Medicinal Chemistry

Chapter 15

OPIOID
NARCOTIC ANALGESICS

Contents

DEFINITIONS

- Opium: a mixture of alkaloids from the poppy plant - papaver somniferum
- Opioid: any naturally occurring, semi-synthetic or synthetic compounds that derived from opium which bind to opioid receptors.
- Opiate: any naturally occurring opioid derived from opium compounds
- Narcotic: Greek word meaning to numb or deaden. denote an opioid but also widely used to describe drugs of addiction and hence includes non opioid compounds

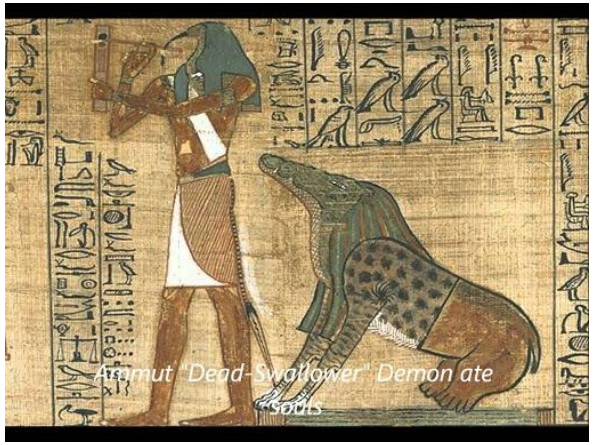
HISTORY

H1: Through ages

Opioids are among the world's oldest known drugs, 5700-5500 BC.

Ideograms on Sumerians clay tablets mention the use of "Hul Gil", a "plant of joy" used for medical, recreational, and religious purposes .

Egyptians lands -mentioned in the Ebers Papyrus- in 4th century BC, used for soothing of children, and for the treatment of breast abscesses.



It was valued by Hippocrates (460-370 BC) as sleep-inducing properties, and treatment of pain.

Avicenna (980–1037 AD) in The Canon of Medicine in five volumes include information on opium's preparation and physical effects, its use to treat a variety of illness, contraindications for its use, its potential danger as a poison and its potential for addiction. Avicenna discouraged opium's use except as a last resort.

H2: Opium conflicts and wars

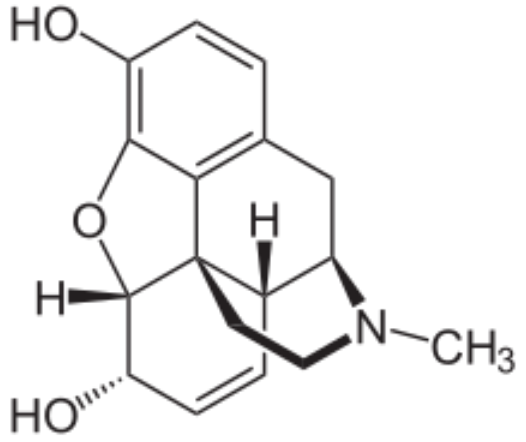
"Arcanum - Laudanum pills", by Paracelsus - 1439-1541 - is often credited with reintroducing opium into medical use in Western Europe. He extolled opium's benefits for medical use and in wars when death was to be cheated.

Laudanum - 17th century: the first medicines liquid tincture of opium, mixture of opium and alcohol, then modified to a mixture of opium, wine, saffron, clove and cinnamon with name of Paregoric, a much milder liquid preparation for children; and Black-drop, a stronger preparation, and Dover's powder.

Opium became a major colonial commodity, moving legally and illegally through trade networks involving India, the Portuguese, the Dutch, the British and China, this led to the First Opium Wars (1839–1842) and Second Opium Wars (1856–1860).

H3: Opium research development

In the 19th century, the beginning of modern scientific drug discovery for opium in two major scientific advances by German pharmacists, the first by isolated morphine from opium. He described the pharmacological. The second by developed morphine glass syringe with a subcutaneous needle made it possible to easily administer controlled.



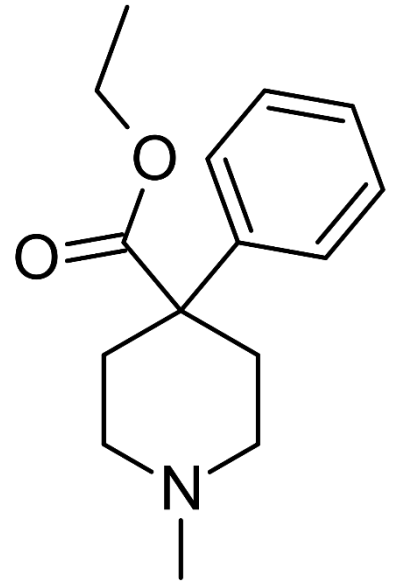
These what hailed morphine as a wonder drug for its ability to ease pain, help people sleep. It was widely prescribed by doctors, and dispensed without restriction by pharmacists.

"Here is a new substance found in opium, does not account for all the effects of morphine and for a long time" - codeine, was discovered in 1832 , when reviewing a method for morphine extraction. this discovery of the alkaloid led to the development of a generation of antitussive and antidiarrheal medicines based on codeine, as ascodeen

H4: Semisynthetic and synthetic opioids

Synthetic opioids were invented, and biological mechanisms for their actions discovered, in the 20th century. Scientists have searched for non-addictive forms of opioids, but have created stronger ones instead as diamorphine (heroin) 1924 at Bayer Laboratories.

Several semi-synthetic opioids were developed in Germany (1910-1972), as oxymorphone and oxycodone, synthesized from thebaine, an opioid alkaloid in opium poppies. At the University of Frankfurt, the hydrocodone derived from codeine, and they synthesized the hydromorphone from morphine.



The first fully synthetic opioid was meperidine (later demerol) by German chemists, it was the first opiate to have a structure unrelated to morphine, but with opiate-like properties, then They developed "Hoechst 10820" (later methadone), after that they developed fentanyl, a synthetic drug with 30 to 50 times the potency of heroin

H5: Criminalization and medical use

Non-clinical use of opium was criminalized in the United States -1914 - by many laws; "The use of opioids was stigmatized, and it was seen as a dangerous substance, to be prescribed only as a last resort for dying patients".

Increasing prescription of opioids caused by the release of OxyContin/Oxycodone and its aggressive marketing fueled a growing black market for codeine & heroin. Between 2000 and 2014 there was an "alarming increase in heroin use across the country and an epidemic of drug overdose deaths". As a result, new guidelines for the prescription of opioids "for chronic pain outside of active cancer treatment, palliative care, and end-of-life care" and the increase of opioid tapering in 2016.

PHARMACOLOGICAL ACTIONS OF OPIOID

Central nervous system

A. Analgesia

- Most effective in relieving dull, continuous and poorly localised pain arising from deeper structures, for example the gut. Less effective against superficial and sharp pain.

B. Sedation

- Drowsiness, feeling of heaviness and difficulty in concentrating are common, sleep may occur , although they are not true hypnotics.

C. Euphoria and dysphoria

- If there is no pain, morphine may cause restlessness and agitation (dysphoria).

D. Hallucinations

- These are more common with kappa agonists

Cardiovascular system

A. Mild bradycardia

- Common as a result of decreased sympathetic drive and a direct effect on the sino-atrial (SA) node. Peripheral vasodilatation

Respiratory system

A. Respiratory depression

- Respiratory rate falls more than the tidal volume and the sensitivity of the brain stem to carbon dioxide is reduced. Its response to hypoxia is less affected but if hypoxic stimulus is removed by supplemental oxygen then respiratory depression may be augmented.
- Codeine suppresses coughing to a degree similar to morphine, but has lesser analgesic activity.
- Morphine and diamorphine are used in paroxysmal nocturnal dyspnoea, as they produce sedation, reduce preload and depress abnormal respiratory drive.

Gastrointestinal System

- Smooth muscle tone is increased but motility is decreased resulting in delayed absorption, increased pressure in the biliary system (spasm of sphincter of Oddi) and constipation.

Ocular effects

- mu and kappa receptors in Edinger-Westphal nucleus of occulomotor nerve are stimulated by opioids resulting in constriction of the pupils (meiosis).

Histamine release and itching

- Some opioids cause histamine release from mast cells resulting in urticaria, itching, bronchospasm and hypotension.

Muscle rigidity

- Large doses of opioids may occasionally produce generalized muscle rigidity especially of thoracic wall and interfere with ventilation.

Immunity

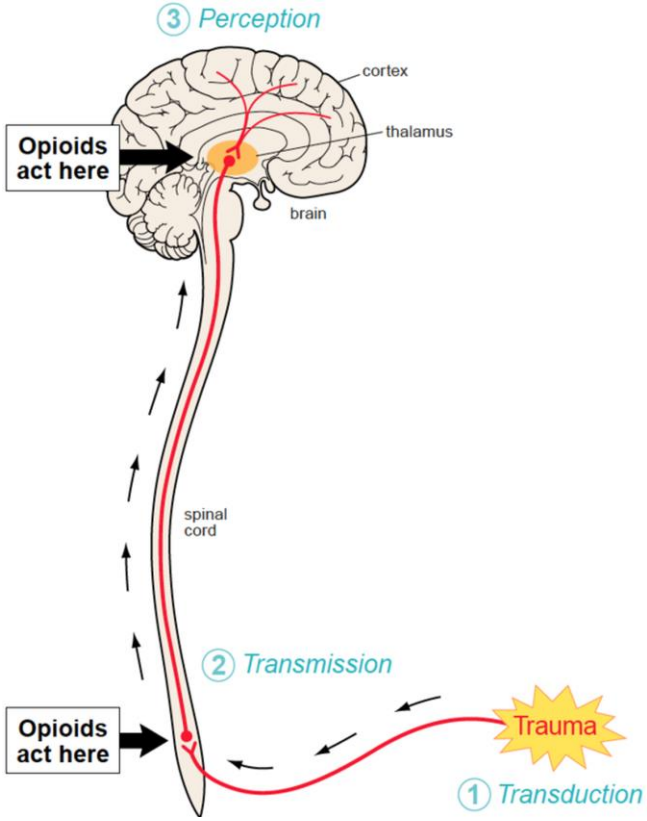
- The immune system is depressed after long-term opioid abuse.

Effects on pregnancy and neonates

- Chronic use by the mother may cause physical dependence in utero and lead to a withdrawal reaction in the neonate at birth that can be life threatening.

MECHANISM OF ACTION

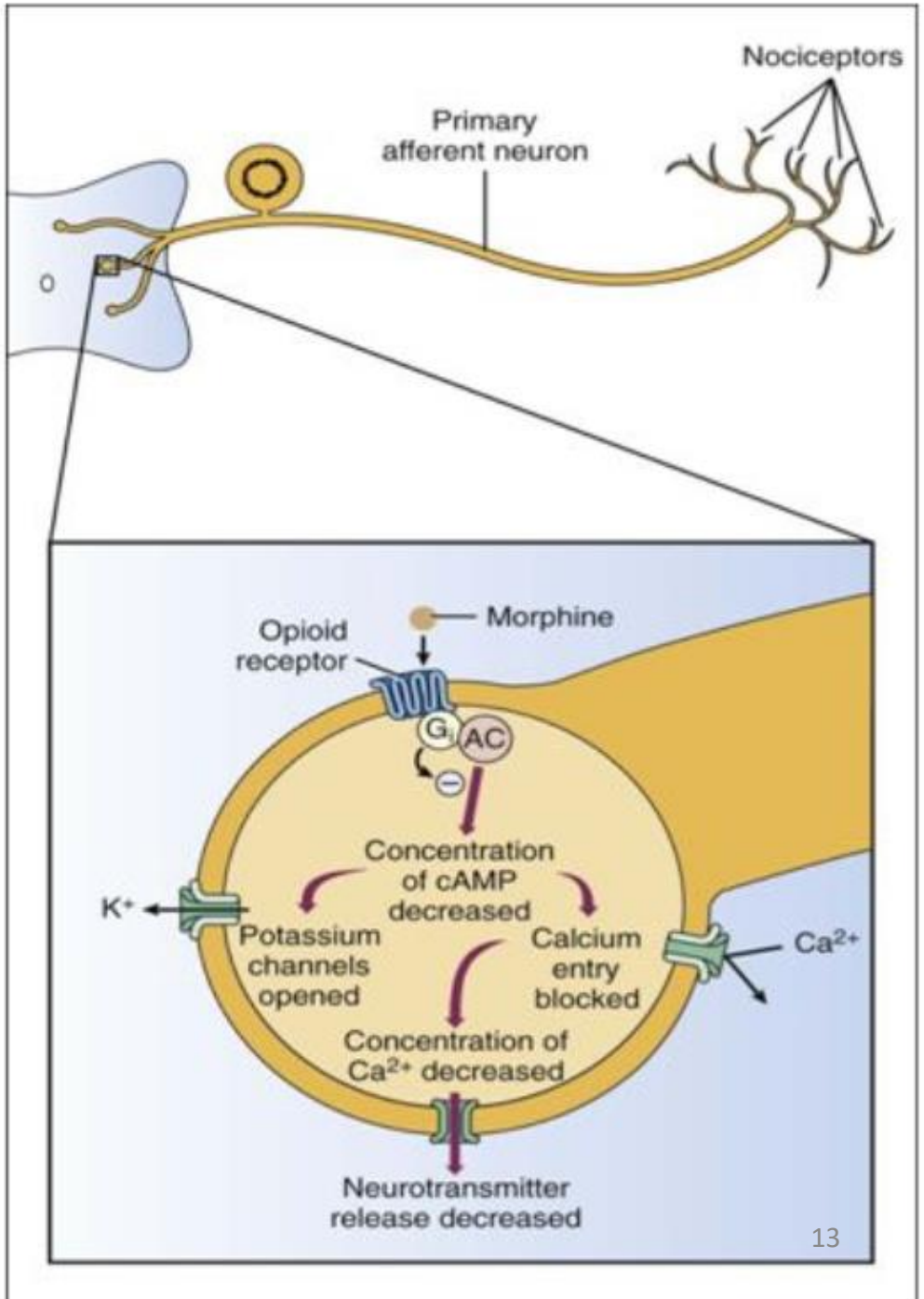
Opioids produce their actions at a cellular level by activating opioid receptors. These receptors are distributed throughout the central nervous system (CNS) with high concentrations in the nuclei of peri-aqueductal grey area (PAG), cerebral cortex, thalamus and the substantia gelatinosa (SG) of the spinal cord. They have also been found on peripheral afferent nerve terminals and many other organs.



<u>These receptors are</u>

- **MOP - μ (mu):** responsible for supraspinal analgesia, physical dependence, respiratory depression, miosis, euphoria, reduced GI motility.
- **KOP - κ (kappa):** spinal analgesia, sedation, miosis, and inhibition of anti-diuretic hormone release.
- **DOP - δ (delta):** responsible for analgesia, euphoria, and physical dependence.
- **SOP (Sigma):** considered to be opioid receptors, but are not usually currently classified as such.

The opioid receptors are prominent members of the **G protein–coupled receptor superfamily**. Activation of opioid receptors leads to inhibition of adenylyl cyclase and a decrease in the concentration of cyclic adenosine monophosphate, an increase in K+ conductance, and a decrease in Ca2+ conductance . The **activated Gαi subunit of the G protein directly inhibits the adenylyl cyclase enzyme,** and the Gβγ subunits are thought to mediate the changes at the Ca2+ and K+ channels. These actions cause both presynaptic inhibition of neurotransmitter release from the central terminations of small-diameter primary afferent fibers and postsynaptic inhibition of membrane depolarization of dorsal horn nociceptive neurons.



- ***Pure opioid agonists*** (morphine, diamorphine, pethidine and fentanyl) bind to opioid receptors avidly and demonstrate high intrinsic activity at the cellular level.
- ***Partial opioid agonists*** (buprenorphine, pentazocine) bind to opioid receptors, but produce a sub-maximal effect compared to pure agonists and so have less intrinsic activity associated with receptor binding.
- ***Opioid antagonists*** (naloxone, naltrexone), have receptor affinity but no intrinsic activity.

Receptors	Endogenous Substance	Agonist	Partial agonist	Antagonist
μ receptors	Endorphin	Morphine	Buprenorphine Butorphanol	Nalorphine Naltrexone
κ receptors	Dynorphin A, B	Butorphanol Nalorphine Pentazocine	---	Naltrexone Naloxone
δ receptors	Enkephalins	Morphine (Weak)	----	Naltrexone (Weak) Naloxone (Weak)

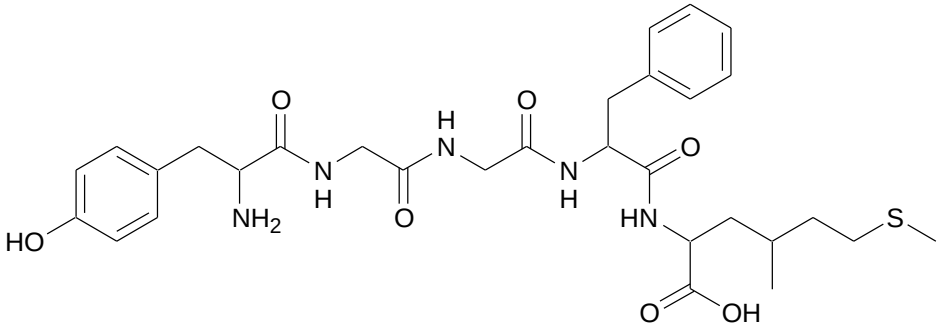
Opioids with their selectivity for different opioid receptors

	Receptor type			
Opioid	**MOP**	**KOP**	**DOP**	**NOP**
Endogenous				
Beta-endorphin	+++	+++	+++	-
Leu-enkaphalin	+	-	+++	-
Dynorphin A& B	++	+++	+	+
OFQ	-	-	-	+++
Clinical drugs				
Agonists				
Morphine	+++	+	+	-
Pethidine	+++	+	+	-
Diamorphine	+++	+	+	-
Fentanyl	+++	+	-	-
Partial agonists				
Buprenorphine	++	+	-	-
Pentazocine	-	++	-	-
Antagonists				
Naloxone	+++	++	++	-
Naltrexone	+++	++	++	-

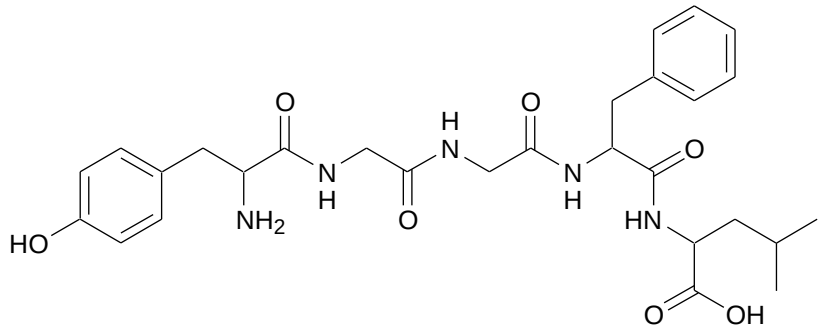
+ = low affinity, ++ = moderate affinity, +++ = high affinity, - = no affinity.

Opioid Peptides

- Greek, kephalē, which means "head" gives the name enkephalins. 2 enkephalins differ in the fifth amino acid one has a Methionine and the other a Leucine residue: Met–enkephalin and Leu–enkephalin
- pro–enkephalin and few more endogenous peptides with opioid activity have been found, the endorphins and the dynorphins,
- The opioid receptor has been subtyped into three distinct types based on these three types of endogenous peptides: (Endorphins –Mu, dynorphins – kappa, enkephalins – delta)
- In all three types of peptides the amino terminus is always the same amino acids (H_2N–Tyr–Gly–Gly–Phe)



H_2N-Tyr-Gly-Gly-Phe-Met-COOH
Met-enkephalin



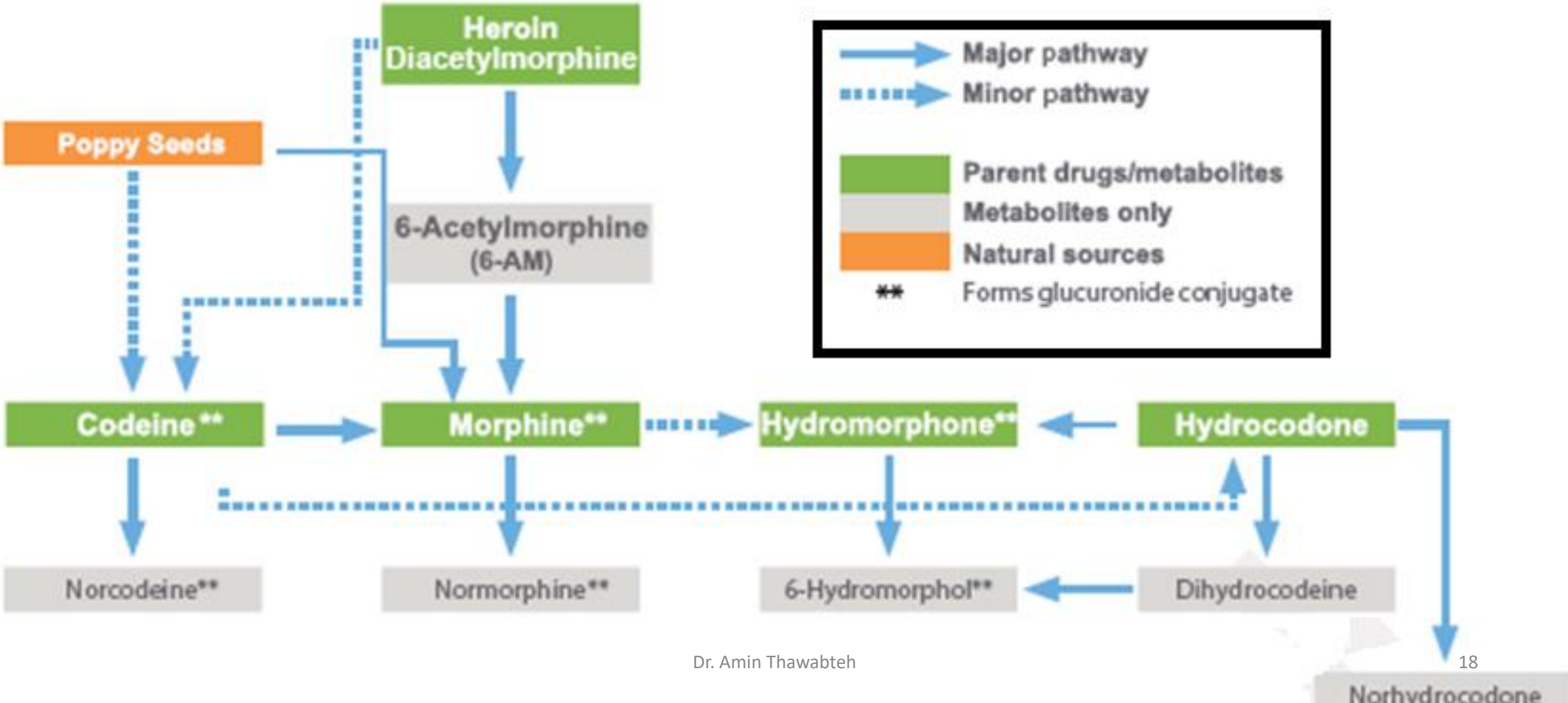
H_2N-Tyr-Gly-Gly-Phe-Leu-COOH
Leu-enkephalin

Opioid Metabolism

- Most opioids are metabolized by hepatic conjugation to inactive compounds that are excreted readily in the urine.
- Opiate metabolites are excreted in the urine, making urine toxicology useful
- Certain opiates (eg, propoxyphene, fentanyl, and buprenorphine) are more lipid soluble and can be stored in the fatty tissues of the body

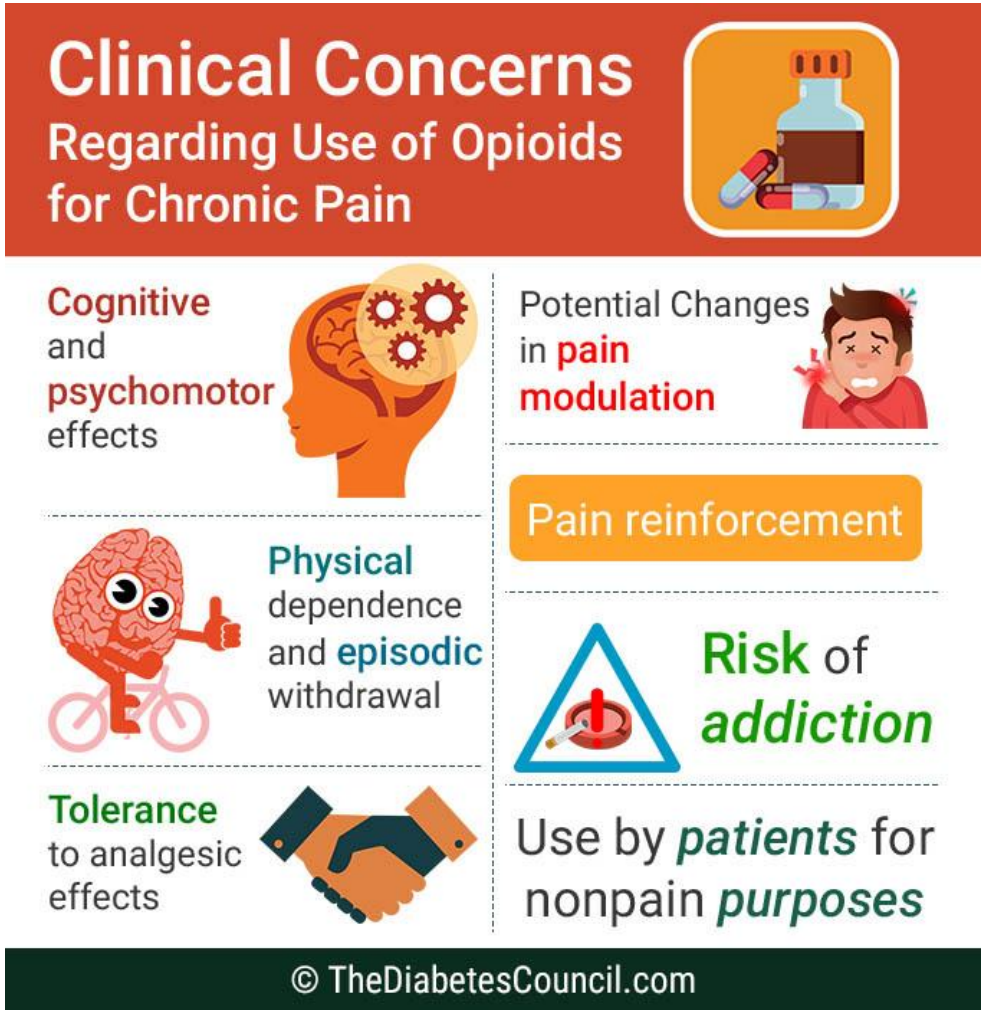
CYP450	CYP Metabolism	Metabolite	Comment
Codeine	CYP-2D6	morphine	Genetic polymorphisms of CYP-2D6 may affect therapeutic efficacy.
Fentanyl	CYP-3A4		Genetic polymorphism of CYP-3A4 may influence metabolism and therapeutic efficacy.
Hydrocodone	CYP-2D6, 3A4	hydromorphone	Genetic polymorphisms of CYP-2D6 and 3A4 may affect therapeutic efficacy.
Methadone	CYP-2D6, 3A4, 2C8, 2C9, 2C19, 2B6, and 1A2		Genetic polymorphisms to CYPs account for wide variability of serum levels for a given dose in different patients.
Oxycodone	CYP-2D6, CYP-3A4	oxymorphone and noroxycodone	Genetic polymorphisms of CYP-2D6 and 3A4 may affect therapeutic efficacy.
Tramadol	CYP-2D6	transmethyltramadol	Genetic polymorphisms of CYP-2D6 may affect therapeutic efficacy.
Glucuronidation			
Hydromorphone			
Morphine			
Oxymorphone			
Tapentadol			

General Opioid Metabolism



Clinical uses

- Management of acute pain, chronic pain, severe pain of acute myocardial infarction, obstetric analgesia
- Cough suppression (Codeine, Dextromethorphan)
- Treatment of diarrhoea (Diphenoxylate, Loperamide)
- Management of acute pulmonary oedema
- Preoperative medication and intraoperative adjunctive agents in anaesthesia (Fentanyl, Alfentanyl, Sufentanyl)
- Maintenance programmes for addicts (Methadone)



Please read more about uses by click here:

Trivedi, M., Shaikh, S., & Gwinnut, C. (2011). Pharmacology of opioids. *Update in Anaesthesia*, 118-124.

