lec. I

4 stage

Organic Pharmaceutical Chemistry II

2020-2019

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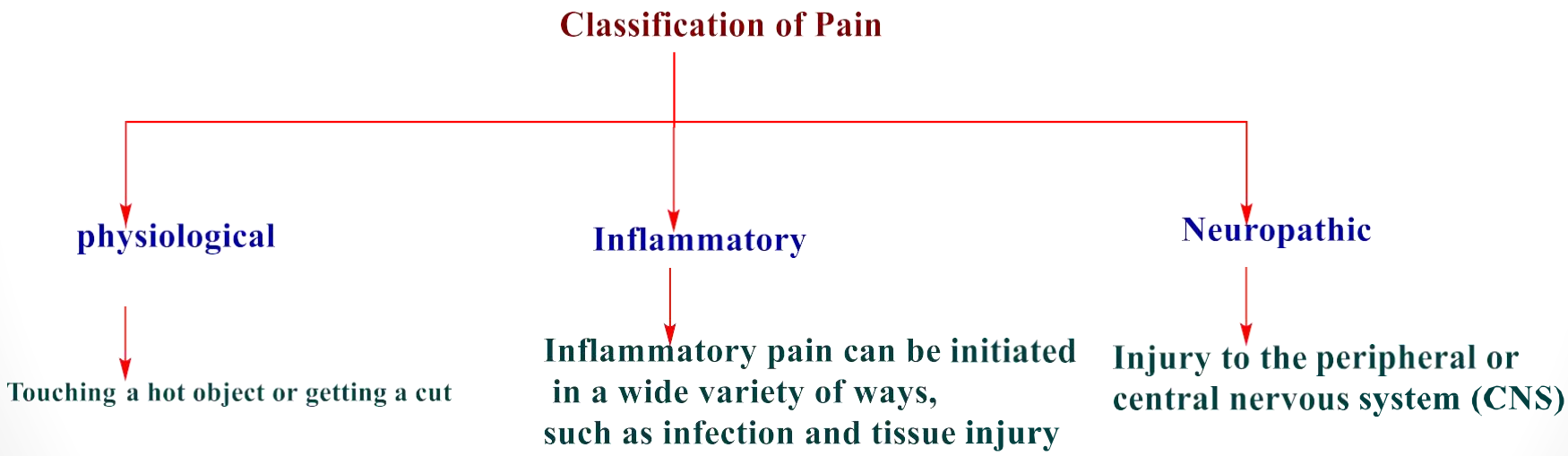
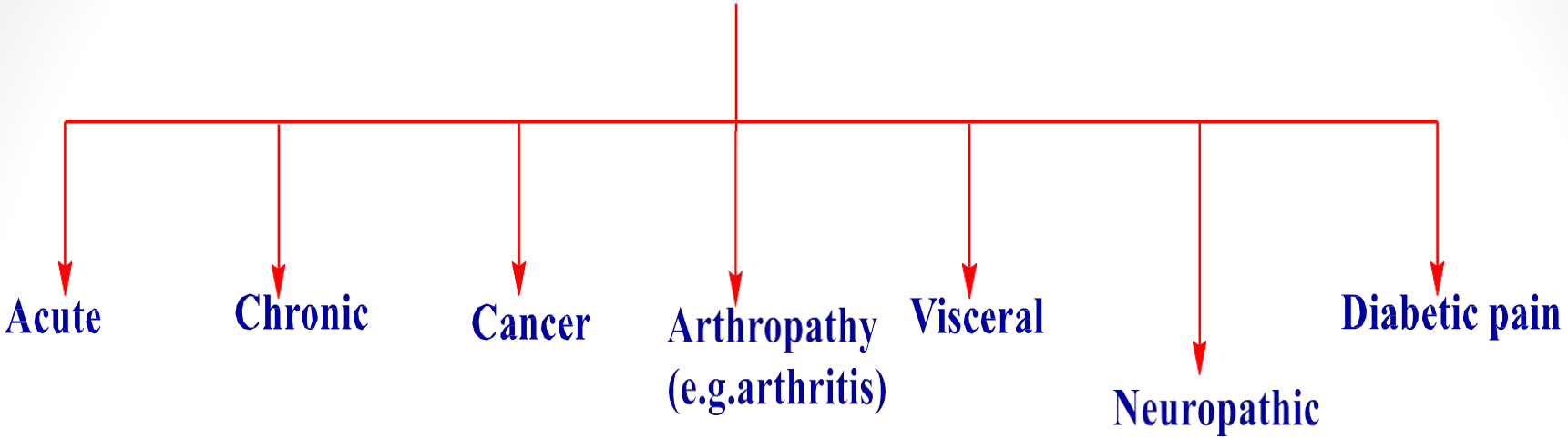
Analgesic Agents

analgesic r̄ medications used to relieve pain w̄out reducing the consciousness of the patient.

