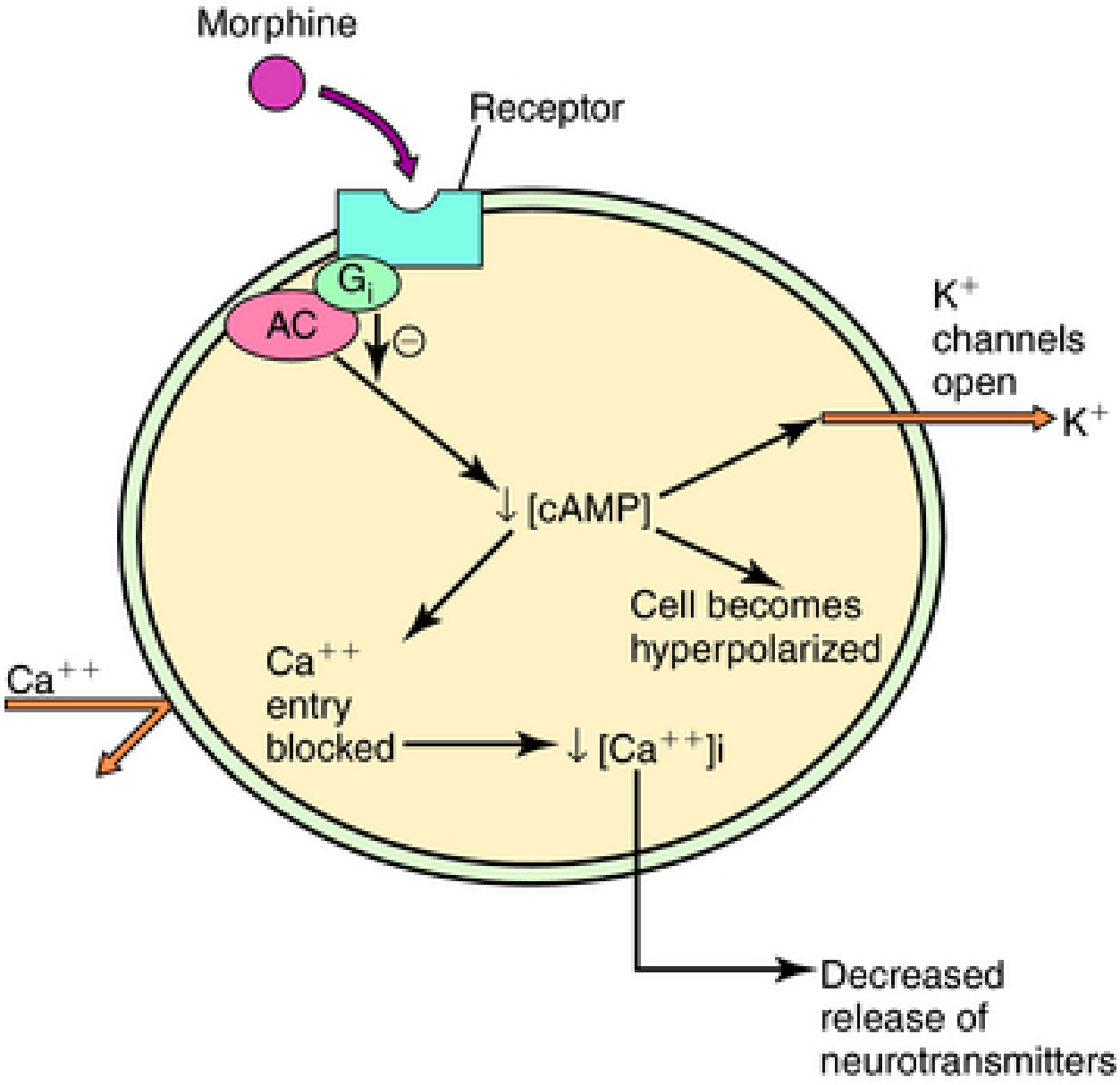
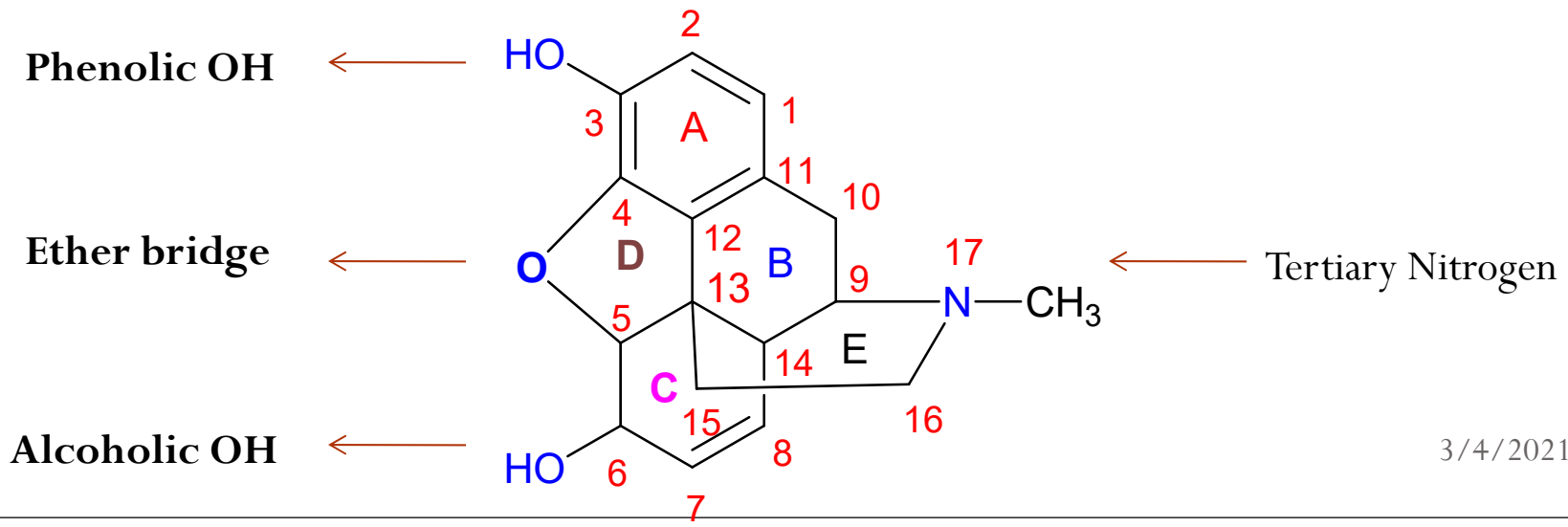
Mechanism of action of Narcotic analgesics