- **Side effects:** Side effects of opioids may include itchiness, sedation, nausea, respiratory depression, constipation, and euphoria. Long-term use can cause tolerance, meaning that increased doses are required to achieve the same effect, and physical dependence, meaning that abruptly discontinuing the drug leads to unpleasant withdrawal symptoms. The euphoria attracts recreational use and frequent, escalating recreational use of opioids typically results in addiction. An overdose or concurrent use with other depressant drugs like benzodiazepines commonly results in death from respiratory depression.

Please read more about the side effects by click here:

Trescot, A. (2013). Clinical use of opioids. In *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches* (pp. 99-110). Springer, New York, NY.

CLASSIFICATION OF OPIOIDS

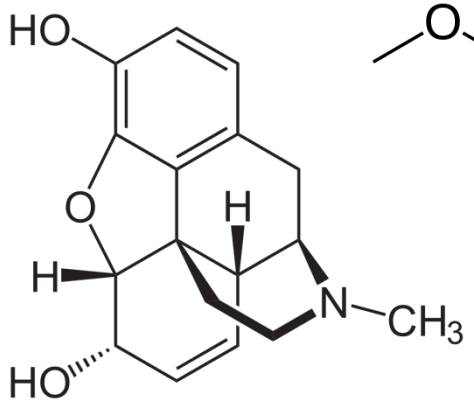
Several classification :

- Traditional : based upon analgesic potency
- Origin of drug : naturally occurring or manufactured
- Function : their action at the opioid receptor
- Based on structure

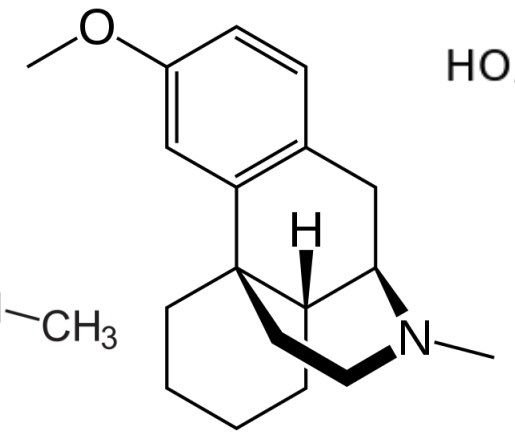
Traditional	Origin	Function
Strong	**Naturally occurring**	**Pure agonists**
Morphine	Morphine	Morphine
Pethidine	Codeine	Fentanyl
Fentanyl	Papavarine	Alfentanil
Alfentanil	Thebaine	Remifentanil
Remifentanil		Sufentanil
Sufentanil	**Semisynthetic**	
	Diamorphine	**Partial agonist**
Intermediate	Dihydrocodeine	Buprenorphine
Buprenorphine	Buprenorphine	
Pentazocine		**Agonists-antagonists**
Butorphanol	**Synthetic**	Pentazocine
Nalbuphine	Phenylpyperidines:	Nalbuphine
	pethidine, fentanyl, alfentanil,	Nalorphine
Weak	sufentanil	
Codeine	Diphenylpropylamines:	**Pure Antagonists**
	methadone, dextropropoxyphene	Naloxone
	Morphinans:	Naltrexone
	butorphanol, levorphanol	
	Benzomorphans:	
	pentazocine	

Based on structure

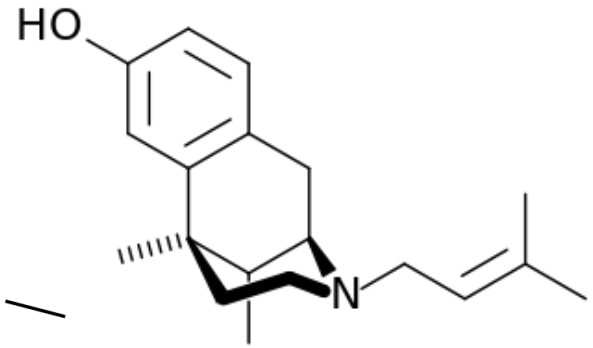
		Eg.
Pentacyclic	Morphines	Codeine ,Buprenorphine, Oxycodone, Diacetylmorphine (Heroin)
Tetracyclic	Morphinan	Levorphanol, butorphanol
Tricyclic	Benzazocine	Pentazocine, Phenazocine
Bicyclic	Phenylpiperidine	Meperidine



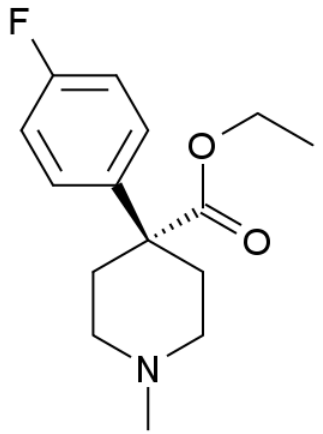
Morphine



Levorphanol



Pentazocine



4-Fluoromeperidine

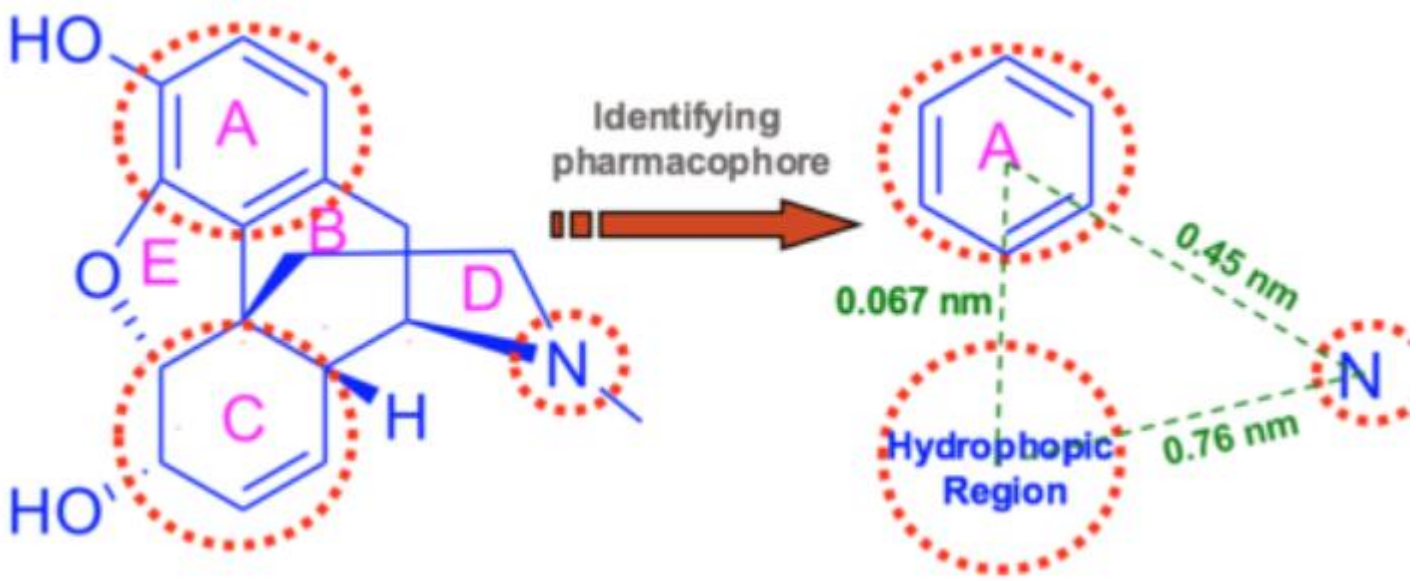
Why you feel “happy”

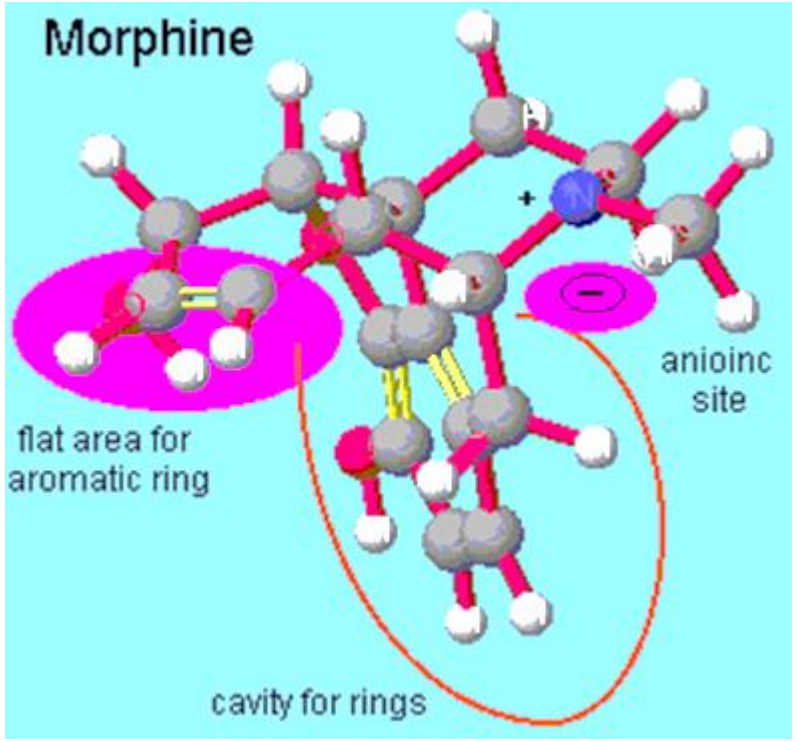
- Opioids modifies the action of dopamine in the brain.
- Once crossing the blood-brain barrier, opioids acts as an agonist.
- This binding inhibits the release of GABA from the nerve terminal, reducing the inhibitory effect of GABA on dopaminergic neurones.
- The increased activation of dopaminergic neurones and the release of dopamine into the synaptic cleft results in activation of the post-synaptic membrane.
- Continued activation of the dopaminergic reward pathway leads to the feelings of euphoria and the ‘high’ associated with heroin use.

PHARMACOPHORE OF MORPHINE

A schematic for an analgesic receptor site may look as shown in the given figure on morphine. Three areas are needed:

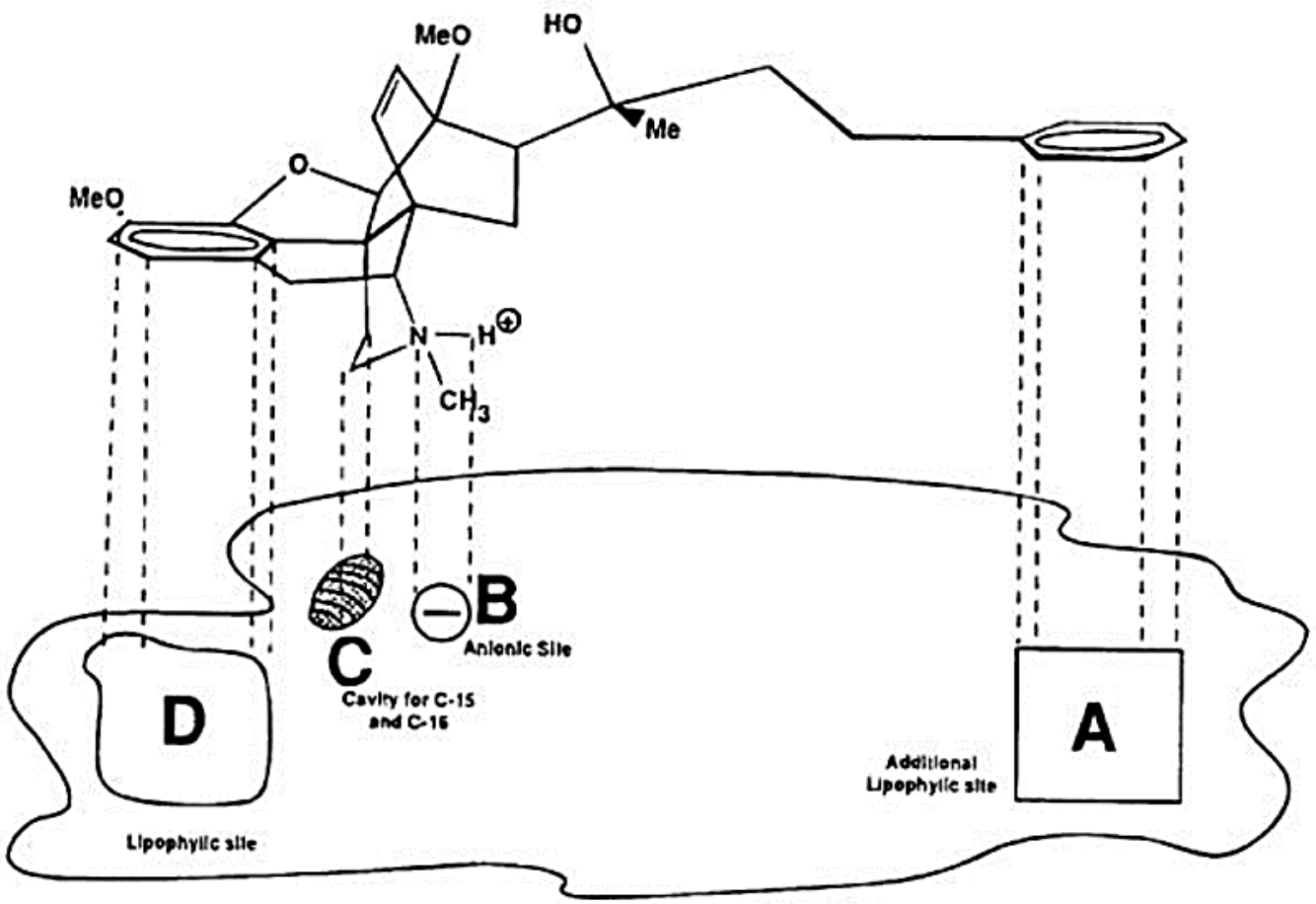
- A flat area to accommodate a flat nonpolar aromatic ring,
- A cavity to accept another series of rings perpendicular
- An anionic site for polar interaction of the amine group





Pharmacophore for opiates.

Schematic Representation of an Opioid Receptor



Site "A" is an atiditional lipophilic site that binds with the phenyl ring on phenylalanipe of the endogenous opioid peptides. This explains receptor interaction of some of the oploid drugs

Site "B" is an anionic site that binds the protonated nitrogen of the pyridine ring (ring "D") found in morphine

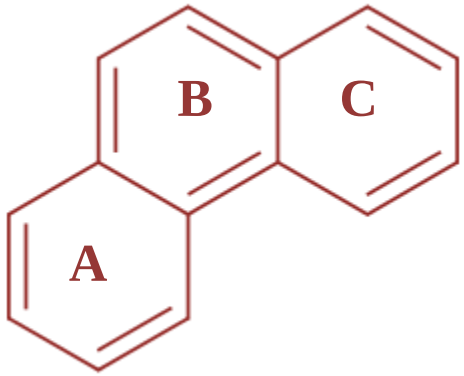
Site "C" is a cavity that accomodates C15 of morphine

Site" D" binds the tyrosine residue of the endogenous opioid peptides: Flat, hydrophobic with an adjacent hydrogen bonding site for hydroxyl on phenyl ring that binds ring "A" of morphine

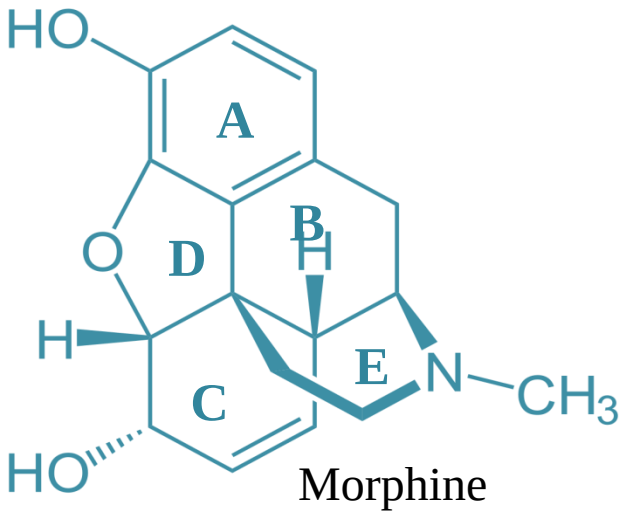
General Structure:

Ring numbering and nomenclature

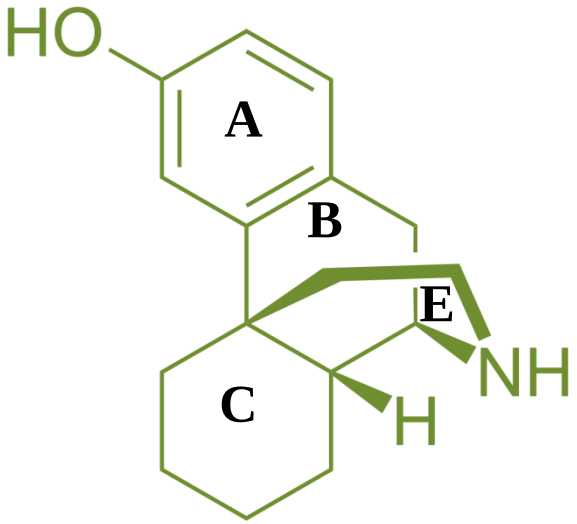
- Based on **phenanthrene** thus these three rings are labeled **A, B and C**, other two are labeled **D and E for Morphine**, while removing **the D ring** of morphine will form **morphinans**.



Phenanthrene



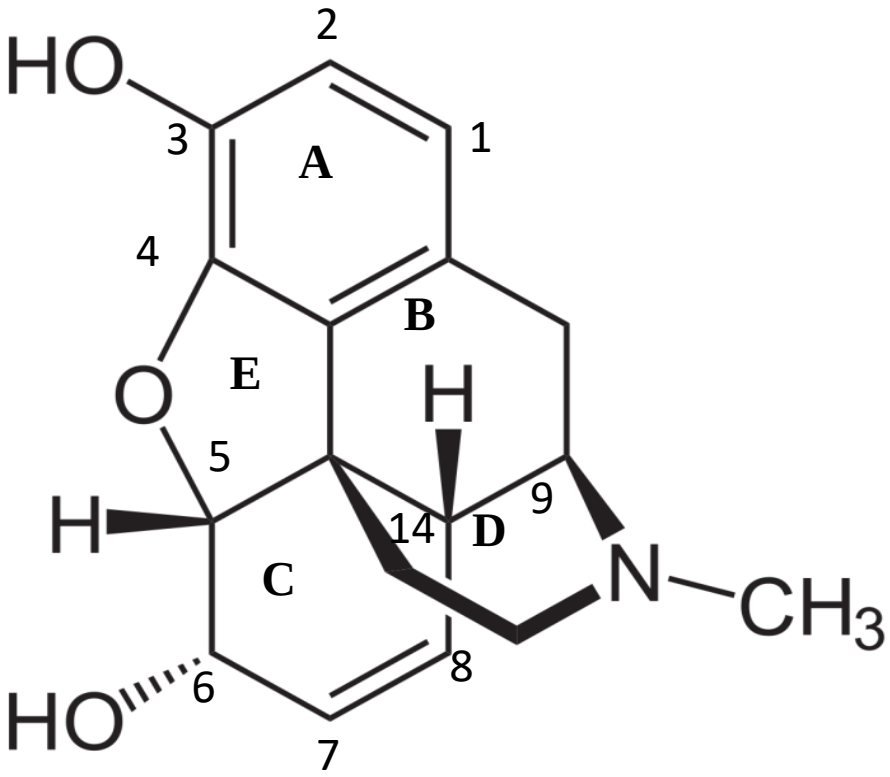
Morphine

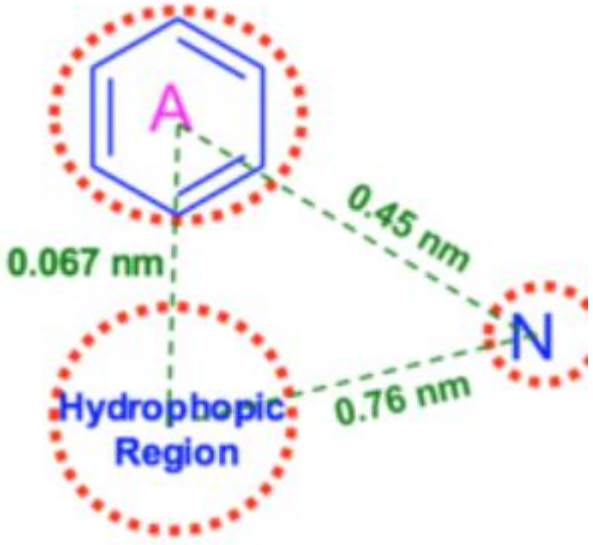


Morphinans

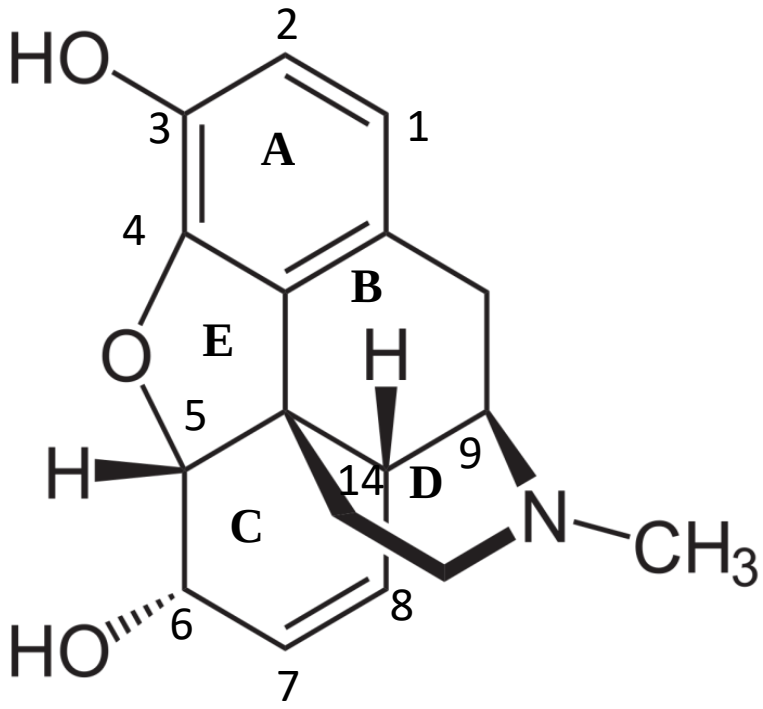
- Rings **B and D** of morphine is termed Morphan, which **ring D** is the nitrogen-containing piperidine ring. **Ring A** is flat aromatic and, **ring C** is in the boat confirmation due to the double bond, **Ring E** is the ether or epoxide

- The configuration at **C9** is the most important, which determines the **orientation and distance** between the protonated nitrogen and the phenyl ring.

