bond with replacement of • alcoholic OH of morphine by C=O(kitone) give compound known as dilaudid (dihydromorphinone) which is more potent than morphine.



Dilaudid(dihydomorphinone, hydromorphone))

4,5-epoxy- 3-hydroxy-17-methyl morphinan-6-one

4-Reduction of 7, 8-double bond with replacement of alcoholic • OH of codiene by C=O (kitone) give compound known as dicodid (dihydrocodeinone) which is more potent than codeine and less potent than morphine(midway between codeine and morphine)



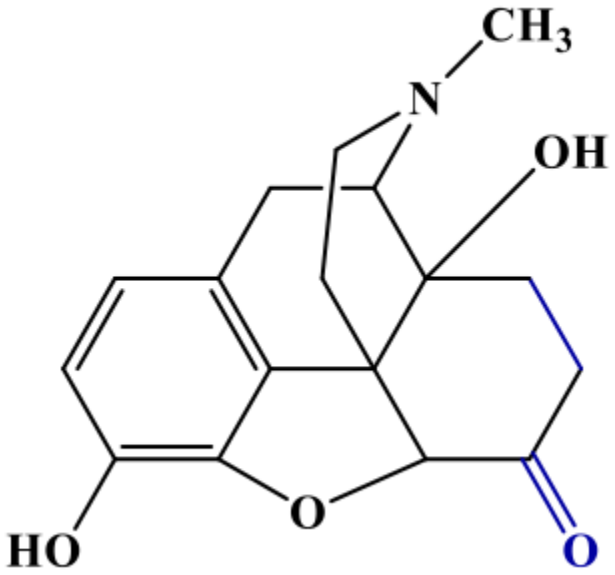
Dicodid(dihydrocodeinone, hydrocodone)

4,5-epoxy- 3-methoxy-17-methyl morphinan-6-one

more potent than codeine

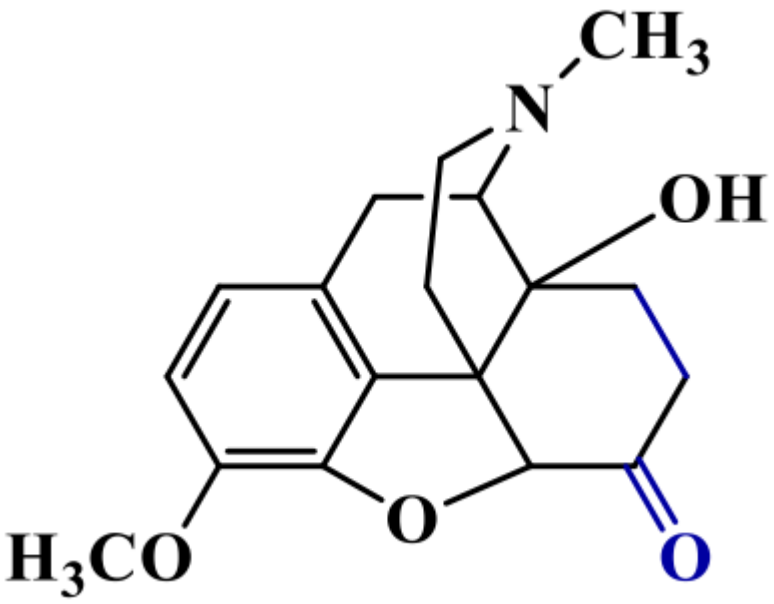
less potent than morphine

5- Addition of hydroxyl group at position 14 of • dihydromorphinone to give dihydrohydroxymorphinone which is as effective as morphine in one-eighth to one-tenth the dosage.



Dihydrohydroxymorphinone(oxymorphone)
4,5-epoxy- 3,14-dihydroxy-17-methyl morphinan-6-one
more potent than morphine

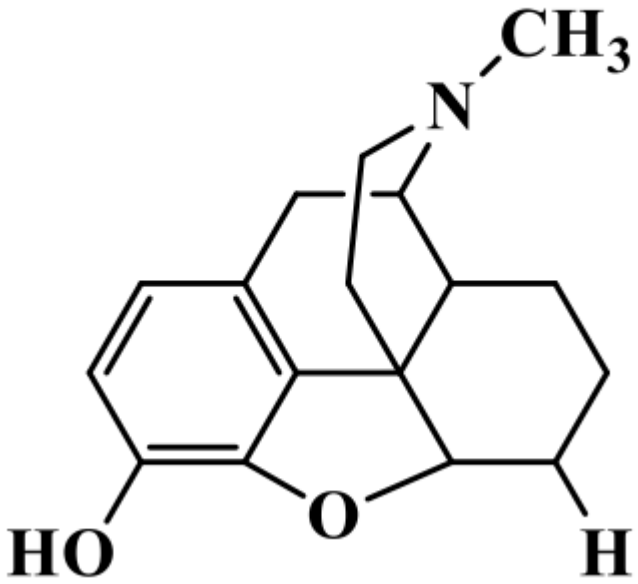
6- Addition of hydroxyl group at position 14 of • dihydrocodeinone to give dihydrohydroxycodeinone which is more active than codeine and morphine.