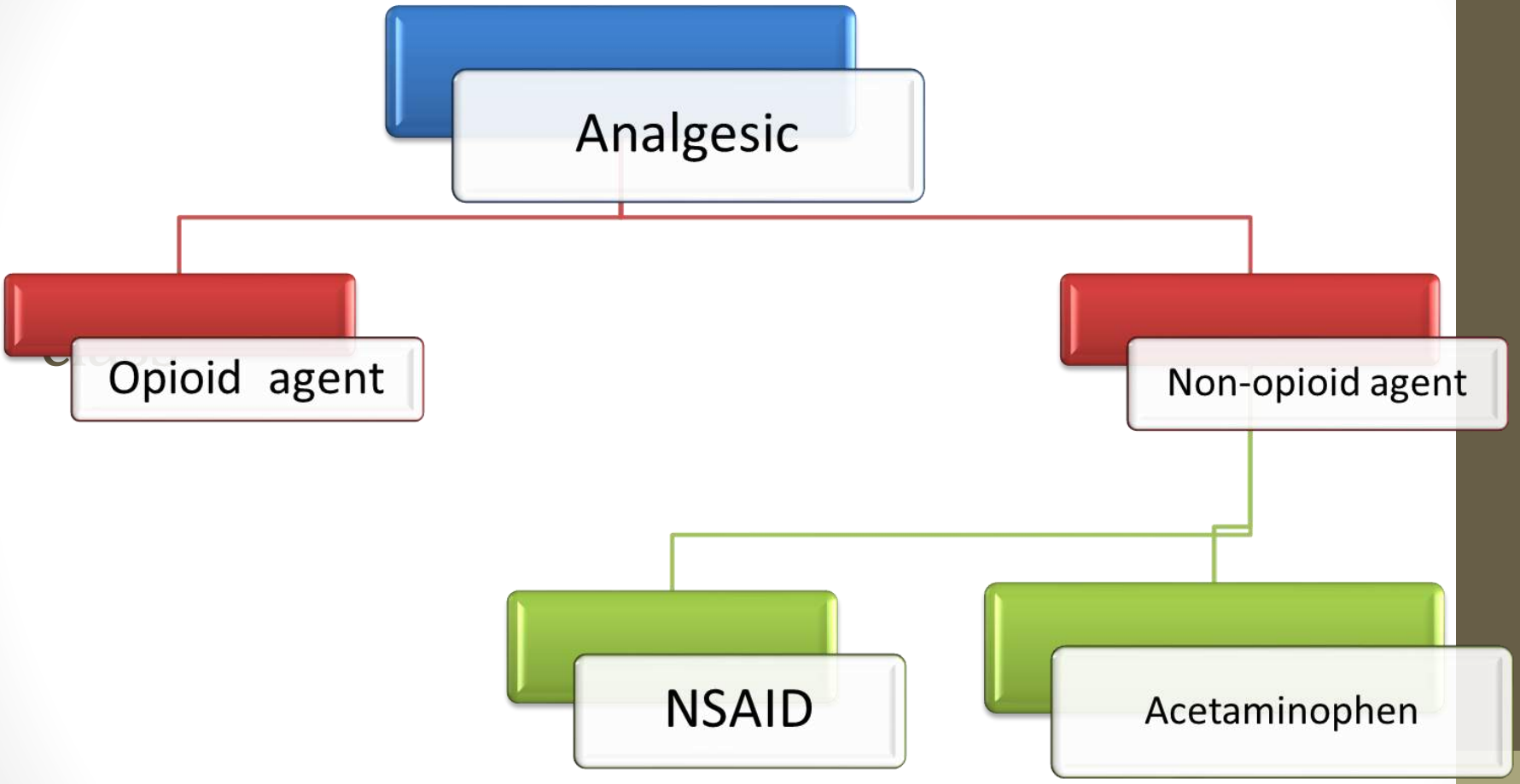
- they work by reducing the amount of the pain felt,not treat the cause of the pain.