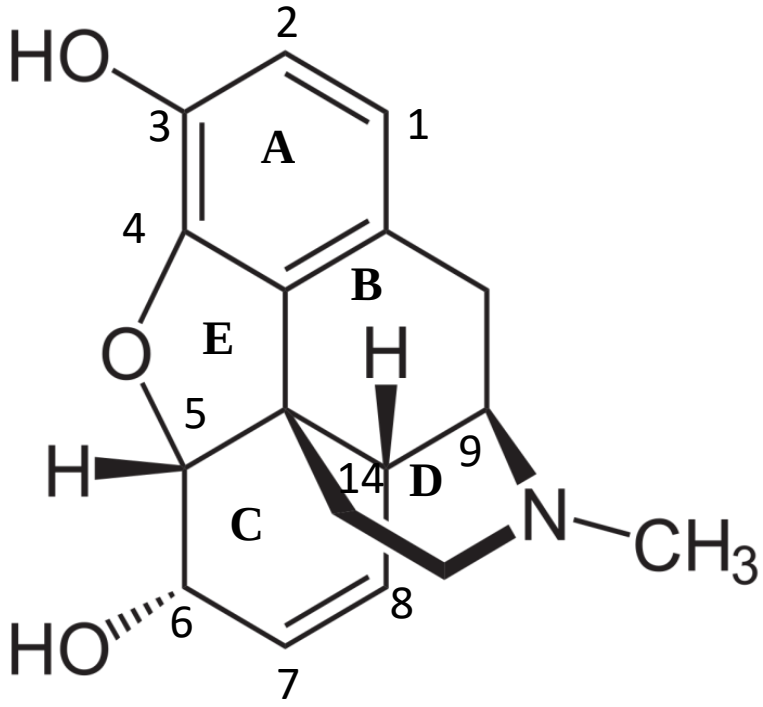




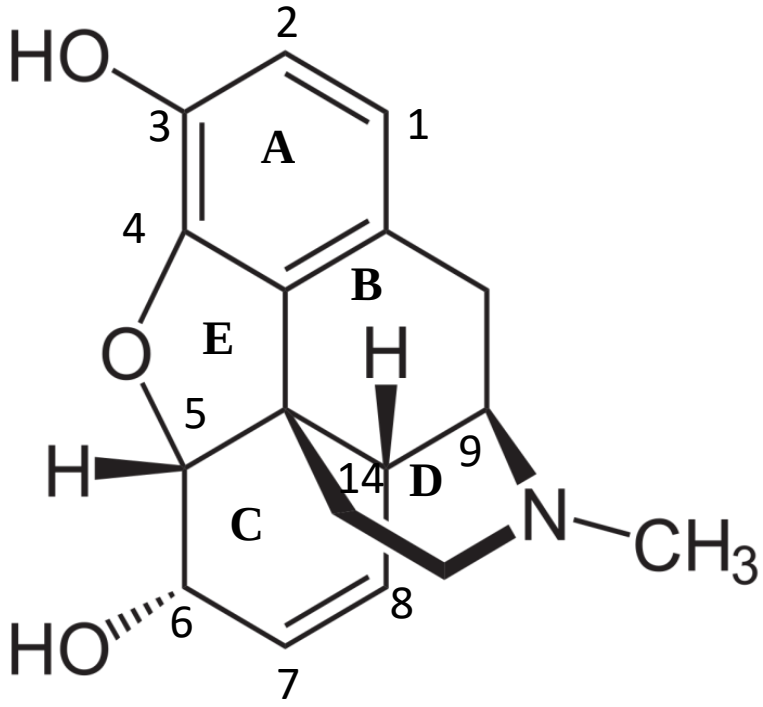
- Modifications involve C3, C6, C7, C8, C14, and the piperidine Nitrogen
- The earliest molecular modifications were simple, such as esterification, etherification, and increasing the length of the N–substituent
- Molecular modifications may be divided into three groups : Ring “A”, Ring “C” Ring “E”
- A free phenolic OH is optimal for μ receptor (analgesia) affinity, but will decrease LWPC and also leads to first pass glucuronidation leading to poorer oral bioavailablity.



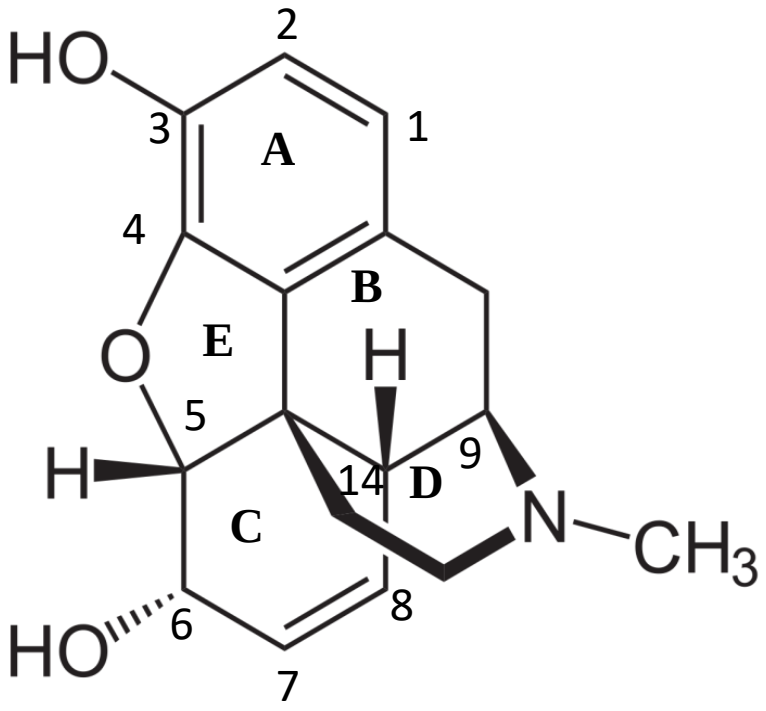
- Conversion of the OH to ether causes decease in μ receptor affinity. Thus codeine is a prodrug for its analgesic effect. The larger the group the slower this proceeds and therefore, the larger the group the less μ receptor affinity.
- However, etherification increases antitussive effectiveness and do not need to remove the alkyl group.
- Etherification also increases LWPC. **The larger the lipophilic substituent the higher the LWPC** and thus increased bioavailability and cannot glucuronidate.



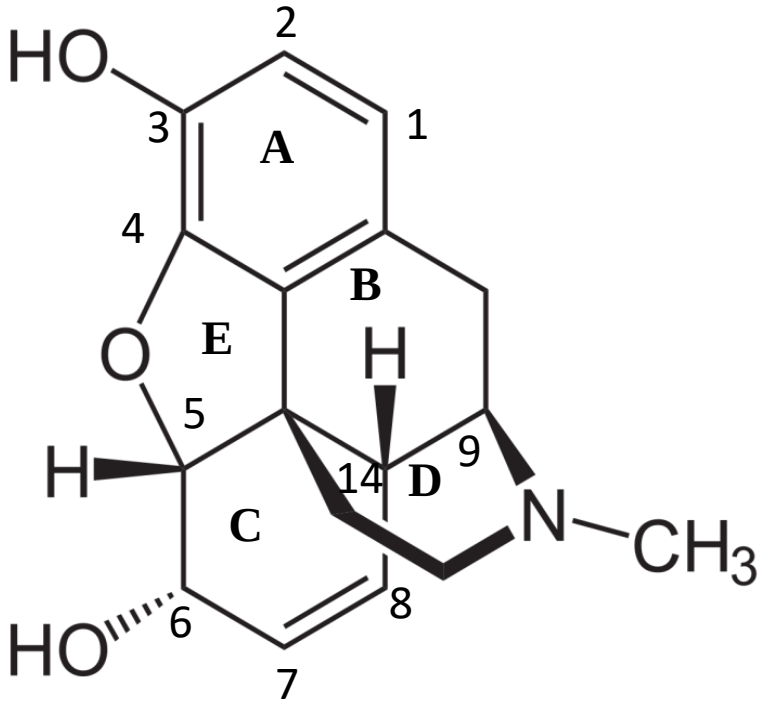
- Conversion to an ester creates a prodrug which must be hydrolyzed at C3 to interact with the receptor. For diacetyl morphine (heroin) the ester at C6 does not have to be removed for the receptor interaction. The C3 is more susceptible to hydrolysis as phenyl is an electron withdrawer
- Removal of ring E increases LWPC. So, in general, all else being equal, a morphinan is overall more potent than the corresponding epoxymorphinan. The ether bridge does not interact with the receptor so does not affect μ receptor affinity.



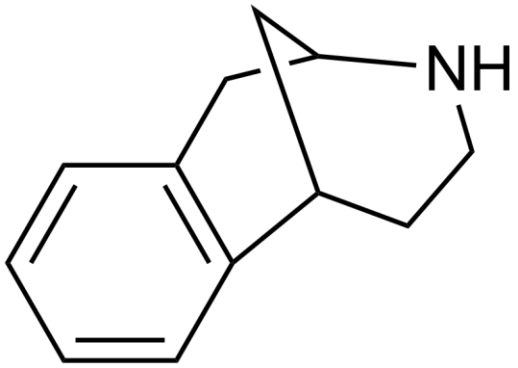
- Oxidation in Ring C decreases analgesic potency , which still possesses a polar oxygen, and apparently interacts more unfavorably with the hydrophobic region on the receptor
- Replacing hydroxyl 6 with methyl or methylene increases μ receptor affinity, again, due to better hydrophobic interaction. Example: nalmefen
- Addition OH at C14 increases μ receptor affinity due to an increased hydrogen bonding



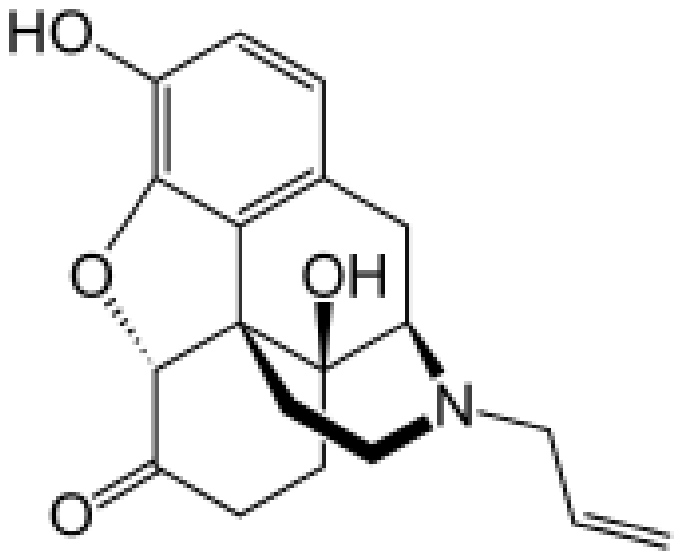
- The C7, C8 (Δ7) olefinic bond saturation changes LWPC and μ receptor affinity. Saturation gives a slight increase in LWPC and also ring "C" goes from boat to chair conformation that changes the 3D position of C6 hydroxyl. This gets rid of the unfavorable hydrophilic–hydrophobic interaction. Thus, this also increases μ receptor affinity
- Oxidation of C6 oxygen produces an increase in μ receptor affinity. The ketone is more rigid and held away from the hydrophobic region.



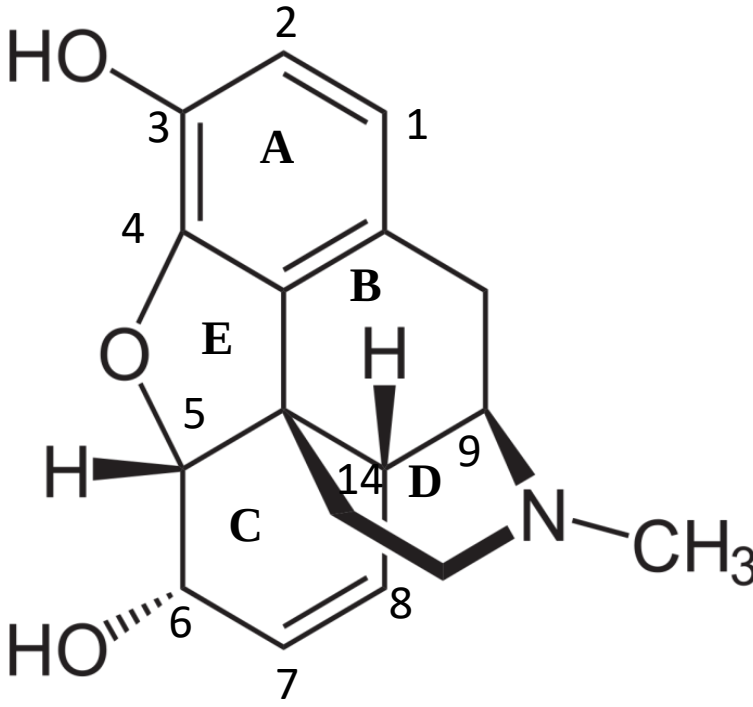
- Removal of ring **C increases LWPC**. Removed C6 hydroxyl does not interact with the hydrophobic site on the receptor unfavorably so it increases μ receptor affinity. So, in general, all else being equal, benzmorphans are more potent than morphinans.



benzmorphans



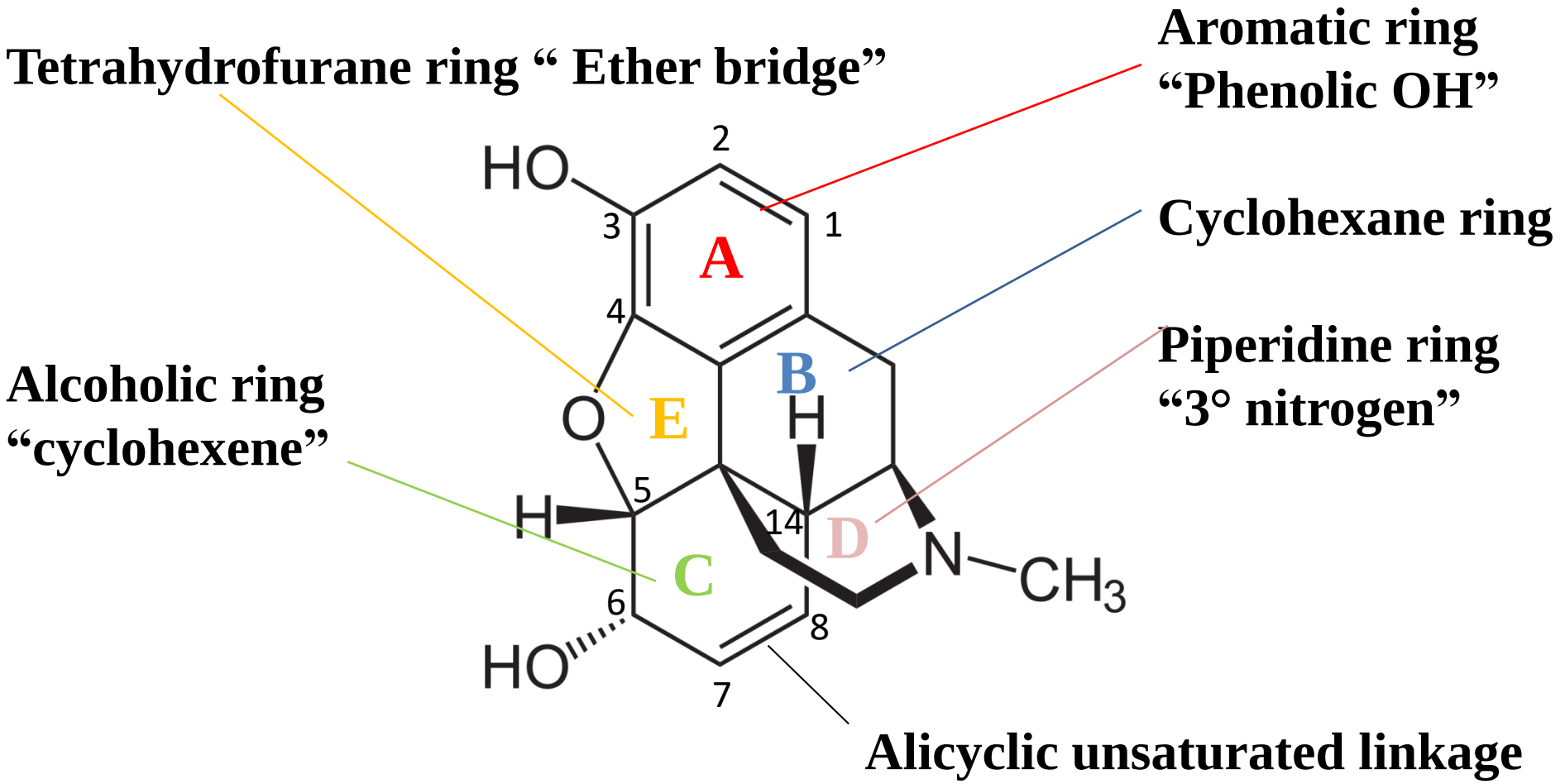
morphinans



POSITION	MODIFICATION	EFFECTS
Phenolic -OH	-OH to -OCH_3 -OH to -OC_2H_5	Less analgesic, Cough suppression.
Alcoholic -OH	-OH to -OCH_3 -OH to -OC_2H_5	5 × morphine. 2.4 × morphine.
Allylic unsaturated linkage	-CH=CH- to –CH_2CH_2-	1.2 × morphine.
Tertiary nitrogen	N-CH_3 to NH N-CH_3 to NCH_2CH_3Ph	< active than morphine 14 × morphine.

MORPHINE & STRUCTURE MODIFICATIONS

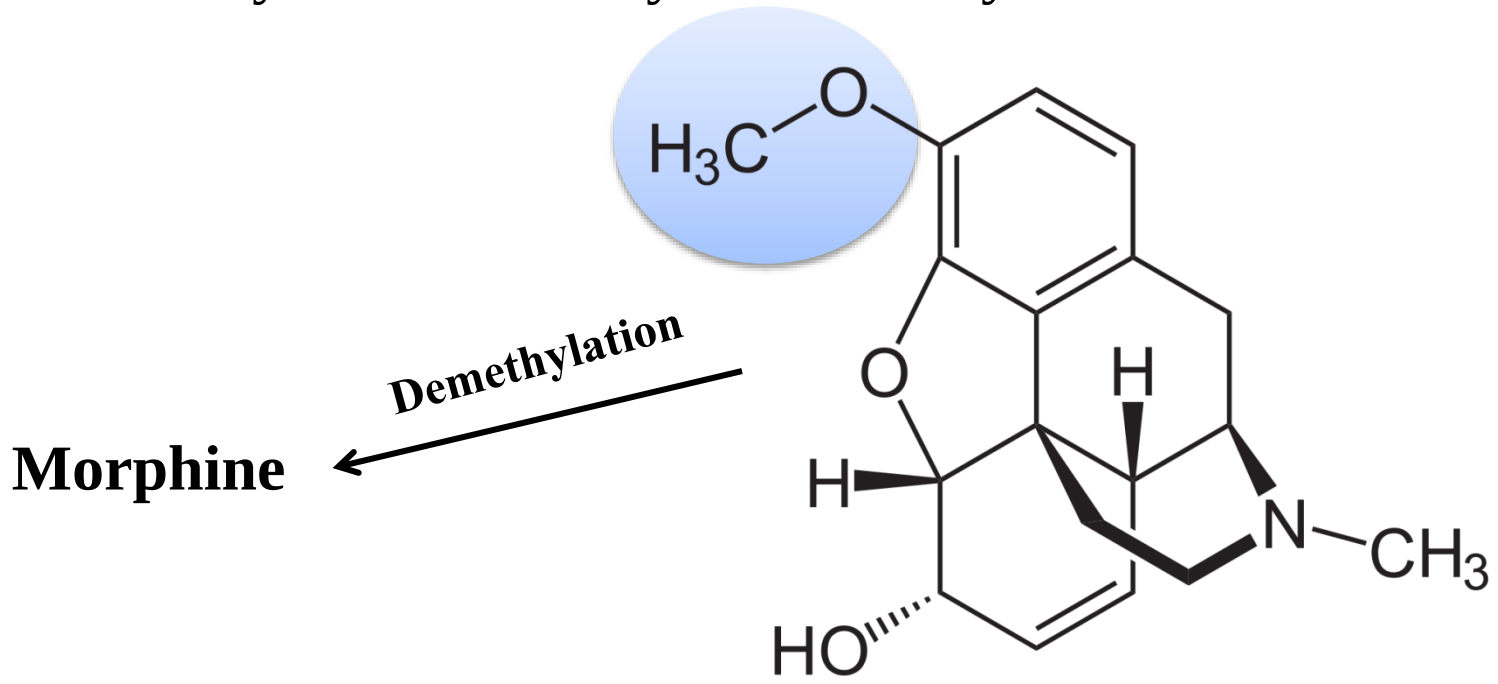
SAR of Morphine



At the 3- and 6-hydroxyl groups:

- Conversion of the 3-OH to a 3-OCH_3 yielding **codeine**, reduces activity to 15% of morphine

- Groups larger than a methoxy reduce activity dramatically.



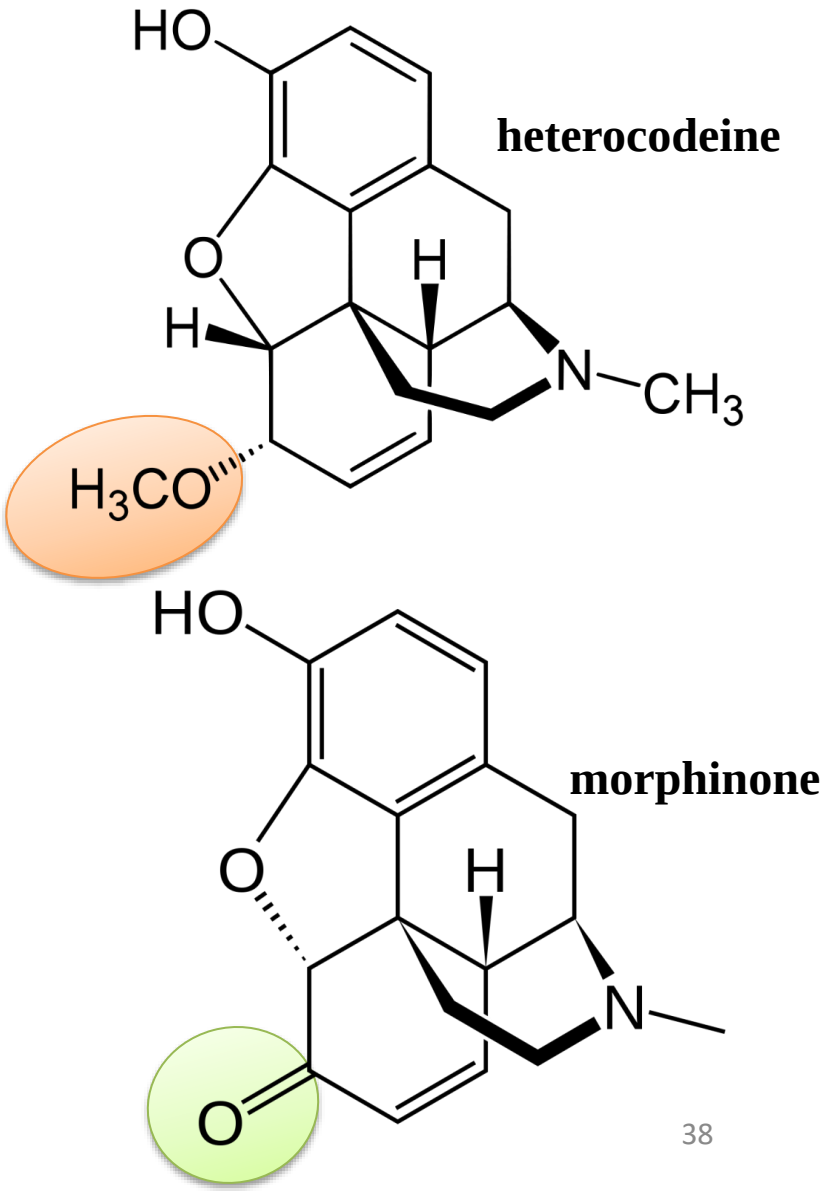
At the 3- and 6-hydroxyl groups:

- Conversion of the 6-OH to a 6-OCH_3 yielding **heterocodeine**, results in a six-fold increase in activity.

- Oxidation of the 6-OH to a ketone

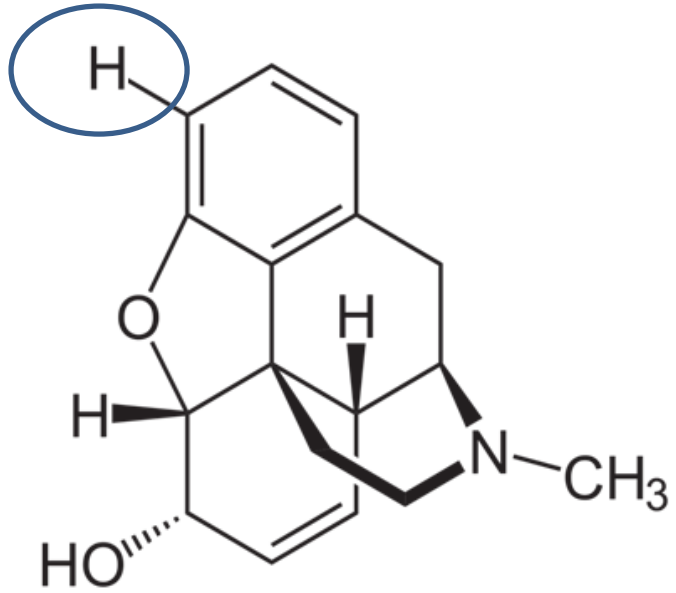
❑ Reduces activity when 7,8-unsaturated: **morphinone** (37% Moph)

❑ Increase activity when 7,8-saturated

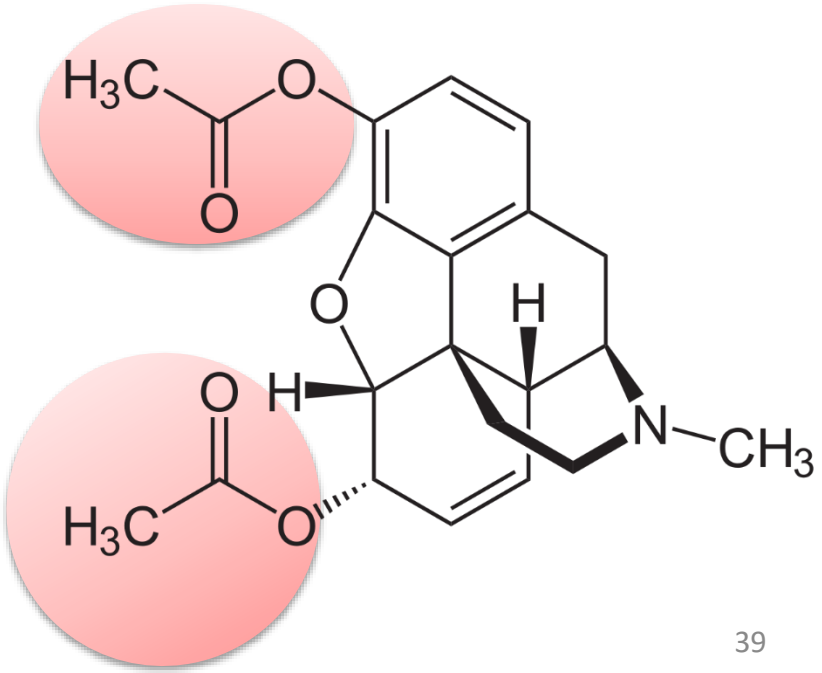


At the 3- and 6-hydroxyl groups:

- Removal of the 6-OH (6-desoxymorphine) increases activity.

