LNCT GROUP OF COLLEGES

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Subject:Medicinal Chemistry(BP-402T)
Unit:V
Topic:SAR of Morphine analogues
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STRUCTURE ACTIVITY RELATIONSHIP

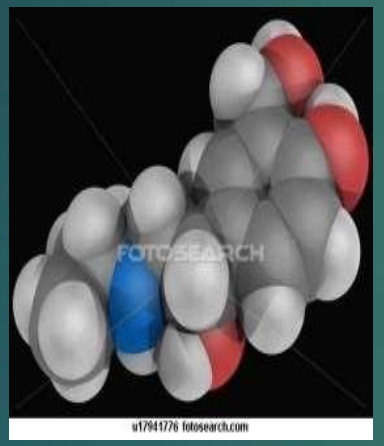
OF OPIOD(Morphine)

- ***The STRUCTURE – ACTIVITY relationship (SAR) is the relationship between the chemical or 3D structure of a molecule and its biological activity.***

- ***Enables the determination of the chemical groups responsible for evoking a target biological effect in the organism***

A chemical structure includes molecular geometry, electronic structure, and crystal structure of a molecule.

Biological activity is an expression describing the beneficial or adverse effects of a drug on living matter.



Biological response

Crude drug

Structure

Receptor

Ligand binding

- *SAR is an advance design to find the relationships between chemical structure and biological activity of studied compounds.*
- *Therefore it is the concept of linking chemical structure to a chemical property or biological activity including toxicity.*
- *The theory of SARs is to produce new drugs with similar structure and effects as the original one but with having more potency and improved side-effects.*

- *Moreover, SARs are essential for toxicological studies on a compound.*
- *SARs have been used since long ago to design chemicals with the commercially wanted properties and thus they are important while designing drugs as the chemicals with desired pharmacological and therapeutic activities are known.*

Factors considered

- *There are various factors that should be considered while developing the mechanism of SARs, these are:*
  - *the size and shape of the carbon skeleton,*
  - *the nature and degree of substitution and*
  - *the stereochemistry.*

- *During modifications on a drug analogue,*
- *effects on water solubility,*
- *transport through membranes,*
- *receptor binding,*
- *metabolism and other pharmacokinetics properties should be considered.*

- *Computer assisted molecular modelling helps to solve this problem by providing accurate targeting*

MODIFICATION OF PARENT COMPOUND

Varying size and shape

Changing the number of methylene groups in chains and rings

- This increases lipophilicity which results in an increased in activity
- Water solubility is reduced as well as activity
- No selective binding due to micelle formation in aliphatic compounds

- *Increasing or decreasing the degree of unsaturation*
  - *A change in the degree of unsaturation causes an increase in rigidity,*
  - *complication of E-Z isomers,*
  - *more sensitivity and increased toxicity.*
- *Introducing or removing a ring system*
  - *This results to an increase in size, shape changes and stability of structure with the substitution of C=C double bonds.*

Modification of Parent compound

1. Univalent atoms and groups

   a. CH_3 NH_2 OH F Cl
   b. Cl PH_2 SH
   c. Br *i*-Pr
   d. I *t*-Bu

2. Bivalent atoms and groups

   a. $-CH_2-$ $-NH-$ $-O-$ $-S-$ $-Se-$
   b. $-COCH_2R$ $-CONHR$ $-CO_2R$ $-COSR$

3. Trivalent atoms and groups

   a. $-CH=$ $-N=$
   b. $-P=$ $-As=$

4. Tetravalent atoms

   a. $-\overset{|}{\underset{|}{C}}-$ $-\overset{|}{\underset{|}{Si}}-$
   b. $=C=$ $=\overset{+}{N}=$ $=\overset{+}{P}=$

5. Ring equivalents

   a. $-CH=CH-$ $-S-$ (e.g., benzene, thiophene)
   b. $-CH=$ $-N=$ (e.g., benzene, pyridine)
   c. $-O-$ $-S-$ $-CH_2-$ $-NH-$

OPIOID

- History:
- first undisputed reference to "poppy juice" is found in the writings of Theophrastus in the third century B.C. the word opium being derived from the Greek word for "juice" the drug being obtained from the juice of the poppy Papaver sominiferum

Source

- *The term opiate refers to compounds structurally related to products found in opium, a word derived from opos, the Greek word for “juice,” natural opiates being derived from the resin of the opium poppy, Papaver somniferum. Opiates include the natural plant alkaloids, such as morphine, codeine, thebaine, and many semisynthetic derivatives.*

- *An opioid is any agent, regardless of structure, that has the functional and pharmacological properties of an opiate. Endogenous opioids, many of which are peptides, are naturally occurring ligands for opioid receptors found in animals.*

OPIOID RECEPTOR

- The major effects of the opioids are mediated by three major receptor families. These are designated by the Greek letters μ (mu), κ (kappa), and δ (delta). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the μ receptors.
- All three opioid receptors are members of the G protein–coupled receptor family and inhibit adenylyl cyclase.
- They are associated with ion channels, increasing postsynaptic K+ effl ux (hyperpolarization) or reducing presynaptic Ca2+ infl ux, thus impeding neuronal fi ring and transmitter release.
- Opioids interact stereospecifically with protein receptors on the membranes of certain cells.