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



major classes of pain relieving drugs

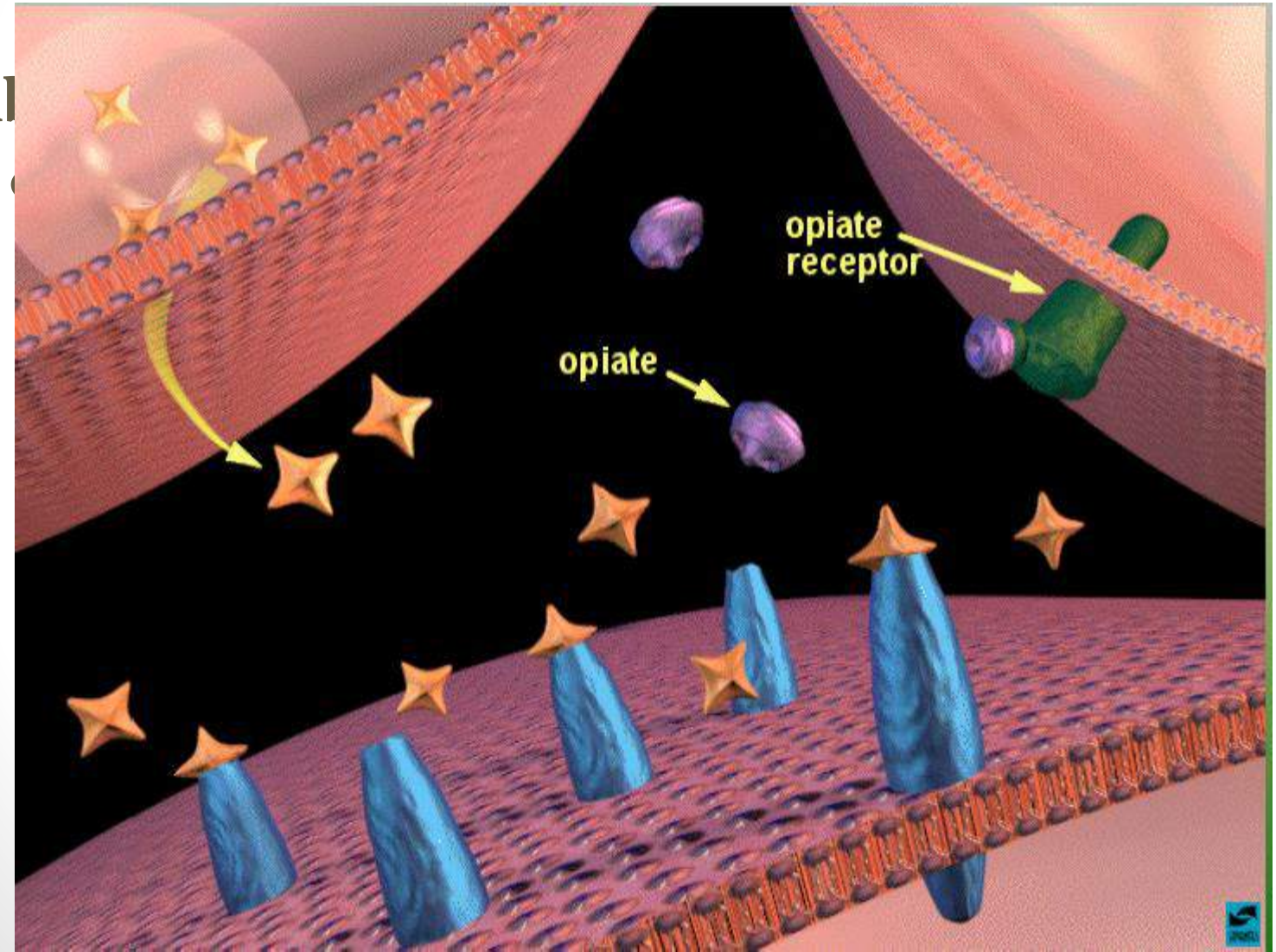


Opioid **receptors**

- group G-protein coupled receptors with opioids as ligands

Sul

μ ,



Opiod Receptor Activation

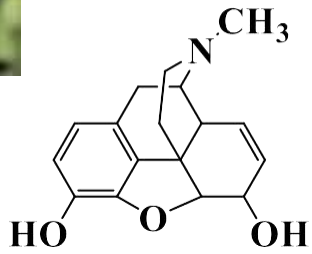
Response	Mu-1	Mu-2	Kappa	Delta	Sigma
Analgesia	★	★	★	★	
Respiratory depression		★			
Euphoria		★		★	
Dysphoria			★		
Decrease GI motility		★			
Physical Dependence		★			
Mania, hallucination					★

