Opioid Analgesics

part 1

Dr. Mai Ramadan

Introduction

Analgesics: Drugs which selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering the consciousness– Opioids and NSAIDS

Opiates: Drugs derived from opium – Natural or semi-synthetic

Opioids: Any drug which binds to the opioid receptors (Pharmacologically related) in the CNS and antagonized by Naloxone

Narcotics: Drugs derived from opium or opium like compounds, with potent analgesic effects associated with significant alteration of mood and behavior, and with the potential for dependence and tolerance following repeated administration.

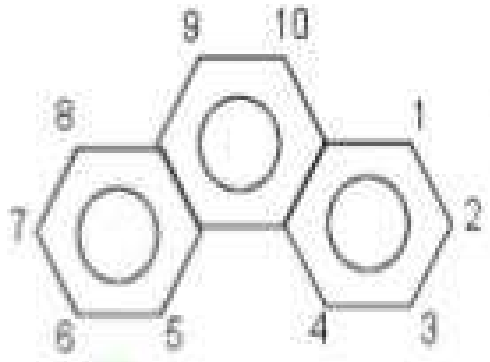
Introduction

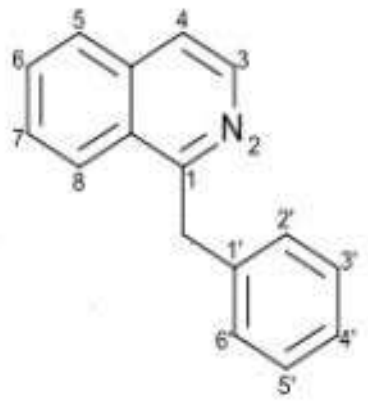
Effects of opioid receptor stimulation

	μ receptor	κ receptor	δ receptor
Q Location	μ1 - supraspinal μ2 - spinal	κ1 - spinal κ3 -supraspinal	Spinal supraspinal
Effects	Analgesia Respiratory depression Sedation Euphoria Miosis Physical dependence Loss of GI motility	Spinal analgesia **Q Dysphoria** Sedation Psychomimetic Physical dependence (nalorphine type)	Spinal analgesia Affective behaviour (Supraspinal) Respiratory depression Reduced GI motility
Agonists	Morphine, Codeine, Fentanyl and pentazocine weakly	Pentazocine	

Introduction

Opium contains alkaloids





OPIUM PHENANTHRENE

Morphine 9-14%

Codeine 0.5-2%

Thebaine 0.2-1%

BENZYLISOQUINOLINE

Papaverine 0.8-1%

Noscapine 3-10%

Narcine 0.2-0.4%

Introduction

Opium: A dark brown, resinous material obtained from poppy (Papaver somniferum) Capsules

Classification of opioid: Source

Natural opioid

Opium Alkaloids:

Morphine and Codeine

Endogenous opioid peptide

Endorphins, Enkephalins, Dynorphins

Semi-synthetic:

Diacetylmorphine (Heroin), oxycodone, oxymorphone

Classification of opioid: Source

Synthetic Opioids:

Phenylpiperidines:

- Pethidine (Mepiridine), Loperamide
- Fentanyl and its congeners – sufentanil, remifentanil and alfentanil

Diphenylheptane

Methadone, Propoxyphene and Dextropropoxyphene

Benzomorphans:

Pentazocine

Morphinan and congeners:

Levorphanol and Butorphanol

Classification of opioid: Chemical structure

Phenanthrene: Morphine

Benzomorphan: Pentazocine

Phenylpiperidine: Fentanyl

Diphenylheptane: Methadone

Phenylpropylamine: Tramadol

Classification of opioid: Pharmacological action

Pure Agonist: has affinity for binding plus efficacy

Pure Antagonist: has affinity for binding but no efficacy; blocks action of endogenous and exogenous ligands

Mixed Agonist-Antagonist: produces an agonist effect at one receptor and an antagonist effect at another

Partial Agonist: has affinity for binding but low efficacy

Classification of opioid: Pharmacological action

Classification of Opioids:

DRUGS	MU	KAPPA
Pure Agonists Morphine, codeine, meperidine, fentanyl , remifentanil, propoxyphene , hydrocodone , oxycodone	Agonist	Agonist
Agonist-Antagonist Nalbuphine, butorphanol, Buprenorphine	Antagonist	Agonist
Pure Antagonists Naloxone, Naltrexone	Antagonist	Antagonist
Partial Agonists Pentazocine	Partial Agonist/weak antagonist	Agonist

Morphine

Opium - History • Friedrich Wilhelm Serturner – A German Pharmacist – Isolated Morphine in 1803 and named it after the Greek god of Dreams "**MORPHEUS**"

Because morphine was poorly absorbed orally, it was little used in medicine until the hypodermic syringe was invented in 1853.

Morphine is agonist of all opioid receptors but affinity is higher for mu

Morphine: Chemical structure

A rigid pentacyclic structure consisting of: Benzene ring (A), Two partially unsaturated cyclohexane rings (B and C), Piperidine ring (D), Tetrahydrofuran ring (E)

Rings A, B and C are the phenanthrene ring system.

Two hydroxyl functional groups: a C3-phenolic OH and a C6-alcoholic OH

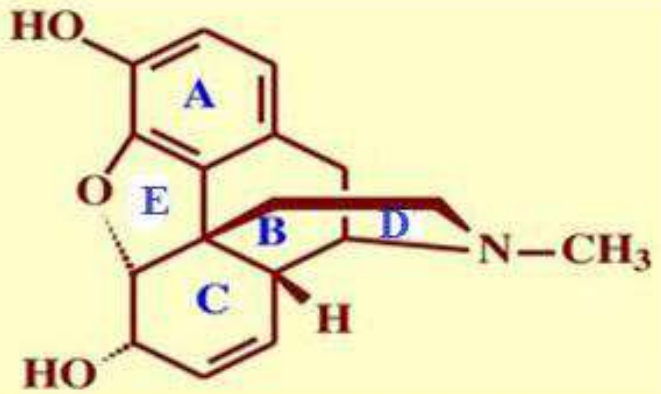
An ether linkage between C4 and C5

Unsaturation between C7 and C8,

A basic, 3^{o}-amine function at position 17

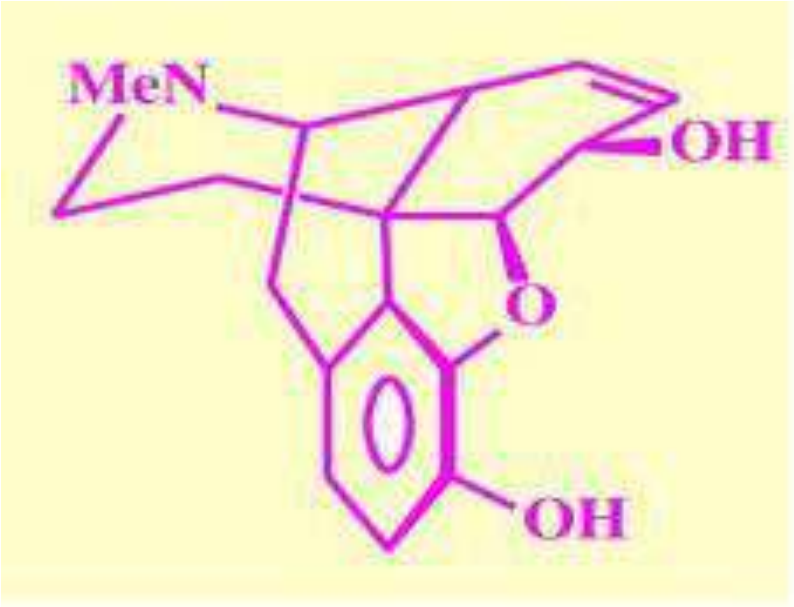
5 centers of chirality (5(R), 6(S), 9(R), 13(S), and 14 (R).)

Morphine: Stereochemistry



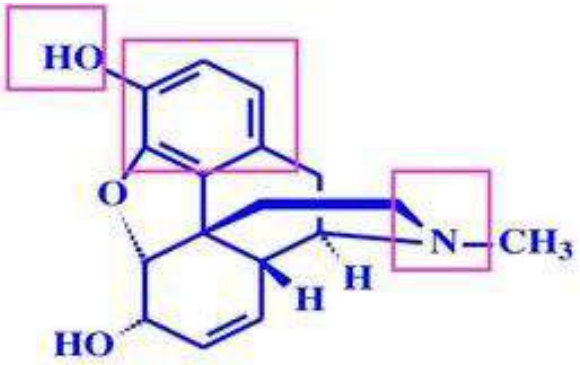
Morphine optical isomers 32 theoretical, in fact only 8 [C6, C14 have epimerization possibility].

Conformation of morphine is a “T” shape with A, B, and E rings forming the vertical portion, and C and D ring forming the top.
Ring C Boot, Ring D Sessel conformation. Alcoholic OH is equatorial



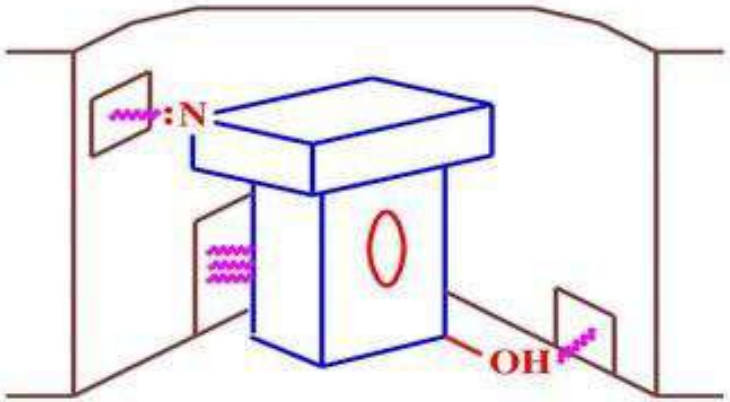
Morphine: Stereochemistry

Morphine is levorotatory with specific rotation -131°

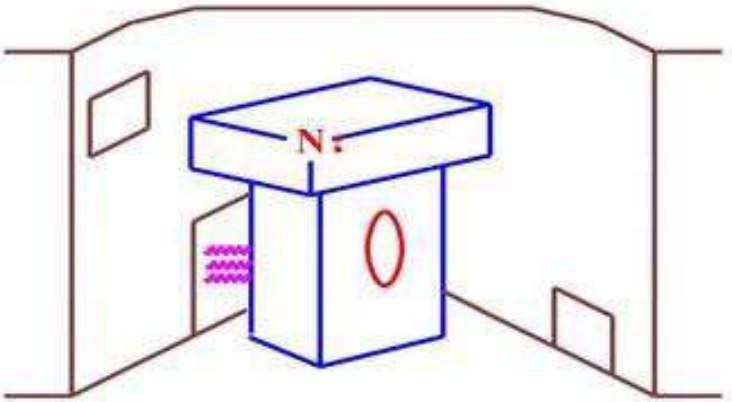


"Natural" Morphine

"Unnatural" Morphine (the mirror image)
No analgesic activity



3 receptor interactions



1 receptor interaction
(OH hidden in diagram)

Morphine: Properties

Morphine:

Amphoteric Base (tert- amine), acidic (phenolic OH)

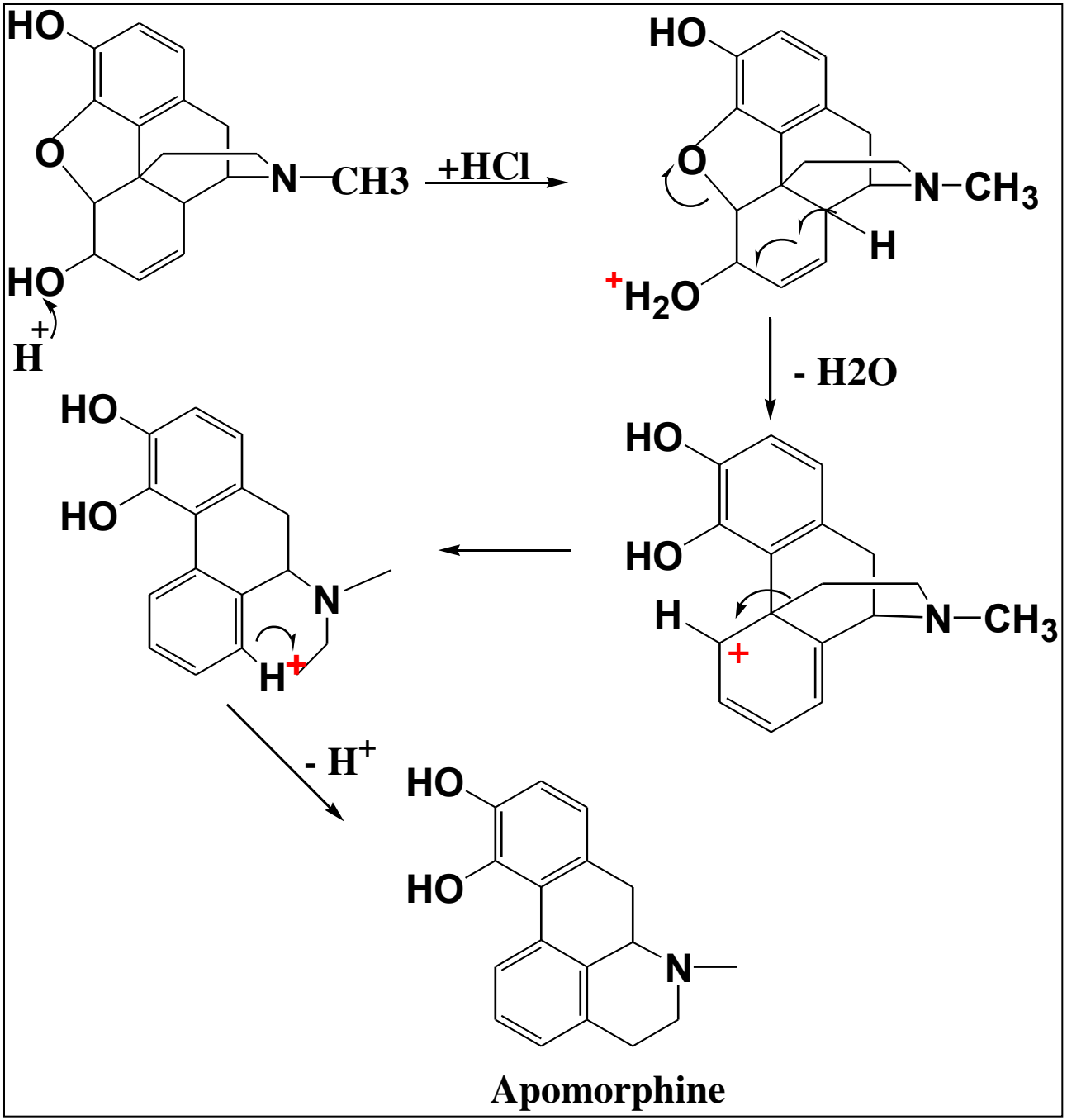
Isoelectric point at pH: 9.1

Slightly soluble in ether, chloroform, ethylacetate, soluble in alcohol and basic solution

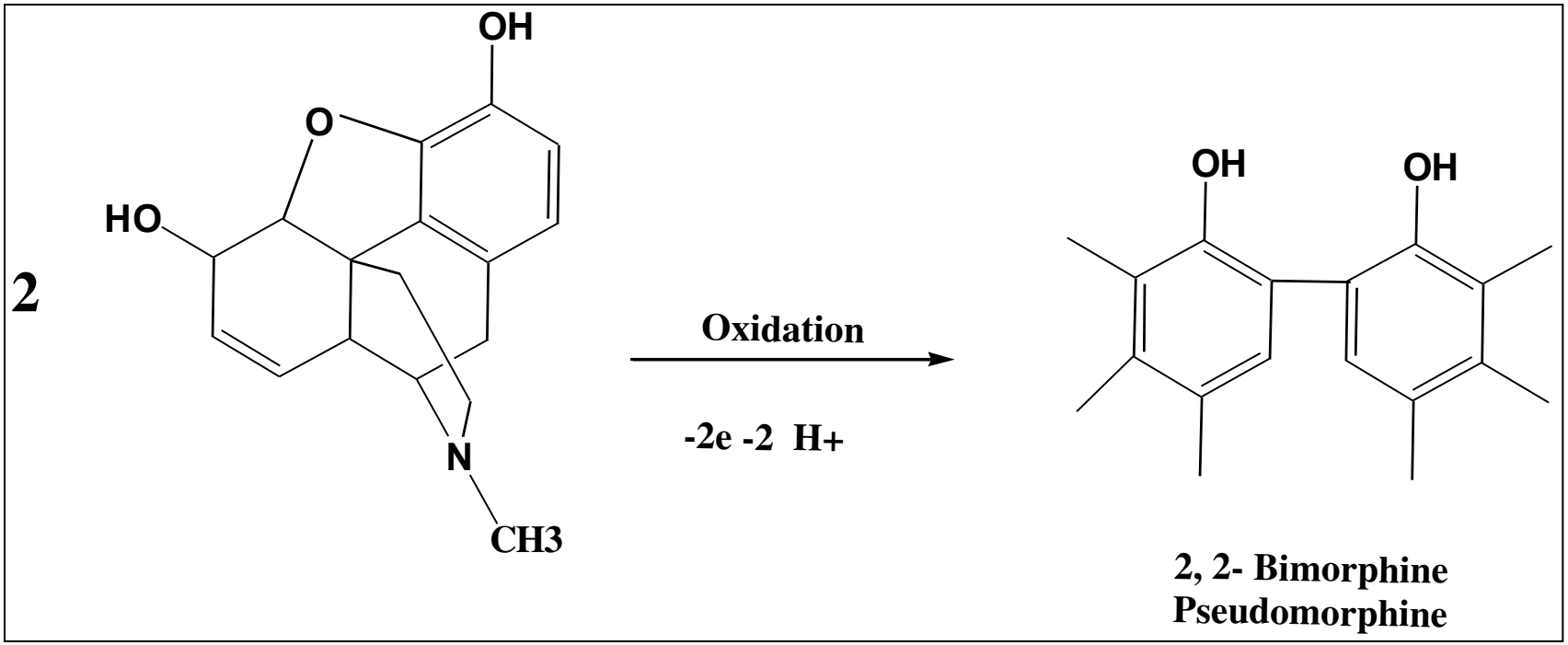
Salts: Hydrochloride and sulfate

Stability: Heating with mineral acids: morphine → **apomorphine**

Oxidation liability → pseudomorphine


HO
O
N—CH3
HO
H+
+HCl
HO
O
N—CH3
H
+H2O
- H2O
HO
HO
H
N—CH3
+
HO
HO
N
H+
- H+
HO
HO
N—
Apomorphine

Oxidation of morphine:



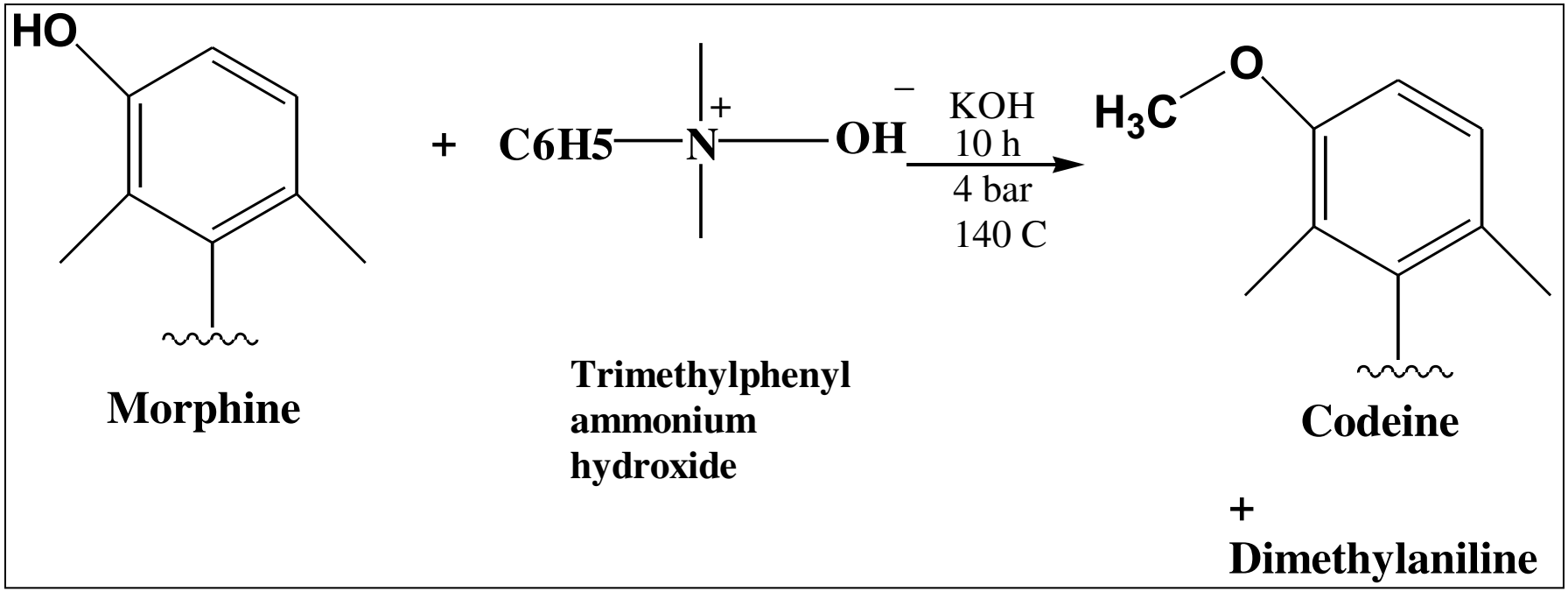
Morphine: Properties

Morphine:

Source mainly is opium, synthesis less efficient

Note: Specific condition are required, affinity for 3°- N amine

Codeine synthesis:



Morphine: Pharmacokinetic

Morphine: orally absorption is slow

Morphine is extensively metabolized by the gut wall & the liver. (First pass effect, **bioavailability 20-40%)**

Metabolism:

Morphine 3 glucuronide (M3G) (60%) – inactive

Morphine-6- glucuronide (M6G)(10%) - analgesic

Sulphate conjugates (3%).

Morphine: Pharmacokinetic

Morphine freely cross the placenta, slowly cross BBB

M6G is normally excreted in urine. M6G accumulates in renal failure & accounts for significantly **increased analgesic effect of morphine***.

Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity.

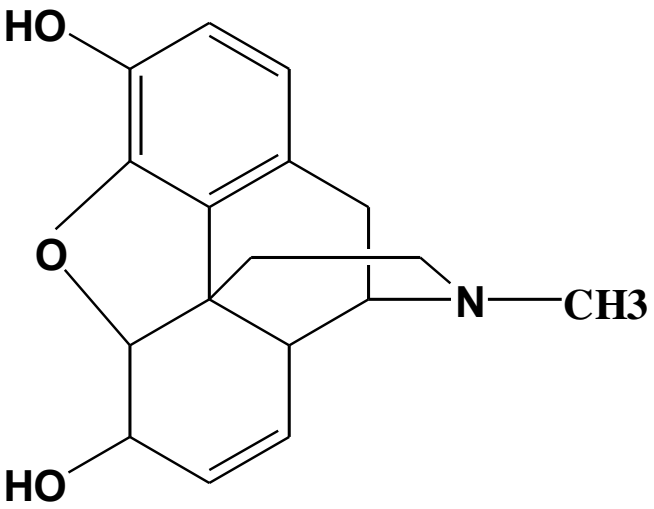
In the **elderly**, owing to reduced volume of distribution, peak plasma level of morphine is higher compared to younger patient.

Duration of action 3-6 h

Doses: PO, IM, IV, Rectal

For equivalent analgesic effect, the oral dose must be 3 times the intravenous (IV) dose

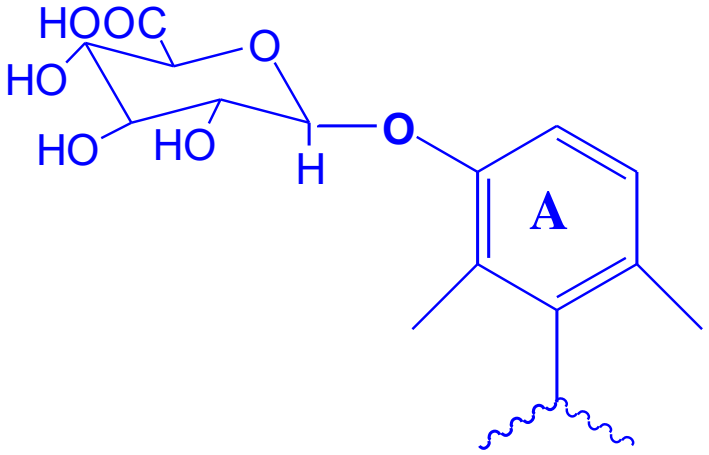
Morphine: Metabolism



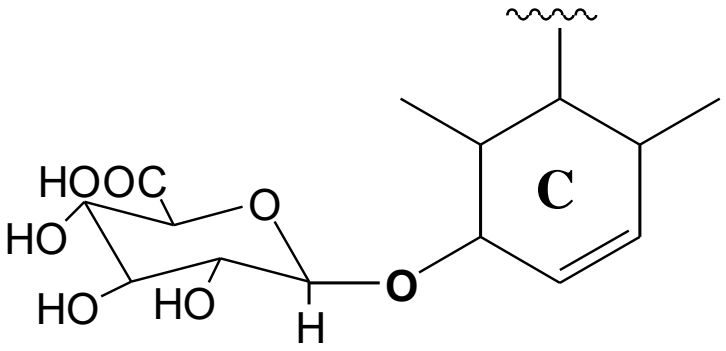
UDP-Glucuronyl transferase

+ UDP glucuronic acid

α-linkage at C1



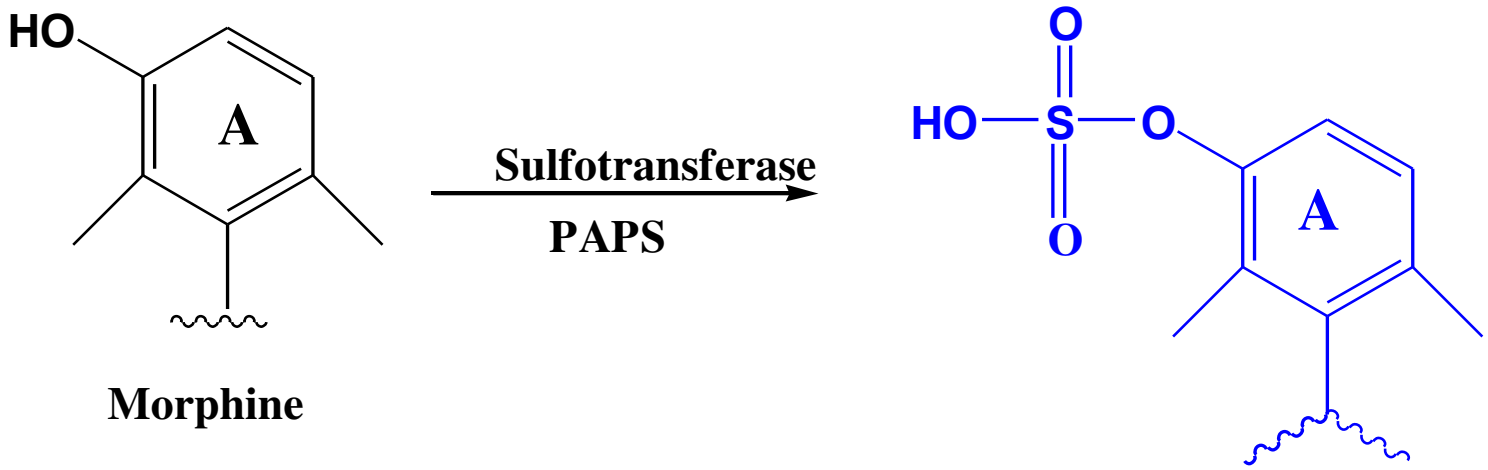
Morphine -3-O- glucuronide
No analgesic activity



Morphine -6-O-glucuronide
Analgesic activity

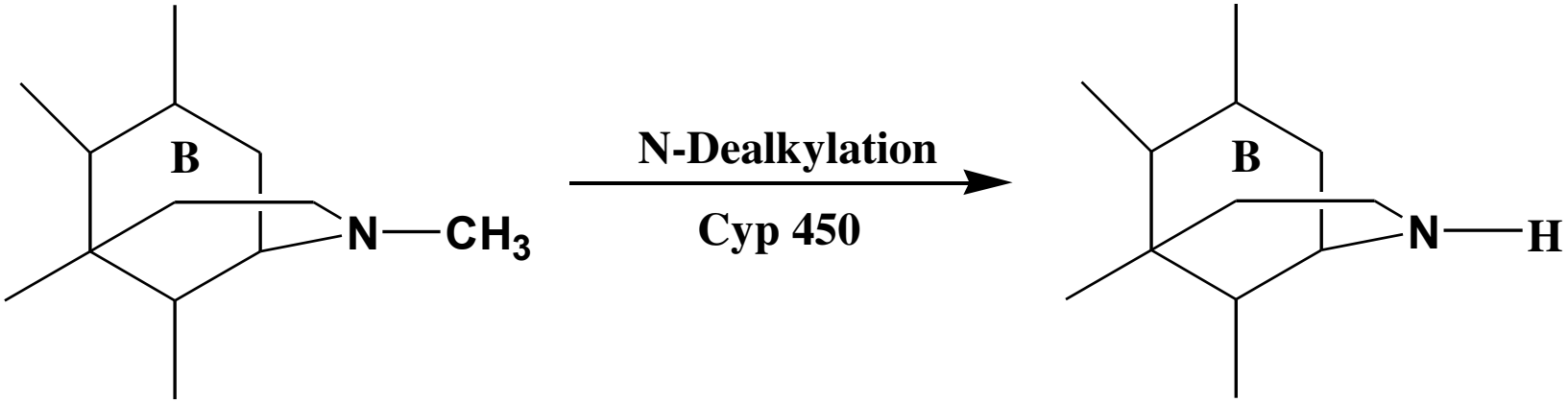
β-linkage at C1 in conjugate

Morphine: Metabolism



Morphine

3-O-Sulfate conjugate
Note 6-O-sulfate conj is active

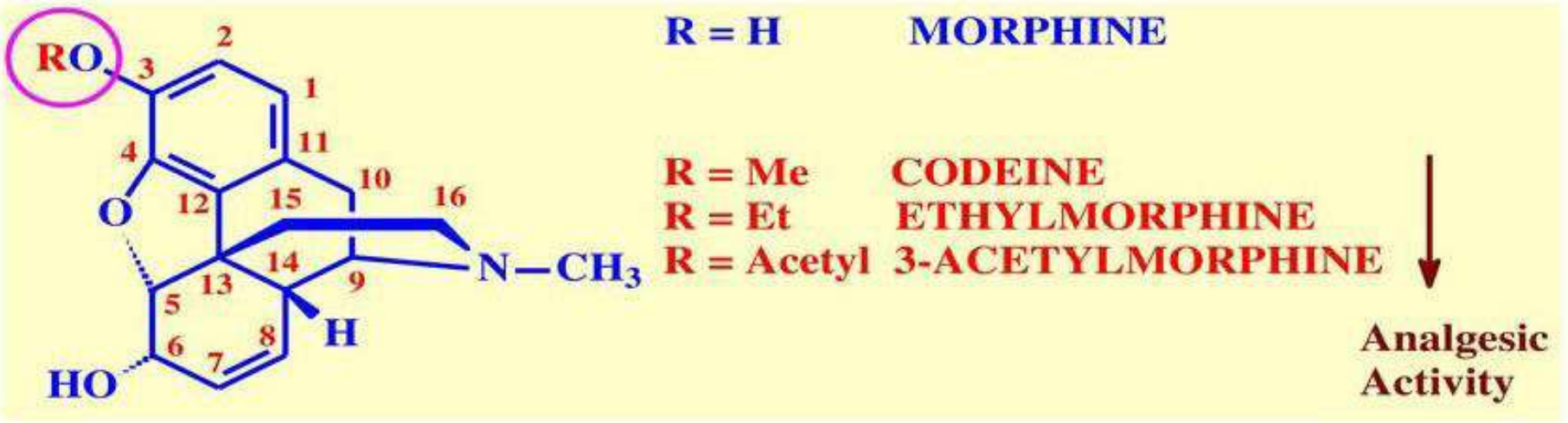


Morphine

Normorphine

SAR and structural modifications

Phenolic OH is essential for analgesic activity



Morphine: Mu, Kappa, Delta Agonist

Codeine (Mu (w), Delta (w))

Methylating phenolic OH (Codeine) decreases analgesic effect.
Codeine is 0.1 percent as active as morphine

SAR and structural modifications

Alcoholic OH is Not Essential for analgesic activity

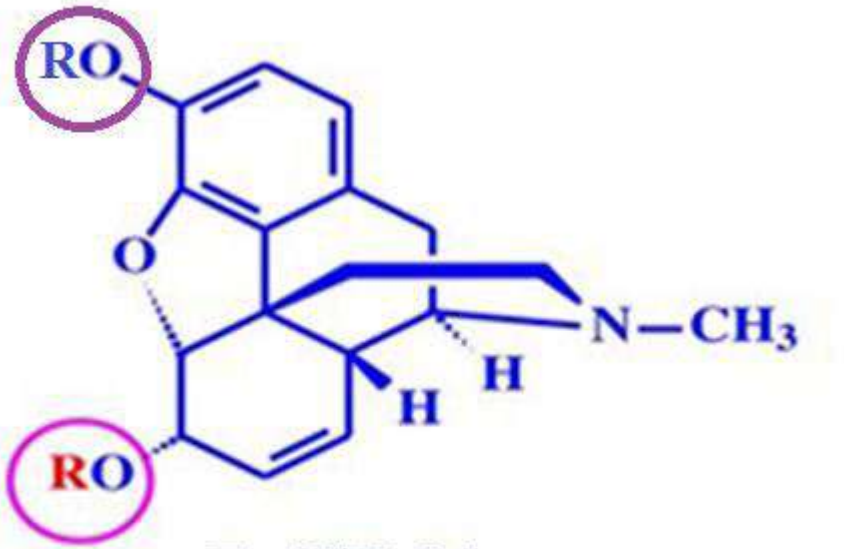
R		Analgesia wrt morphine
Me	Heterocodeine	5x
Et	6-Ethylmorphine	greater
Acetyl	6-Acetylmorphine	4x

Increasing lipophilicity of compounds increase analgesic effect

6-O-Sulfate and 6-O-glucuronide are more potent than morphine

SAR and structural modifications

Alcoholic and phenolic OH : Heroin



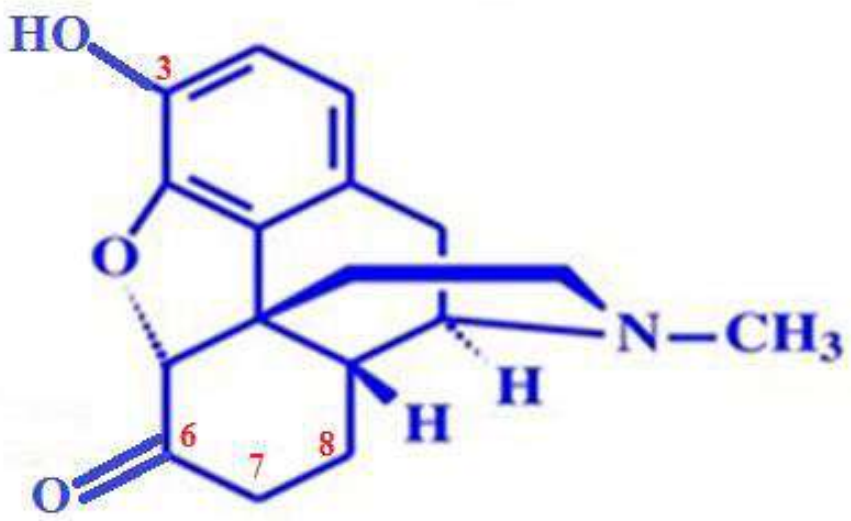
R: CH3 CO-
R: CH3CO-

3,6-Diacetylmorphine Heroin increase analgesic action. Heroin pass BBB quicker than morphine. By esterase enzyme in brain 3-acetyl morphine (inactive), and 6-acetylmorphine which is 2 to 3 times more potent at μ -receptor than morphine

Fast onset and intense euphoric action

SAR and structural modifications

Alcoholic OH and double bond at 7,8

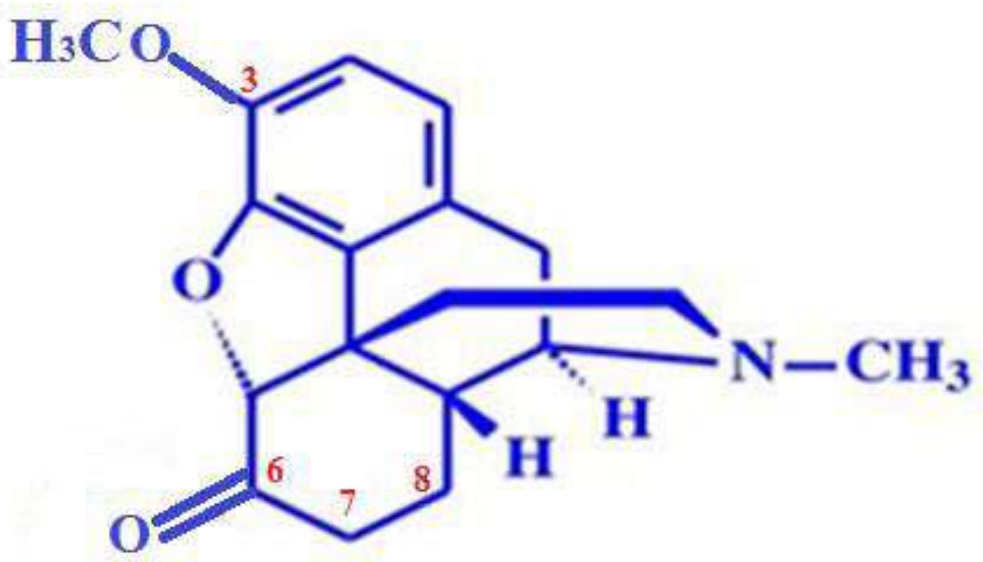


Hydromorphone

Alcoholic OH at 6 is not essential, double bond is not essential
Modification OH to ketone and saturation of double bond at 7,8 increase activity (**approximately 5 times as potent as morphine**).