Location of opioid receptors

OPIOID receptors

- CNS distribution is not uniform
- they are at areas concerned with pain
- receptor locations beginning with highest concentration areas
- 1. cerebral cortex
- 2. amygdala
- 3. septum
- 4. thalamus
- 5. hypothalamus
- 6. midbrain
- 7. spinal cord

Receptor Stimulation

- **mu**
  - **P** hysical dependence
  - **E** uphoria
  - **A** nalgesia (supraspinal)
  - **R** espiratory depression

- **kappa**
  - **S** edation
  - **A** nalgesia (spinal)
  - **M** iosis

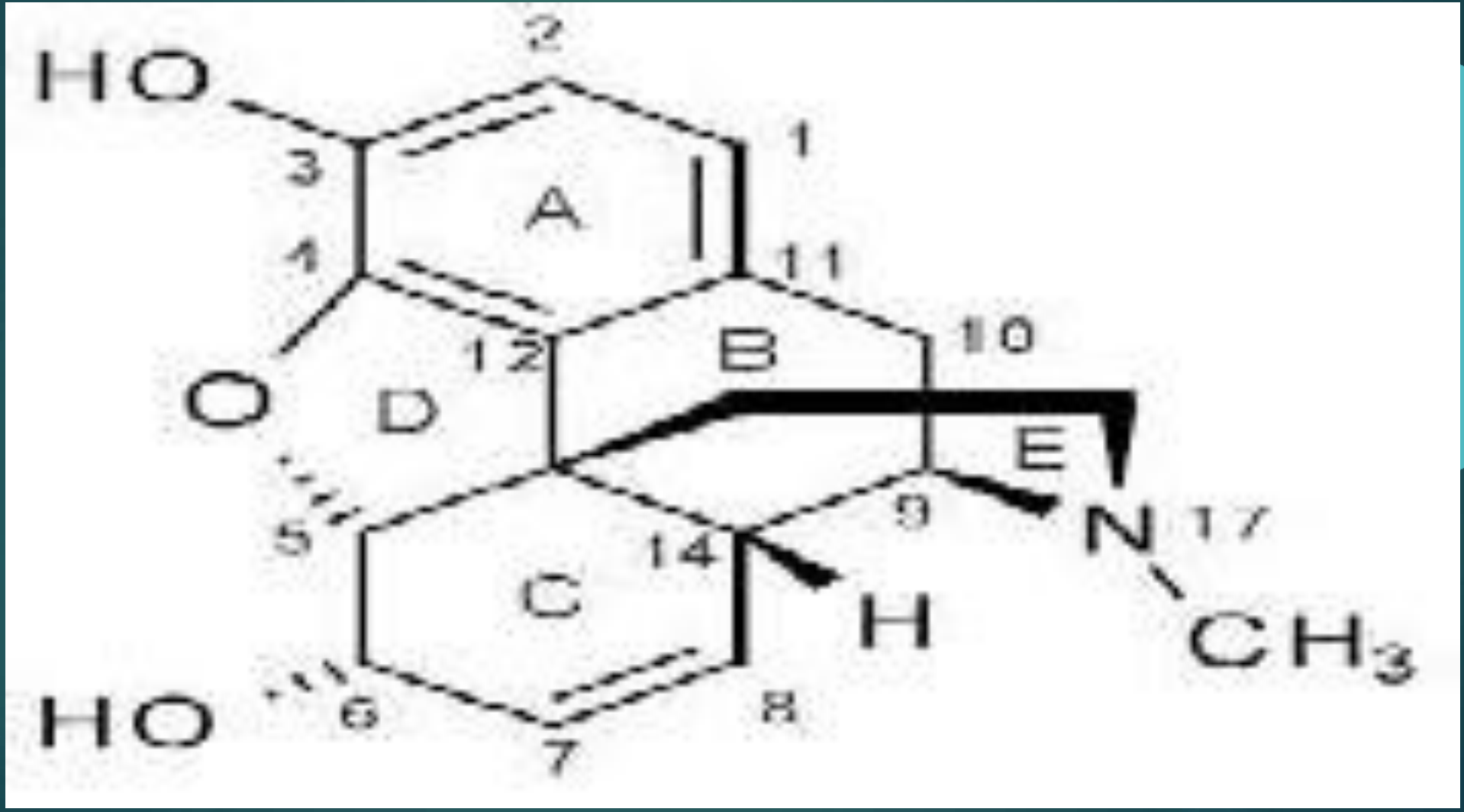
- **delta**
  - **a**nalgesia (spinal & supraspinal)
  - **re**lease of **g**rowth **h**ormone
- **sigma**
  - dysphoria (opposite of euphoria)
  - hallucination (both visual & auditory)
  - respiratory and vasomotor stimulation
  - mydriasis

Endogenous opioid peptides

- Three distinct families of peptides have been identified
- ENKEPHALINS , ENDORPHINS ,DYNORPHIN.

- These are now designated as Proenkephalin (proenkephalin A),
- Proopiomelanocortin (POMC) and
- Prodynorphin (proenkephalin B).