Opioid drugs

Opium

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

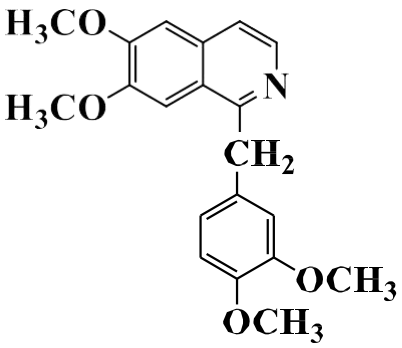
Phenanthrene (morphine)



acts principally on

CNS as a depressant and stimulant

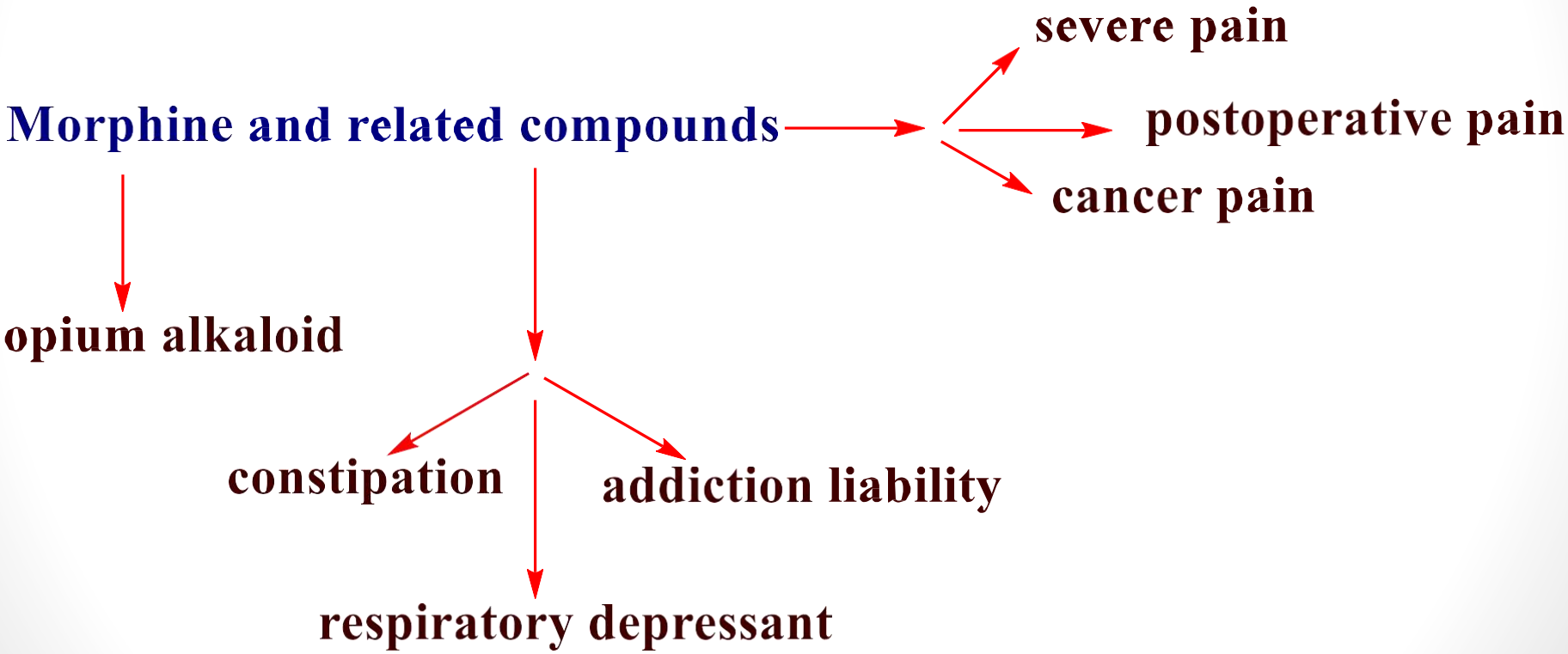
Benzylisoquinoline(papaverine)