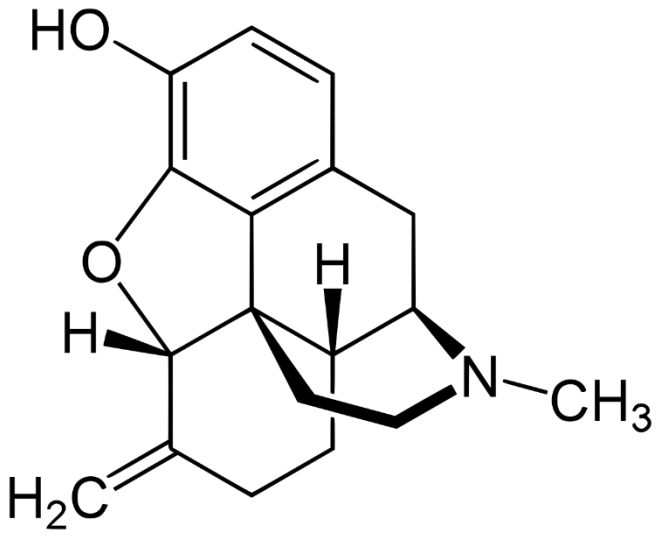


- Acetylation of both the 3- and 6-OH produces heroin, Heroin is 2-3 times more potent than morphine. This increase is due to increased lipid solubility, which leads to enhanced and rapid CNS penetration.

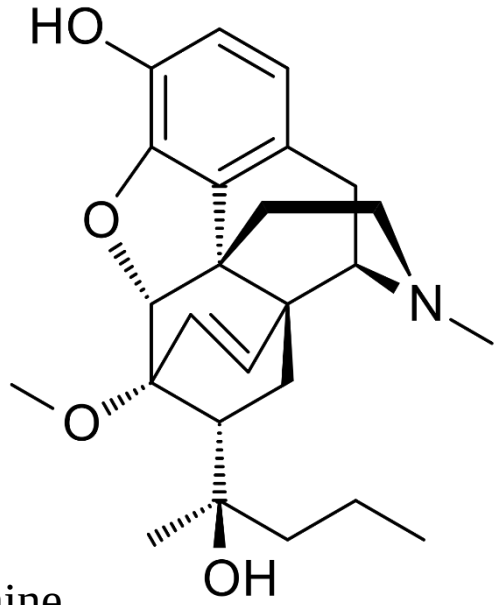


At the 3- and 6-hydroxyl groups:

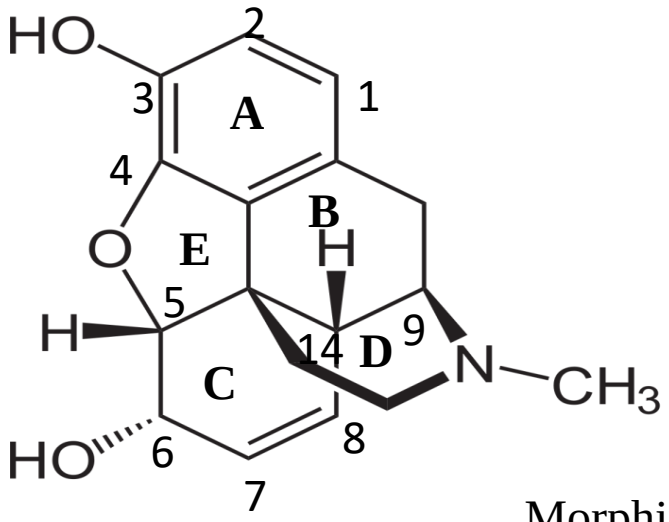
- If the 6 position is substituted with a methylene substituent, as in the structure above (6-methylene-dihydromorphine), the resulting analogue has 80 times the potency of morphine.



- The addition of a two-carbon bridge between carbons 6 and 14 (e.g., 6,14-ethano, 6,14-etheno, or 6,14-ethyno), and which significantly distorts the C ring, may increase potency 1,000 to 10,000 times, or greater, compared to morphine, as in etorphine, and others.



Etorphine

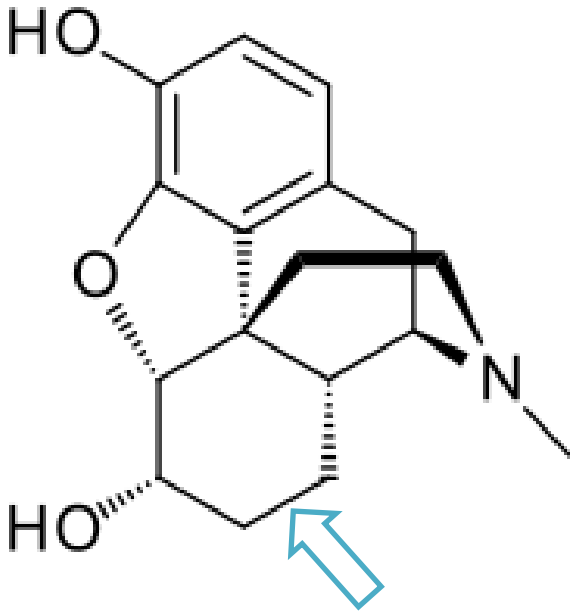


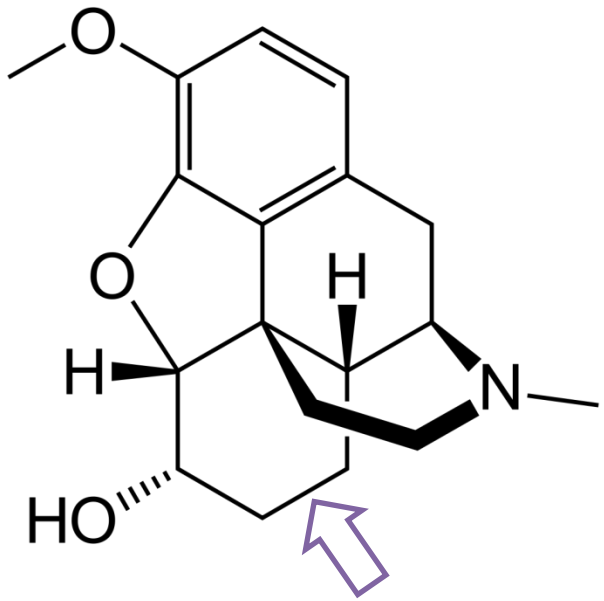
Morphine

Modifications at the 7,8-double bond:

- Reduction of the 7,8-double bond results in a slight increase in activity, as in dihydromorphine and dihydrocodeine.

dihydromorphine





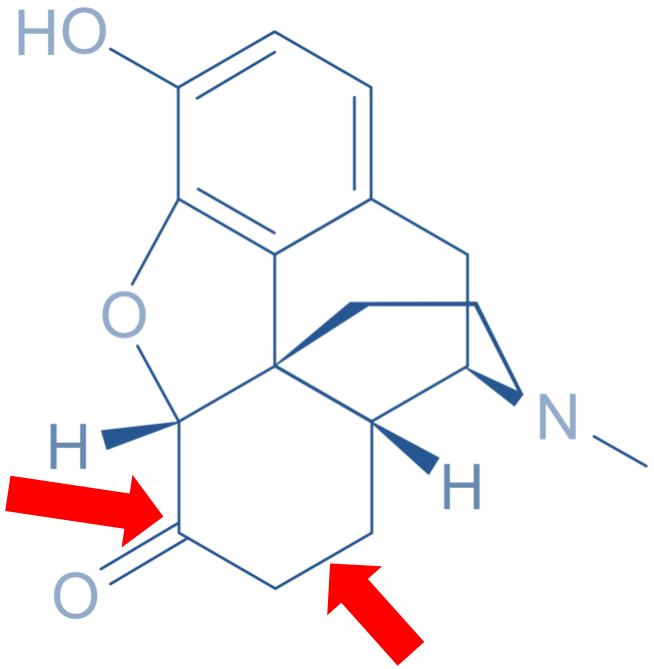
dihydrocodeine

Modifications at the 7,8-double bond:

- Saturation of the 7,8-double bond has the greatest effect when combined with modifications at the 6-position (as in dihydromorphinone).

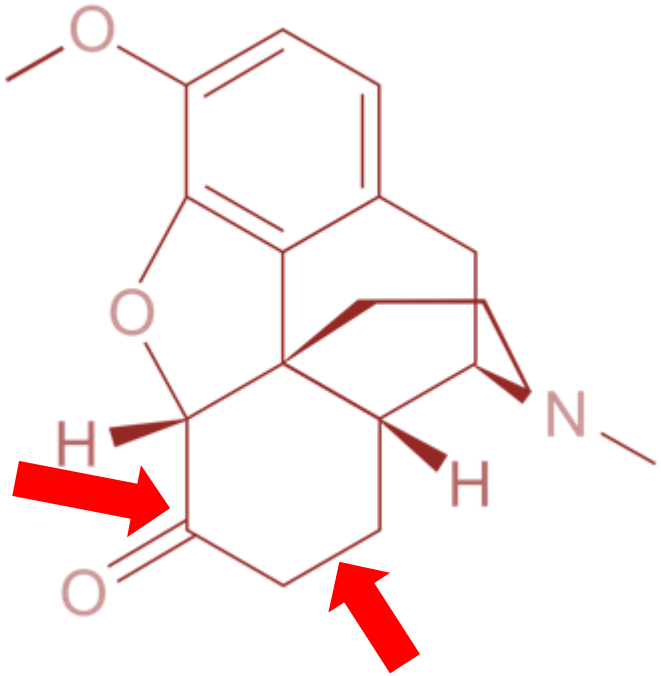
❑ Dihydromorphinone, have 6-C=O

is 6X potent as dihydromorphine.



❑ Dihydrocodeinone, have 6-C=O

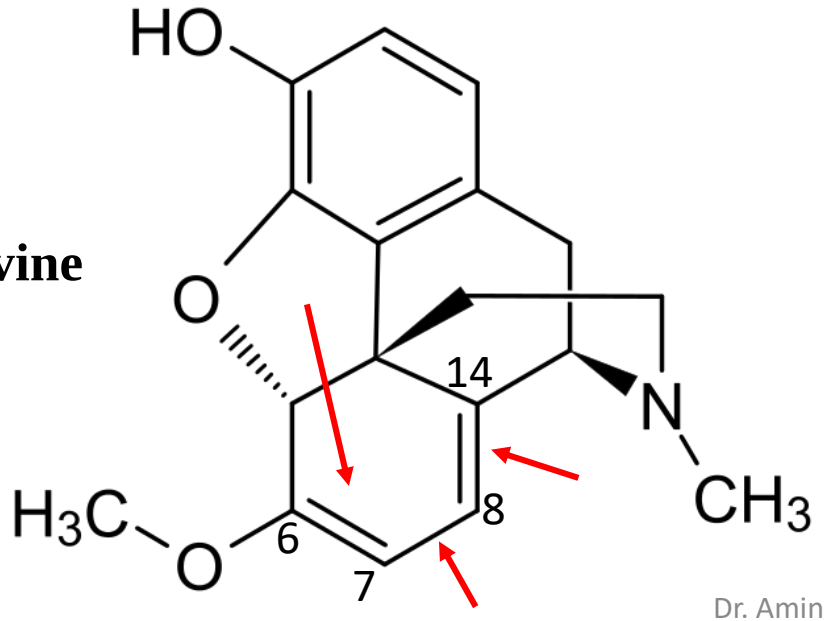
is 4X potent as dihydrocodeine.



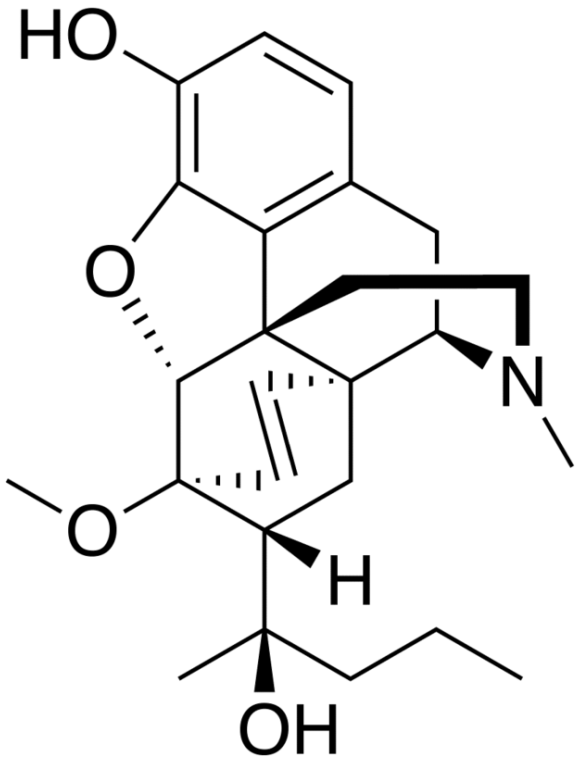
Modifications at the 7,8-double bond:

The oripavine derivative etorphine is a representative of a particularly potent class of morphine analogues. Etorphine is approximately 1000 times as potent as morphine, and arguably is too potent to be released for human therapy. It is currently used as a tranquilizer for large animals.

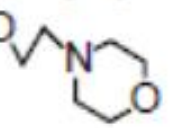
Oripavine



Etorphine

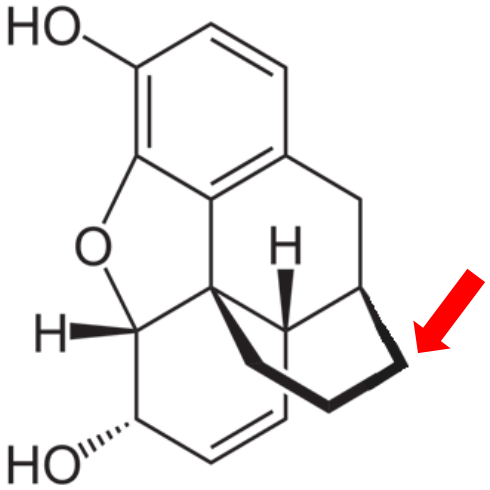


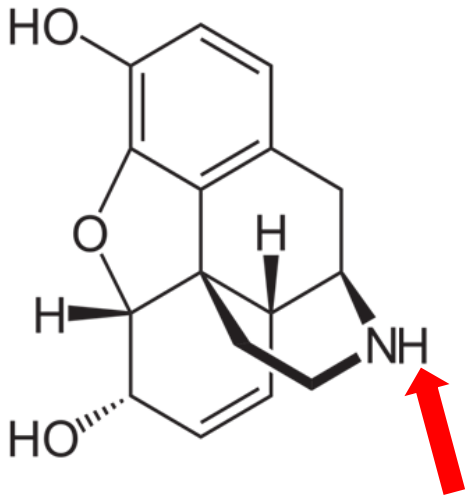
Summarized SAR of Morphine " 3,6,7,8 positions

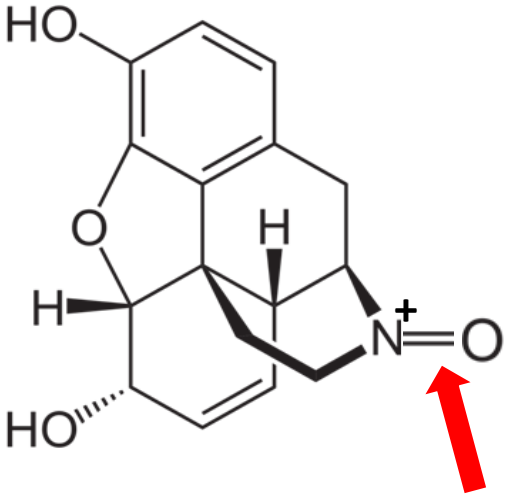
Functional group	Modification	Observed Effects
Phenolic hydroxyl –OH	(i) –OH–H	Less analgesic effect
	(ii) –OH to $-COCH_3$	Less analgesic effect
	(iii) –OH to OCH_3	Less analgesic effect
	(iv) OH to OC_2H_5	Less analgesic effect
	(v) OH to –O 	Less analgesic effect
Alcoholic hydroxyl –OH	(i) OH to OCH_3	More active than morphine
	(ii) OH to OC_2H_5	More active than morphine
	(iii) OH to $OCOCH_3$	More active than morphine
	(iv) OH to = O	Less active than morphine
	(v) OH to H	More active than morphine
Alicyclic Unsaturated Linkage –CH = CH–	–CH = CH to – CH_2–CH_2	More active than morphine

Modifications of the nitrogen substituent:

- Methyl is the optimal substituent for agonist activity, and ethyl is passable.
- If the nitrogen substituent is a hydrogen, analgesic effect is reduced 75%, and addiction liability is lowered.
- Removal of N-methyl & N-oxide decreases LWPC, is more polar through resonance where there is an N^{+} and O^{-} form.



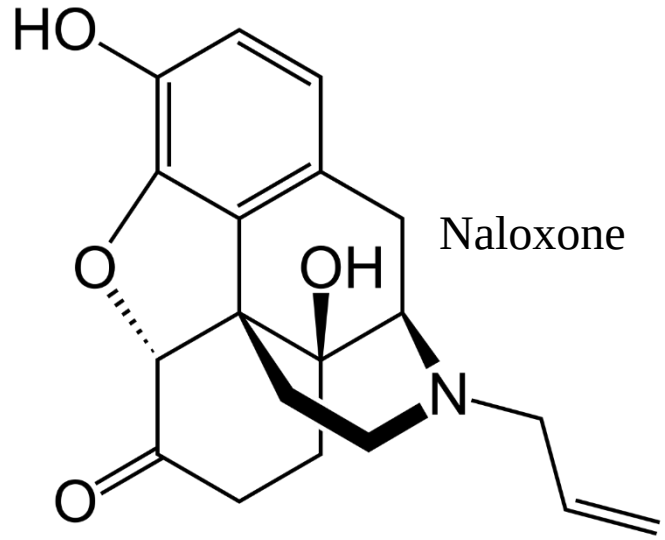




Modifications of the nitrogen substituent:

- 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.

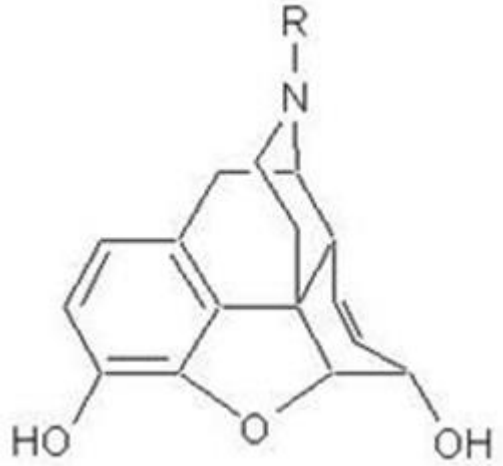
- Branching, unsaturation or strained ring structures in the N-alkyl substituent leads to antagonists or, at the very least, partial agonist (Naloxone, Naltrexone).



Naloxone

Summarized SAR of Morphine "N of mophine structure"

Functional group	Modification	Observed Effects
Tertiary nitrogen N—CH_3	(i) N–CH_3 to NH	
	(ii) N–CH_3 to N–CH_2–CH_2–Ph	Less active than morphine More active than morphine
	(iii) N–CH_3 to *N*-allyl, propyl	Morphine antagonist



R = CH_3 Morphine

= CH_2CH_3

= $CH_2CH_2CH_3$

= $CH_2CH_2CH_2CH_3$ No activity

↓ Agonist activity decreases
antagonist activity increases

= $(CH_2)_4CH_3$

= $(CH_2)_5CH_3$

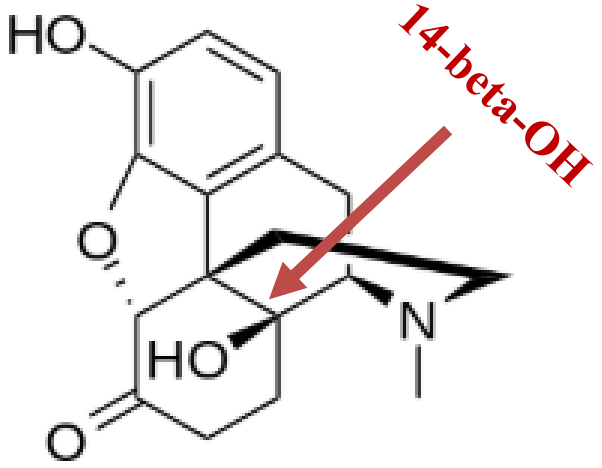
= CH_3CH_2– 

↓ Agonist activity increases

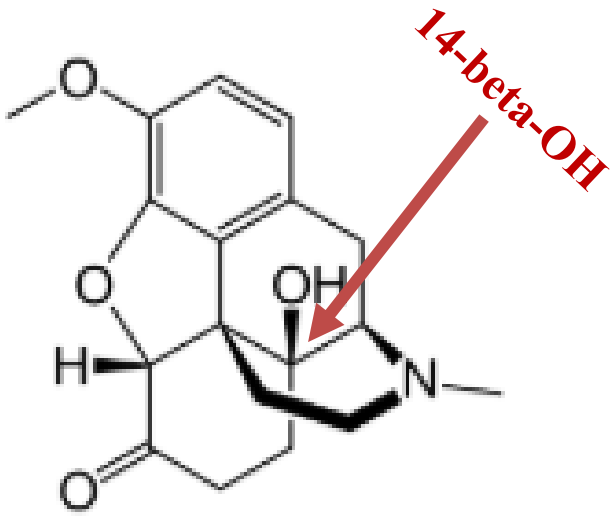
↓ 14x morphine

Modifications of Ether bridge

- **Opening up** the ether linkage (E ring) to form the catechol-type ring system shown **below will reduce activity by 90%.**
- Addition of a **14-beta-OH** results in a dramatic **increase in activity** in the dihydromorphinone series and penetration of BBB, but **decreasing in antitussive action**.



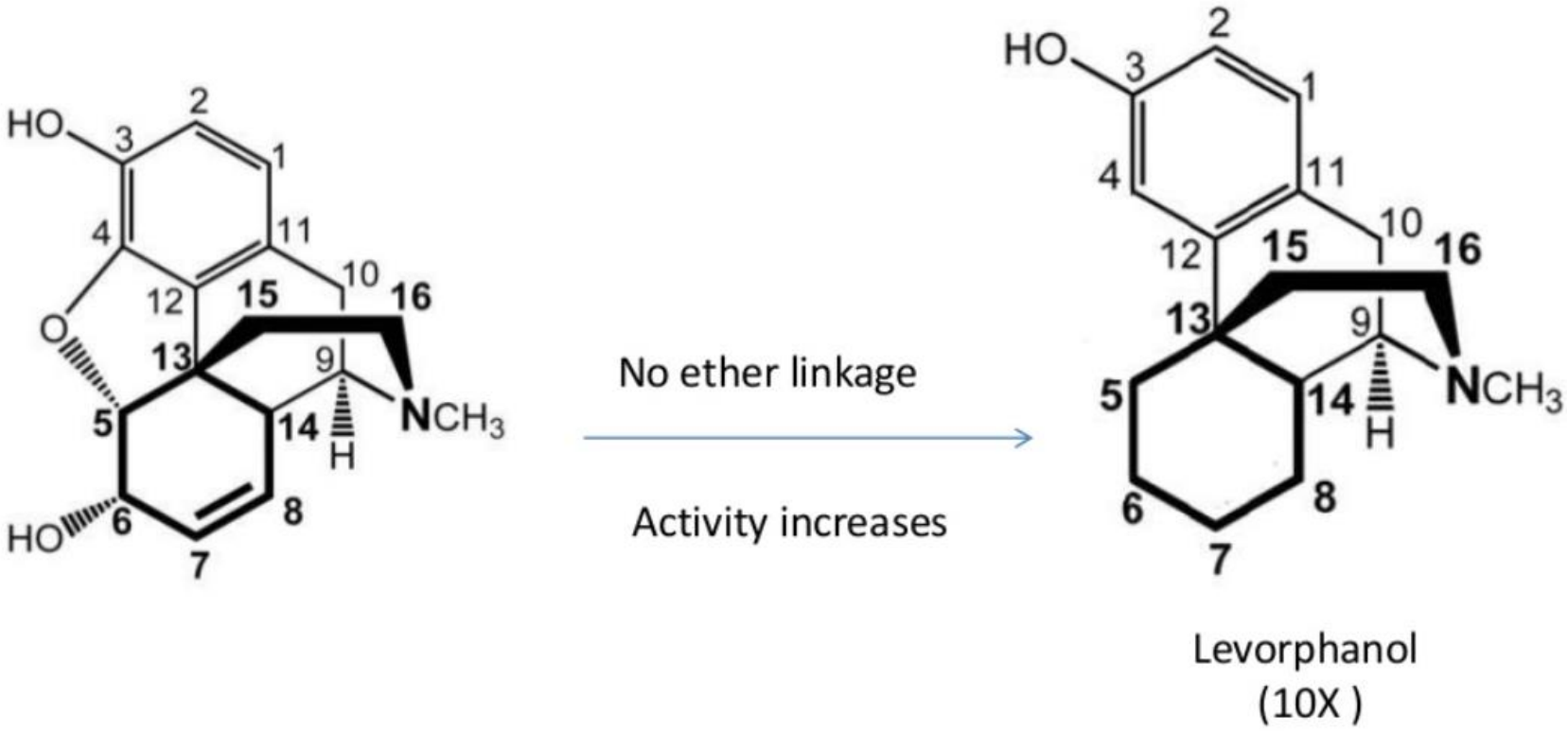
Oxymorphone



Oxycodone

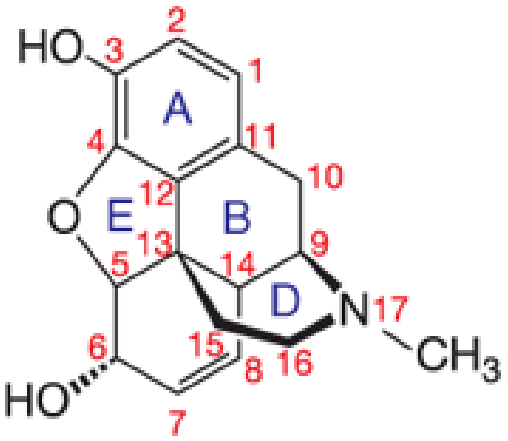
Modifications of Ether bridge

- Removal of Ether linkage produces compounds called Morphinans that has increase activity



Morphine and its analogues

Nonproprietary name	Chemical radicals and position[a]			Other changes†
	3	6	17	
Morphine	—OH	—OH	$-CH_3$	—
Heroin	$-OCOCH_3$	$-OCOCH_3$	$-CH_3$	—
Hydromorphone	—OH	=O	$-CH_3$	(1)
Oxymorphone	—OH	=O	$-CH_3$	(1), (2)
Levorphanol	—OH	—H	$-CH_3$	(1), (3)
Levallorphan	—OH	—H	$-CH_2CH=CH_2$	(1), (3)
Codeine	$-OCH_3$	—OH	$-CH_3$	—
Hydrocodone	$-OCH_3$	=O	$-CH_3$	(1)
Oxycodone	$-OCH_3$	=O	$-CH_3$	(1), (2)
Nalmefene	—OH	$=CH_2$	$-CH_2$—cyclopropyl	(1), (2)
Nalorphine	—OH	—OH	$-CH_2CH=CH_2$	—
Naloxone	—OH	=O	$-CH_2CH=CH_2$	(1), (2)
Naltrexone	—OH	=O	$-CH_2$—cyclopropyl	(1), (2)
Buprenorphine	—OH	$-OCH_3$	$-CH_2$—cyclopropyl	(1), (4)
Butorphanol	—OH	—H	$-CH_2$—cyclobutyl	(1), (2), (3)
Nalbuphine	—OH	—OH	$-CH_2$—cyclobutyl	(1), (2)

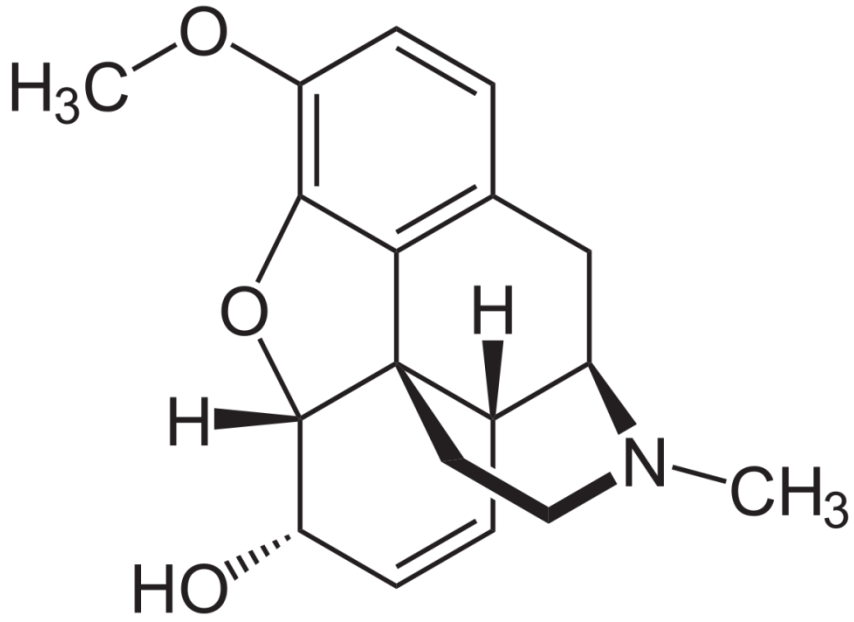


Morphine

Codeine

- Codeine, or 3-methylmorphine, is an alkaloid found in the opium poppy, the name codeine is derived from the Greek word kodeia for "poppy head".