Dihydrohydroxycodeinone
analgesic and cough depressant
more active than codeine and morphine

Modification at 1929 by Small and Eddy

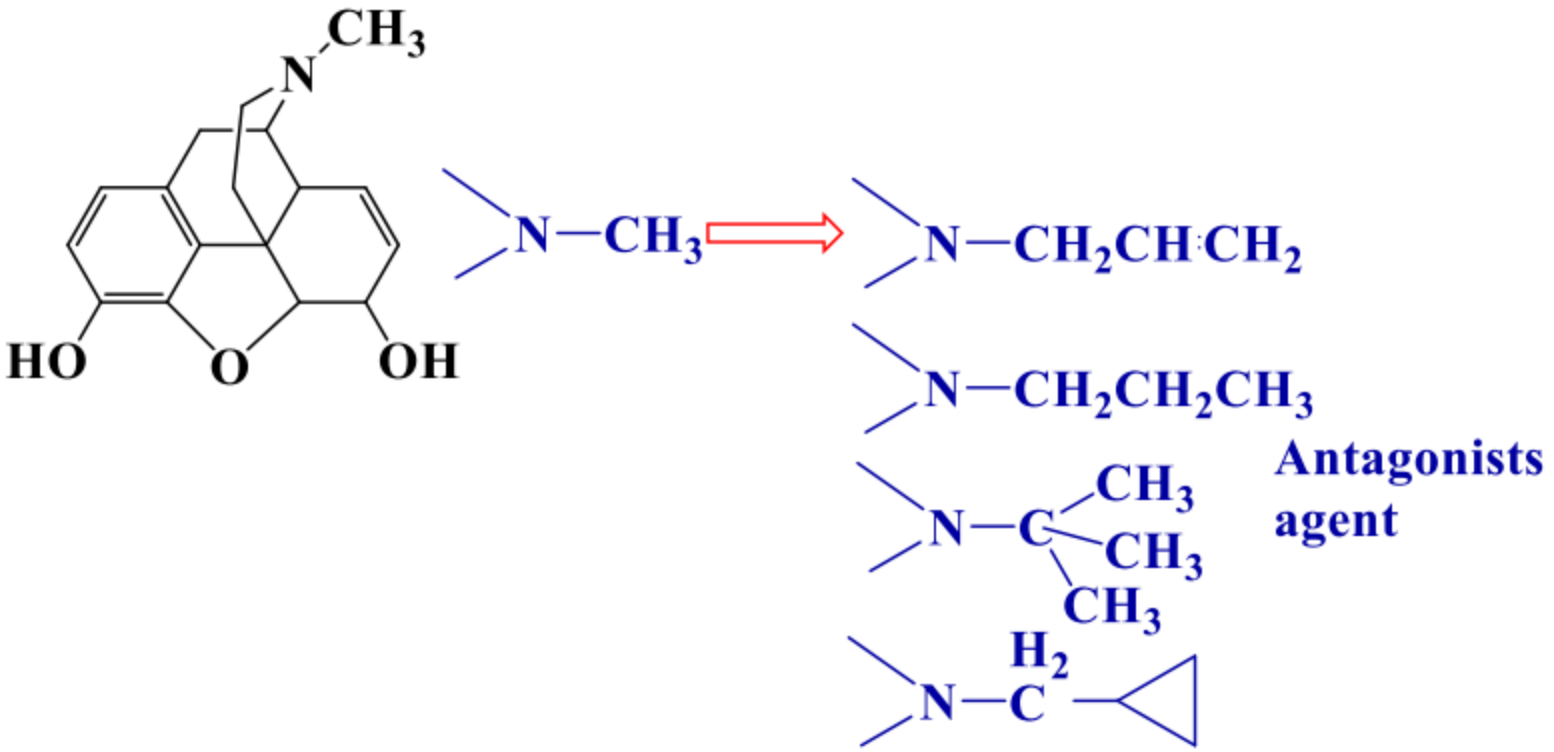
G- Replacement of hydroxyl group at position 6 by hydrogen and reduction of 7,8-double bond, result in increase in activity.