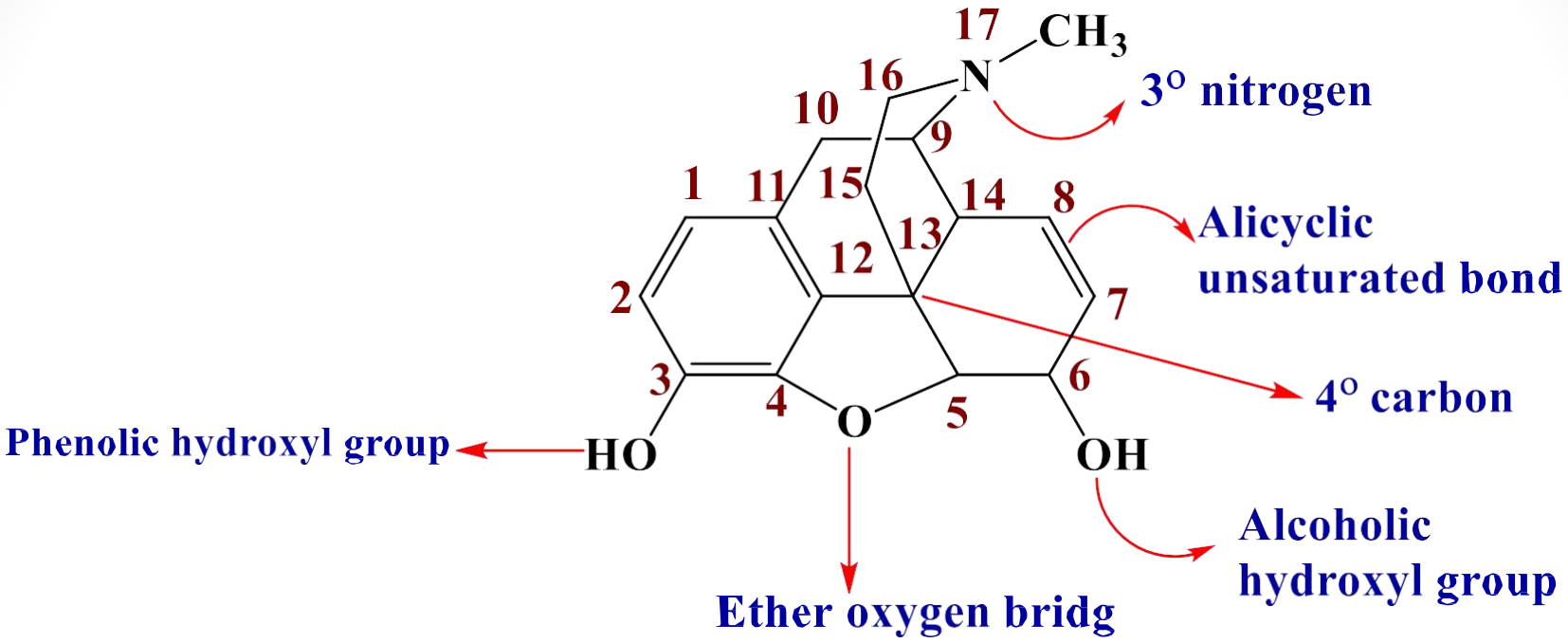
act on

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.