SAR and structural modifications

Alcoholic OH and double bond at 7,8



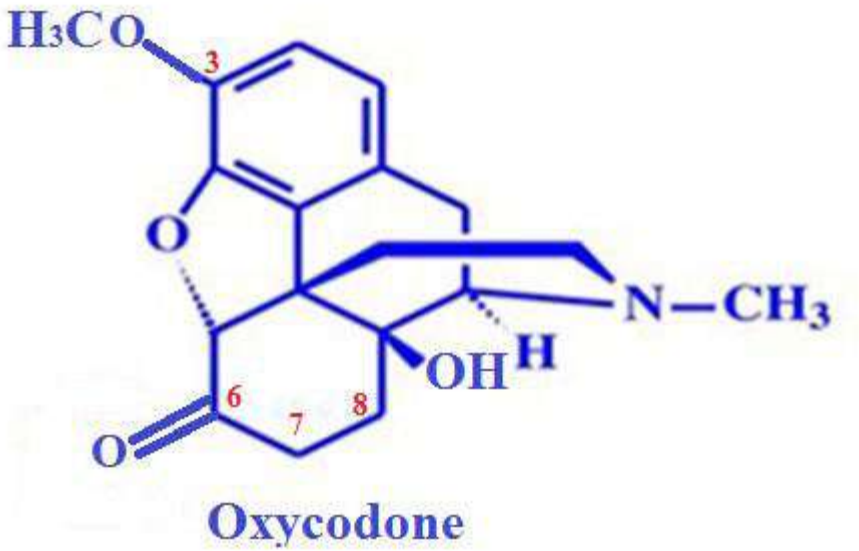
Hydrocodone

Hydrocodone is the 3 methoxy version of hydromorphone.
The loss of the 3-OH group yields a compound that is approximately 4 to 5 times less potent than hydromorphone, thus about equal to morphine.

SAR and structural modifications

Replace Alcoholic OH at 6 with H and reduction of double bond at 7, 8 increases activity

Replace H at 14 with β-OH



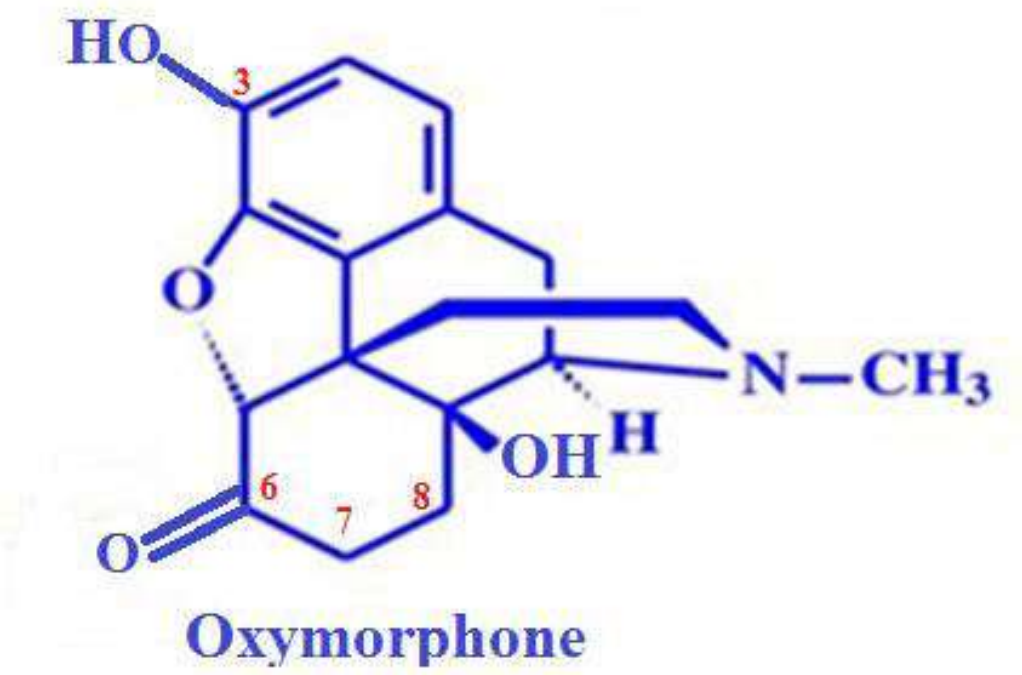
Oxycodone

14 beta-hydroxyl version of hydrocodone

Oxycodone greater potency (1.5 times orally) than hydrocodone

SAR and structural modifications

Replace H at 14 with β-OH



Oxymorphone

14 beta-hydroxyl version of hydromorphone

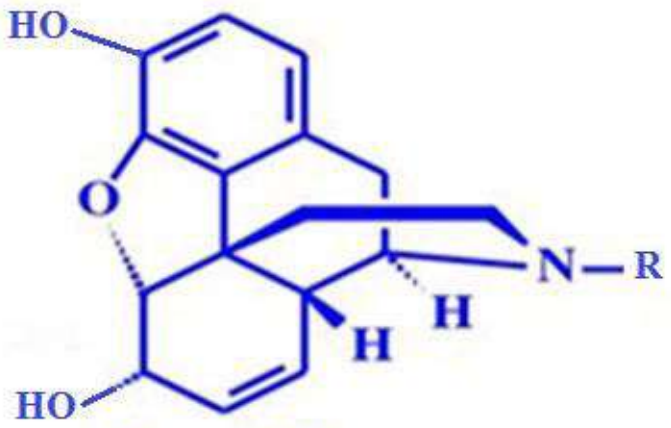
Oral bioavailability of oxymorphone is lower than that of hydromorphone (less potent)

Injectable Oxymorphone is more potent than hydromorphone

SAR and structural modifications

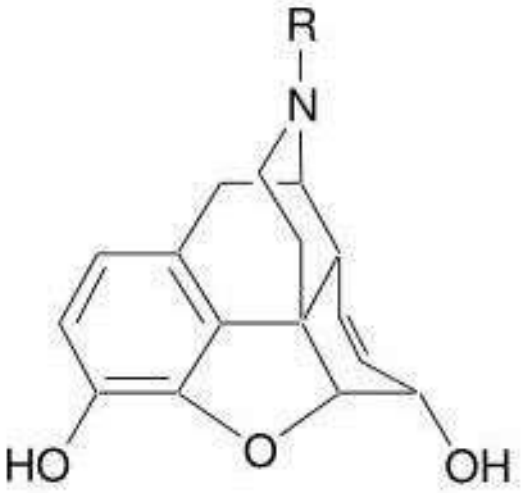
Nitrogen is essential for activity

- Replace NR by CHR the compound is inactive
- Normorphine is polar and cross BBB more slowly
- Ionized compound can not cross BBB
- As the alkyl group is increased in size from a methyl to a butyl group, the activity drops to zero.
- When substituent at N R is pentyl or hexyl the activity recovers slightly.



NR	CHR		inactive
NR	NH	Normorphine	25% active
NR	$\overset{+}{N}$ CH3 (O)		inactive
NR	$\overset{+}{N}Me_2$		inactive

SAR and structural modifications



$R = CH_3$ Morphine

$= CH_2CH_3$

$= CH_2CH_2CH_3$

Agonist activity decreases
antagonist activity increases

$= CH_2CH_2CH_2CH_3$ No activity

$= (CH_2)_4CH_3$

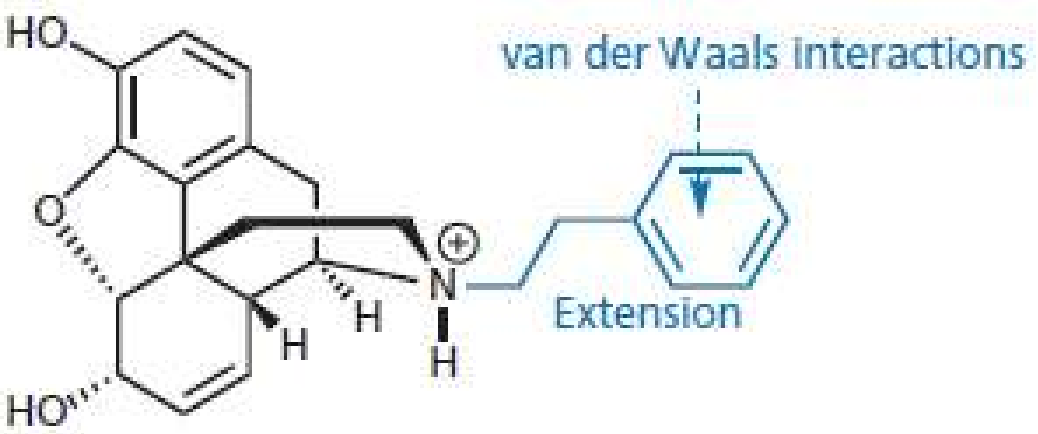
$= (CH_2)_5CH_3$

Agonist activity increases

$= CH_3CH_2$ 

14x morphine

SAR and structural modifications

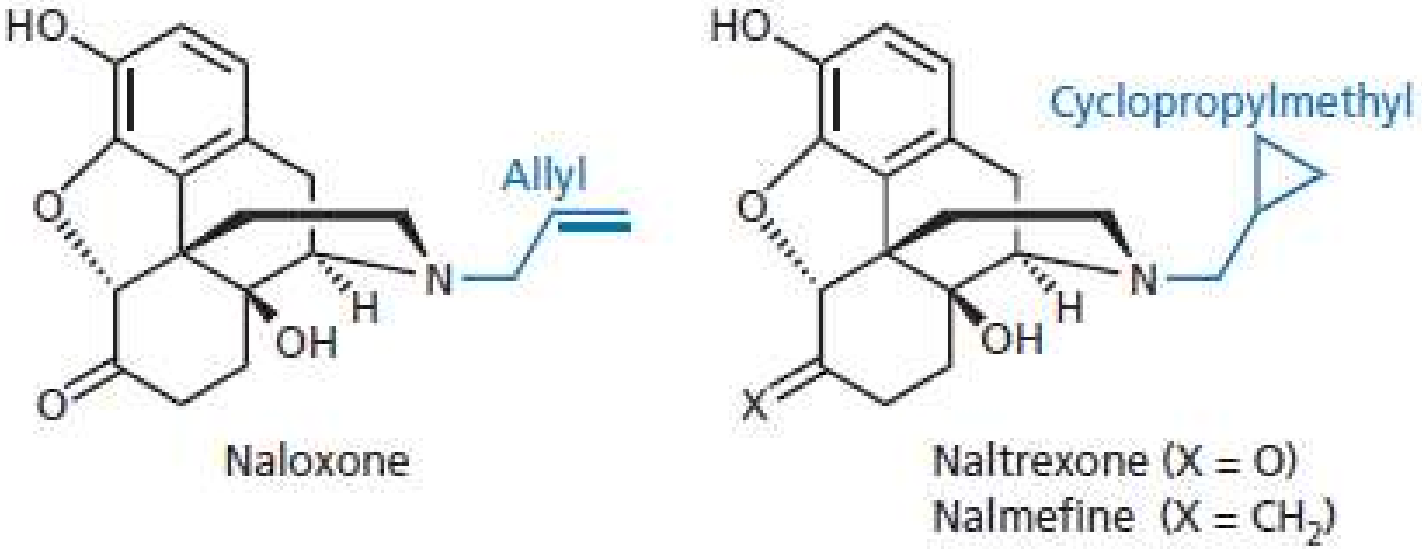


N-Phenethylmorphine
(14 × activity of morphine)

- Larger substituent at N return agonist [phenylethyl] 10X more potent as mu agonist than CH3

SAR and structural modifications

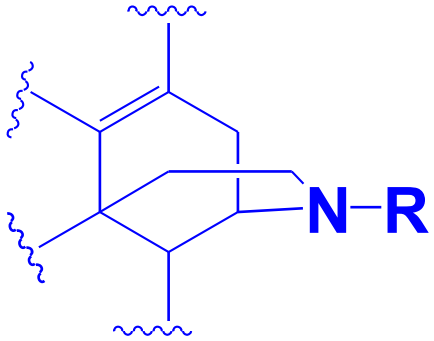
Nitrogen is essential for activity



- Unsaturated or carbocyclic substituents (3C) produces pure antagonist
- Naltrexone is eight times more active than naloxone as an antagonist.
- Nalmefine binds more strongly to opioid receptor than naltrexone.

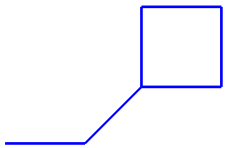
SAR and structural modifications

R at N



R: Dimethylallyl

R: Cyclobutylmethyl



Antagonism at Mu receptor decreaes and agonism increases at kappa receptor

Mixed agonist antagonist

SAR and structural modifications

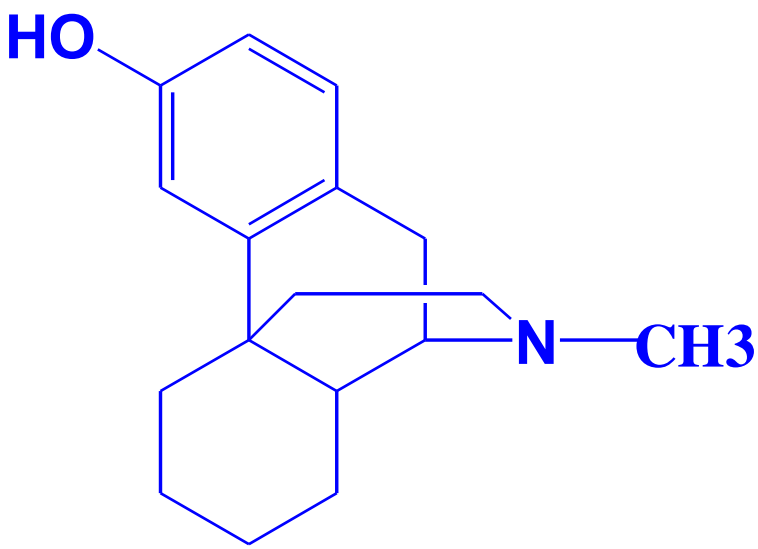
Removal of C4-C5 ether link increases activity

Removal of ether link at C4-C5 produce **morphinans**

Ether link is not essential

Only levo (-) isomers posses opioid activity.

Levorphanol is **7.5 times** more potent than morphine

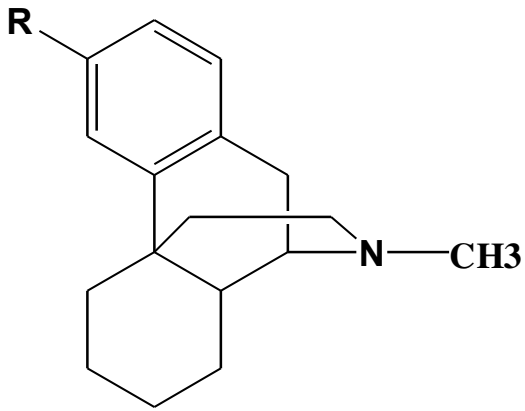


Levorphanol

SAR and structural modifications

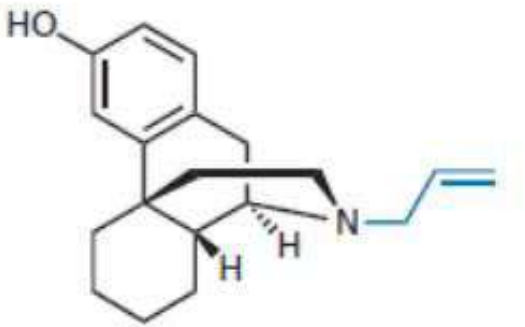
Dextromethorphan is antitussive.

Morphinans are more potent and longer-acting than their morphine counterparts, but they also have higher toxicity and comparable dependence characteristics

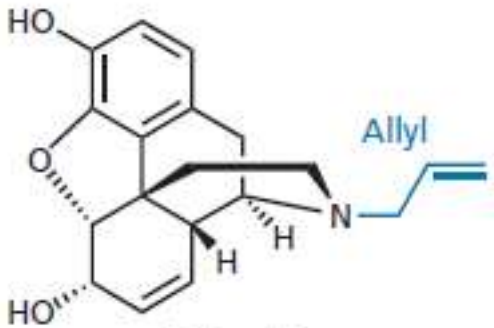


R: OH Levorphanol
R: OCH3 Dextromethorphan

Morphinan derivatives



Levallorphan
(Antagonist 5 × more potent than nalorphine)



Nalorphine

Nalorphine is **antagonist at μ-receptor**
Analgesic effect **agonist κ- receptor**

SAR and structural modifications

Changes on Morphine that increase analgesic activity	Changes on Morphine that produce antagonists
C6 - OH to OAc	N - CH_3 to $CH_2CH{=}CH_2$
C3 and C6 - OH to OAc	N - CH_3 to CH_2–cyclopropyl
C6 - OH to O-Sulfate or O-glucuronide	
C6 - OH to =O and C7-C8 single bond	
C6 - OH to H and C7-C8 single bond	
C14 - H to βOH	
N - CH_3 to CH_2CH_2Ph	
N - CH_3 to CH_2CH_2furan	
N - CH_3 to $CH_2C{=}OPh$	
Removal of C4-C5 ether link	

Figure 24.6 • Summary of functional group changes on morphine structure.

Opioid analgesics

Part 2

Dr. Mai Ramadan

4,5-α- Epoxymorphinan derivative (μ-agonist)

Opioid	Log $D_{pH7.4}$	Oral bioavailability %
Codeine	0.82	
Hydrocodone	1.36	
Oxycodone	0.38	60-90
Morphine	0.48	
Hydromorphone	1.56	
Oxymorphone	0.32	10
Levorphanol	**1.76**	

What is Log $D_{pH7.4}$?????

What is 4,5-α- Epoxymorphinan derivative ????

Remember Levorphanol is morphinan derivative

Summary of SAR for 4,5-α epoxymorphinan

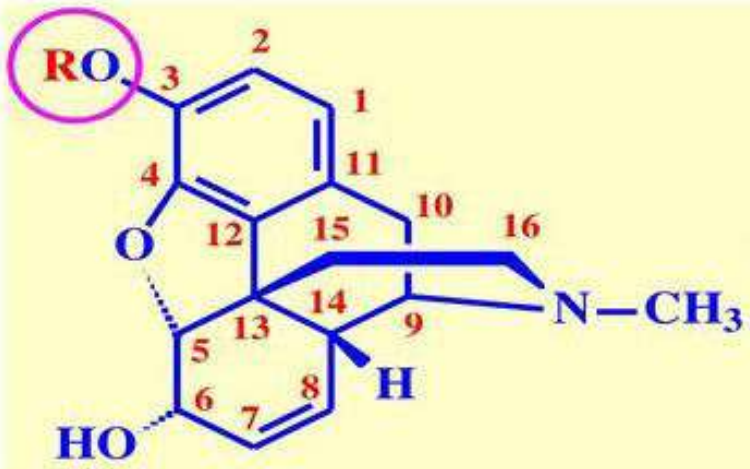
At Ring A:

- A free phenolic OH is essential for μ receptor (analgesia) affinity, but as a polar group leads to poorer oral bioavailablity (first pass glucuronidation) e.g. morphine

- Conversion of the 3-OH to ether 3-OR causes decease in μ receptor affinity and analgesic effect. Codeine is a prodrug for its analgesic effect. However, etherification increases antitussive effectiveness, Log D and bioavailability.