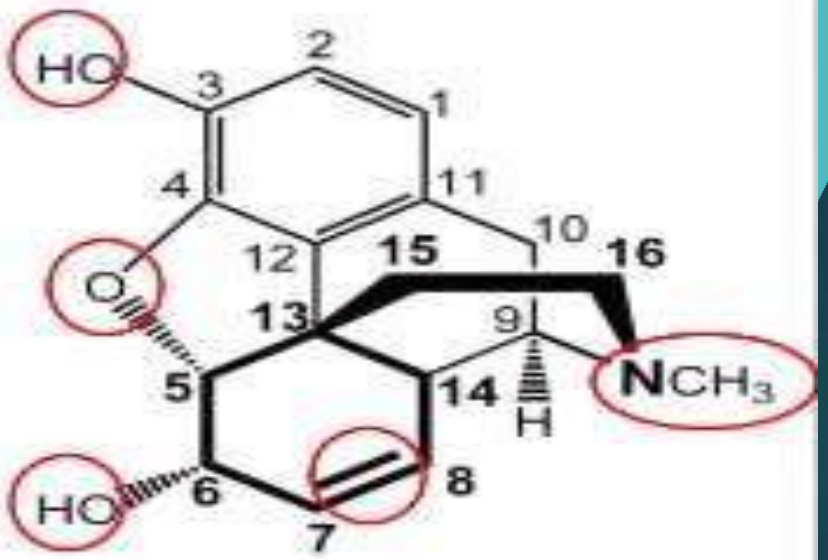
Structure of morphine

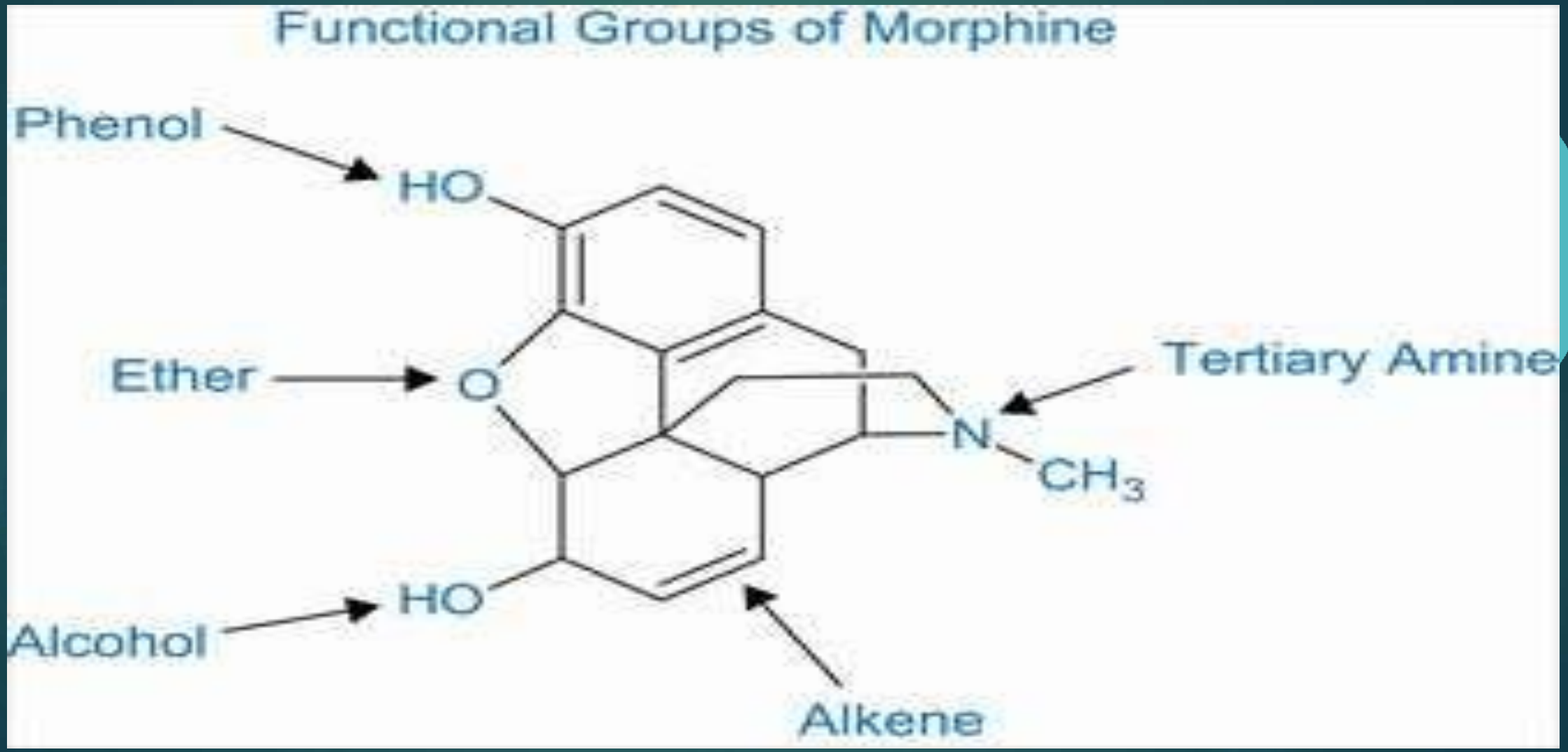


- Morphine, $C_{17}H_{19}NO_3$, is the most abundant of opium's 24 alkaloids, accounting for 9 to 14% of opium-extract by mass.
- Named after the Roman god of dreams, Morpheus, the drug morphine numbs pain, alters mood and induces sleep.
- The three dimensional structure of morphine is fascinating.
- It consists of five rings, three of which are approximately in the same plane.
- The other two rings, including the nitrogen one, are each at right angles to the other trio