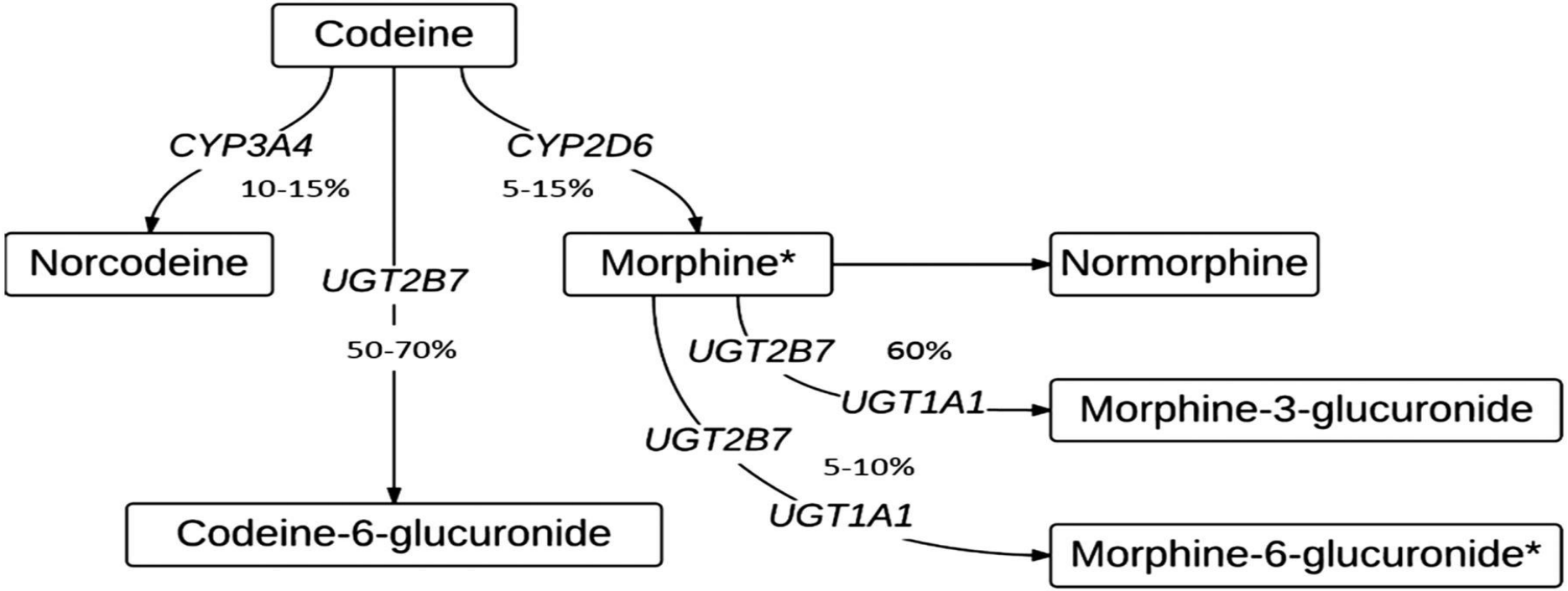
- It is the second-most predominant alkaloid in opium.
- It is classified both as a medical and legal narcotic.
- On its own, it is a Schedule II drug, but in certain formulations it’s less strictly-controlled. Although this narcotic medication is very widely-used.



- Medical used: it is often combined with other non-narcotic painkillers, or cough medications and works by affecting the parts of the brain which control coughing and pain. It’s used as • Analgesic • Hypnotic properties• Antitussive • suppress coughing• Antidiarrheal • Antianxiety• Antihypertensive • Sedative

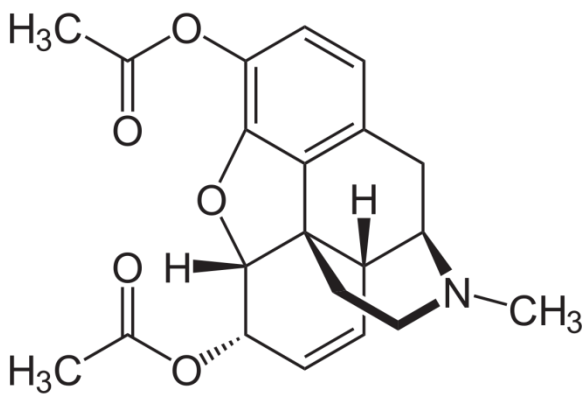
- Is Codeine Addictive?• Yes, codeine is addictive. In fact, codeine is the most widely-used, naturally-occurring narcotic in the world, making it easier to access and become addicted to than other, more tightly-controlled narcotics. However, codeine is more likely to be addictive to people who have a history of drug or alcohol abuse.

Metabolism: 50-70% codeine normally converted to glucuronide, eliminated by kidney. 5-15, 10-15% codeine is metabolized into morphine by CYP2D6 and to norcodeine by CYP3A4



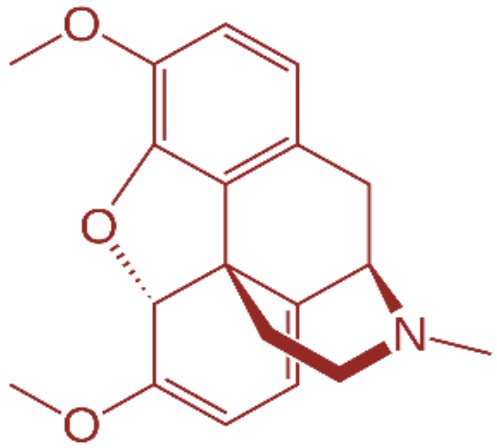
Heroin

- Heroin is a highly addictive and illegal drug. It is a depressant drug. The resin of poppy plants are used to make heroin.
- Heroin originated in 1874 by an English chemist. then produced by the Bayer Pharmaceutical Company, a German chemical company in 1898.
- How is it used? Heroin is usually injected into the body, but it can also be snorted or smoked. When injected, heroin quickly reaches the brain.
- Classification: Heroin is a level 5 drug which puts it in the narcotic analgesics group.

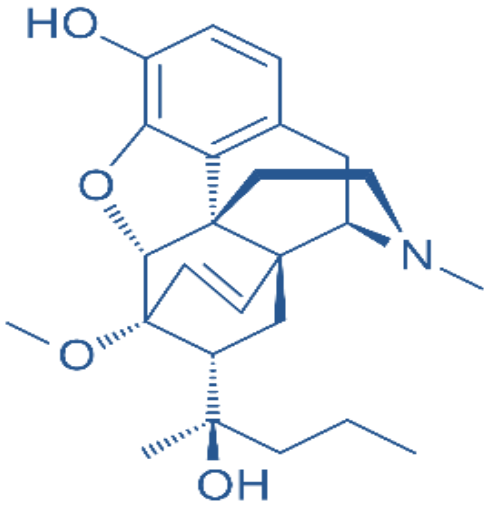


- Ingredients: The two major chemicals found in heroin are morphine and Acetic Anhydride.
- Effects of Use: Heroin slows down the Central Nervous System when it depresses nerve transmission in the brain and spinal cord (CNS). Heroin can reach the brain in just 6 to 8 seconds when injected. This will disrupt the cardiovascular system and the respiratory system, as the CNS controls breathing and heart rate. Because of this, the brain won't receive enough oxygen or blood, and brain damage can result.
- Using heroin and alcohol at the same time is deadly because both heroin and alcohol slow down the CNS.

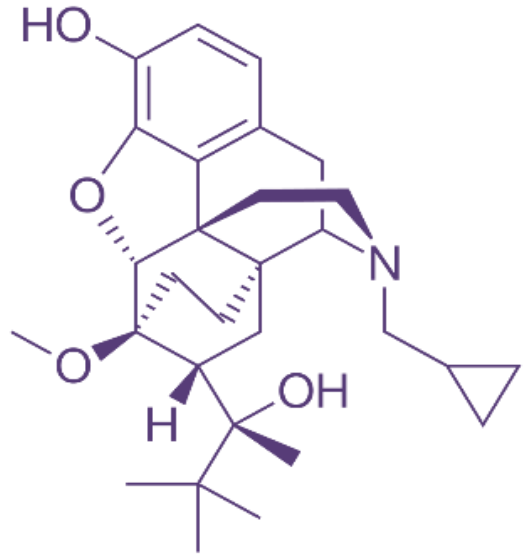
Thebaine (paramorphine): is an opiate alkaloid. A minor constituent of opium, thebaine is chemically similar to both and, but produces stimulatory, with strychnine-like convulsions, rather than depressant effects. Thebaine is not used therapeutically, but is converted industrially into a variety of compounds including, oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine and etorphine. It is controlled i in Schedule ll of the Controlled Substances Act as well as under international law.



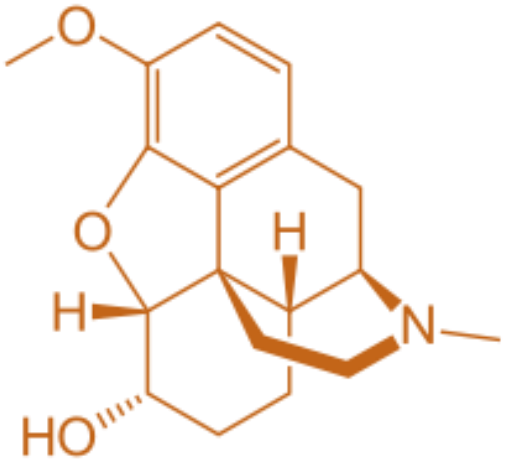
Etorphine: is a semi-synthetic opioid possessing an analgesic potency approximately 1,000–3,000 times that of morphine, which could be interpreted as having a better or a tighter fit to receptors. It is used primarily in veterinary medicine to immobilize large animals.



Buprenorphine: synthesis from thebaine, Buprenorphine is a more complex molecule than morphine, which would interact with the opioid receptor (analgesic) and because of its complex structure it would not interact with other receptors that produce side effects as respiratory depression (decreased breathing), sleepiness, adrenal insufficiency, QT prolongation, low blood pressure, allergic reactions, and opioid addiction and used as potent analgesic.



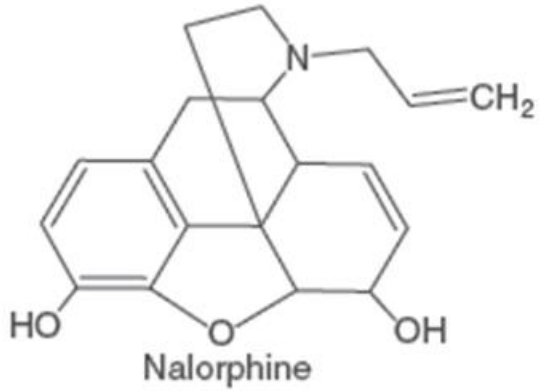
Dihydrocodeine is a opiate painkiller. It's used to treat moderate to severe pain, such as after an operation or a serious injury. It's also used for long-standing pain when weaker painkillers, such as paracetamol, ibuprofen and aspirin, have not worked. It also comes mixed with paracetamol, this is called co-dydramol. It comes as standard tablets, slow-release tablets and as a liquid that you swallow.



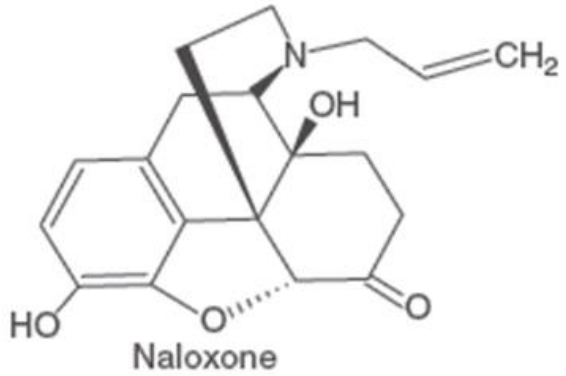
Narcotic / Morphine antagonists

- The euphoria accompanying with use of heroin and other narcotics reinforces repeated drug-seeking behaviour. Once tolerance develops, the opiate-dependent individual avoids painful withdrawal symptoms by continuously increasing the amounts of opiate consumed.

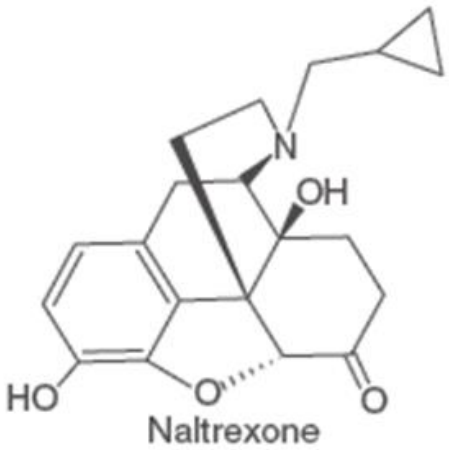
- Narcotic antagonists: Prevents or abolishes excessive respiratory depression caused by the administration of morphine or related compounds. They act by competing for the same analgesic receptor sites. They are structurally related to morphine with the exception of the group attached to nitrogen.



Nalorphine



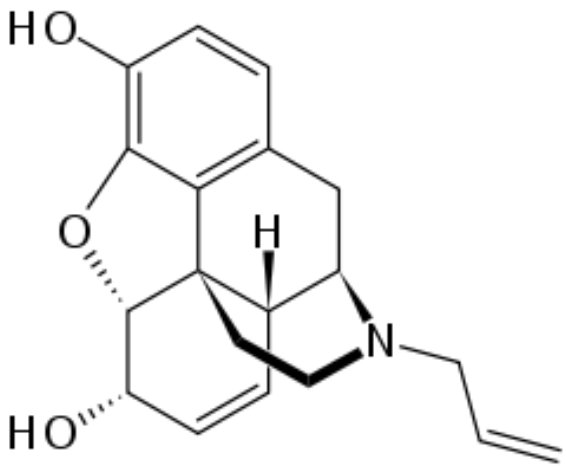
Naloxone



Naltrexone

Nalorphine

- Synthesis from morphine in presence of cyanogen bromide
- Has a direct antagonistic effect against morphine, meperidine, methadone, and levorphanol. It has little antagonist effect towards barbiturate or general anaesthetic depression. However, it has strong analgesic properties, but it is not acceptable for such use owing to the high incidence of undesirable psychotic effects.
- It acts at two opioid receptors — the μ-opioid receptor (MOR) where it has antagonistic effects, and at the κ-opioid receptor (KOR) where it exerts partial agonist characteristics. Due to potent activation of the KOR, nalorphine produces side effects such as dysphoria, anxiety, confusion, and hallucinations, and for this reason, is no longer used medically.



Naloxane

- Is a pure antagonist with no morphine like effect. It blocks the euphoric effect of heroin when given before it.
- Synthesis from Thebaine in presence of H2O2
- It is almost seven times more active than nalorphine in antagonizing the effects of morphine. It shows no withdrawal effects after long term administration. It lacks not only the analgesic activity shown by other antagonists, but also all of the other agonist effects.

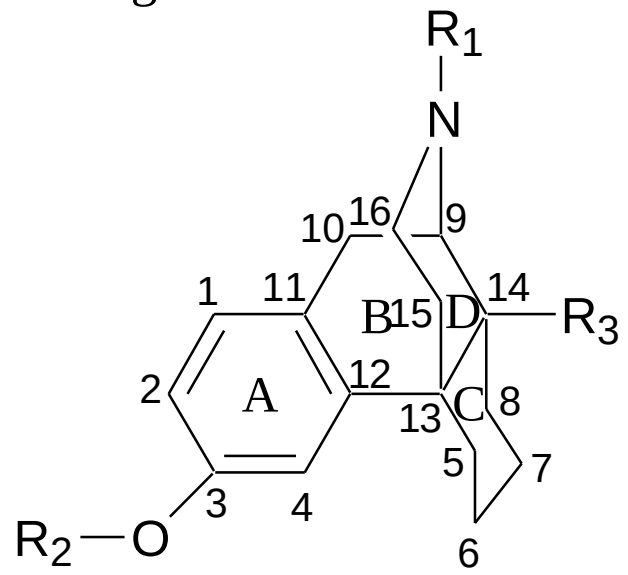
Naltrexone

- It became clinically available in 1985 as a new narcortic antagonist. Its action resembles those of naloxone, but naltrexone is well absorbed orally, and is long acting,
- it is at least 17 times more potent than nalorphine in morphine-dependent humans and twice as potent as naloxone in precipitating withdrawal symptoms.
- Synthesis from Oxymorphone in presence of Acetic anhydride

MORPHINANS

Morphinan is the prototype chemical structure of a large chemical class of psychoactive drugs, consisting of opiate analgesics, cough suppressants, and dissociative hallucinogens, among others.

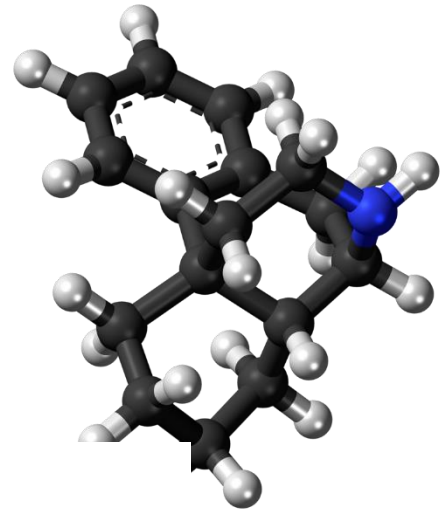
The morphinans were introduced in 1946. They are morphine without the ether link but are produced synthetically. Numbering system is the same as with morphine. Since these compounds are synthetic they are obtained as racemates. The more potent isomer has an R configuration α to the nitrogen (C9 is R)



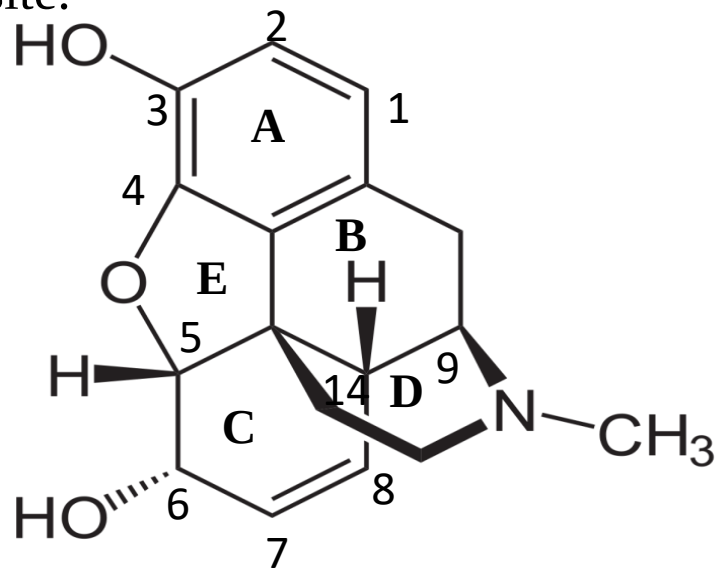
Numbering system is similar to morphine

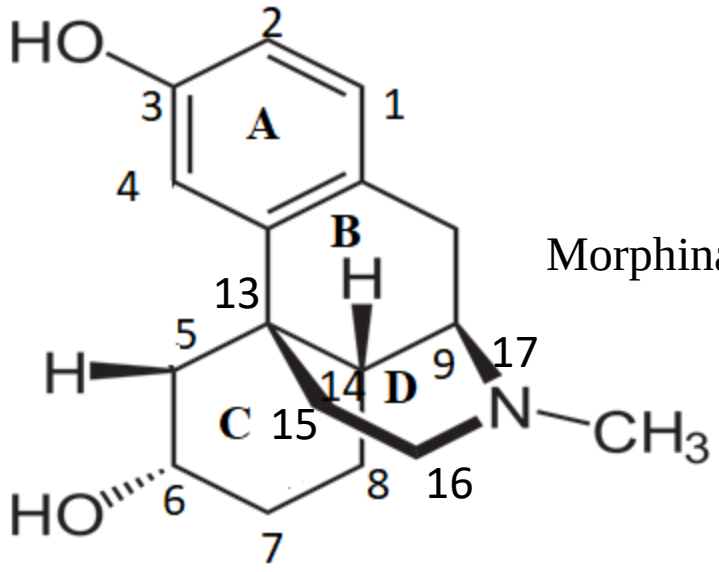
Chemical Structure

Morphinan has a phenanthrene core structure with the A ring remaining aromatic and the B and C rings being saturated, and an additional nitrogen-containing, six-membered, saturated ring, the D ring, being attached to carbons 9 and 13 of the core, and with the nitrogen being at position 17 of the composite.



Morphine





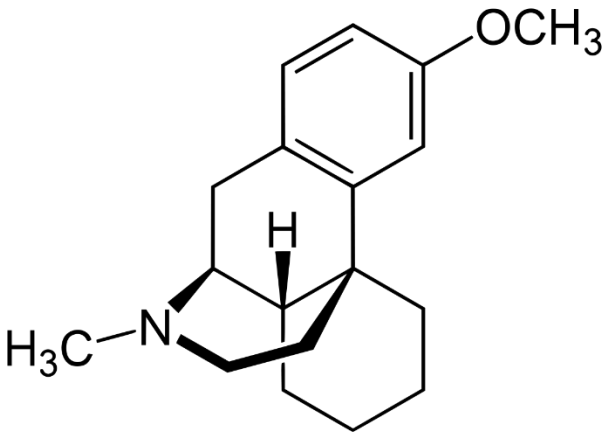
Morphinan

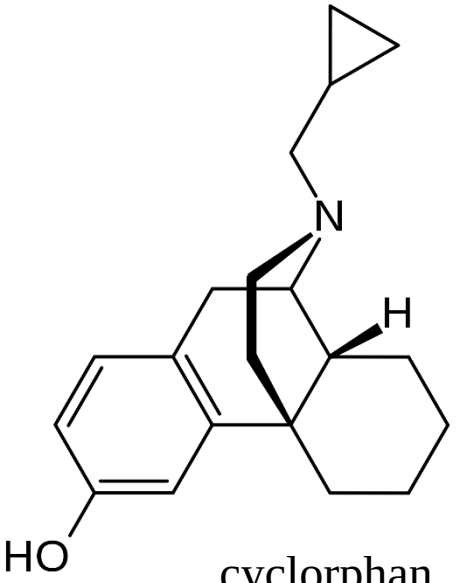
Structure/Activity Relationships

Epoxymorphinans and morphinans interact with the receptor in a similar fashion and thus exhibit similar pharmacological profiles and SARs especially in the C3 hydroxy, C14 hydroxy, and the N–substituent. (–)–N–Methylmorphinan possess high degree of analgesic activity, i.e., the ether bridge is not necessary for activity, introduction of a phenolic OH increases potency

- Small groups are usually found on morphinan derivatives at carbons 3 &6.
- The substitution of certain bulky groups on nitrogen 17 converts an opioid agonist into an opioid antagonist, the most important of which is cyclorphan, a non-selective opioid antagonist with no opioid agonist properties whatsoever.