- Esterification of 3-OH decreases analgesic effect. It must be hydrolyzed at C3 to produce free OH and interact with receptor.

Remember



R = H MORPHINE

R = Me CODEINE
R = Et ETHYLMORPHINE
R = Acetyl 3-ACETYLMORPHINE

Analgesic Activity

Morphine: Mu, Kappa, Delta Agonist

Codeine (Mu (w), Delta (w))

Summary of SAR for 4,5-α epoxymorphinan

At Ring A:

- Esterification at 3-OH and 6-OH

Heroin (Diacetyl morphine) has increased log D and enhanced penetration through BBB. 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 . 6-Acetyl morphine is 2-3 folds more potent than morphine. It has intense euphoric make it popular for abuse.

Example: heroin

Remember

Heroin (Diacetyl morphine)

R: CH3 CO-

R: CH3CO-

Summary of SAR for 4,5-α epoxymorphinan

At Ring C

- 6-α-OH is a polar and **not essential** for receptor interaction. Modify 6-OH to 6-OCH_3 increases lipophilicity and μ receptor affinity (Analgesic effect). Example: Heterocodeine, a structural isomer of codeine, which is more potent than even morphine.

- Esterification of 6-OH increases lipophilicity and analgesic effect . Example 6-acetylmorphine is more potent than morphine.

- Removal of 6-OH and replacement with H increases lipophilicity and μ receptor affinity. Activity increases 10 folds.

- Replacing hydroxyl with methyl or methylene increases μ receptor affinity. Example: nalmefen

Remember
Alcoholic OH at 6

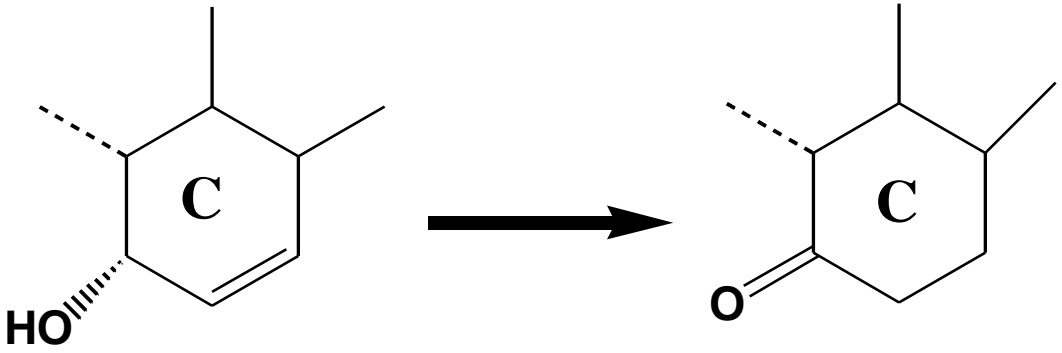
R		Analgesia wrt morphine
Me	Heterocodeine	5x
Et	6-Ethylmorphine	greater
Acetyl	6-Acetylmorphine	4x

Summary of SAR for 4,5-α epoxymorphinan

Ring C Modifications

- Oxidation of 6-OH to keto group (Polar group, H-bond acceptor) decreases analgesic effect (1/3 effect)

- Changing natural 7,8-dehydro-6α-ol to 7,8-dihydro-6-one results in **6 times** gain analgesic potency and increase Log D. e.g. Hydromorphone



7,8-dehydro-6α-ol **7,8-dihydro-6-one**

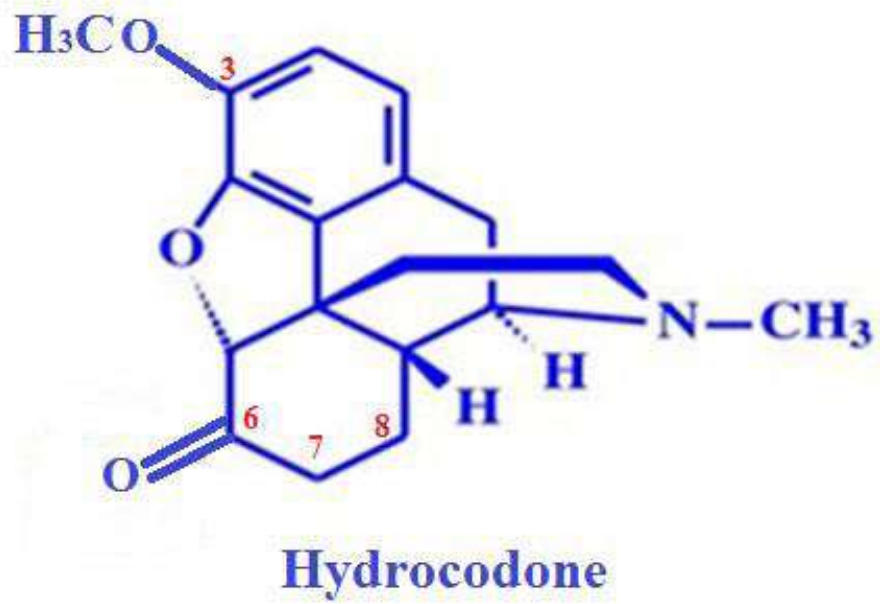
The C ring is more flexible (no double bond) and can take chair conformation and position keto group for high affinity binding. Examples: Hydromorphone, hydrocodone

Remember

Ring C: 7,8-dihydro-6-one

Hydromorphone

Log D at pH7.4 : 1.56



Hydrocodone

Log D at pH7.4 : 1.36

Summary of SAR for 4,5-α epoxymorphinan

At C-14

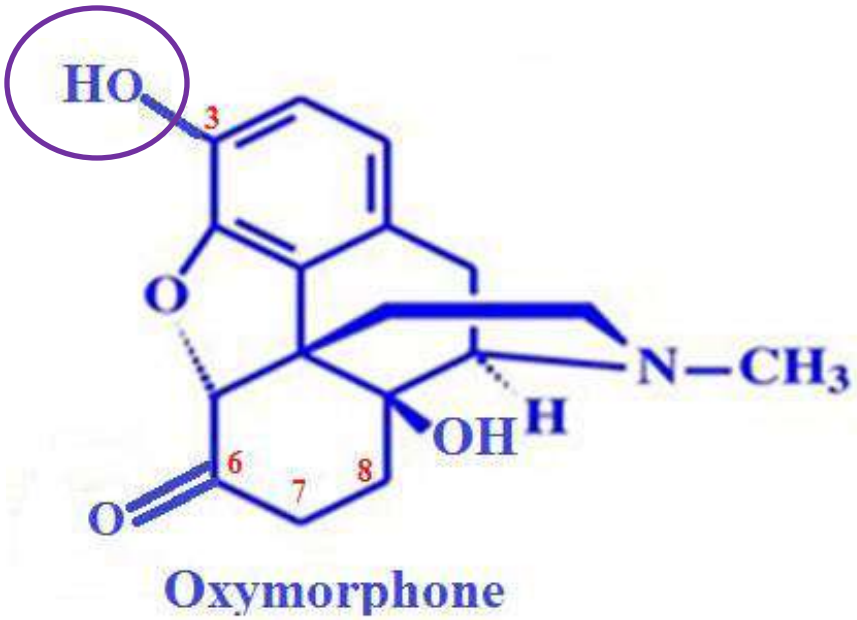
- 14β-OH at C-14 decreases log D but enhances μ receptor affinity. At μ receptor, 14 β-OH bonds very effectively with Tyr residue. At κ receptor the bonding residue is Glu.

- 14β-OH derivative are more potent (2-3 folds analgesia) and have decreased antitussive action.

- Oxycodone is more potent than hydrocodone

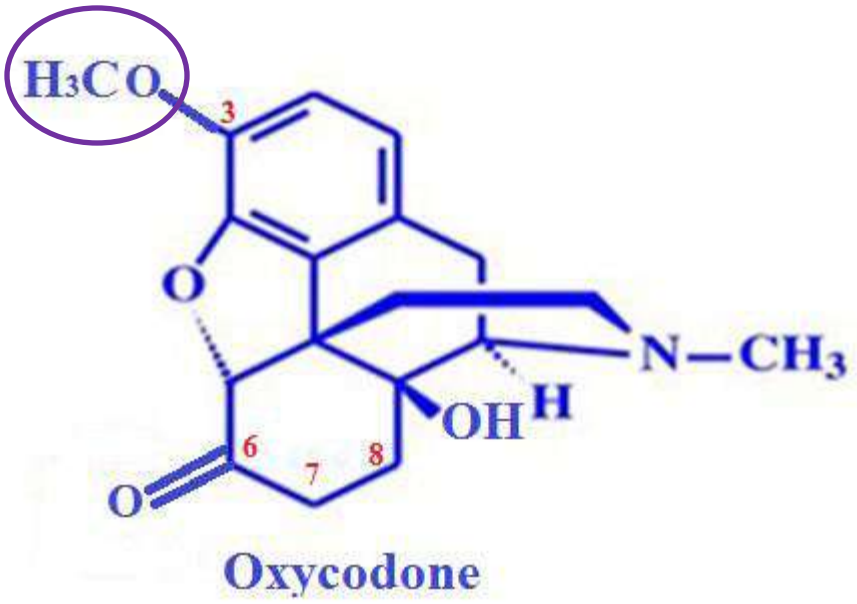
Remember

Ring C: 7,8-dihydro-6-one & 14β-OH at C-14



Oxymorphone

Log D at pH7.4 : 0.32

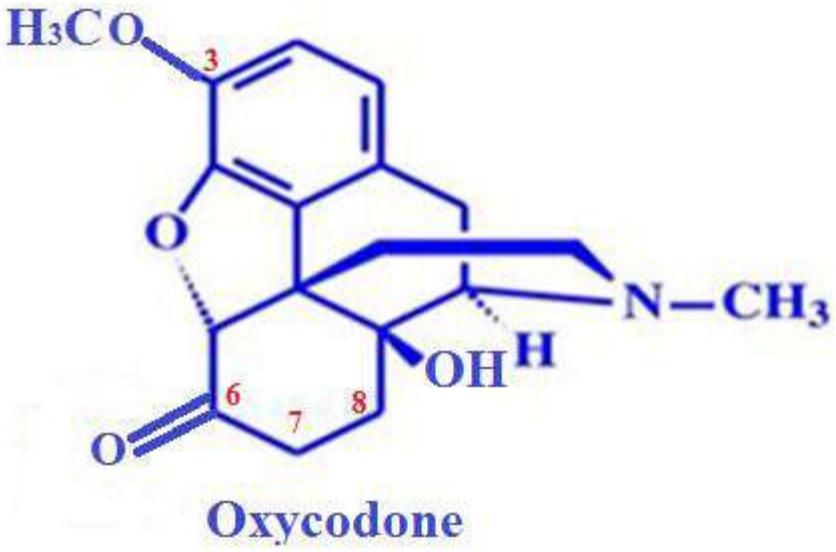


Oxycodone

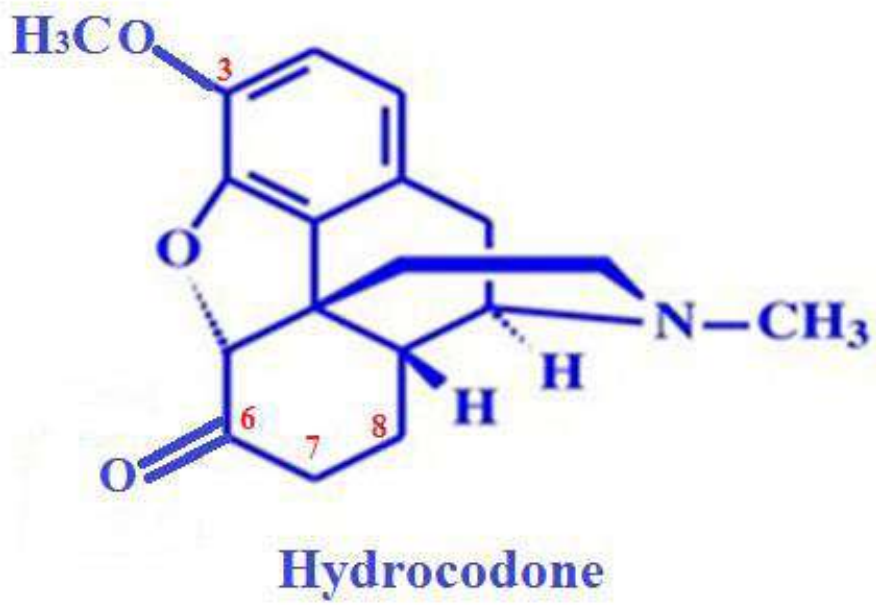
Log D at pH7.4 : 0.38

Remember

Oxycodone is more potent than hydrocodone



Oxycodone



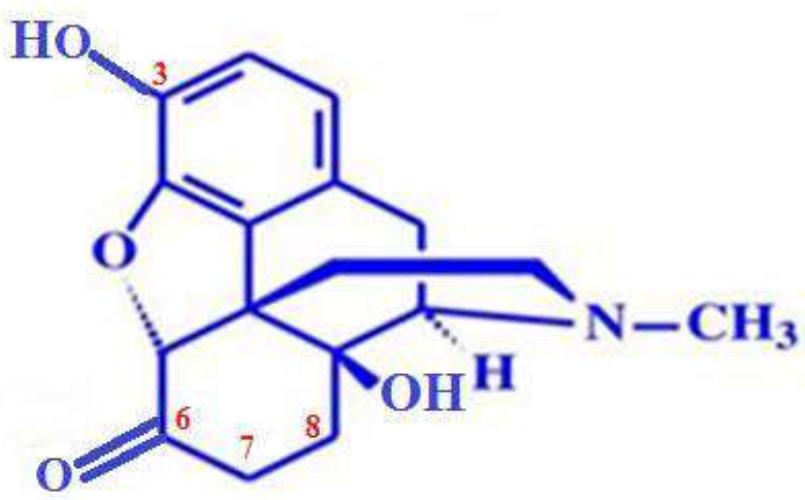
Hydrocodone

Log D at pH7.4 : 0.38

Log D at pH7.4 : 1.36

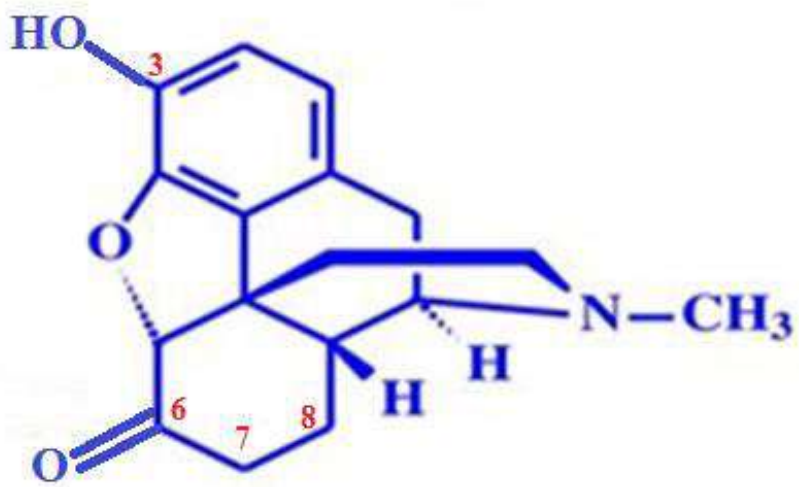
Remember

Oxymorphone is more potent than Hydromorphone injectable



Oxymorphone

Log D at pH7.4 : 0.32



Hydromorphone

Log D at pH7.4 : 1.56

Summary of SAR for 4,5-α epoxymorphinan

At Ring D

- Tertiary amine is **essential** for activity. Replace –NR by –CHR results in loss of activity.

- Removal of N-methyl decreases lipophilicity and activity (Normorphine)

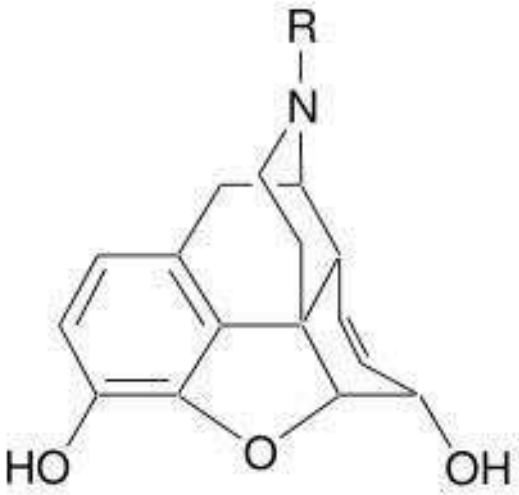
- Quaternerization decreases lipophilicity and loss of activity.

- When alkyl group (N-alkyl) increases in size (C2-5), decreases μ receptor affinity through steric hindrance. When R is of 4C inactive

- When R is more than 5C, hexyl, aralkyl the potency is increased. R:(-CH2CH2Ph) the compound has 14X potency of morphine.