Biological action of opiods

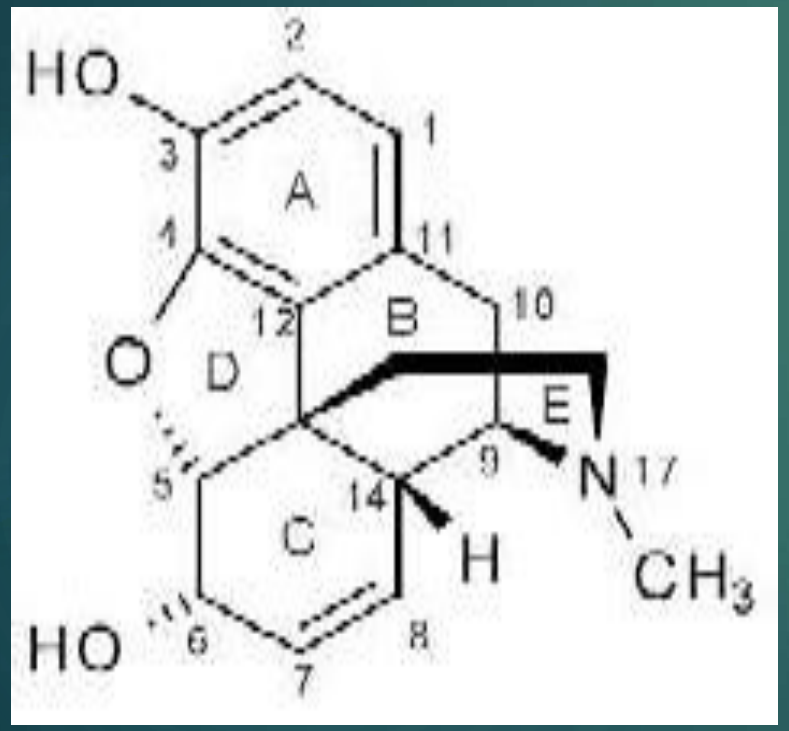
- depends on
  1. **Phenolic hydroxyl group**
  2. **6 hydroxyl**
  3. Double bond between 7 & 8 c
  4. **N-methyl group**
  5. Ether (E) bridge
  6. Aromatic ring




Functional Groups of Morphine
Phenol
HO
Ether
O
Tertiary Amine
N
CH3
HO
Alcohol
Alkene

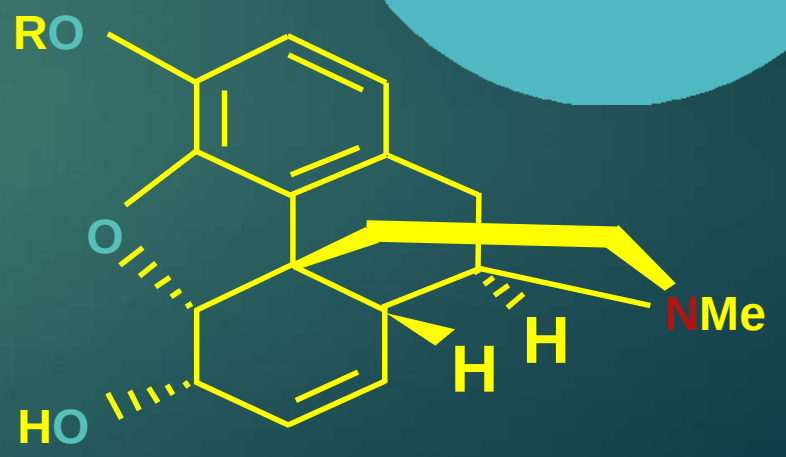
- Mask or remove a functional group
- Test the analogue for activity
- Determines the importance or other wise of a functional group for activity