Dextromethorphan

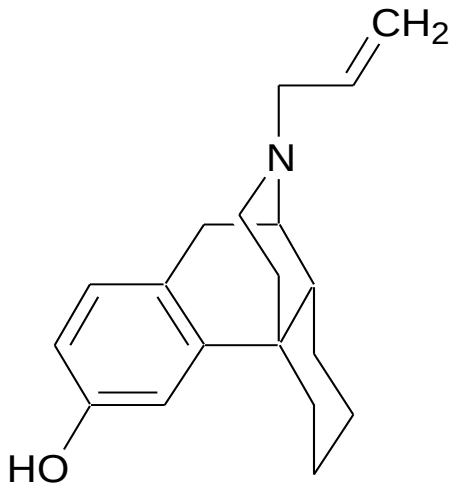




cyclorphan

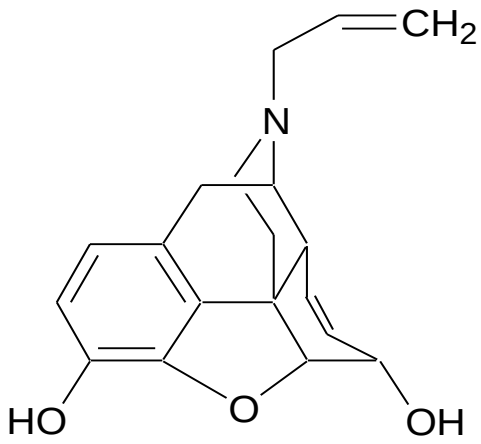
Structure/Activity Relationships

- Substitution of certain very bulky groups on carbon 6 converts cyclorphan into a peripherally-selective opioid antagonist with no centrally-selective antagonist properties. As the same rule of naloxone and naloxegol.
- The N–allyl derivative, levallorphan is a potent antagonist at μ receptors, five times as potent as nalorphine



Levallorphan

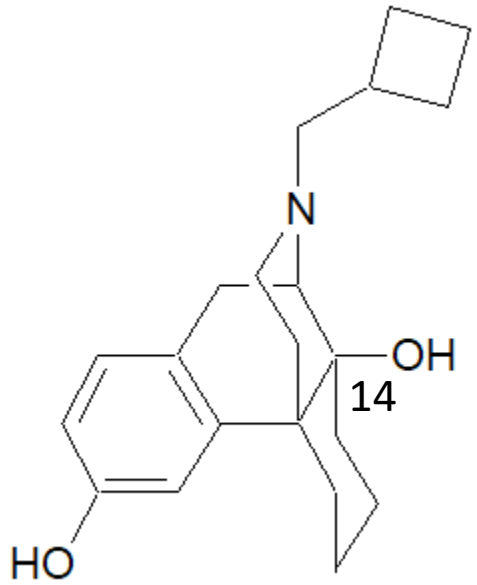
>>



Nalorphine

Structure/Activity Relationships

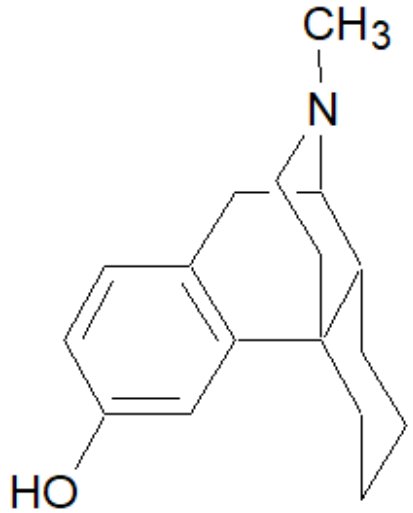
- Butorphanol has higher μ receptor affinity compared to morphine due to the C14 hydroxyl but with little dependence liabilities and limited respiratory depression.



- This drug is a mixed agonist/antagonist - κ agonist, μ antagonist.
- κ Agonists have lower ceiling analgesia effects and are not as effective as μ agonist in severe pain.

Structure/Activity Relationships

- The levorotatory isomer with R configuration alpha to the nitrogen is known as levorphanol. It is 6 to 8 times as potent an analgesic as Morphine. It is also a potent antitussive.

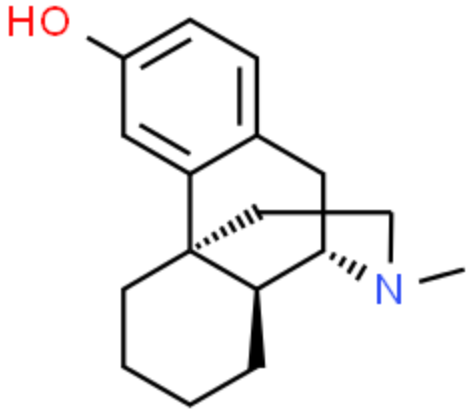


- This high potency is due to
- (a) a higher LWPC (1300 vs 8)
- (b) loss of the ether oxygen and the C6 hydroxyl
- (c) It also has higher receptor affinity.

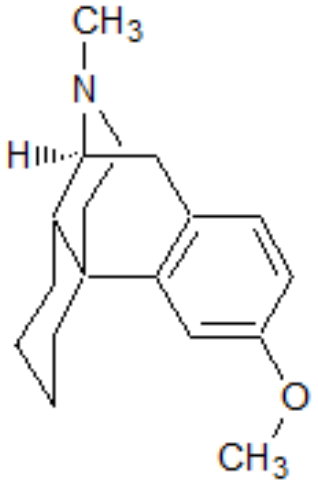
- Advantages over Morphine include better oral bioavailability and a longer duration of action, but it has higher toxicities

Structure/Activity Relationships

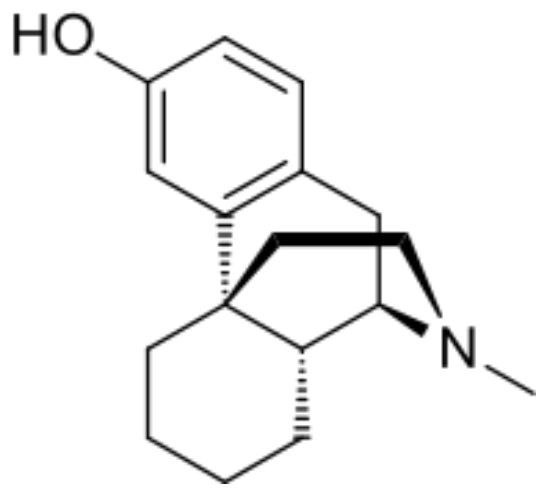
- The *dextro* isomer, dextrorphan is devoid of analgesic activity and associated liabilities but remains a potent antitussive. It is further substantiating the belief that analgesia and antitussive effect are mediated through different receptors.



- The *dextro* isomer was O 3 –methylated to increase its antitussive potency which is marketed as dextromethorphan.
- Dextromethorphan is said to be as potent as Codeine as an antitussive without respiratory depression and associated side effects



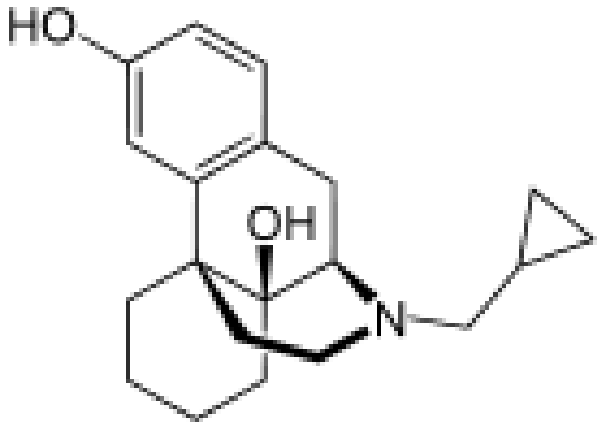
Levorphanol



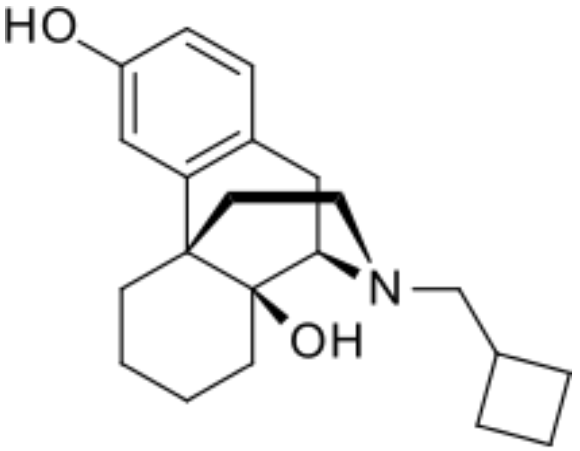
- Levorphanol acts predominantly as an agonist of the μ-opioid receptor (MOR), but is also an agonist of the δ-opioid receptor (DOR), κ-opioid receptor (KOR), and the nociceptin receptor (NOP), as well as an NMDA receptor antagonist and a serotonin-norepinephrine reuptake inhibitor (SNRI).
- Levorphanol, similarly to certain other opioids, also acts as a GABA receptor antagonist at very high concentrations. Levorphanol is 6 to 8 times as potent as morphine at the MOR.
- The duration of action is generally long compared to other comparable analgesics and varies from 4 hours to as much as 15 hours. For this reason levorphanol is useful in palliation of chronic pain and similar conditions.

- Levorphanol's exceptionally high analgesic efficacy in the treatment of neuropathic pain is also conferred by its action on serotonin and norepinephrine transporters, similar to the opioids tramadol and tapentadol, and mutually complements the analgesic effect of its NMDA receptor antagonism.
- Levorphanol is listed under the Single Convention On Narcotic Drugs 1961 and is regulated like morphine in most countries. In the U.S., it is a Schedule II Narcotic controlled substance

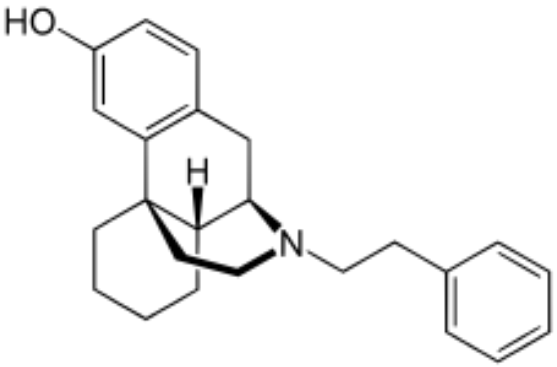
Oxilorphan is an opioid antagonist of the morphinan family that was never marketed. It acts as a μ-opioid receptor (MOR) antagonist but a κ-opioid receptor (KOR) partial agonist, and has similar effects to naloxone and around the same potency as an MOR antagonist. and can produce hallucinogenic/dissociative effects at sufficient doses, indicative of KOR activation



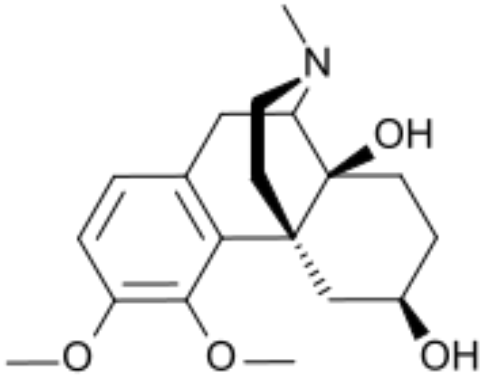
Butorphanol is an agonist–antagonist opioid analgesic, exhibits partial agonist and antagonist activity at the μ-opioid receptor, as well as partial agonist activity at the κ-opioid receptor. The most common indication for it is management of migraine using the intranasal spray formulation. It may also be used parenterally for management of moderate-to-severe pain, as a supplement for balanced general anesthesia, and management of pain during labor.



Phenomorphan is an opioid analgesic. It is not currently used in medicine, but has similar side-effects to other opiates, which include itching, nausea and respiratory depression. It is a highly potent drug due to the N-phenethyl group, which boosts affinity to the μ-opioid receptor, and so phenomorphan is around 10x more potent than levorphanol, which is itself 6-8x the potency of morphine



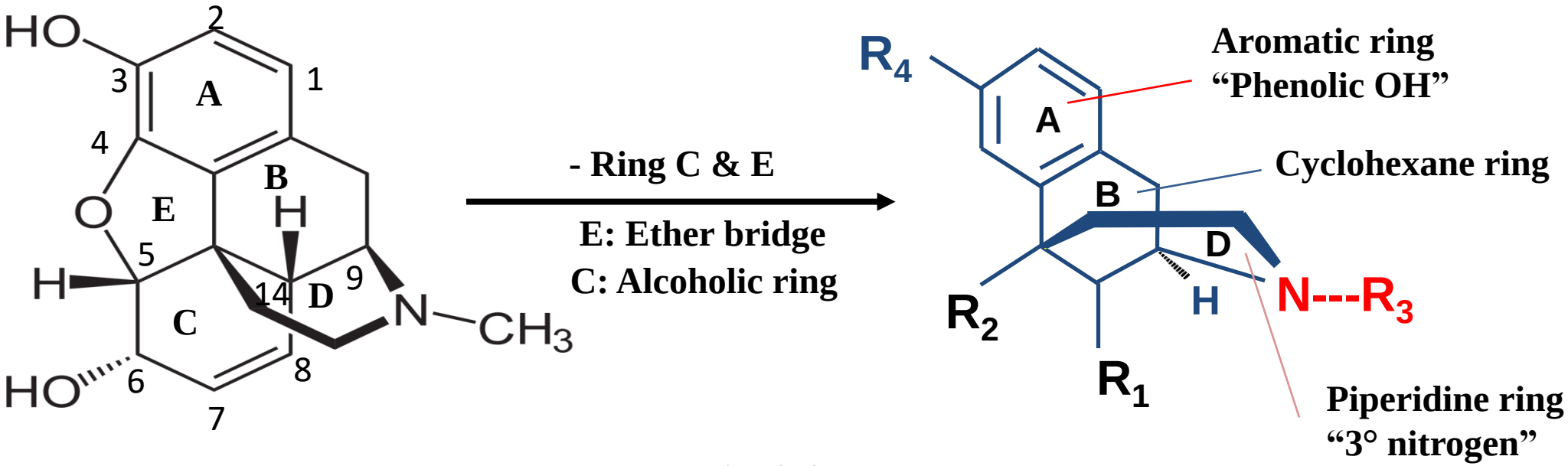
Drotebanol has powerful antitussive (cough suppressant) effects, and is around 10x more potent than codeine in producing this effect. It also has analgesic effects several times stronger than codeine, but weaker than morphine. In animal studies it was found to be moderately addictive and produced limited physical dependence, but not as severe as that seen with morphine or pethidine.



BENZOMORPHANS

- It is the base for a series of analgesic drugs which produces analgesia because of its agonistic action on kappa opioid receptors

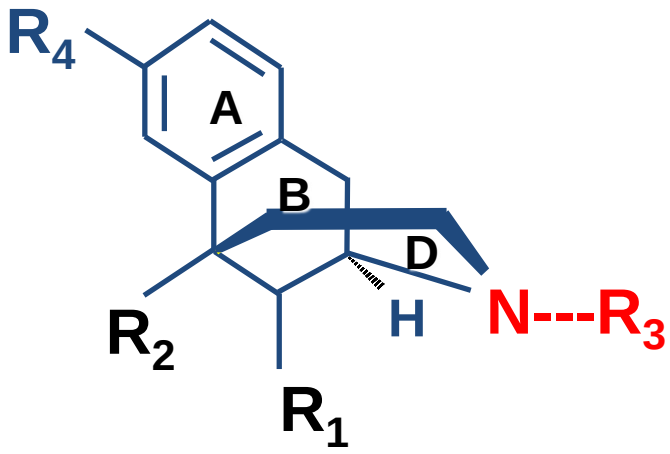
- The benzomorphans, which were first introduced by May in 1960, are also similar in structure to the morphine analogues, but lack the C and E rings found in the naturally occurring opioids.



Structure/Activity Relationships

- R1 and R2 substituents must be present to supply vestiges of the C ring. These are usually methyl, or a similar lower alkyl.

- R1 and R2, are essential for μ receptor affinity. R2 is down because the piperidine ring is up but R1 may be up or down. The cis (R1 & R2) isomers are called α and the trans isomers are called β. The α isomers are superimposable on morphine, however, the β isomers have higher μ receptor affinity than the α isomers. Still, α isomers have higher μ receptor affinity compared to morphine (b > a > morphine)

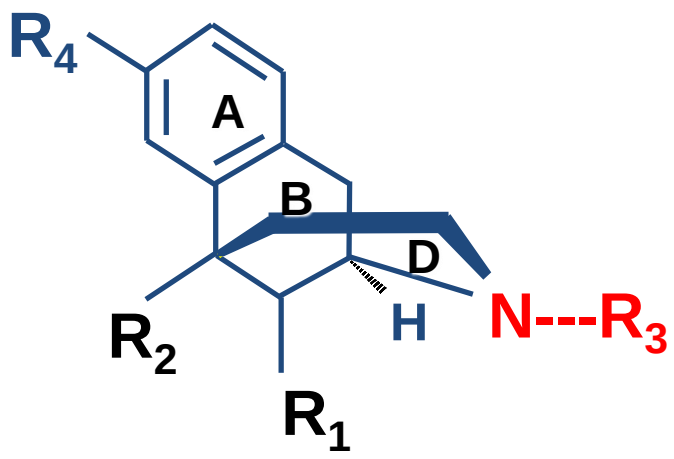


- Both α and β benzomorphans also have a higher LWPC than morphine further adding to their overall potency. The β isomers have higher dependence liabilities than α isomers. Therefore, clinically the weaker α isomers are used.

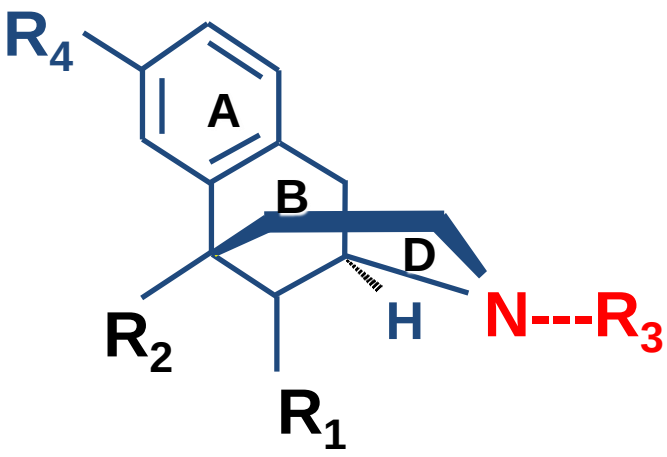
- The nitrogen substituent (R3) follows the same rules as the morphinans and morphines. However, antagonist substituents produce analogues with a higher agonist/antagonist ratio,

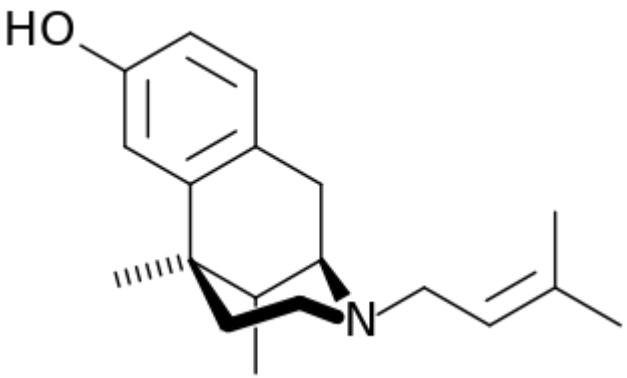
- R4 must be OH or methoxy.

- Its also called, Morphan or benzazocin derivatives



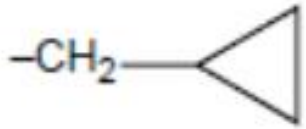
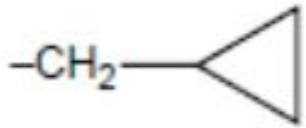
- Placement of N- phenyl ethyl results in more activity than N-methyl compound.
- Placement of methyl group in R1 position increases the activity. However -OH group decreases the activity.
- The trimethyl compound (R1= R2= R3 = CH3) is more active than dimethyl (R1=H, R2,R3 = CH3) compound.
- Pentazocine produces analgesia because of its agonistic action on kappa opioid receptors. Pentazocine is a week antagonistic at μ receptors.

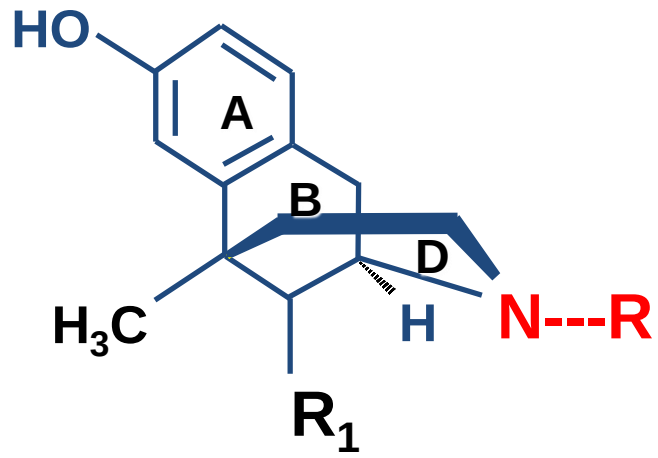




Pentazocine

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	$-CH_3$	$-CH_3$

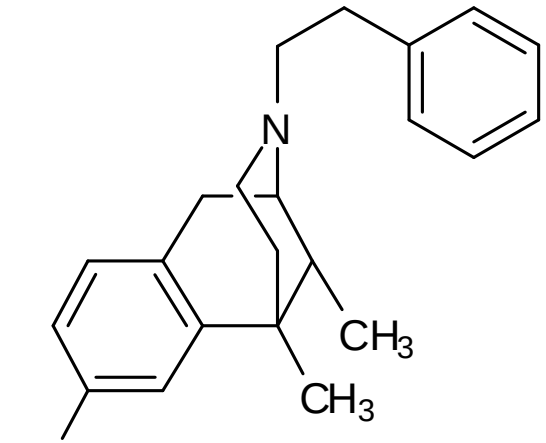


Phenazocine

- Phenazocine appears to be a much stronger analgesic with fewer side effects than pentazocine, probably due to a more favorable μ/κ binding ratio. Phenazocine is a much more potent analgesic than pentazocine and other drugs in the benzomorphan series, most probably due to the presence of an N-phenethyl substitution, which is known to boost μ-opioid activity in many classes of opioid analgesics.

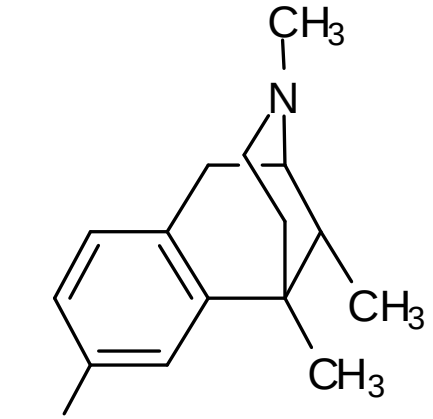
- Consequently, phenazocine has four times the potency of morphine as an analgesic. Also it more suitable than morphine for the treatment of biliary or pancreatic pain.

- It remains a Schedule II substance under the Comprehensive Drug Abuse Control & Prevention



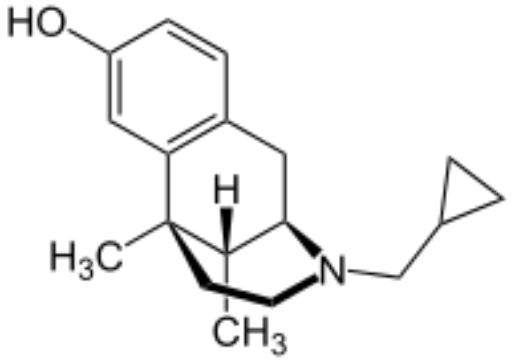
Phenazocine

- **Metazocine** is the prototype. The LWPC is higher than morphine, mediated through a mixed agonist–antagonist action at the mu opioid receptor, its clinical use is limited by dysphoric and hallucinogenic effects which are most likely caused by activity at kappa opioid receptors (where it is a high-efficacy agonist)



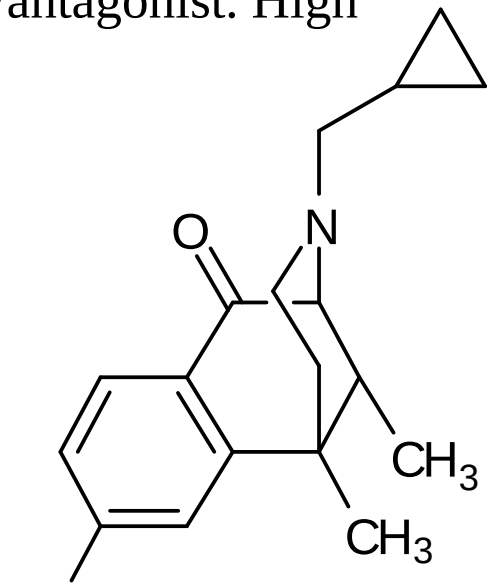
Metazocine

- **Cyclazocine** (methylcyclopropyl) is a potent mixed agonist/antagonist. High LWPC and high incidence of hallucinations.



Cyclazocine

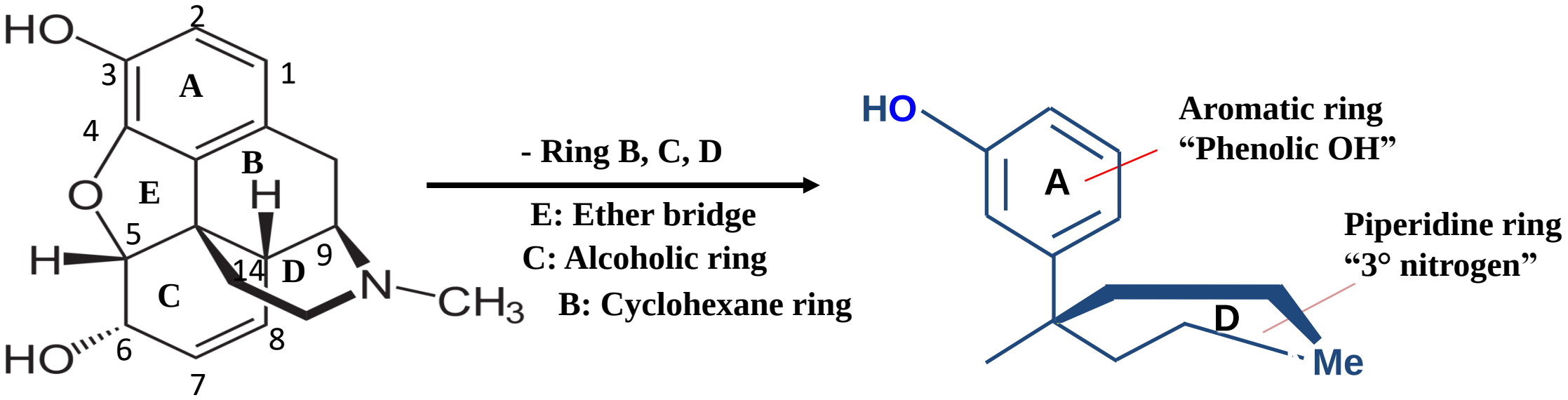
- **Ketazocine**, not marketed in the US, has high affinity for the κ receptor and gives the receptor its name



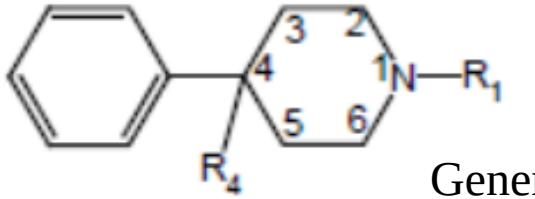
Ketazocine

PHENYL (ETHYL) PIPERIDINES

- Also called 4-Phenylpiperidines
- The representitive 4-phenylpiperidine, meperidine was first prepared as an antispasmodic, and in addition to this activity it was found to be analgesic at about 20% the potency of morphine.
- The 4-phenylpiperidine, are also similar in structure to the morphine analogues, but lack the B, C, E rings.