Remember

Summarizing the Effects of altering chain length on N of morphine structure



$R = CH_3$ Morphine

$= CH_2CH_3$

$= CH_2CH_2CH_3$

Agonist activity decreases
antagonist activity increases

$= CH_2CH_2CH_2CH_3$ No activity

$= (CH_2)_4CH_3$

$= (CH_2)_5CH_3$

Agonist activity increases

$= CH_3CH_2$– 

14x morphine

Summary of SAR for 4,5-α epoxymorphinan

At Ring D

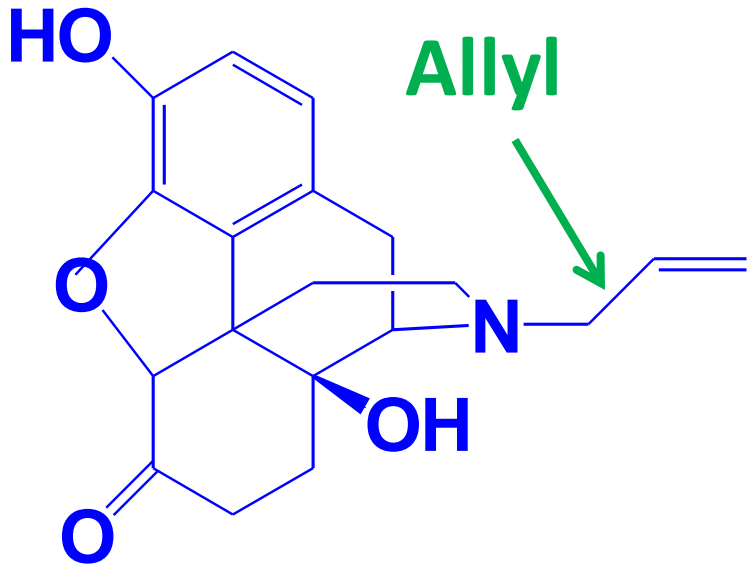
- N-Alkyl substituent is **branching, unsaturated or strained ring results in antagonism**

- Optimal antagonism at μ receptor when N-R is of **3C like allyl** (Naloxone) and **cyclopropylmethyl** (Naltrexone)

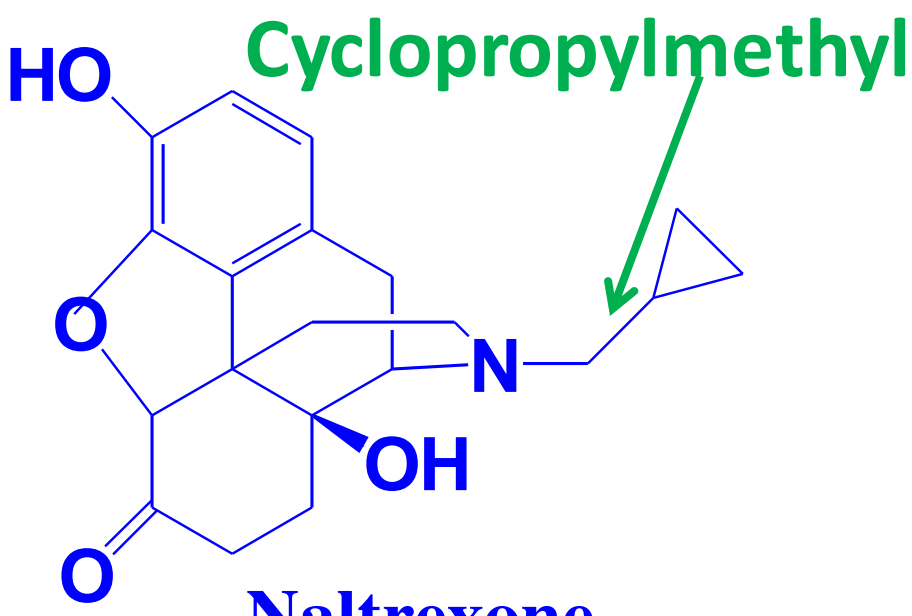
- When N-R is cyclobutylmethyl or dimethylallyl the antagonism is weak .

- Removal of C15 (breakage of ring D) decreases μ-receptor affinity.

Remember



Naloxone

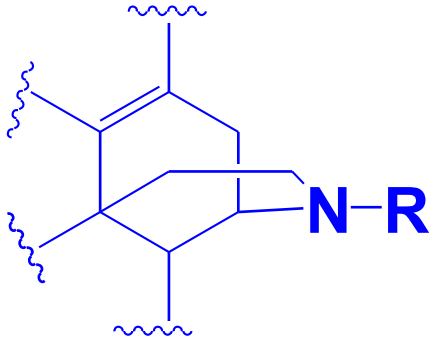


Naltrexone

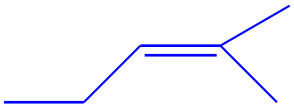
Pure antagonist

Remember

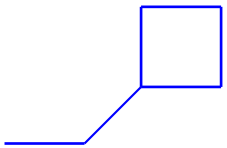
R at N



R: Dimethylallyl



R: Cyclobutylmethyl



Antagonism at Mu receptor decreaes and agonism increases at kappa receptor

Mixed agonist antagonist

Summary of SAR for 4,5-α Epoxymorphinan

At Ring E

- 4,5α-epoxy bond is **not essential** and does not affect μ receptor affinity

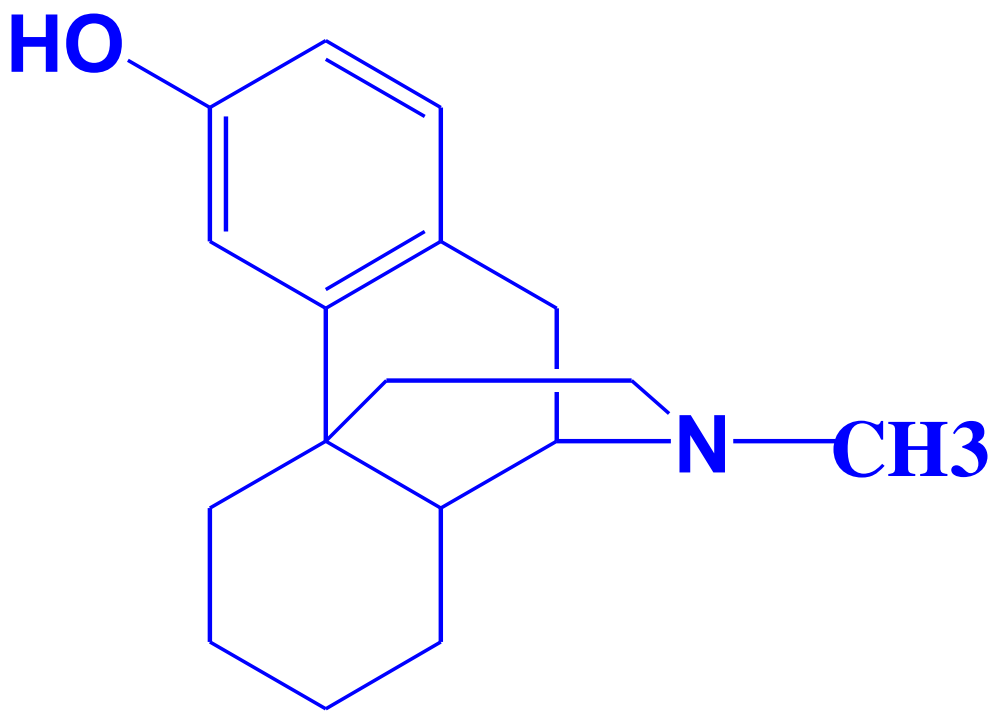
- Removal of 4,5α-epoxy (Removal of ring E, Tetracyclic opioid, Morphinan) increases Log D. In general, a morphinan is overall more potent than the corresponding 4,5-α-epoxymorphinan.

Example: Levorphanol is 7.5 times more potent than morphine

Remember

Removal of ring E

Tetracyclic opioid



Levorphanol

Opioid Analgesics

Part 3

Dr. Mai Ramadan

- **Semi-synthetic opioid**

Codeine, Heroin, Hydromorphone, Hydrocodone, Oxymorphone, Oxycodone

4,5-α –Epoxymorphinan (μ-agonist)

Codeine:

Natural opioid.

Source: opium, semisynthesis from morphine

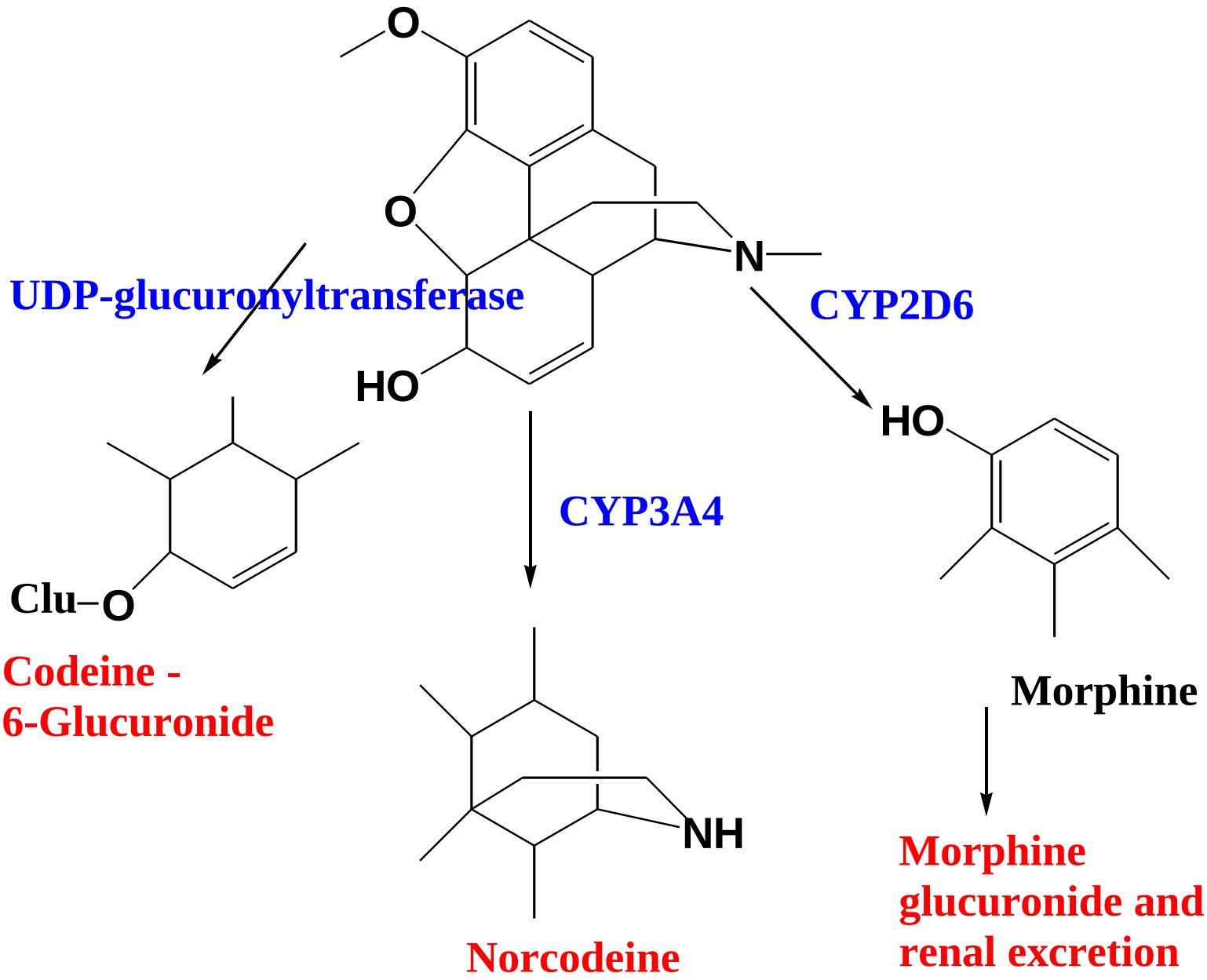
Drug used as salts: sulfate, phosphate

Antitussive
In combination with paracetamol and ibuprofen for moderate pain.

Ca 5% of codeine is metabolized to morphine via CYP2D6 (genetic polymorphism)

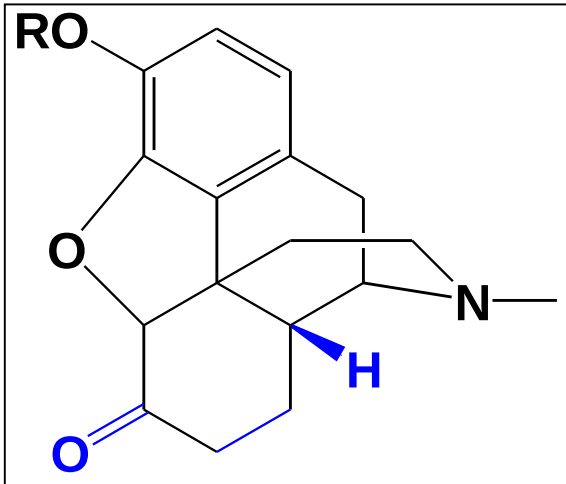
Codeine is a prodrug of morphine more lipophilic with better bioavailability.

4,5-α- Epoxymorphinan

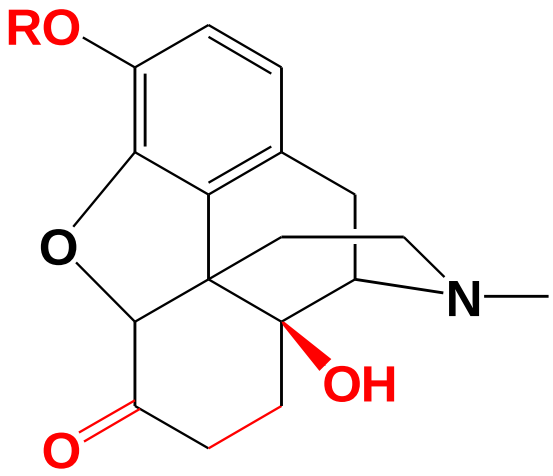


4,5α -Epoxymorphinan

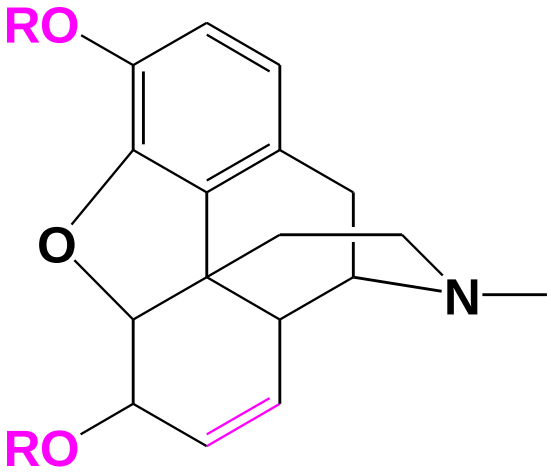
(μ-agonist)