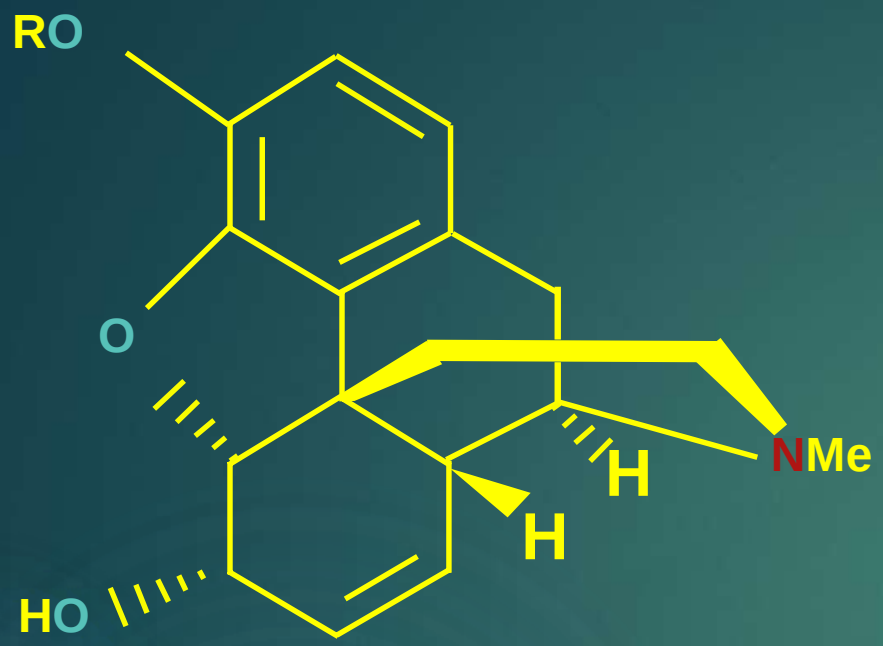
Morphine



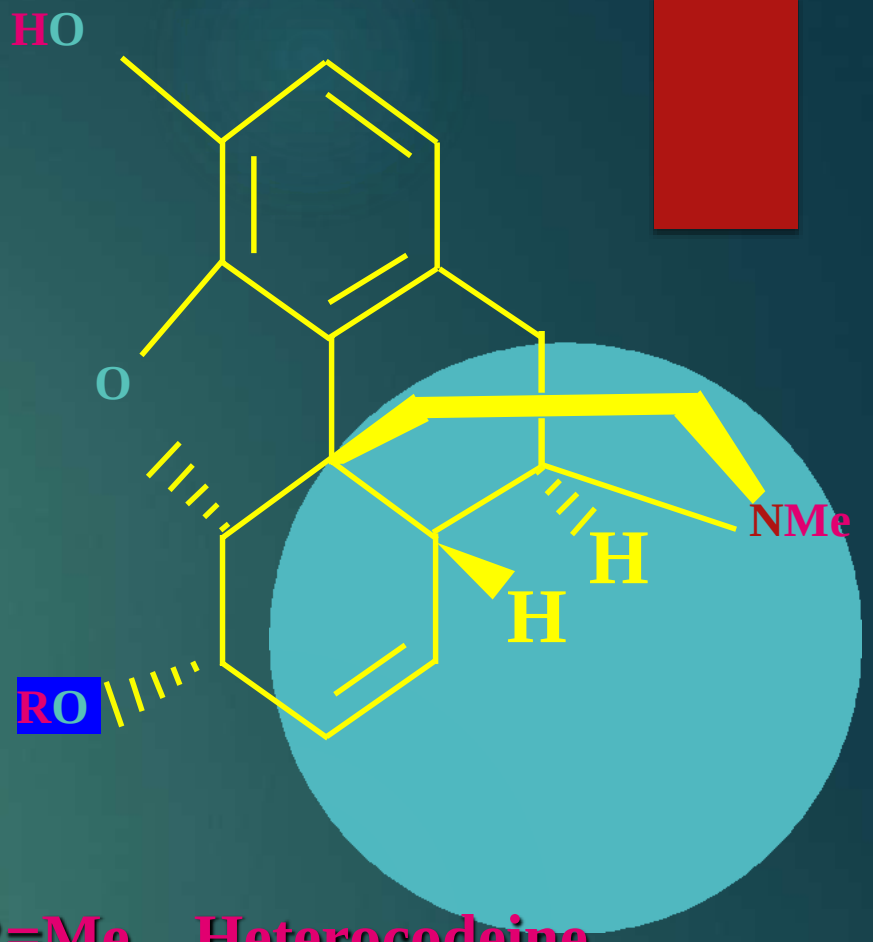
Codeine

- R = methyl group
- Codeine It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine. It is less potent than morphine (1/10th as analgesic), also less efficacious; is a partial agonist at μ opioid receptor