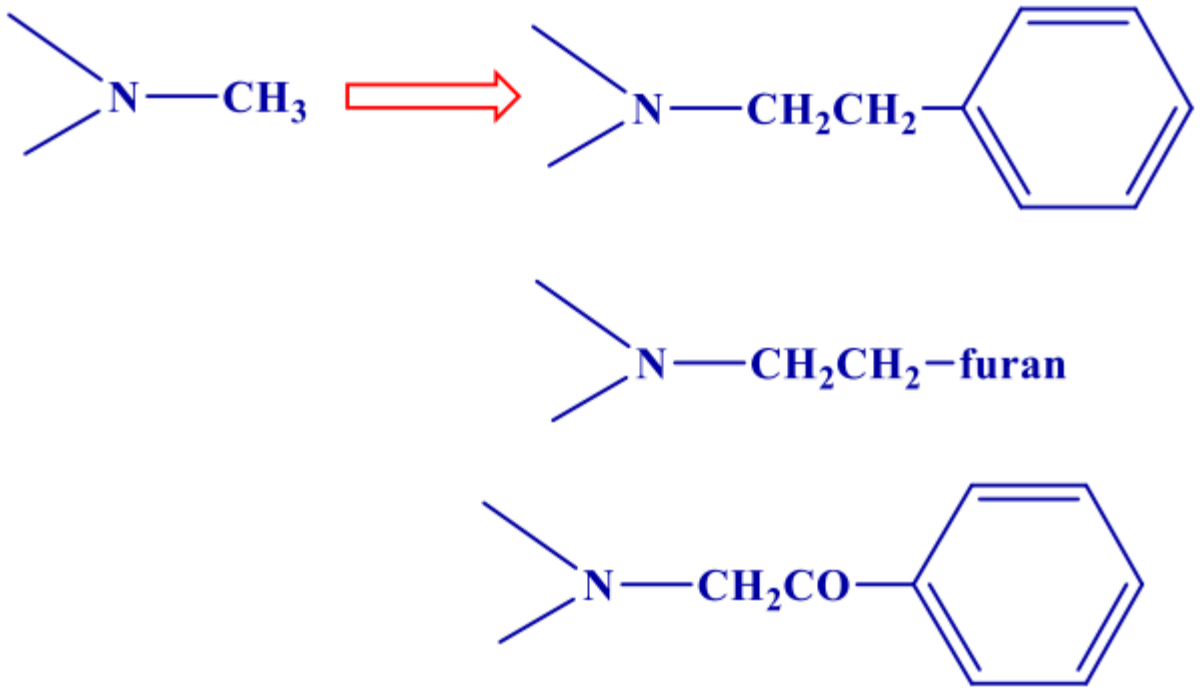
dihydrodesoxymorphine

Replacement of the N-methyl group in morphine by larger alkyl groups not • only lowers analgesic activity, but also confers morphine-antagonistic properties on the molecule.

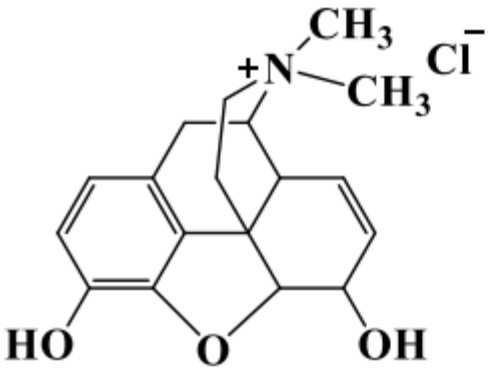
1- Replacement of methyl group at position 17 by $CH_2CH{=}CH_2$, CH_2-cyclopropyl groups, isobutyl, result compound that act as antagonists (reversal of activity).

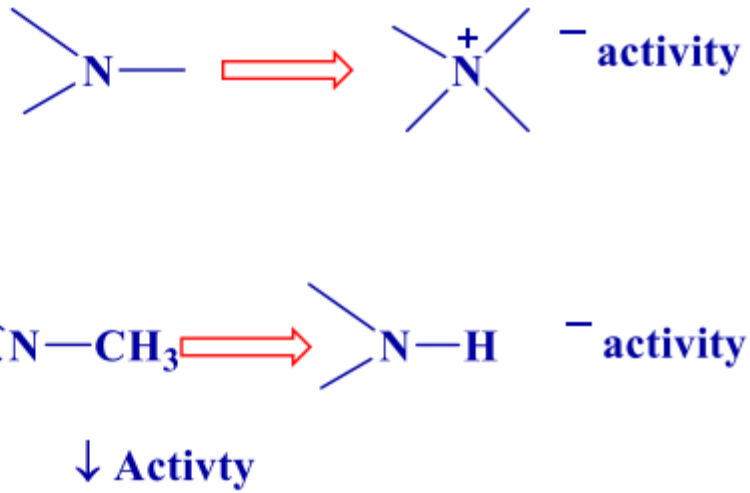


Replacement of methyl group at position 17 by phenyl ethyl • group, ethyl furane (CH_2CH_2 furan), and CH_2 C=O phenyl, result in increase in activity which is an exception to the above rule.



Quaternization of nitrogen or replacement of N-methyl group by • N-H group, result in decrease in activity.





Cl or Br substitution at position • 1
NH_2 substitution at position •2
result in decrease in activity•.