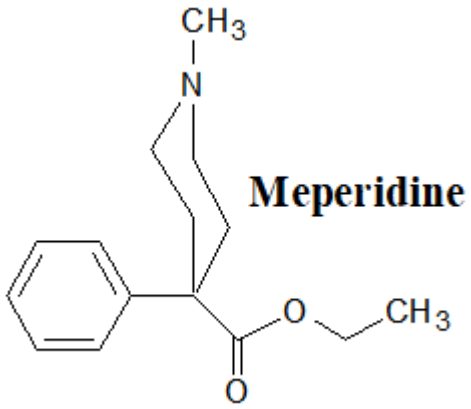


Structure/Activity Relationships

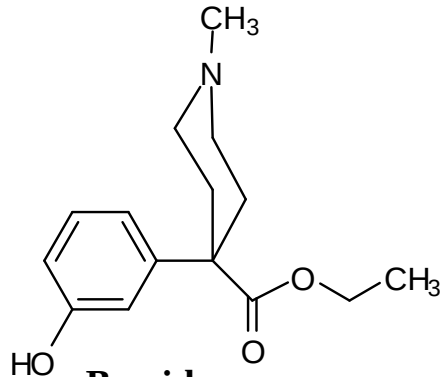


General

- Meperidine - 4-phenyl piperidine - proved to be a typical mu agonist with about one-fourth the potency of morphine on weight basis.
- The replacement of C-4 phenyl group of meperidine by hydrogen, alkyl, other aryl, aralkyl, and hetero cyclic groups reduces analgesic activity by decrease affinity for site “A” .
- The presence of phenyl and ester group at 4th position of 1 methylpiperdine results in optimum activity.
- Insertion of a meta hydroxyl does increase potency by 50%. Thus Bemidone has higher affinity for the “A” site than meperidine possibly due to hydrogen bonding to an adjacent site



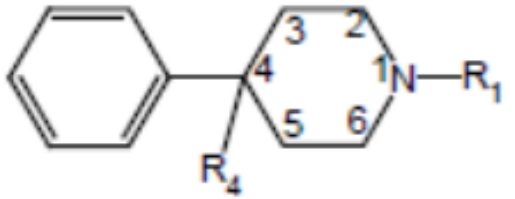
Meperidine



Bemidone

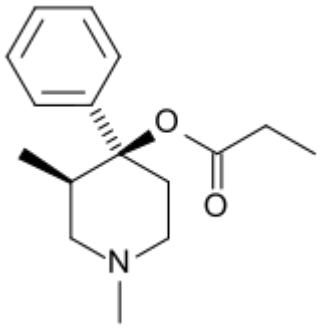
Structure/Activity Relationships

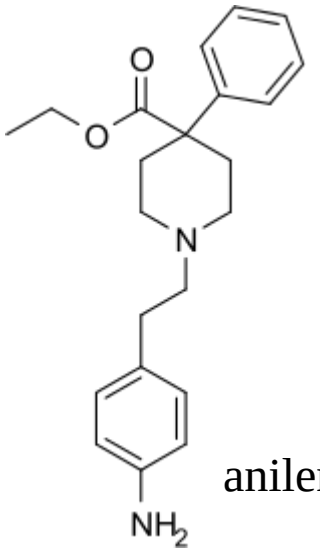
- Replacement of the carbethoxy group in meperidine by acyloxy group provides better analgesic, as well as spasmolytic (alphaprodine).
- Replacement of phenyl group by phenyl ethyl derivatives is seen to be about three times as active as the meperidine.
- The amino analogue, anileridine is about four, times more active.
- Expansion or contraction of the ring to seven or five members gives compounds with analgesic activity but less μ receptor affinity due to a change in relationship between the nitrogen and the phenyl ring



General

alphaprodine

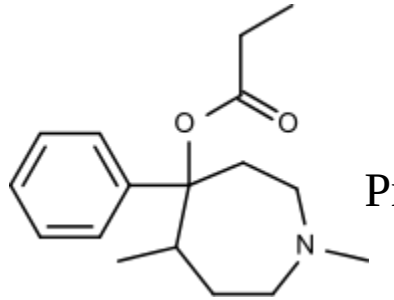




anileridine

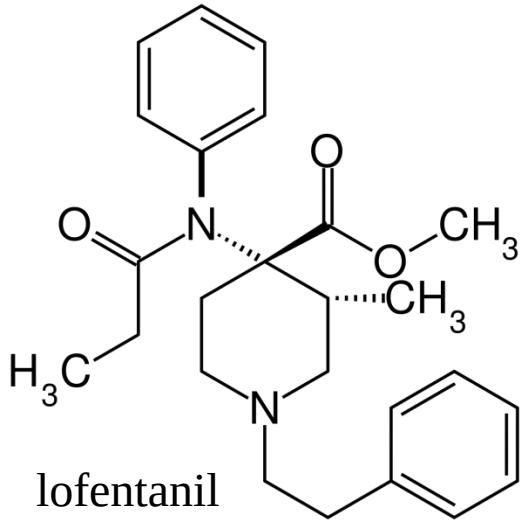
Structure/Activity Relationships

- Enlargement of piperidine ring to a 7-membered hexa hydroazepine yield active compounds with low incidence of side effects. For example, Proheptazine.



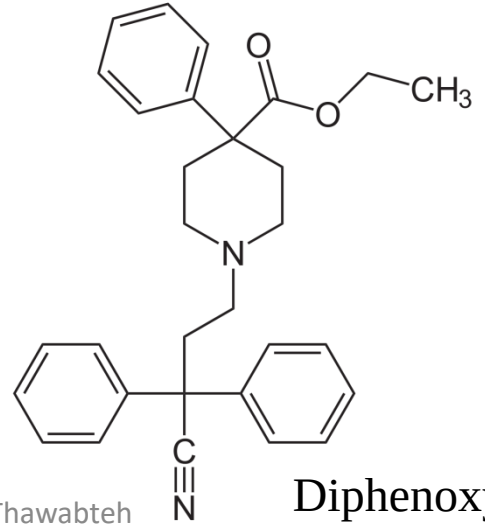
Proheptazine

- The C-3 methyl analogue with an ester group at the C-4 position like lofentanil 8,400 times more potent than meperidine as an analgesic.



lofentanil

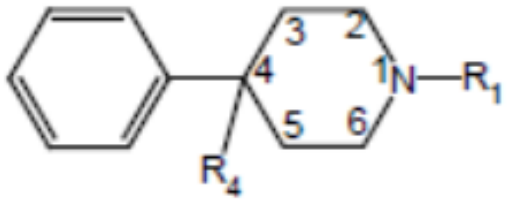
- Diphenoxylate, a structural hybrid of meperidine and methadone types, lacks analgesic activity. It is effective as an intestinal spasmolytic and is used for the treatment of diarrhoea.

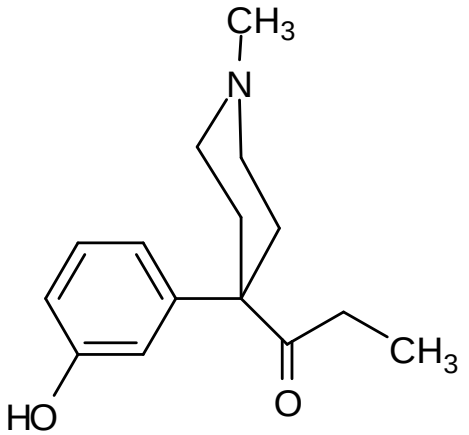


Diphenoxylate

Structure/Activity Relationships

- The SARs for the N–substituent are similar to epoxymorphinans. Introduction of aralkyl substituents markedly increase potency
- Separation of the phenyl and the ester groups decrease potency. This modifications result in a change in the distance between the nitrogen and the phenyl ring, a critical feature. This decreases the ability to bind site "A" and "B" simultaneously.
- Conversion of the ester to a ketone increases potency and duration of action by increasing metabolic stability, esters can be hydrolyzed but ketones cannot. Example: ketobemidone

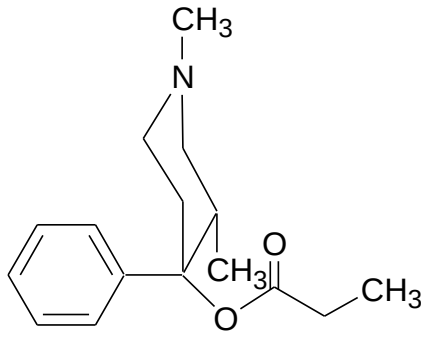




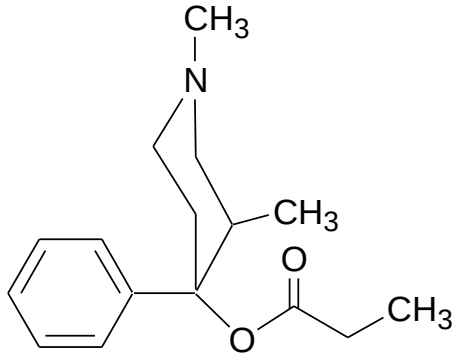
Ketobemidone

Structure/Activity Relationships

- Introduction of a methyl at position 3 results in stereoisomers having different potencies. The trans methyl is called Alphaprodine and the cis isomer is Betaprodin. Their respective potencies are 5 and 14 times Meperidine, The 3–methyl affects the conformation of the phenyl ring with respect to the nitrogen decreasing μ receptor affinity



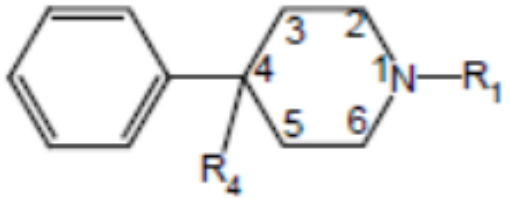
Alphaprodine



Betaprodine

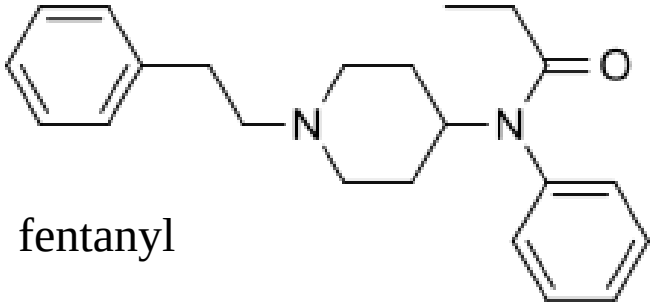
Structure/Activity Relationships

- The related p-chloro analogue (loperamide) has been shown to bind to opiate receptors in the brain, but not to penetrate the blood-brain barrier sufficiently to produce analgesia.

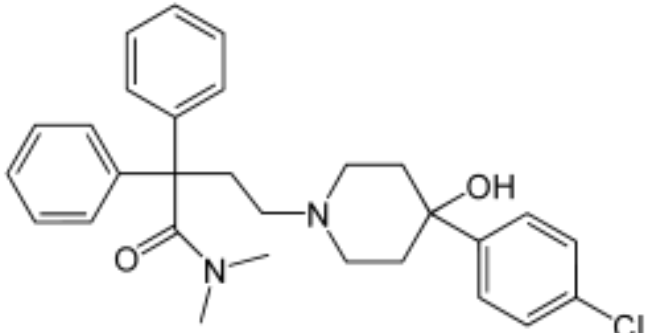


General

- In fentanyl, the phenyl and acyl groups are separated by nitrogen. It is 50 times stronger than morphine with minimal side-effects. Its short duration of action makes it well suited for use in anaesthesia.

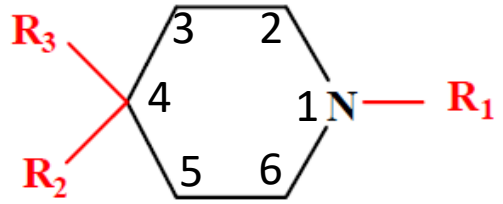


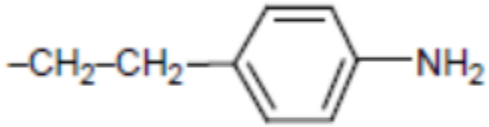
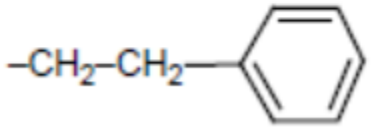
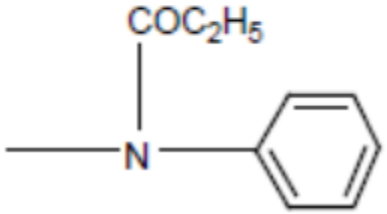
fentanyl



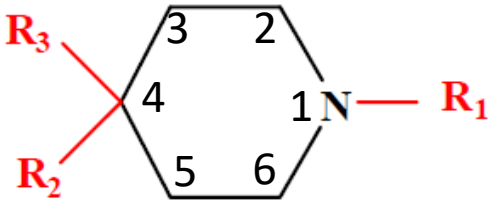
Loperamide

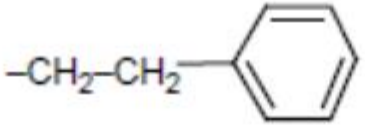
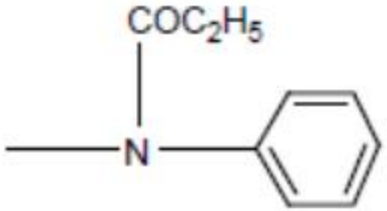
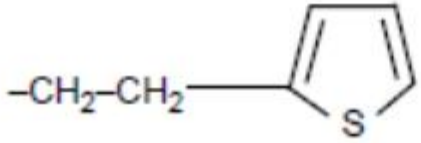
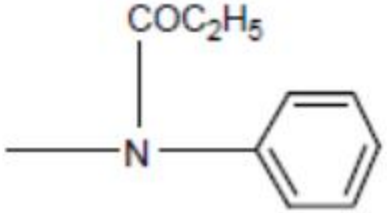
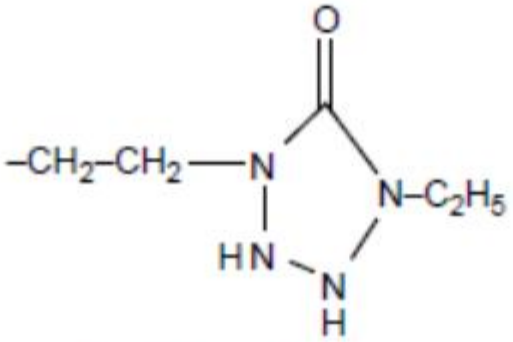
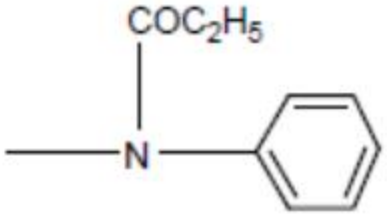
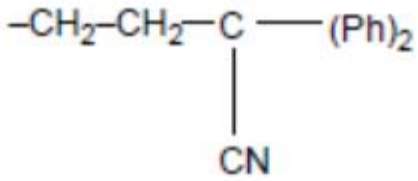
4-Phenylpiperidines analogues



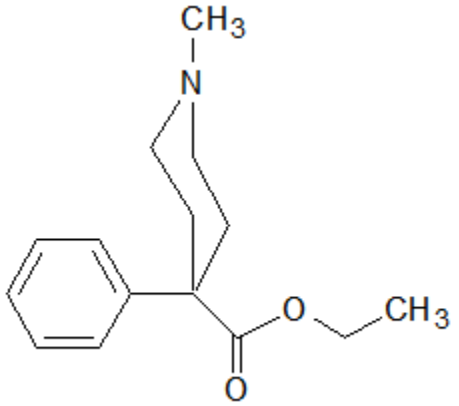
S. No.	Name	R_1	R_2	R_3
1.	Meperidine	$-CH_3$	$-C_6H_5$	$-COOC_2H_5$
2.	Bemidone	$-CH_3$	$-C_6H_4OH$	$-COOC_2H_5$
3.	Properidone	$-CH_3$	$-C_6H_5$	$-COCH(CH_3)_2$
4.	Ketobemidone	$-CH_3$	$-C_6H_4OH$	$-COC_2H_5$
5.	Anileridine		$-C_6H_5$	$-COC_2H_5$
6.	Fentanyl		$-H$	

4-Phenylpiperidines analogues



S. No.	Name	R_1	R_2	R_3
7.	Lofentanil		$-COOCH_3$	
8.	Sufentanil		$-CH_2OCH_3$	
9.	Alfentanil		$-CH_2OCH_3$	
10.	Diphenoxylate		$-C_6H_5$	$-COOC_2H_5$

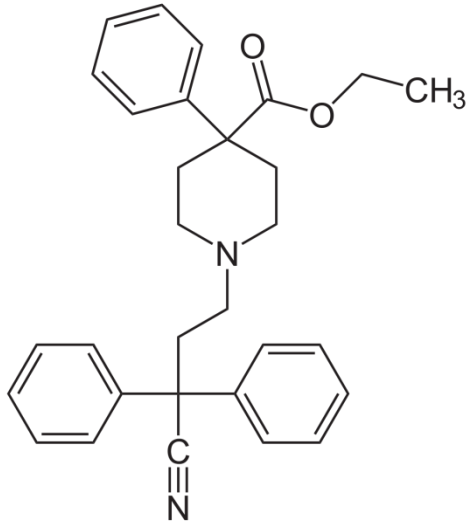
Meperidine is the prototype; potency about 20% of morphine and higher LWPC. Short duration of action due to metabolism of its ester and 40 - 60% bioavailable. About 1/3 as potent orally as compared to parenteral. Meperidine is believed to bind with site “A” and the anionic site “B”. Binding with site “A” is not as effective as binding to site “D”



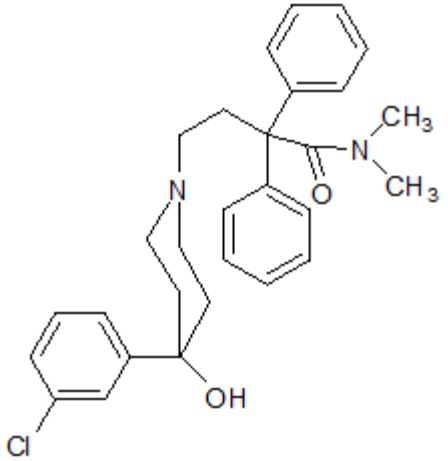
Diphenoxylate is highly lipophilic. However, in regular doses has no CNS activity due to

(a) highly protein bound and sequester in the lipid bilayer,

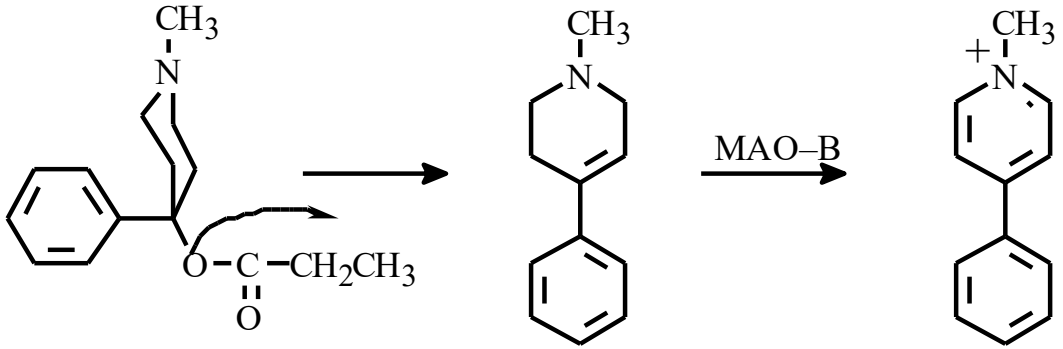
(b) rapidly hydrolyzed to the carboxylic acid Diphenoxin which can not penetrate the blood brain barrier



Loperamide has high LWPC and also free of all CNS effects due to high protein binding and twice as potent as Diphenoxylate. Further, the high lipophilicity result in slow dissolution resulting in slow absorption and 40% bioavailability. The lack of water solubility prevents drug abuse because it can not be injected

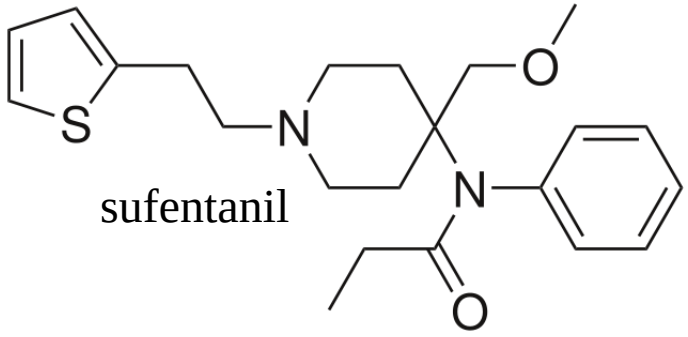


Another molecular modification that stabilizes the molecule is reversal of the ester. The Meperidine reverse ester (MPPP, N–methyl phenyl–4–propionoxy piperidine) has a longer duration of action due to increased resistance to ester hydrolysis.



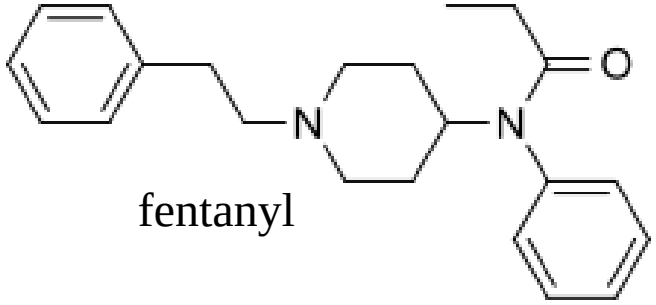
Sufentanil, sold under the brand names Dsuvia and Sufenta, is a synthetic opioid analgesic drug approximately 5 to 10 times more potent than its parent drug, **fentanyl**, and 500 times as potent as **morphine.**

Structure: its differs from fentanyl through the addition of a methoxymethyl group on the piperidine ring (which is believed to reduce duration of action), and the replacement of the phenyl ring by thiophene.



sufentanil

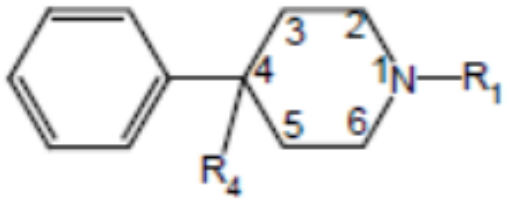
Used: Because of its extremely high potency, it is often used in surgery and post-operative pain management for patients that are heavily opioid dependent/opioid tolerant because of long term opiate use for chronic pain or illicit opiate use. Currently sufentanil is the strongest opioid painkiller available for use in humans.