- ✓Narcotic analgesics produce their actions at a cellular level by by activating on **opioid receptors.**
- ✓e.g. 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 .
- ✓Opioid receptors are coupled with **inhibitory G- proteins** and their activation has number of actions like **closing of voltage sensitive calcium channels, stimulation of potassium efflux** leading to hyperpolarization which causes reduction in neuronal cell excitability.


Morphine
Receptor
G_i
AC
K^+ channels open
K^+
↓ [cAMP]
Cell becomes hyperpolarized
Ca^{++}
Ca^{++} entry blocked
↓ $[Ca^{++}]i$
Decreased release of neurotransmitters

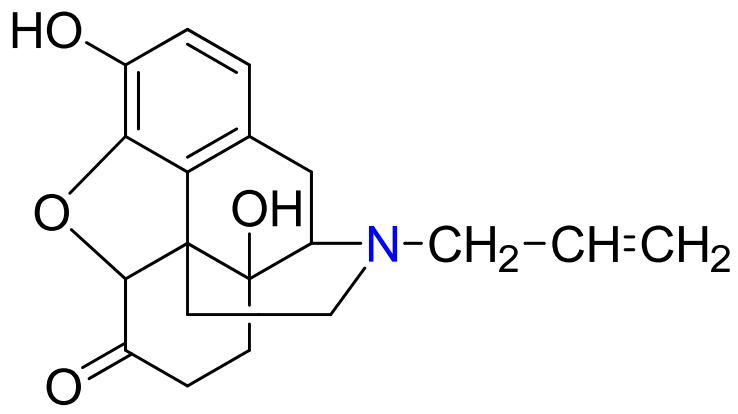
Structure activity relationship of morphine

- The structure of morphine is composed of five fused rings and have 5 chiral centers.
- the levo (-) rotary form is the active form while dextro (+) morphine is inactive.
- The A ring and the basic nitrogen are the two necessary component in every potent opoid receptor agonist.
- The aromatic A ring and the tertiary nitrogen may be connected by an ethylene/propelene linkage.