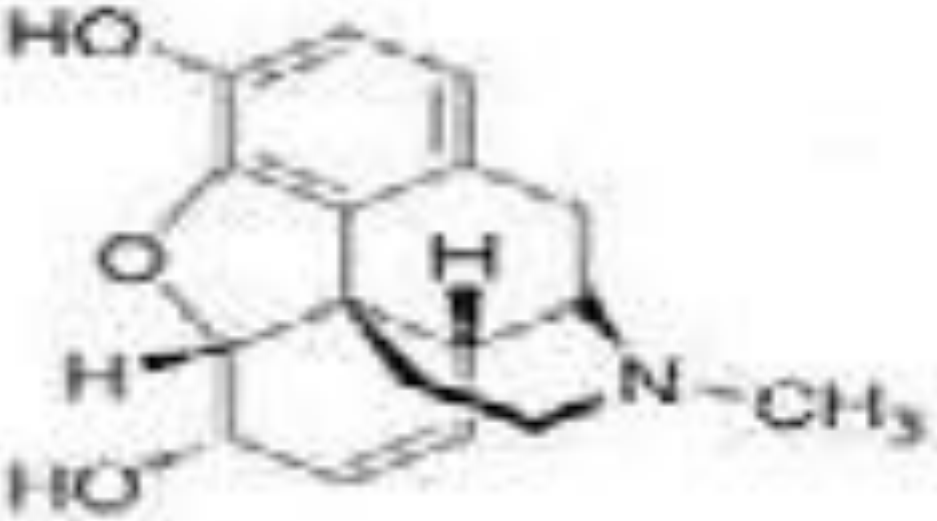


Codeine



R=Me Heterocodeine

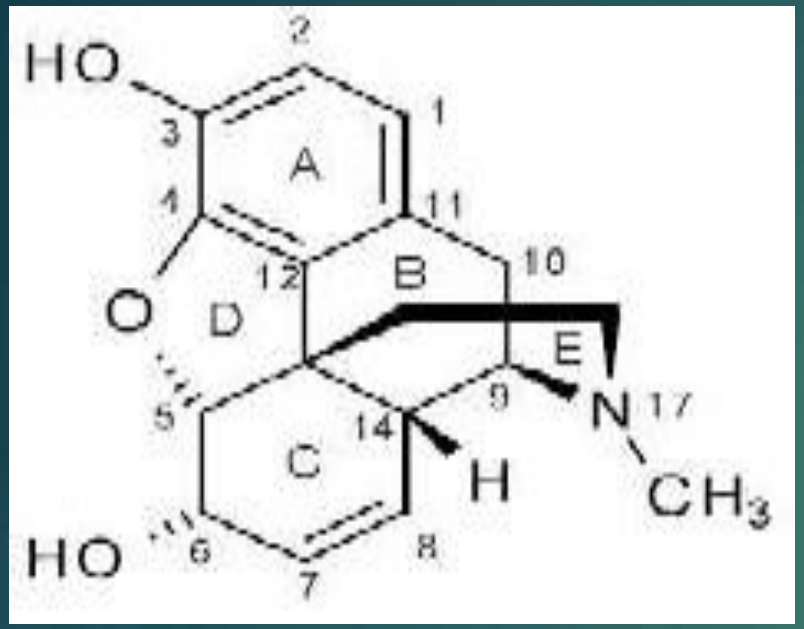
5 x activity



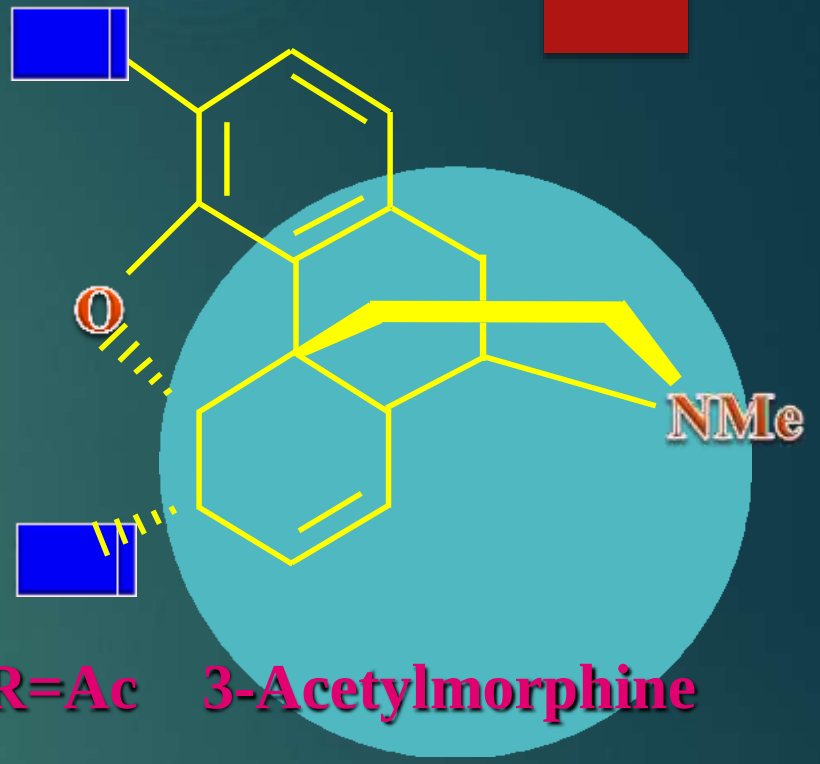
morphine

heroin

- Heroin (Diamorphine, Diacetylmorphine) It is about 3 times more potent than morphine;
  more lipid soluble, therefore enters the brain more rapidly, here in brain acetyl group are hydrolysed to produce morphine ,
  but duration of action is similar.
  It is considered to be more euphorient (especially on i.v. injection) and highly addicting