R: H **Hydromorphone**
R: CH3 **Hydrocodone**

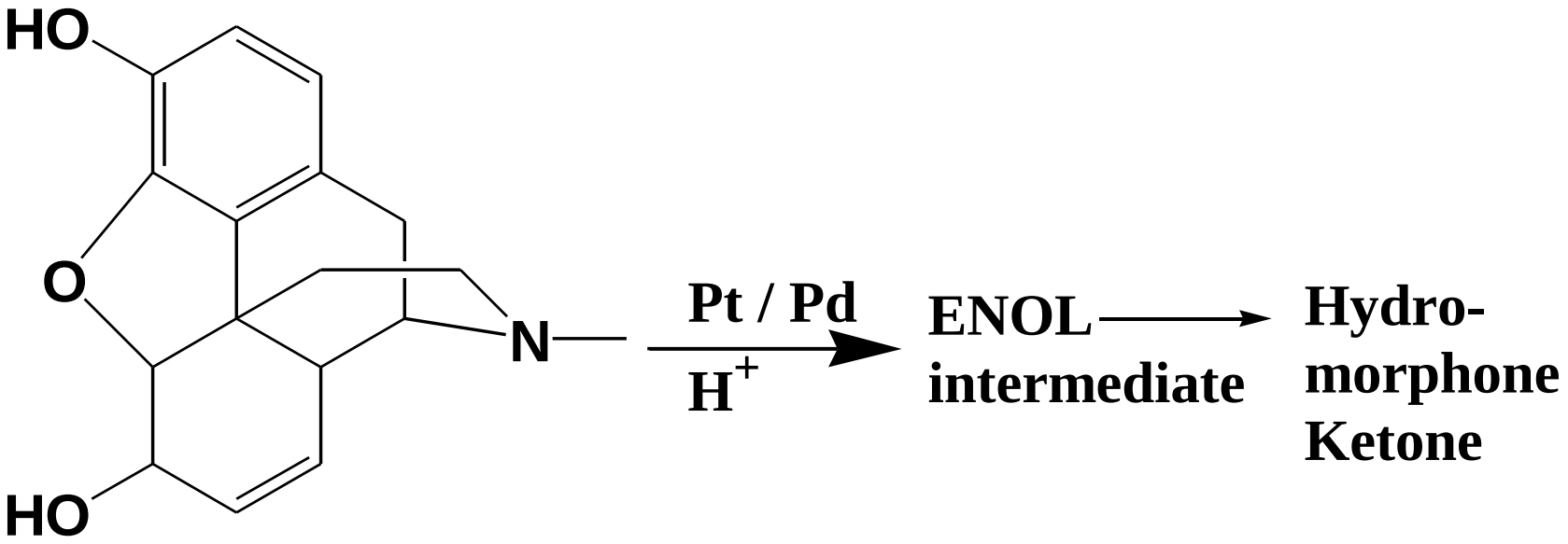


R: H **Oxymorphone**
R: CH3 **Oxycodone**



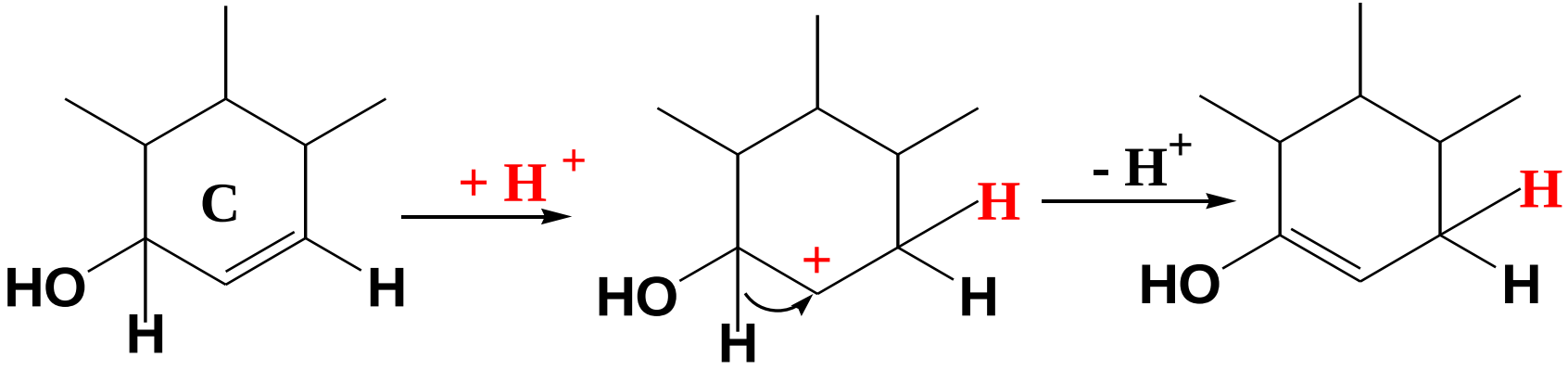
R: -COCH3 **Heroin**

Synthesis of Hydromorphone: Semisynthetic opioid

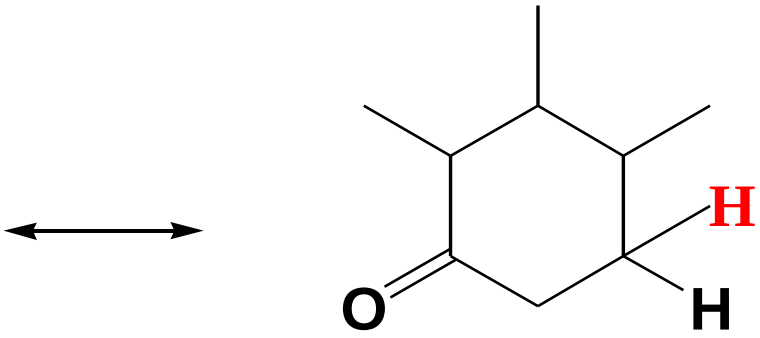


Morphine

Synthesis of Hydromorphone: Semisynthetic opioid



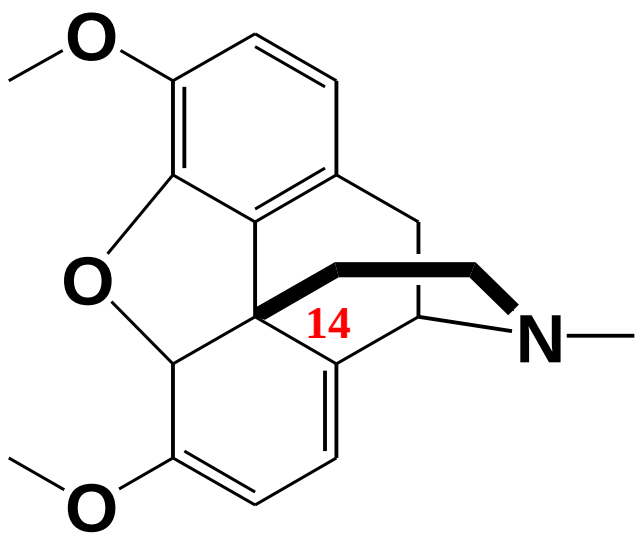
Morphine



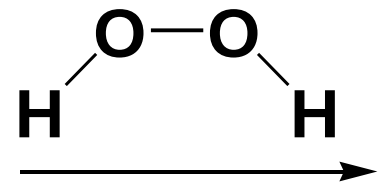
Hydromorphone

Synthesis of Oxycodone: Semisynthetic opioid

Synthesis of Oxycodone: Semisynthetic opioid

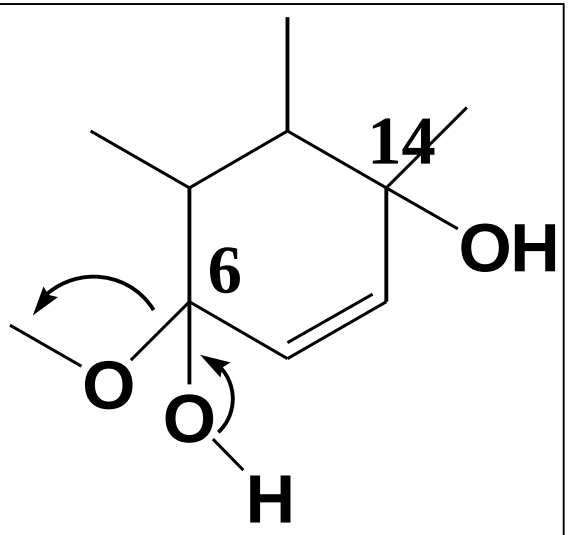


Thebaine



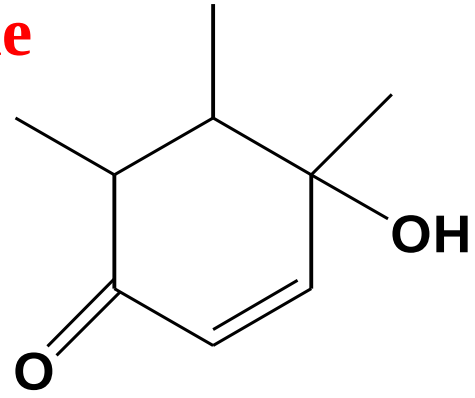
+ CH_3COOH

1,4-Addition



Hemiketal

- CH_3OH



14-hydroxycodeinone

H_2 / Pt

Oxycodone

Semisynthetic opioid: Heroin

Synthesized in 1898 by Bayer company in Germany as an alternate analgesic to morphine

Salicylic acid + $(CH_3CO)_2O$ ⟶ Aspirin [F. Hoffman, 1897]

Morphine + $(CH_3CO)_2O$ ⟶ Heroin [H. Dresser]

The product named heroin because it made the test subjects, including some of the chemists, feel "heroic." It is 2X potent than morphine

Heroin in **BP** (Monograph) as **Diamorphine HCl**

Tests:

IR

UV

Heroin + C_2H_5OH $\xrightarrow{+ H^+}$ Smell of ethylacetate

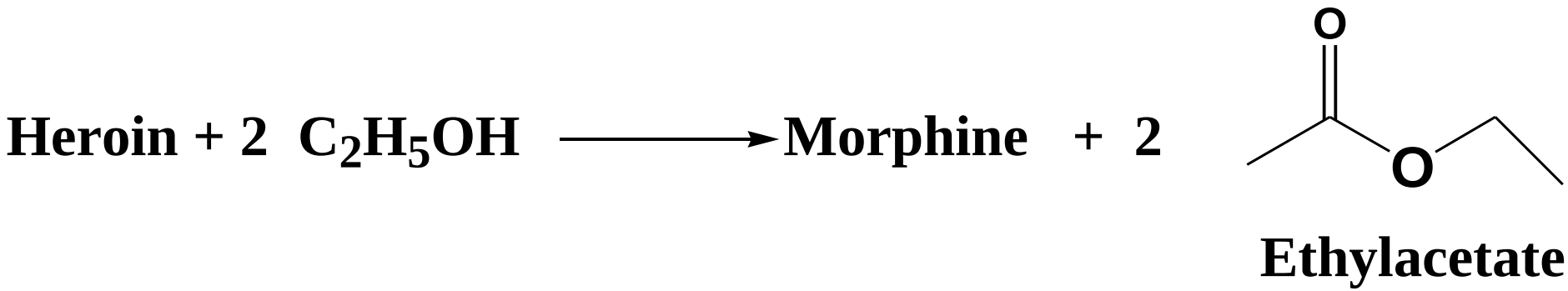
Heroin + H_2SO_4 + $K_3[Fe(CN)_6]$ $\xrightarrow{+Fe^{+3}}$ Blue colored complex

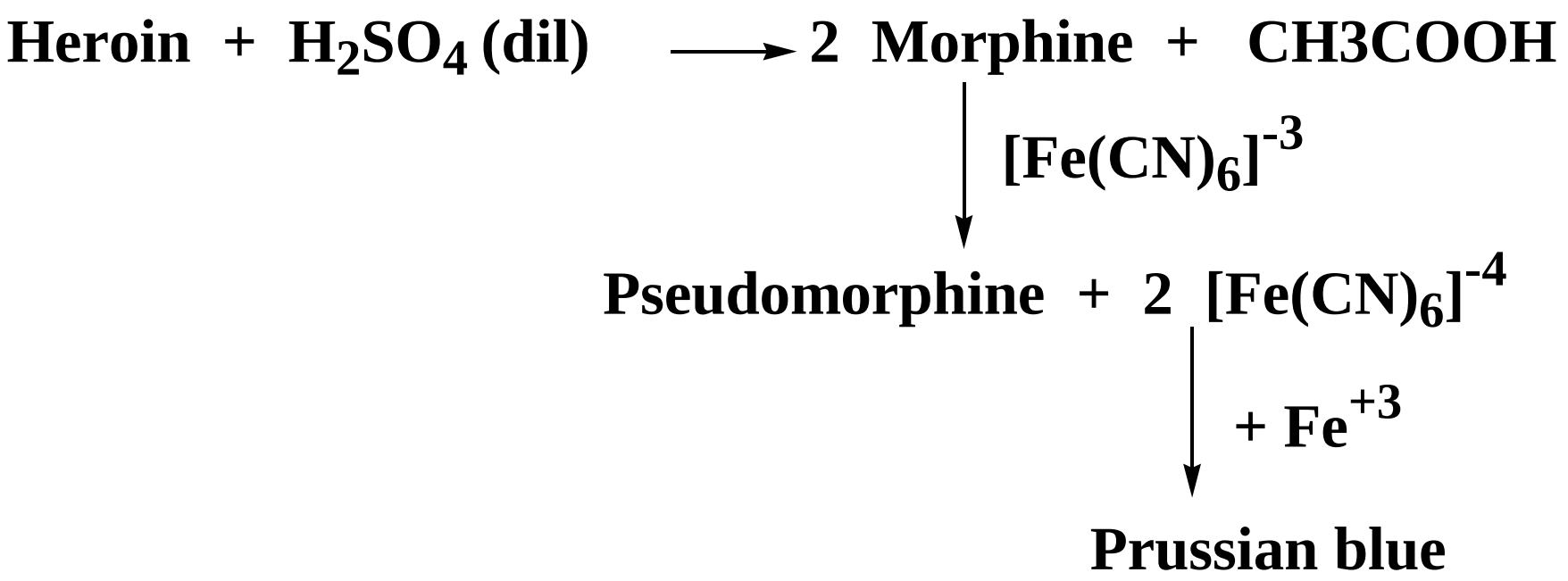
Pass through BBB quicker than morphine

In brain rapid metabolism to 3-acetylmorphine (inactive) and 6-Acetylmorphine (2X potent as morphine)

Semisynthetic opioid: Heroin

What is characteristics between IR spectrum of morphine and heroin?





Semisynthetic opioids

Hydromorphone vs Oxymorphone

Oxymorphone is 14-β-hydroxy of hydromorphone, more potent (2-3 folds, **IV**) than hydromorphone.

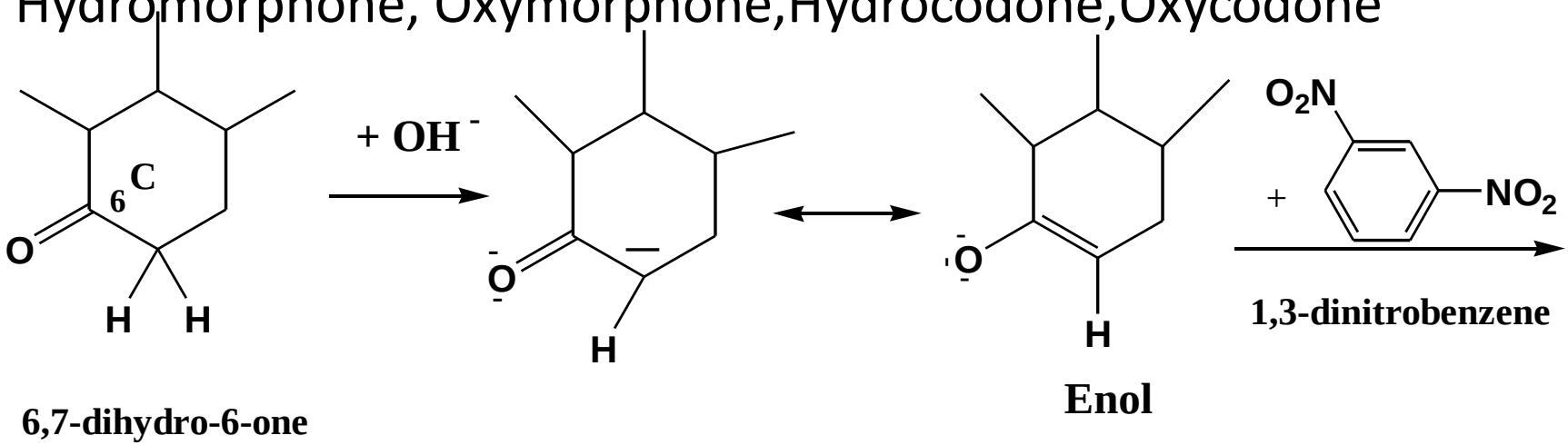
Oral bioavailability of oxymorphone (10%) is lower than that of hydromorphone (35%) because of decreased absorption (Log D) and increased first-pass metabolism

Oxycodone is the 14 beta-hydroxyl version of hydrocodone. This additional functional group gives oxycodone greater potency (1.5 times **orally**) than hydrocodone.

Codeine, hydrocodone, oxycodone are prodrugs must be demethylated to phenolic 3-OH by CYP2D6 for binding with opioid μ receptor. They have enhanced bioavailability.

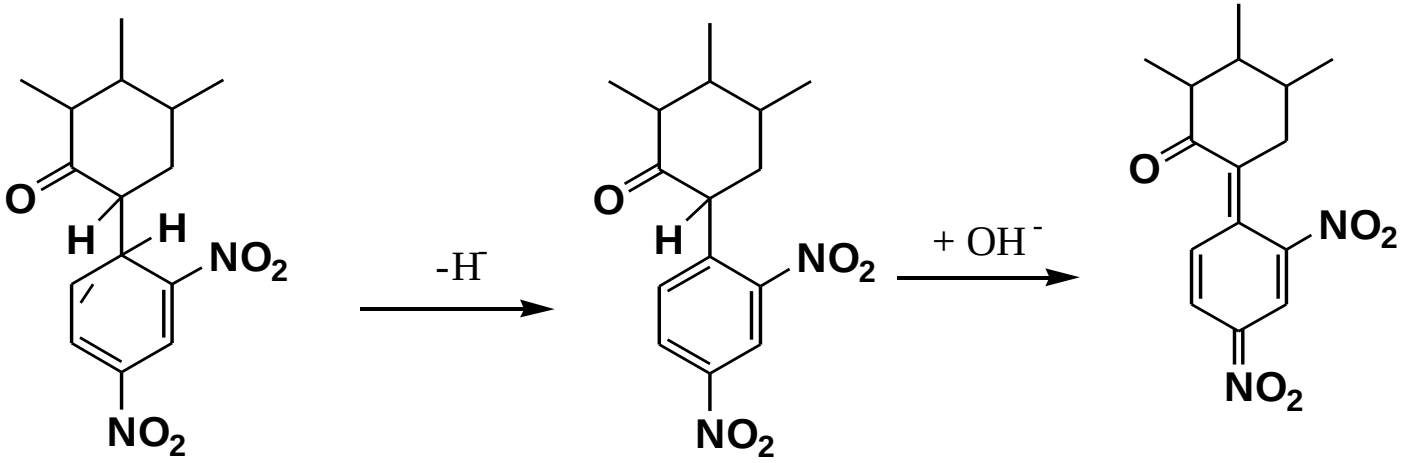
Semisynthetic opioids: A common test for 6-keto derivatives

Hydromorphone, Oxymorphone,Hydrocodone,Oxycodone



6,7-dihydro-6-one

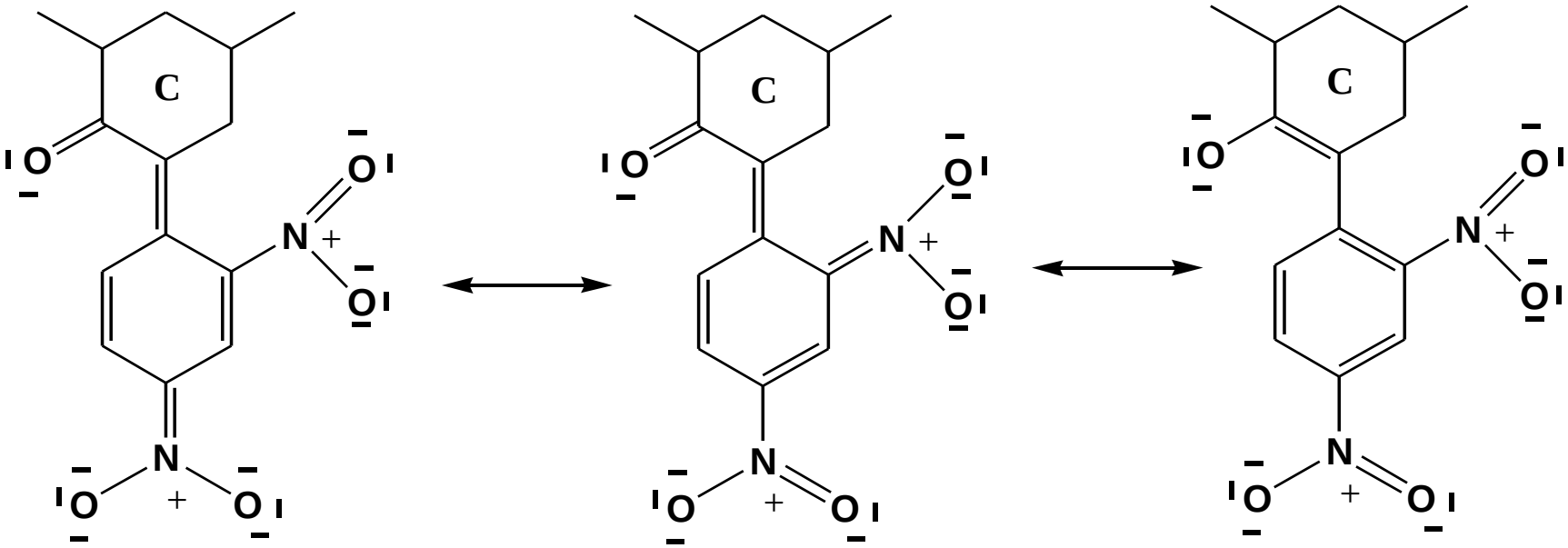
Enol



Zimmerman product
colored compound

Semisynthetic opioids: A common test for 6-keto derivatives

Hydromorphone, Oxymorphone, Hydrocodone, Oxycodone



Zimmerman product, colored compound

Opioid Analgesics
Part 4

Dr. Mai Ramadan

- Synthetic opioid

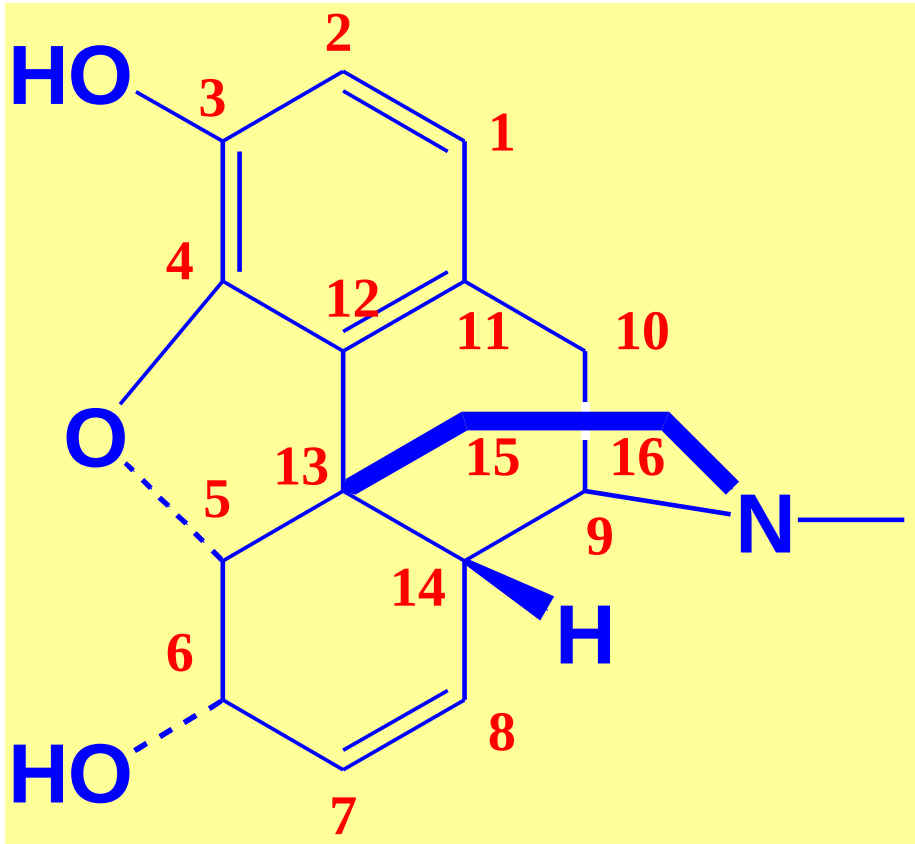
Morphinan

Levorphanol

Butorphanol

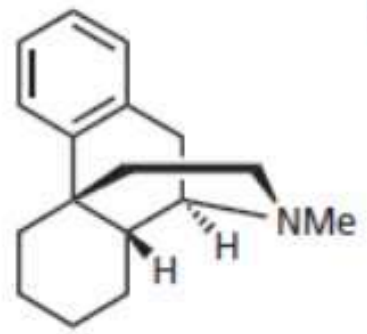
levallorphan

❑ Remember all the time structure of morphine (5 ring system)