Tertiary nitrogen atom

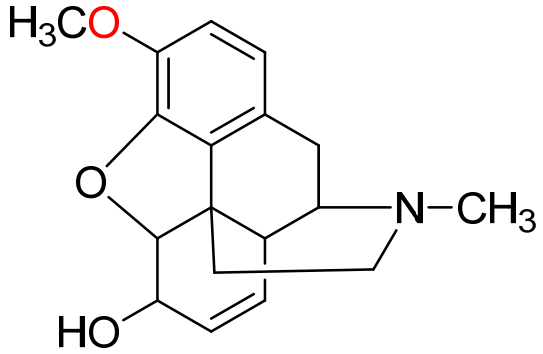
- The substituent on nitrogen of morphine and morphine like structure is critical to degree and type of activity.
- N-methyl substituents generally results in compound with good **agonist proporties**.
- Increasing the size of the N-substituent results in **antagonist** e.g. naloxone



Naloxone

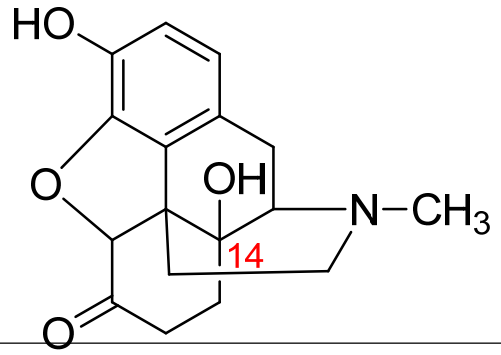
Hydroxyl Group

- Masking the phenolic hydroxyl group by etherification to methyl ether **decrease** the analgesic activity about ten fold. e.g. Codeine



Codeine

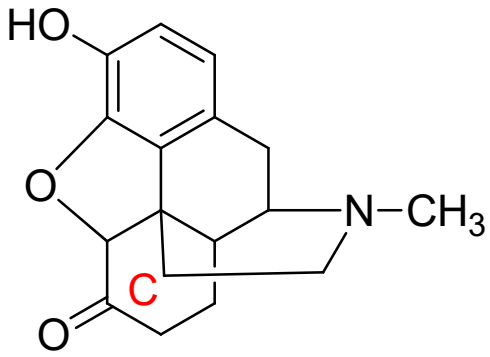
- Esterification of hydroxyl group leads to **more active** compound than morphine. e.g. Heroin
- introduction of hydroxyl group at 14th position lead to **increase** in activity e.g. oxymorphone



Oxymorphone

Ring C

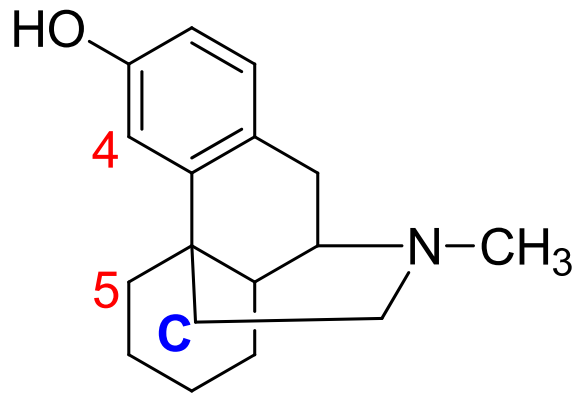
- Change in the C-ring chemistry of morphine can lead to compounds with increased activity. e.g. Hydromorphone is 8-10 times more potent than morphine.



Hydromorphone

4,5-Epoxide bridge

- Removal of 4,5-epoxide bridge in the morphine structure results in **mophinans**.
- only levo isomer of morphinan possess opoid analgesic activity while dextro isomer have antitussive actvity.
- 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. e.g. Benzomorphans.