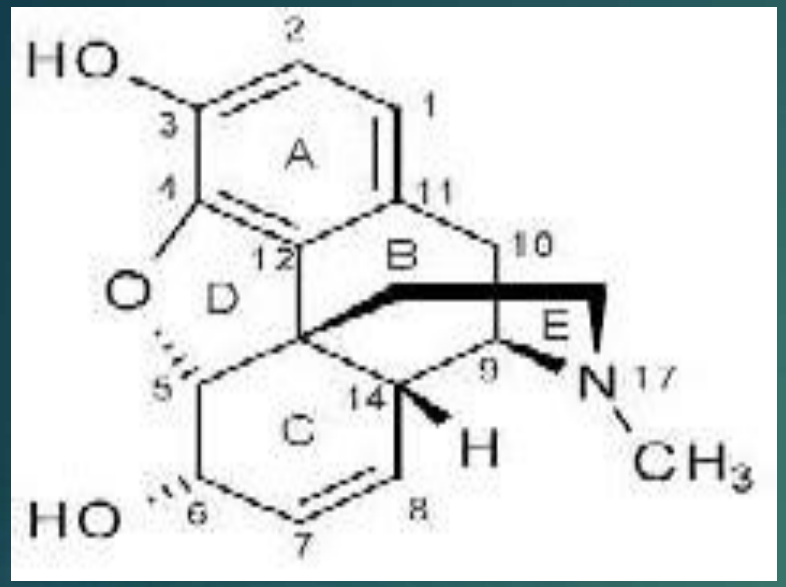
Morphine

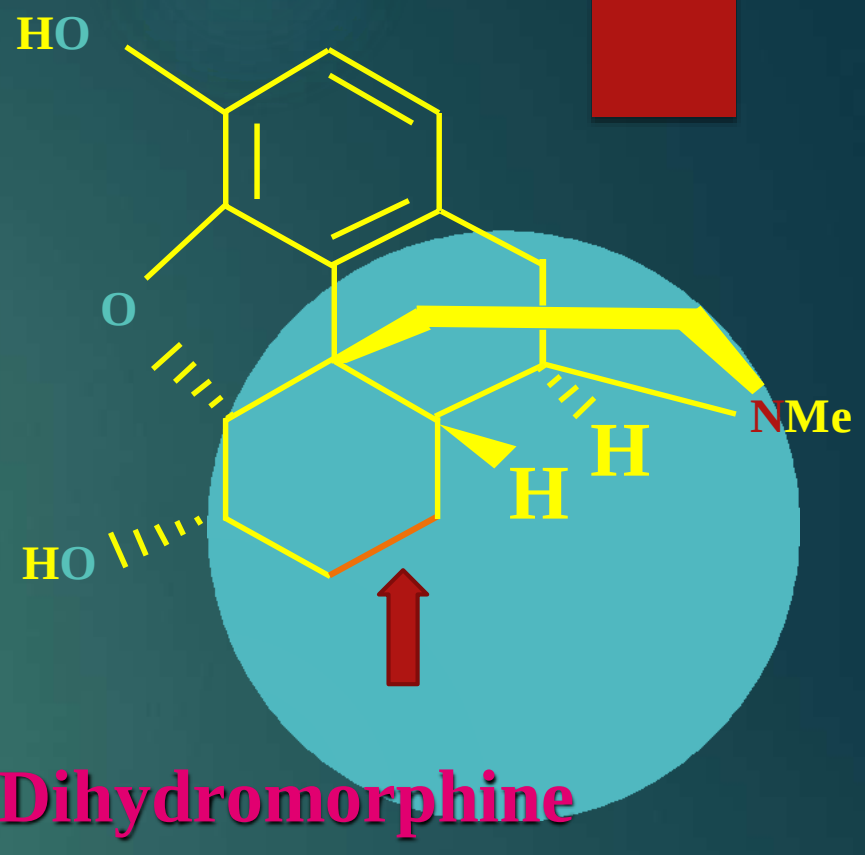


R=Ac 3-Acetylmorphine

Decreased activity

- ACETYL MASKS THE POLAR PHENOL GROUP
- COMPOUND CROSSES THE BLOOD BRAIN BARRIER MORE EASILY
- ACETYL GROUP IS HYDROLYSED IN THE BRAIN TO FORM MORPHINE