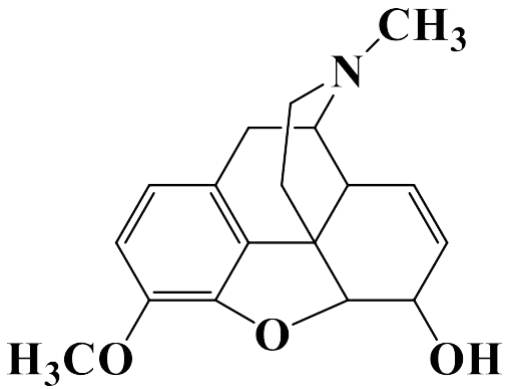
SAR of morphine



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

SAR

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



Codeine

analgesic effect less than morphine

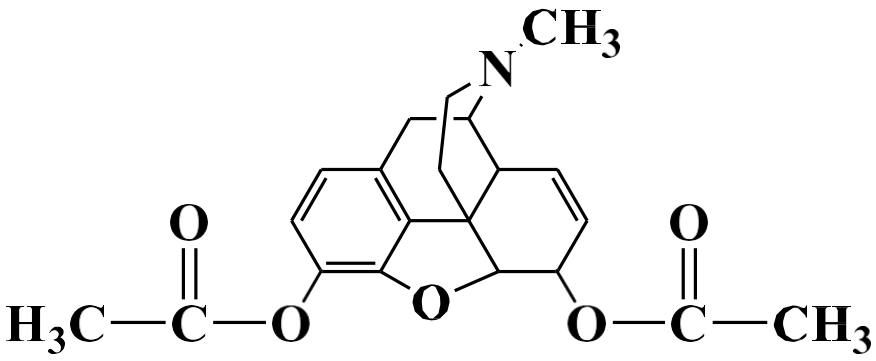
cough depressant(antitussive effect)

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

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

C6-OH to OAc ↑ activity

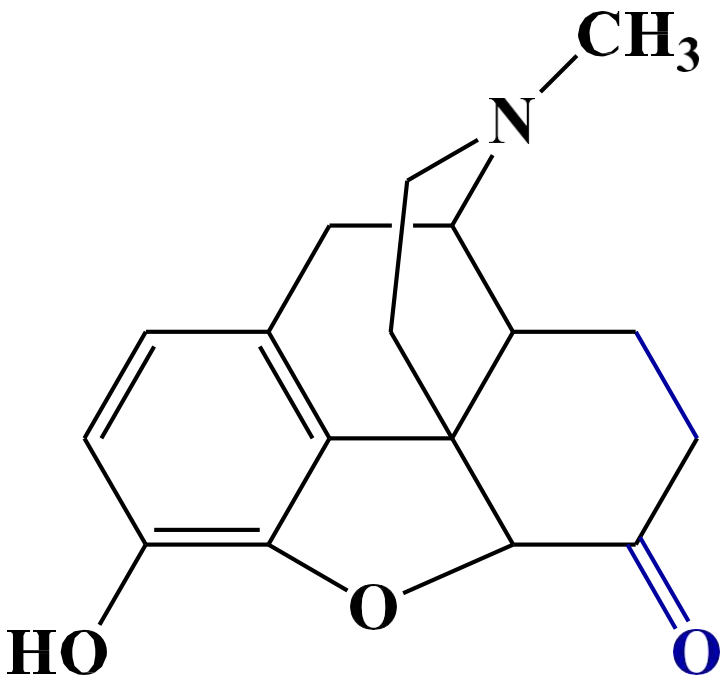
C3 and C6-OH to OAc ↑activity



Heroin

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

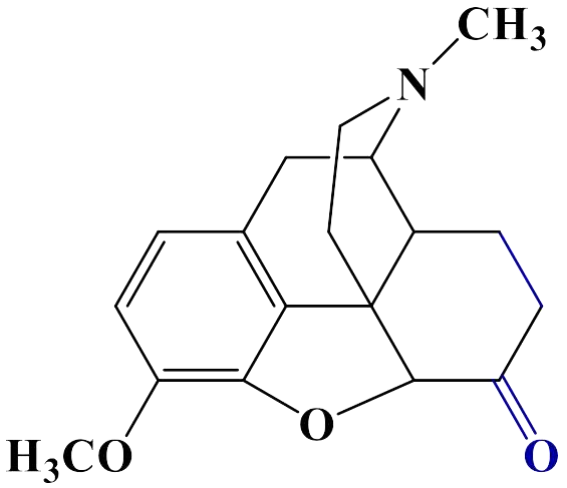
3- Reduction 7,8-double bond with replacement of alcoholic OH of morphine by C=O(ketone) give compound known as dilaudid (dihydromorphinone) which is more potent than morphine.



Dilaudid(dihydomorphinone, hydromorphone))

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

4- Reduction of 7,8-double bond with replacement of alcoholic 6-OH of codiene by C=O (ketone) give compound known as dicodid .