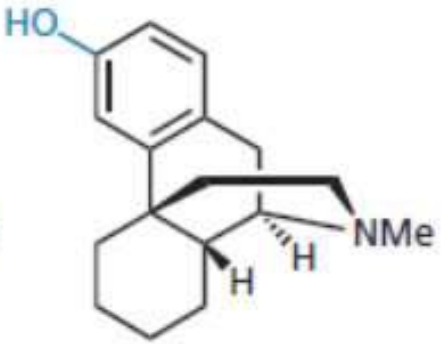


Synthetic opioids: Morphinan

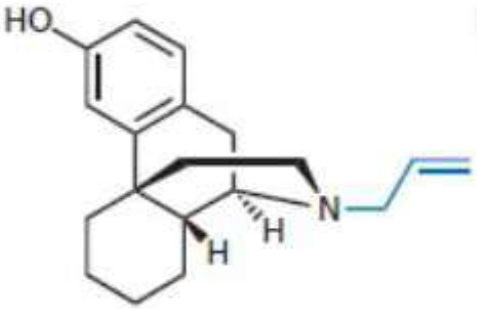
SAR of morphinan Like 4,5-α-epoxymorphinan



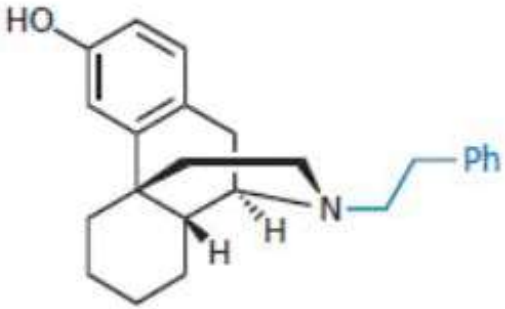
N-Methylmorphinan
(20% activity of morphine)



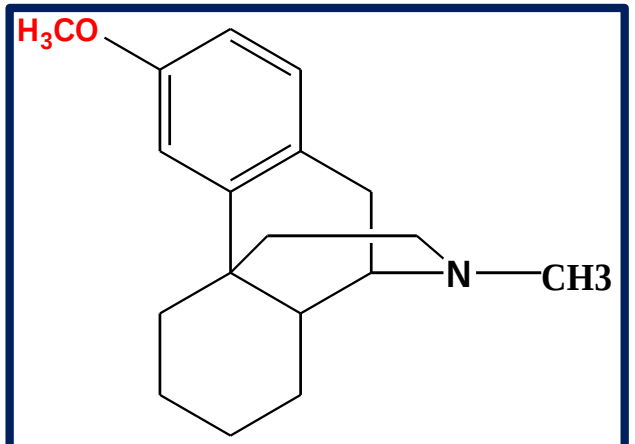
Levorphanol
(5 × more potent than morphine)



Levallorphan
(Antagonist 5 × more potent than nalorphine)



N-Phenethyllevorphanol
(15 × more potent than morphine)



(+) Dextromethorphan

Antitussive

Synthetic opioids: Morphinan

***N* –Methylmorphinan:**
Only 20% as active as morphine

Levorphanol:
(Phenolic –OH) five times more active than morphine

Dextrorphan :
Enantiomer of levorphanol insignificant analgesic activity

N-Alkyl substituent: CH3 is optimal

adding an allyl substituent on the nitrogen gives antagonists.
Adding a phenethyl group to the nitrogen greatly increases potency.

14 hydroxyl group:
Adding a 14-hydroxyl group increases affinity to μ receptor

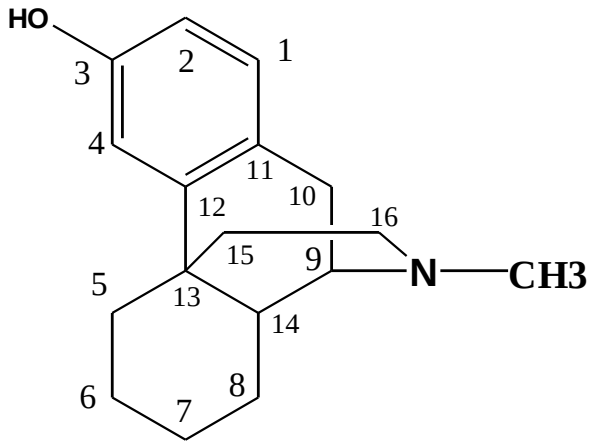
Synthetic opioids: Morphinan

Morphinans are more potent and longer-acting than their morphine counterparts, but they also have higher toxicity and comparable dependence characteristics

Modifications carried out on the morphinans have the same structure–activity relationship (SAR) results as they do with morphine. This implies that morphine and morphinans are binding to the same receptors in the same way

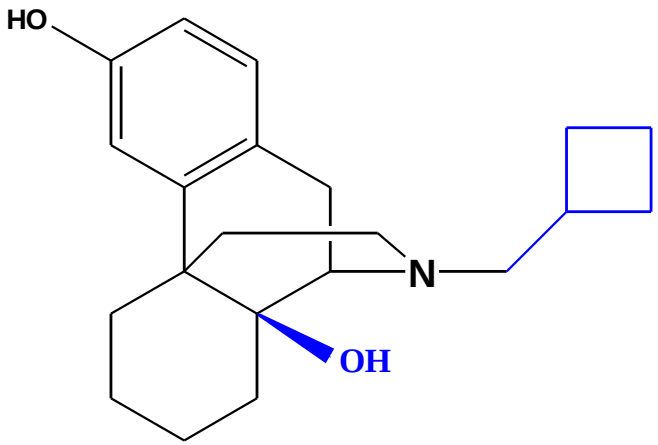
Morphinans are easier to synthesize as they are simpler molecules with fewer rings and chiral centers

Synthetic opioids: Morphinan



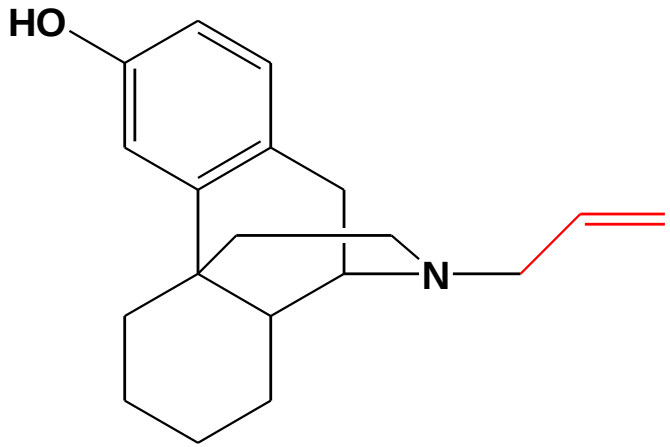
Levorphanol

Agonist, levo-isomer



Butorphanol

Mixed agonist antagonist



Levallorphan

Antagonist

Synthetic opioids: Morphinan

Levorphanol:

Levorphanol tartarate , Levorotary isomer, Tetracyclic opioid

Analgesic activity is 7.5 more potent than morphine

Log $D_{pH7.4}$: 1.76 (Loss of polar groups: Ring E, 6-OH)

More flexible molecule (loss of ring E, No double bond at C7,8)

Duration of action 6-8 h (twice that of morphine)

Renal excretion

Synthetic opioids: Morphinan

Butorphanol: Mixed κ-agonist, μ-antagonist

High affinity for the κ -receptors is proposed to give butorphanol its analgesic properties and CNS side effects.

Little dependence liability

Limited respiratory depression

No oral dosage forms (first pass effect)

Nasal spray, and injection

- Synthetic opioids:

Benzomorphan

Pentazocine

Phenazocine

Bremazocine

Synthetic opioids: Benzomorphan

Benzomorphan: Loss of ring E and C

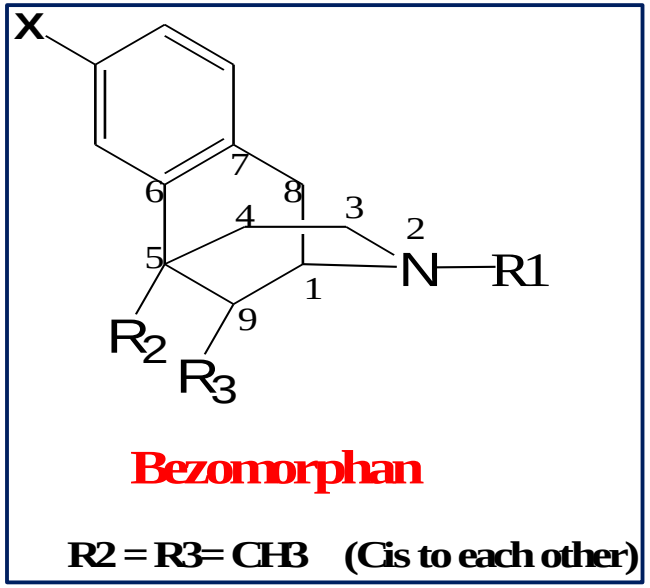
Tricyclic opioid

Metazocine: The same analgesic activity as morphine

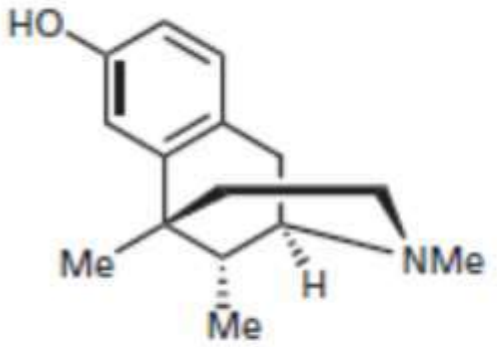
Phenazocine

Pentazocine

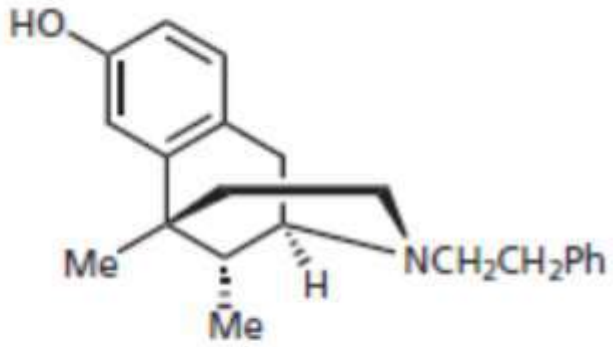
Bremazocine



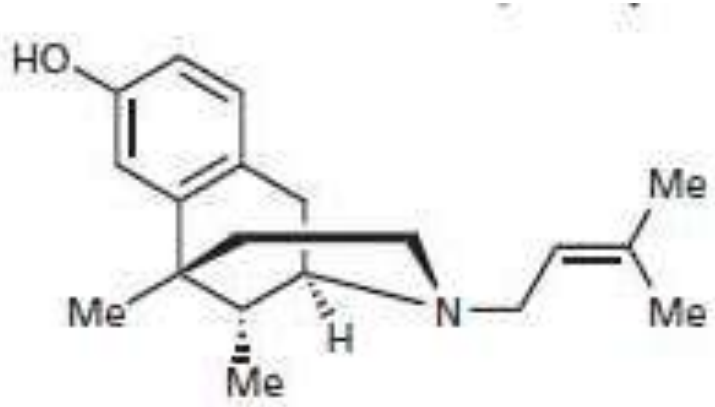
Synthetic opioids: Benzomorphan



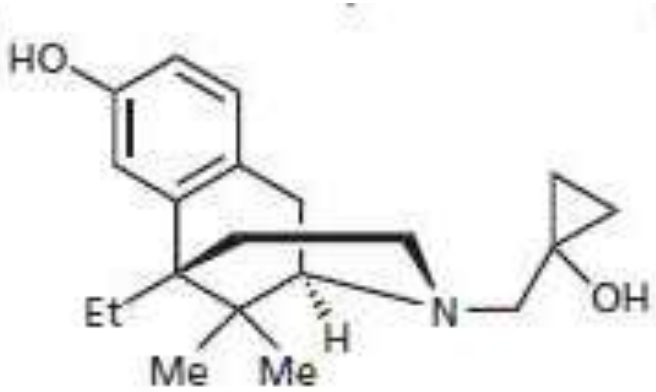
Metazocine
(same potency as morphine)



Phenazocine
(4 × more potent than morphine)

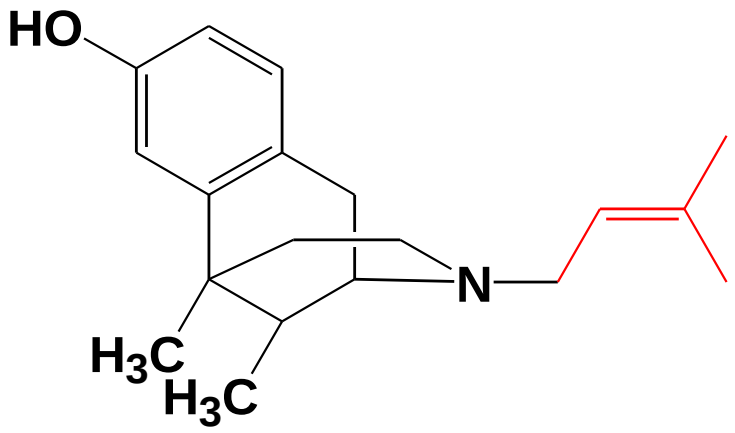


Pentazocine
(33% activity of morphine, short duration, low addiction liability)



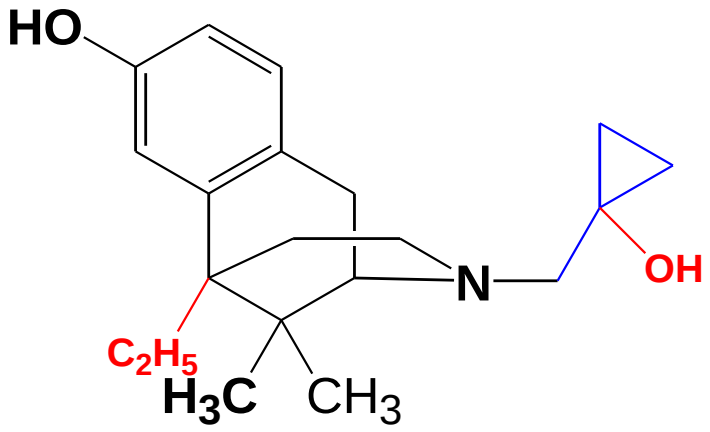
Bremazocine

Synthetic opioids: Benzomorphan

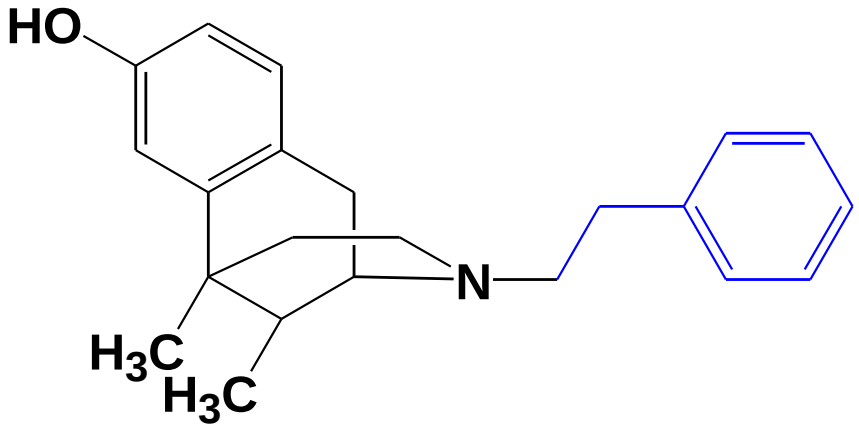


Pentazocine

Mixed agonist antagonist



Bremazocine
200X morphine



Phenazocine
Agonist 4X morphine

Synthetic opioids: Benzomorphan

Pentazocine: Mixed κ-agonist, μ-antagonist

N substituent Dimethylallyl produce a weak antagonist at μ receptor, full agonist at **κ- receptor**

Only **levorotatory isomer** is analgesic (where are chiral centers)

Analgesic effect is 33% that of morphine.
Hallucinogenic and psychotomimetic side effects as a result of activating the κ receptor

Phenazocine is not more used in USA, England

Synthetic opioids: Benzomorphan

Bremazocine:

longer duration, has 200 times the activity of morphine

No addictive properties, and does not depress breathing

What is the benefit of the composition in Talwin NX tablet (Pentazocine 50-mg, naloxone 0.5 mg)?

Synthetic opioids: Benzomorphan

- ❑ Rings C and E are not essential to analgesic activity

- ❑ Analgesia and addiction are not necessarily co-existent
- ❑ 6,7-benzomorphans are clinically useful compounds with reasonable analgesic activity, less addictive liability, and less tolerance

- ❑ Benzomorphans are simpler to synthesize than morphine and morphinans

- ❑ Benzomorphans bind to opioid receptors in the same manner as morphine and morphinans.

❑ Synthetic opioids:

4-phenylpiperidine

Meperidine (Pethidine)

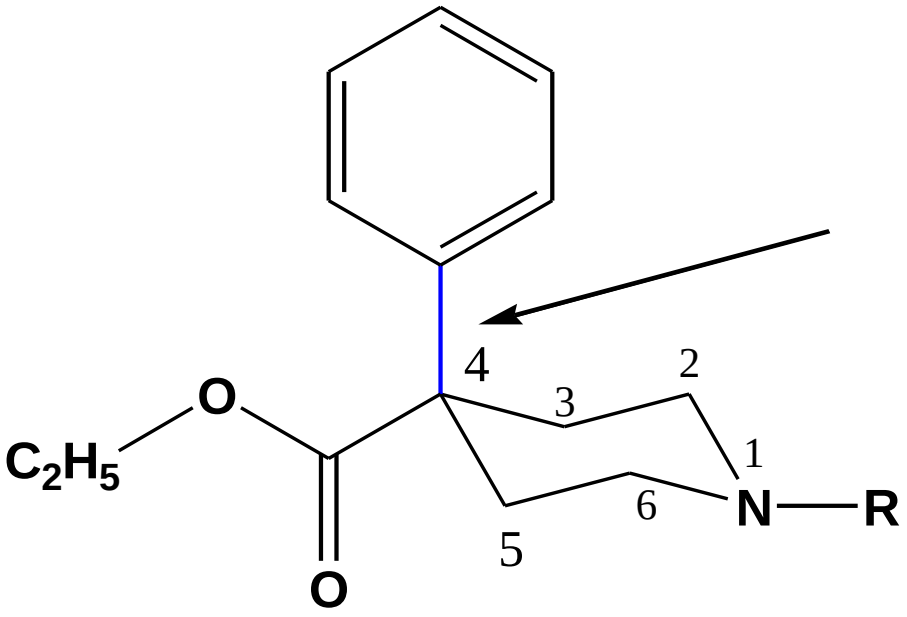
Ketobemidone

Loperamide

Synthetic opioids: 4-Phenylpiperidine

Meperidine (Pethidine): [loss of ring B,C, E]

4-phenylpiperidine



R: CH3 Meperidine

Flexible Rotation around single bond

Aromatic ring can be equatorial to piperidine ring
In multicyclic opioid axial position restriction of rotation

No chiral centers

No phenolic OH

Synthetic opioids: 4-Phenylpiperidine

Meperidine (Pethidine):

1/10 potency of morphine

Flexible Mu and kappa agonist

Poor oral bioavailability

Metabolism: Neurotoxic metabolite (Normeperidine, seizures)

Used in obstetrics (rapid onset and a shorter duration of action.)