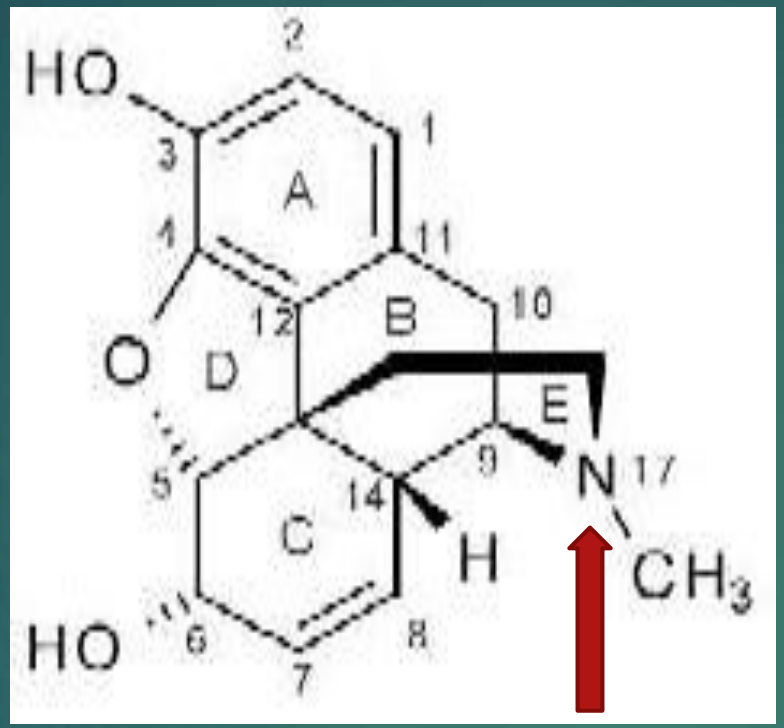
Dihydromorphine

Increased activity

THE ALKENE GROUP IS NOT IMPORTANT TO BINDING

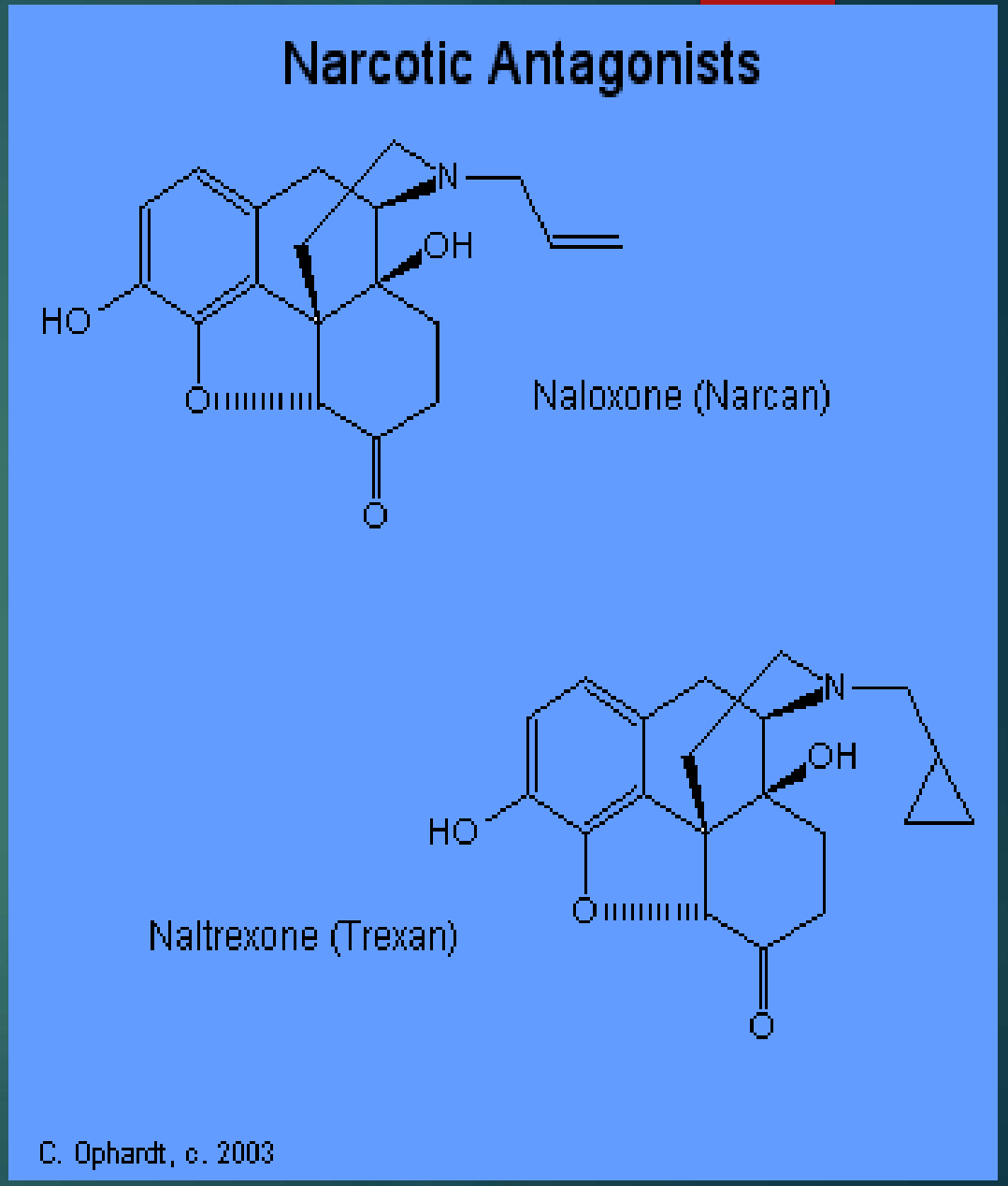
SAR - Methyl group on nitrogen

R =	Me, Et, Pr	Bu	Amyl, Hexyl	CH_2CH_2Ph
	Agonism decreases Antagonism increases	Zero Activity	Agonists	14 x Activity wrt morphine



NITROGEN IS ESSENTIAL FOR BINDING

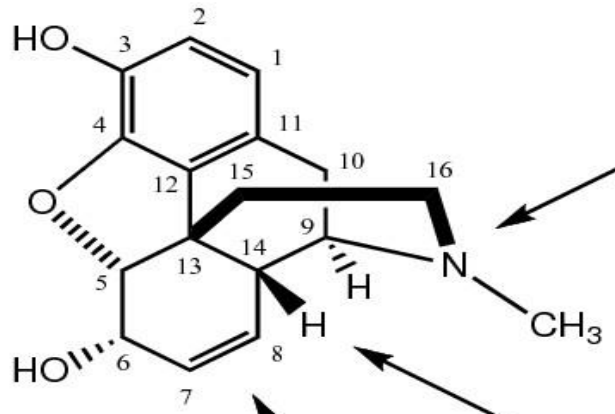
The pure opioid antagonist drugs naloxone, naltrexone, and nalmefene are morphine derivatives with bulkier substituents at the N17 position. These agents have a relatively high affinity for μ-opioid binding sites. They have lower affinity for the other receptors but can also reverse agonists at δ and κ sites.



Summary of structure-activity relationships (SAR's)

Removal of OH reduces activity

Removal increases activity



N-CH_2CH_2Ph increases
N-$CH_2CH{=}CH_2$ creates antagonist

Introduction of OH increases activity

Oxidation, coupled with reduction of 7,8 C=C, increases activity
Acetylation increases activity

Reduction increases activity

CONCLUSSION

- *Medicinal chemistry has and will continue to play an important role in today's society as it deals with development, synthesis and design of pharmaceutical drugs.*
- *These results are then used to give us a better way of preventing and curing diseases.*
- *Although medicinal chemistry is about creating new drugs, the properties and quantitative structure activity relationships (QSAR) of existing drugs is important to see if a combination of these biological properties can be mixed with a new hit to produce the latest drug that will help fight against various diseases.*

- *As the majority of medicinal chemistry is based around the discovery of new drugs and development, many companies spend a considerable amount of money in maintaining and improving their database of information to ensure that each test is run as efficient as possible.*
- *Of course, thousands of compounds related to the morphine structure have been prepared and many without activity, and no compound has been found to halt the terrible addictive morphine properties.*
- *When Used correctly, the morphine family is an important class of analgesics, and their study represents an important contribution to the understanding of medicinal activity.*

THANK YOU