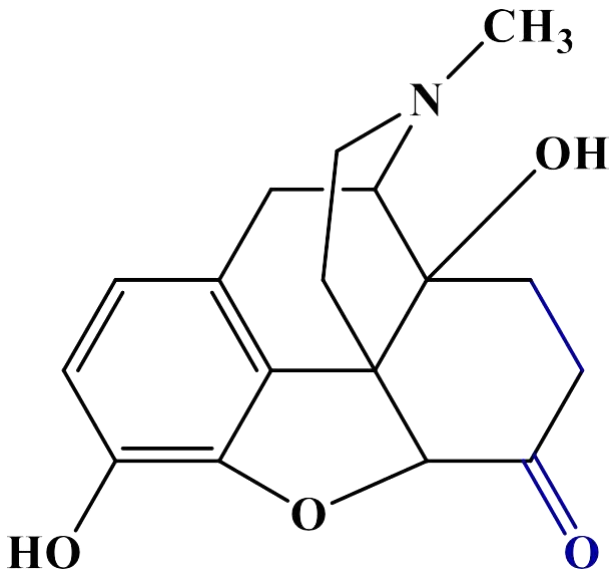
Dicodid(dihydrocodeinone, hydrocodone)

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

more potent than codeine

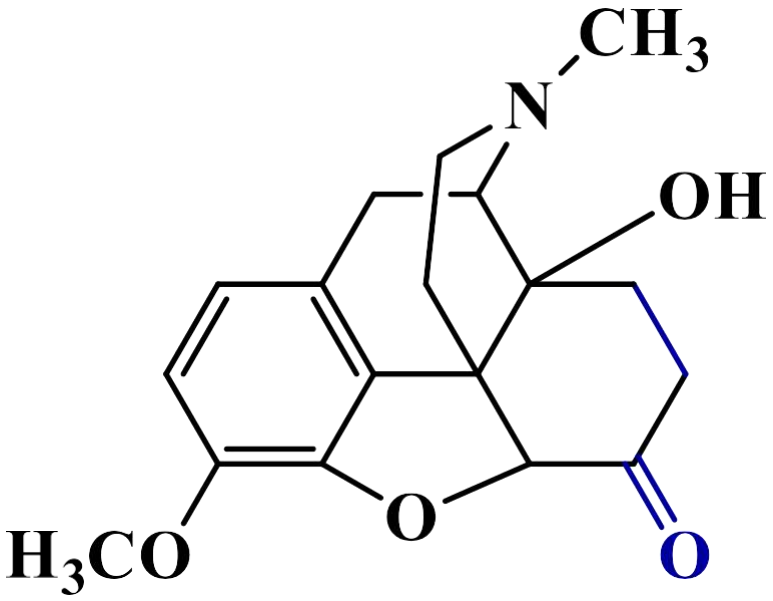
less potent than morphine

Addition of hydroxyl group at position 5- 14-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

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



Dihydrohydroxycodeinone
analgesic and cough depressant
more active than codeine and morphine

1929 Modification at

by Small and Eddy

G- Replacement of hydroxyl group at position 6 by H.

↑ activity

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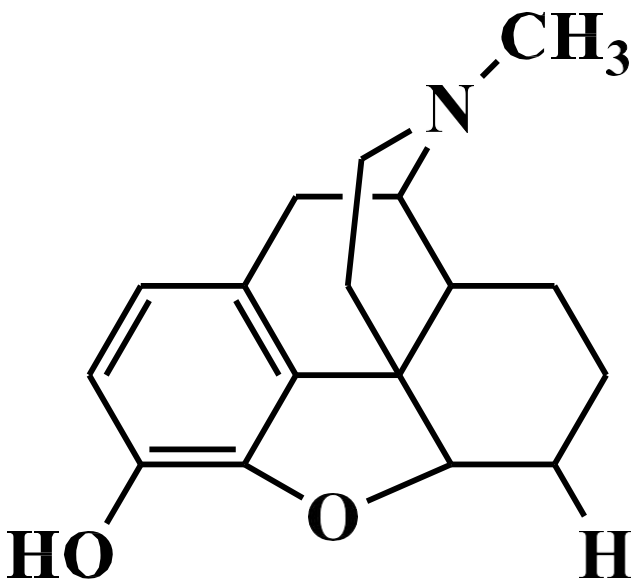