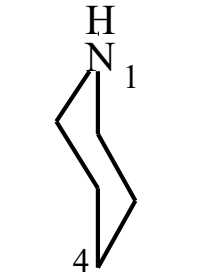


fentanyl

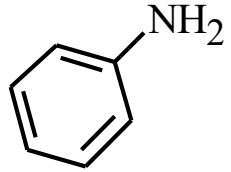
ANILIDOPIPERIDINES

- Moving the phenyl ring from direct attachment to the piperidine ring by one atom to nitrogen on the side chain allows for the phenyl ring to assume the more favorable axial conformation.
- Thus, the phenyl ring of the anilidopiperidines binds the "D" site similar to the morphine "A" ring. 3-OH is not essential for binding to this site. This class includes some of the most potent synthetic analgesics

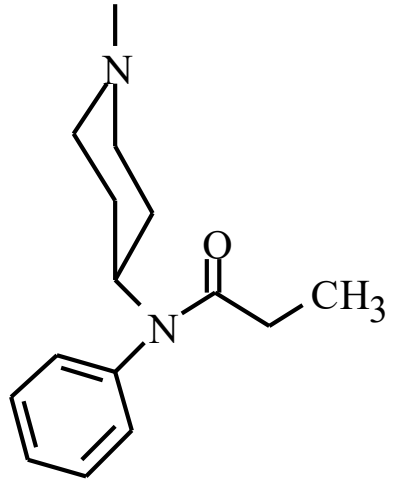


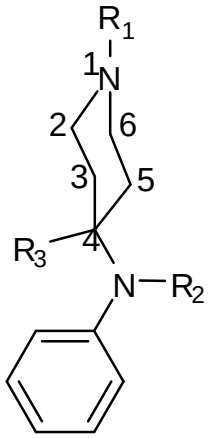


piperidine



aniline

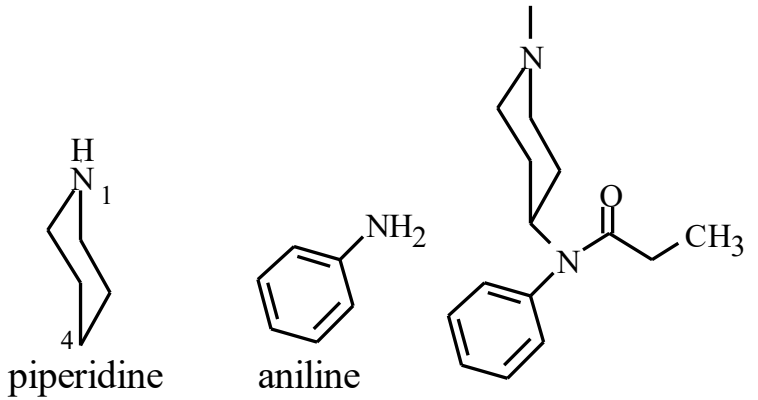


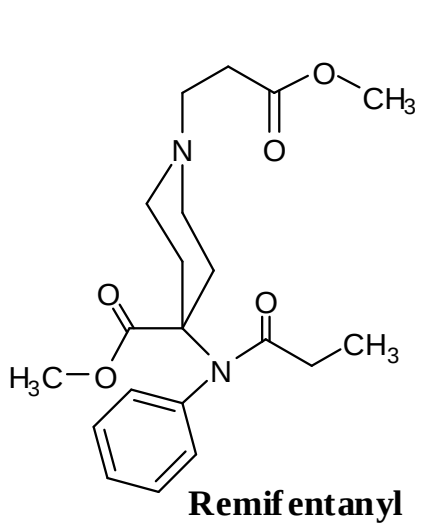


Anilidopiperidine

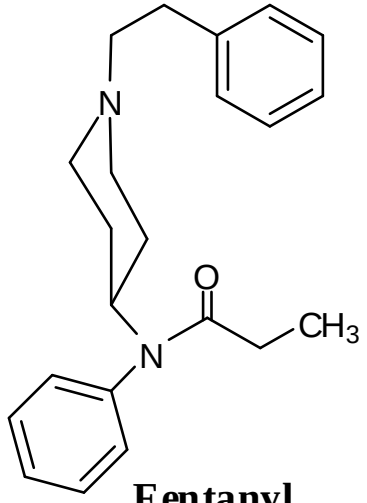
ANILIDOPIPERIDINES

- **Fentanyl**: 50 to 100 times more potent than morphine. It has high μ receptor affinity due to binding at "A", "B" "C" and "D" sites. High LWPC and thus can be absorbed through skin or oral mucosa. N at C4 and the alkyl through NCO bond increases μ receptor affinity by correctly orienting the phenyl ring
- **Remifentanyl**: Esters on N and at C4 lead to rapid inactivation by plasma esterases in consistent with the soft drug / antedrug concept





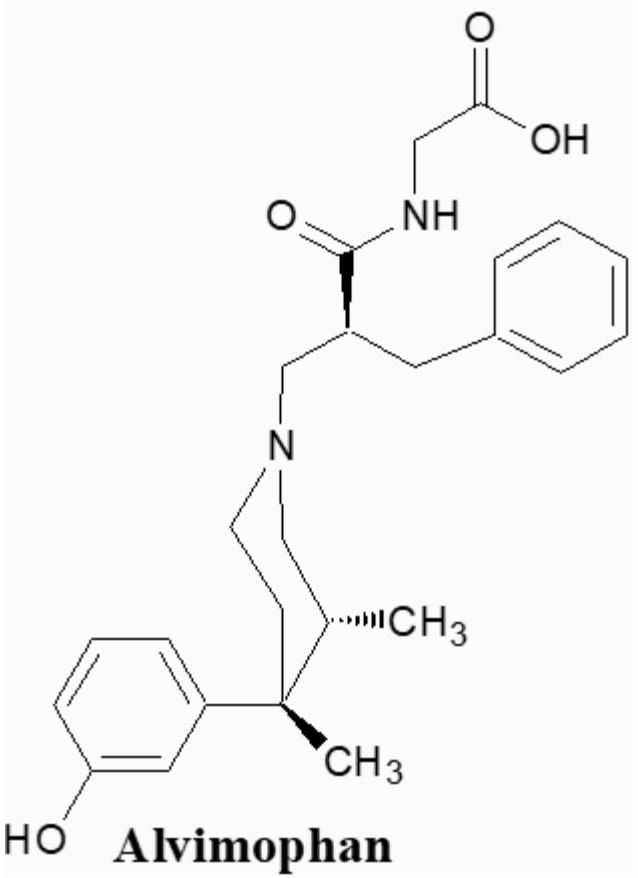
Remifentanyl



Fentanyl

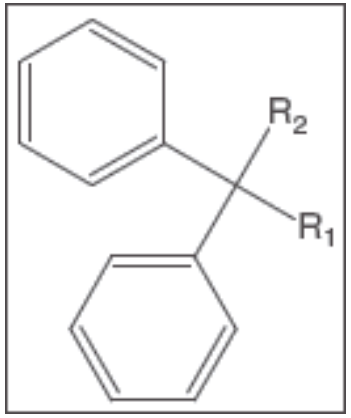
4-Phenylpiperidines type Antagonist

Alvimophan (Entereg) is the first phenyl piperidine type μ-antagonist with limited CNS effect and thus lower opioid drug induced side effects especially constipation. It does not affect the analgesia precipitate withdrawing syndrome. It got FDA approval in May 2008. It binds the GI μ-receptor strongly but dissociates slowly thus exhibiting selective peripheral activity. Thus unlike methylnaltrexone, which can not deliver into brain due to positive charge, its selectivity is kinetically controlled.

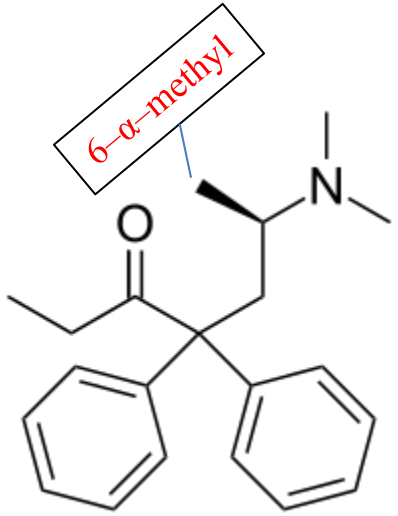


Alvimophan

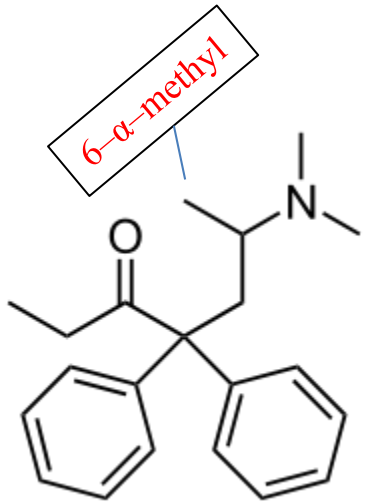
DIPHENYL HEPTANONES



- Also called phenylpropylamines
- The prototype is Methadone, can be viewed as a ring "D" opened phenylpiperidines. When ring D of Morphine was opened there is a total loss of activity but racemic Methadone "Levomethadone" is equal to Morphine in analgesic potency.
- Both phenyl rings required for potency. Removal of one sharply reduces potency, may help correct positioning of one phenyl with correct spacing to the protonated amine for the anionic site



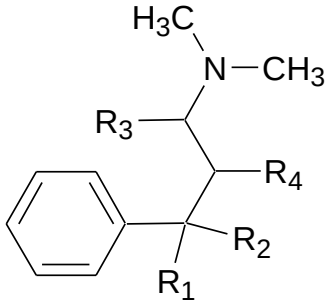
Levomethadone



Methadone

Structure/Activity Relationships

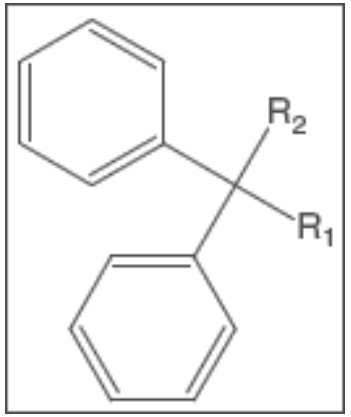
- The phenyl ring of the phenylpropylamines binds the "D" site analogous to the "A" ring of morphine rather than the "A". They have high LWPC, low first pass due to metabolically stable; it is not an ester but a ketone. Also has a long half-life



Phenylpropylamine

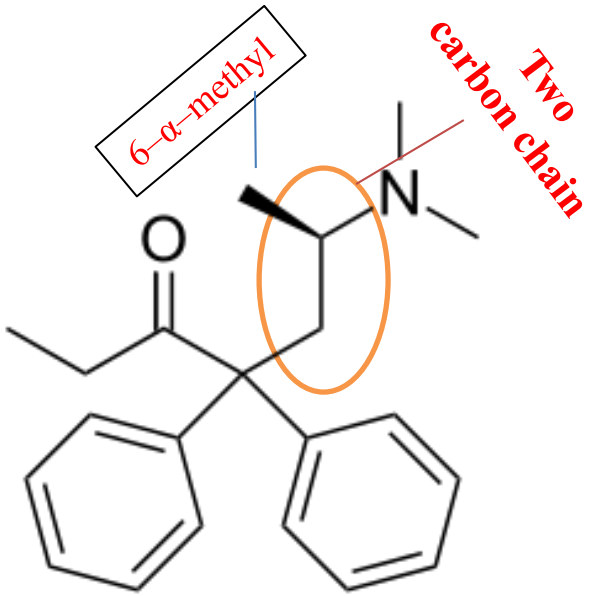
N-substitution "R1":

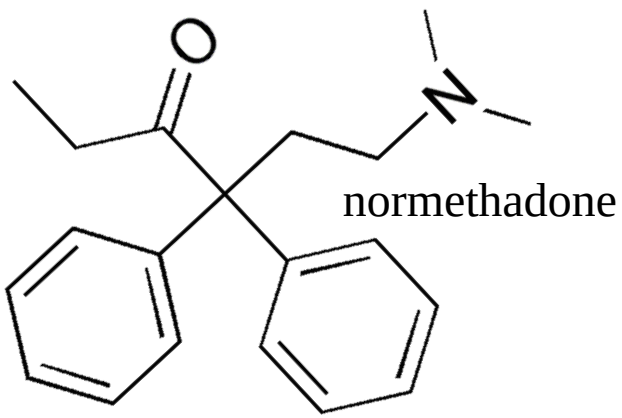
- Generally the dimethylamino gives optimal potency. The diethylamino derivative is less potent but 5 and 6 membered alicyclic basic units have comparable activity to the dimethylamino group



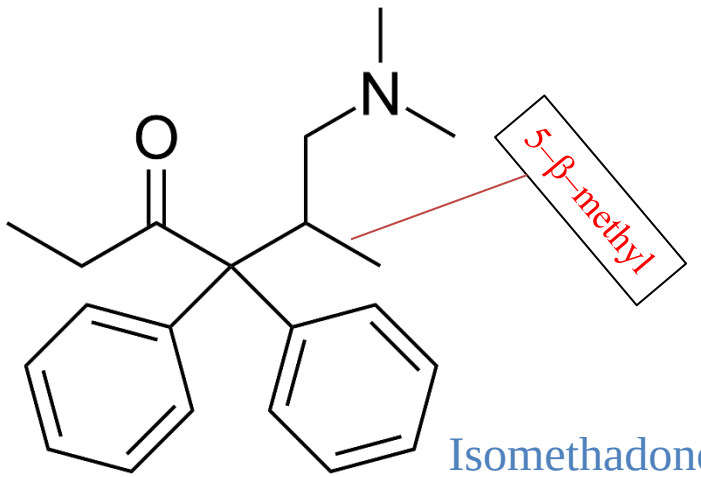
Structure/Activity Relationships

- The two carbon chain between the basic nitrogen and the quaternary carbon is the optimal length
- Removal of the 6–α–methyl (normethadone) decreases potency
- Moving the 6 (a)-methyl to position 5 (β) gives Isomethadone which has 65% of the potency





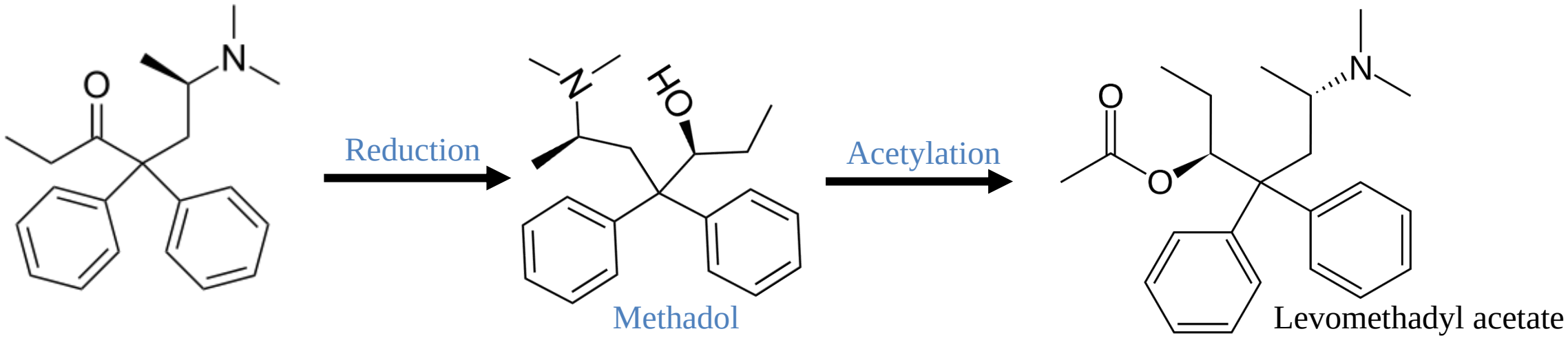
normethadone



Isomethadone

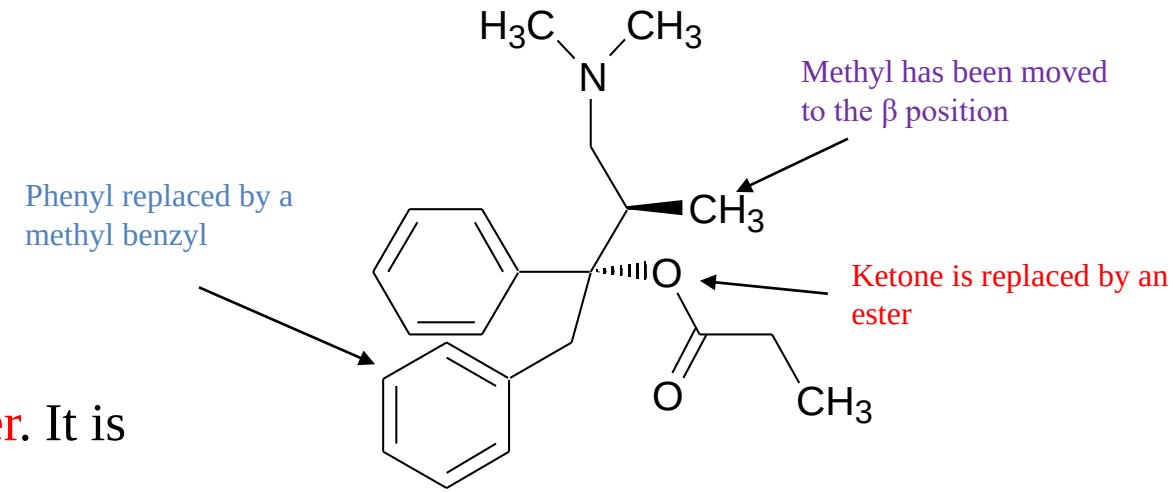
Structure/Activity Relationships

- Ketone side chain is important for activity, removal or altering its length abolishes or significantly decrease potency
- Reduction of the ketone produces Methadol with decreased potency
- Acetylating the alcohol of Methadol produce Levomethadyl acetate which more potent analgesic



Propoxyphene

- The introduction of a benzyl creates a second chiral center with four possible isomers



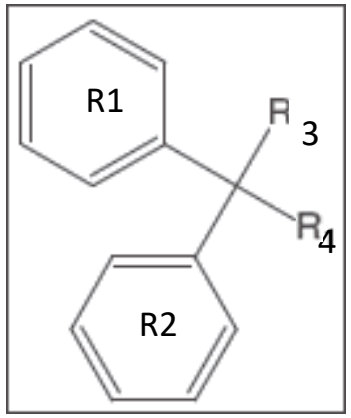
Propoxyphene

- The analgesic activity resides primarily in the (+) isomer. It is marketed as Darvon™. It has 1/8 the potency of Methadone and 2/3 of Codeine. Has lower addiction liabilities and toxicities

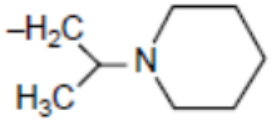
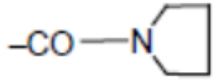
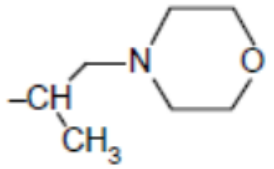
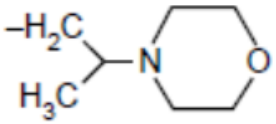
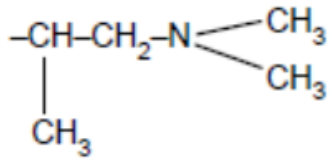
- The (–) isomer was used as an antitussive called Novrad™ which lacks the classical opioid characteristics and a pure antitussive
- The napsylate salt is used because it is water insoluble and is less likely to be abused by injection

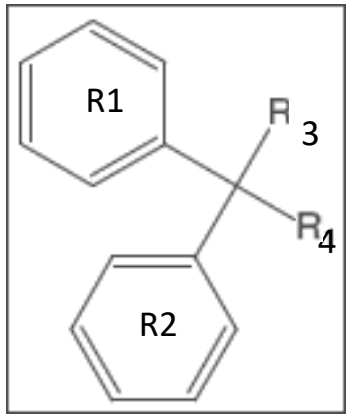
phenylpropylamines analogues

S.No	Drug	R_1	R_2	R_3	R_4
1.	Methadone	–Ph	–Ph	$-COC_2H_5$	$-CH_2-CH(CH_3)-N(CH_3)_2$
2.	Isomethadone	–Ph	–Ph	$-COC_2H_5$	$-CH(CH_3)-CH_2-N(CH_3)_2$
3.	Normethadone	–Ph	–Ph	$-COC_2H_5$	$-CH_2-CH_2-N(CH_3)_2$
4.	Alpha acetyl methadone	–Ph	–Ph	$-CH(C_2H_5)(OCOCH_3)$	$-CH_2-CH(CH_3)-N(CH_3)_2$



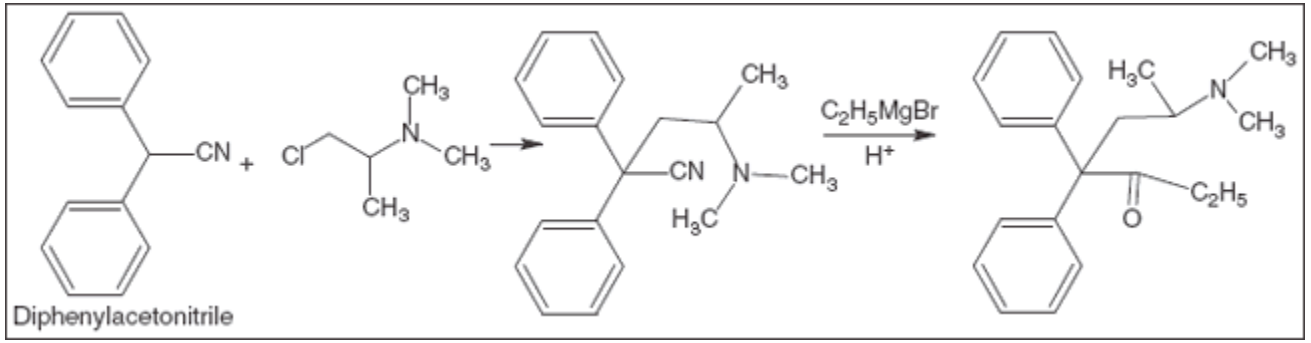
phenylpropylamines analogues

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	$-CH_2-C_6H_5$	$-COC_2H_5$	



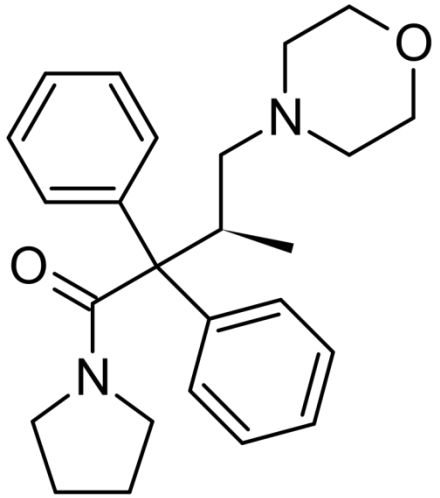
Methadone

- Is a potent analgesic that has a longer duration of action than morphine
- Has a very long half life and accumulates in the body with continued dosing
- Well absorbed from the GI tract and is very effective when given orally
- used for opioid maintenance therapy in opioid dependence and for chronic pain management
- also used in drug treatment programs during detoxification from heroin and other opioids
- Methadone synthesised by alkylation of diphenylacetonitrile using dimethyl-aminopropylchloride in the presence of sodamide.



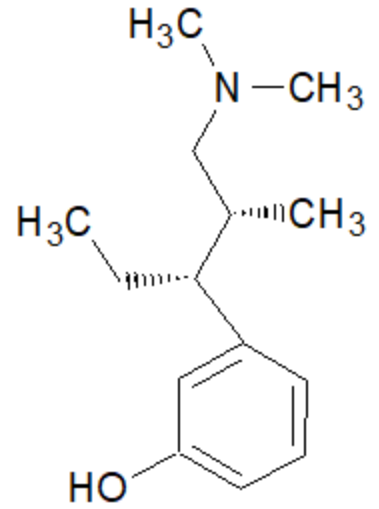
Dextromoramide

- Dextromoramide was discovered and patented in 1956
- Synthesised by alkylation of diphenylacetonitrile using morpholinyl-chloropropane in the presence of sodamide
- The main advantage of this drug is that it has a fast onset of action when taken orally, and has a high bioavailability which means that oral dosing produces almost as much effect as injection.
- It also has a relatively low tendency to cause constipation which is a common problem with opioid analgesics used for cancer pain relief, and tolerance to the analgesic effects develops relatively slowly compared to most other short-acting opioids.

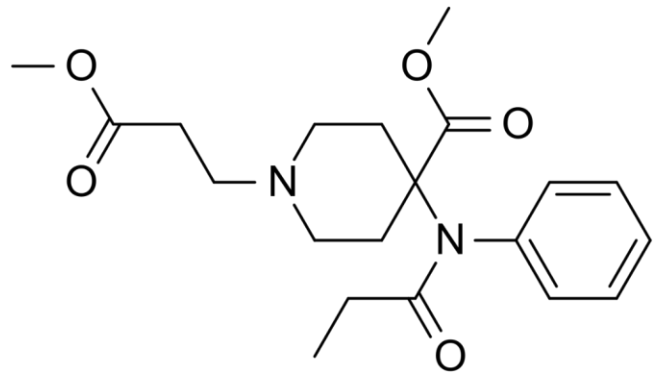


NEWER DRUGS

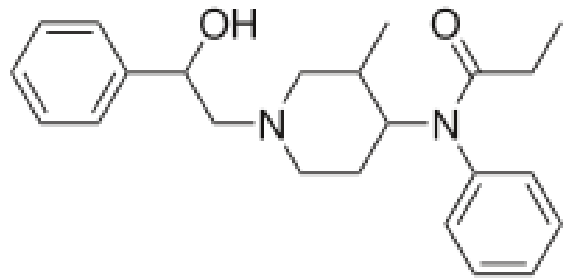
Tapentadol (Nucynta) is a simplified structure approved in November 2008 as narcotic analgesic. It has a dual mechanism of action as a μ-opioid agonist as well as a NE reuptake inhibitor with analgesic potency comparable to that of morphine with a more tolerable side effect profiles.



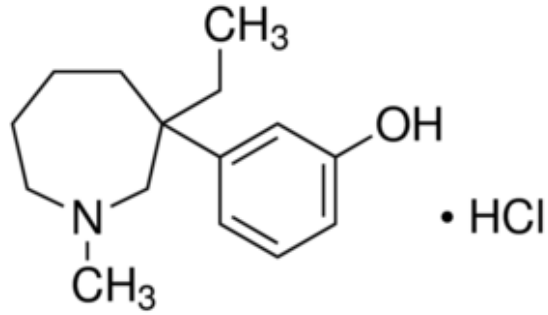
Remifentanil: It is a potent ultrashort-acting synthetic opioid analgesic drug. It is given to patients during surgery to relieve pain and as an adjunct to an anaesthetic. Remifentanil is used for sedation as well as combined with other medications for use in general anaesthesia. Remifentanil has a similar potency to fentanyl.



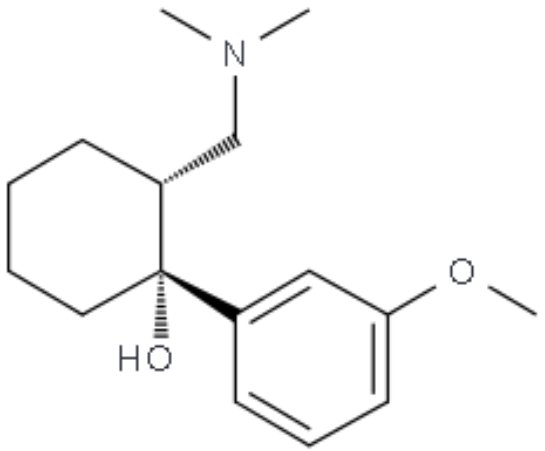
Ohmefentanyl: It (β-hydroxy-3-methylfentanyl) is an extremely potent analgesic drug that selectively binds to the μ-opioid receptor. In mouse studies, the most active isomer 3R,4S,βS-ohmefentanyl was 28 times more powerful as a painkiller than fentanyl, the chemical from which it is derived, and 6,300 times more effective than morphine.



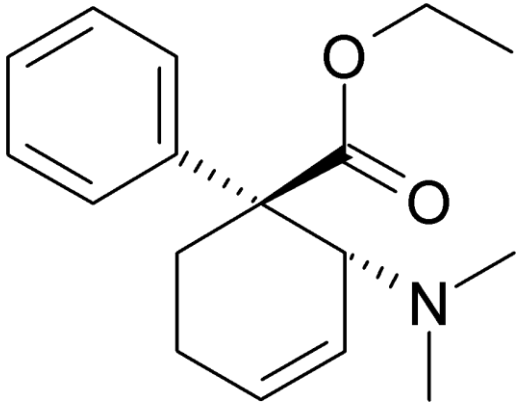
Meptazinol: It is an opioid analgesic for use with moderate to severe pain, most commonly used to treat pain in obstetrics (childbirth). A partial μ-opioid receptor agonist, its mixed agonist/antagonist activity affords it a lower risk of dependence and abuse than full μ agonists like morphine. Meptazinol exhibits a short onset of action, but also a shorter duration of action relative to other opioids such as morphine, pentazocine, or buprenorphine.



Tramadol: Is a centrally acting analgesic whose mechanism of action is based on blockade of serotonin reuptake. it is believed to be only a weak m-receptor agonist. It is surprising that no clinically significant effects on respiration or the cardiovascular system have thus far been reported. Tramadol may serve as an adjunct with pure opioid agonists in the treatment of chronic neuropathic pain.



Tilidine



Nexeridine