dihydrodesoxymorphine

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

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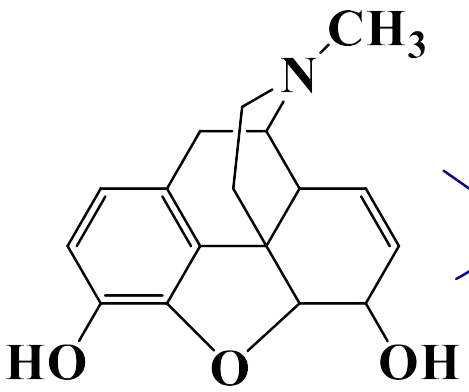
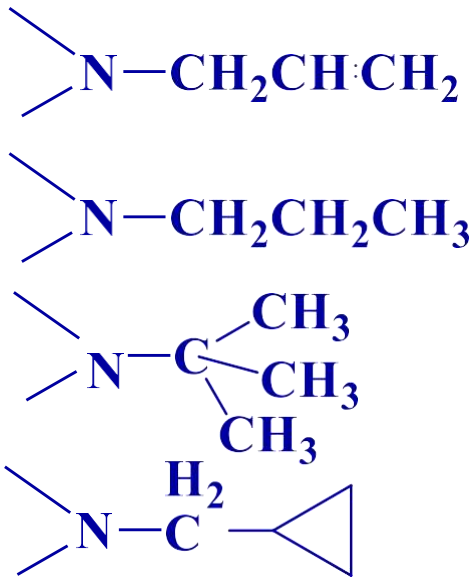
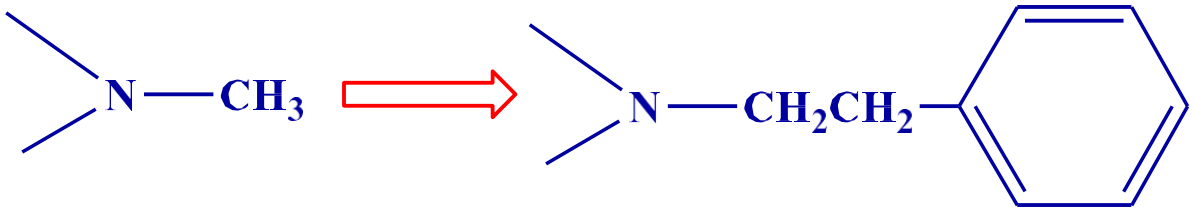
17- CH_3 grp. ⇨ replacement by - $CH_2CH=CH_2$, -CH2-cyclopropyl . isobutyl, result compound that act as antagonists (reversal of activity

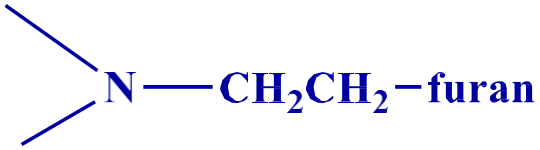


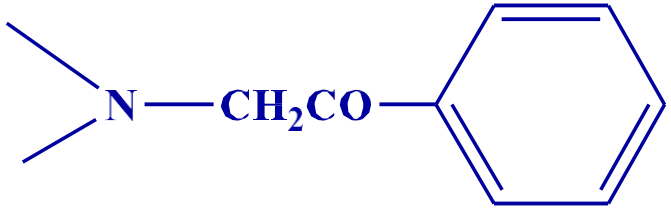


Antagonists agent

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.

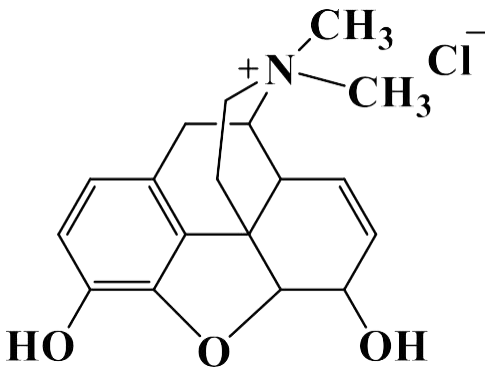


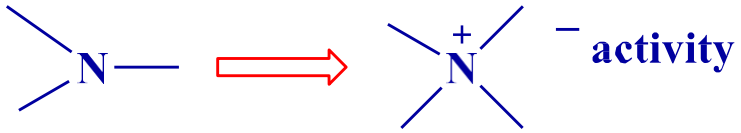


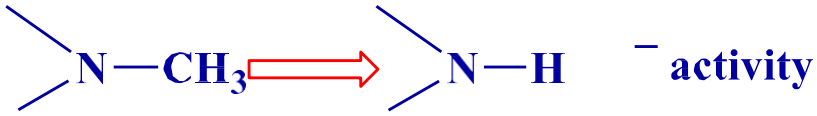


↑ **Activity**

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







↓ Activty

Cl or Br substitution at position 1 •

. NH_2 substitution at position 2 •

result in decrease in activity•