Not more favored

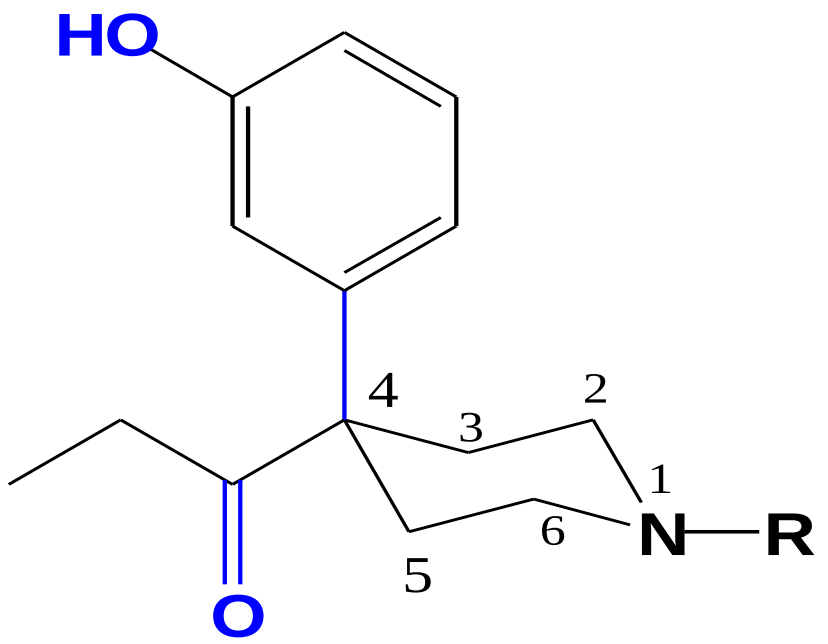
Synthetic opioids: 4-Phenylpiperidine

Ketobemidone:

Ketobemidone 6X activity of morphine

IV, Oral

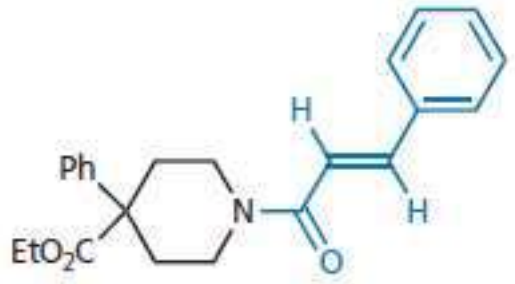
It also has some NMDA-antagonist properties. This makes it useful for some types of pain that don't respond well to other opioids.



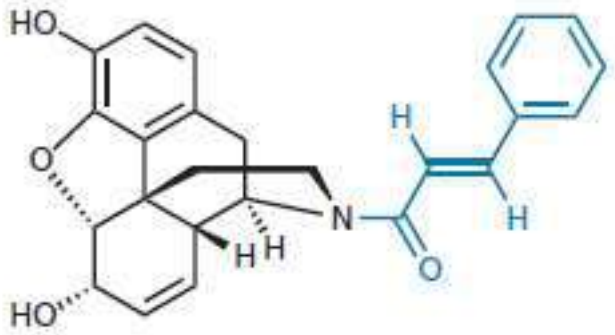
R: CH3 Ketobemidone

Synthetic opioids: 4-Phenylpiperidine

4-phenylpiperidine bind to opioid receptor in different mode than morphine



N-Cinnamoyl analogue of pethidine
30 × more potent than pethidine

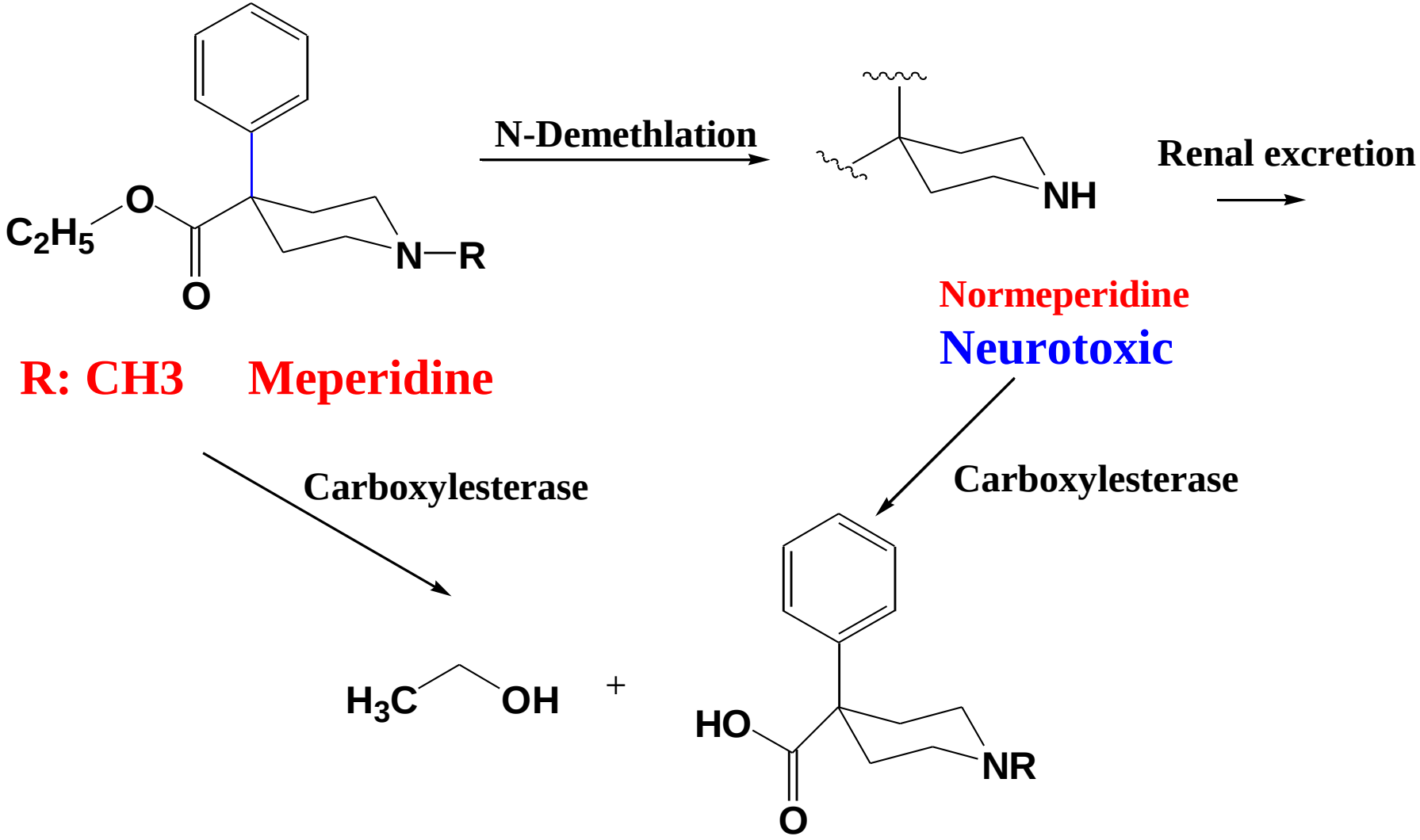


N-Cinnamoyl analogue of morphine
Zero activity

Adding allyl or cyclopropyl groups does not give antagonists.
The replacement of the methyl group of pethidine with a cinnamic acid residue increases the activity 30-fold, whereas putting the same group on morphine eliminates activity.

Synthetic opioids: 4-Phenylpiperidine

Meperidine: Metabolism



Synthetic opioids: 4-Phenylpiperidine

Loperamide:

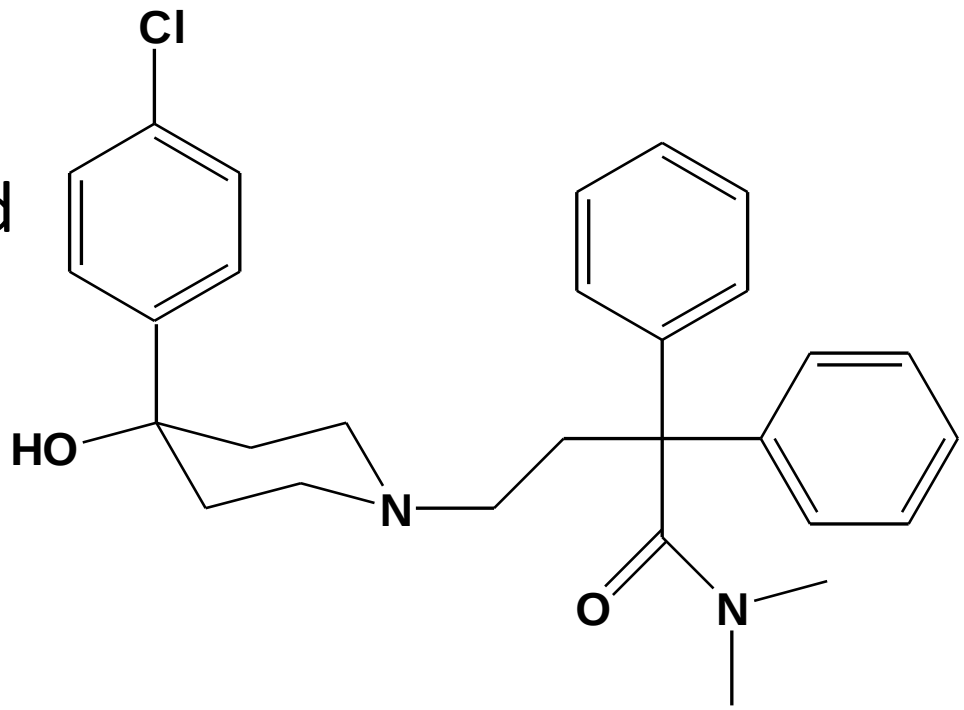
Lipophilic compound.

Because of poor water solubility—little is absorbed from the intestines

Antidiarrheal (Local effect on peripheral μ opioid in GIT)

Penetrate BBB but efflux by p-Gp.

No abuse liability



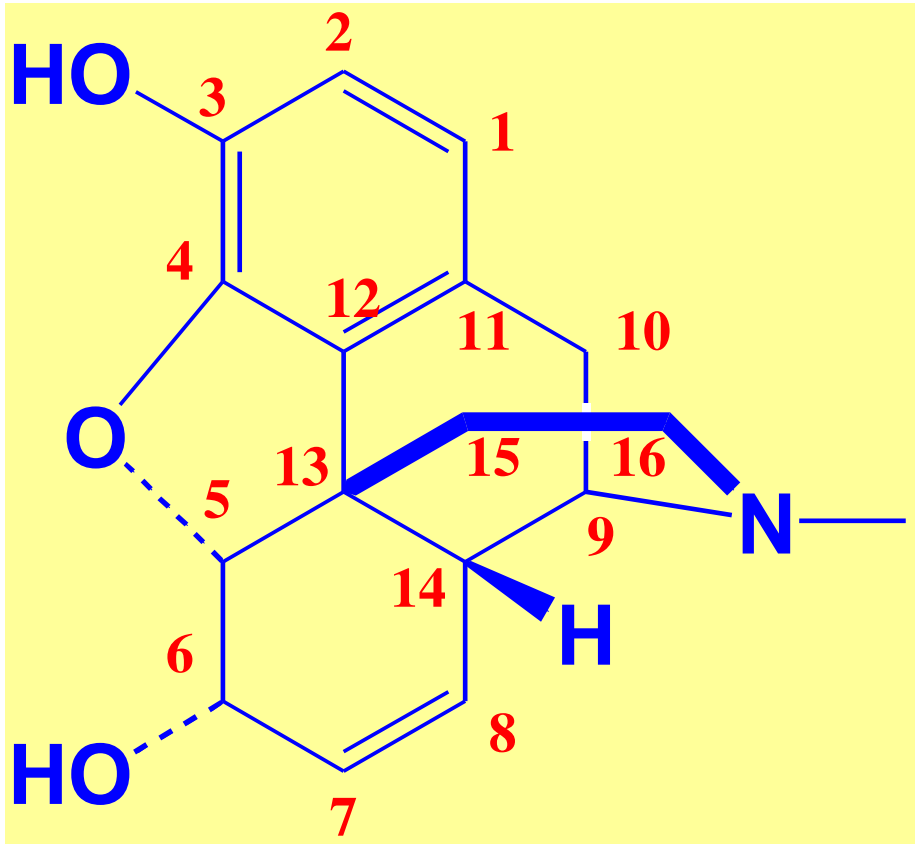
Loperamide

Study the structure!!!!

Opioid Analgesics
Part 5

Dr. Mai Ramadan

❑ Remember all the time structure of morphine (5 ring system)



Further simplification of morphine and opioid analgesic

❑ Synthetic opioids:

4-Anilidopiperidine

Fentanyl

Sufentanil

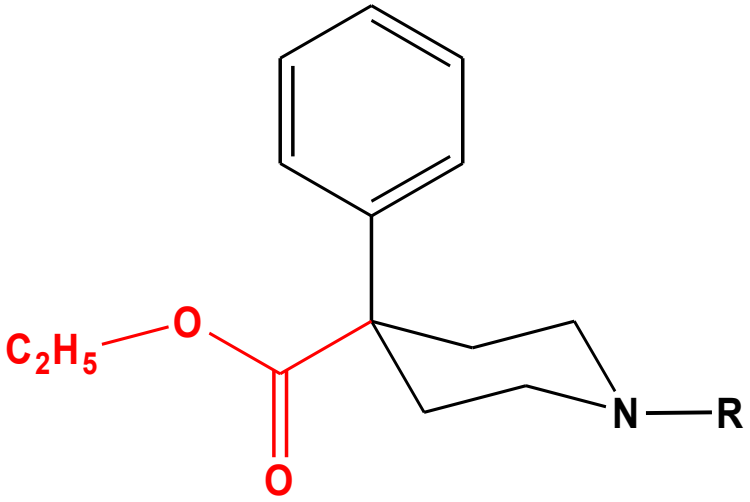
Alfentanil

Remifentanil

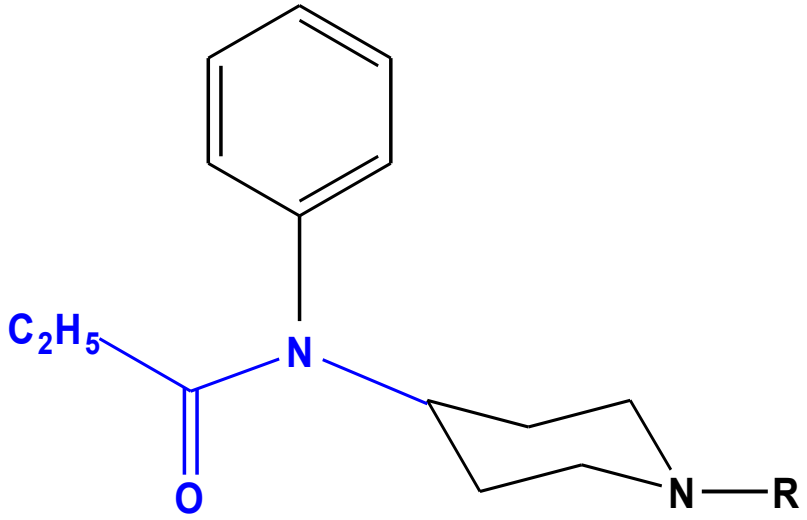
Synthetic opioids: 4-Anilidopiperidine

Fentanyl: Loss of rings B,C, E

Lipophilic, No phenolic OH, Flexible, most potent μ-receptor agonist



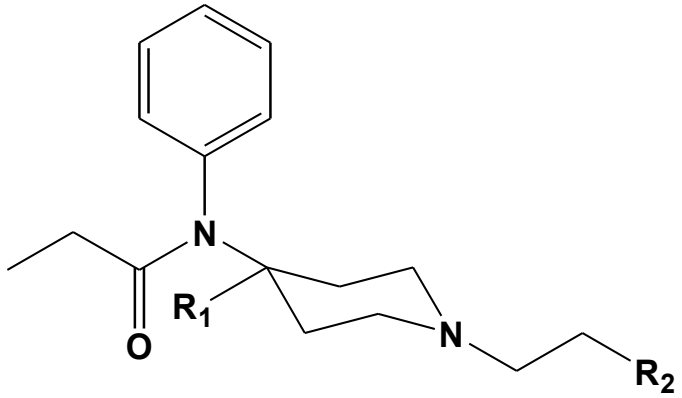
R: CH3 Meperidine



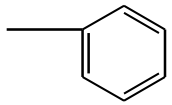
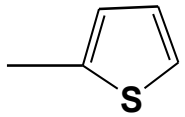
R: -CH_2CH_2Ph Fentanyl

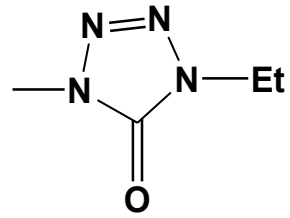
100 X activity of morphine

Synthetic opioids: 4-Anilidopiperidine



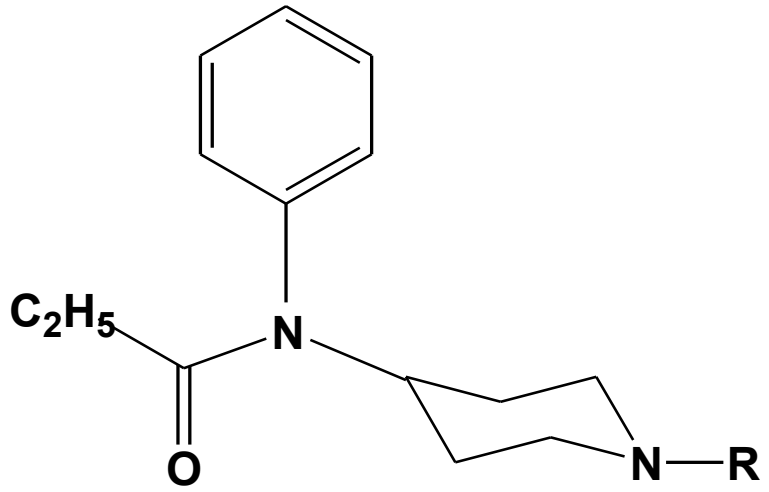
4-Anilidopiperidine derivatives

	R 1	R 2
Fentanyl	H	
Sufentanil	—CH2OCH3	

	R 1	R 2
Alfentanil	—CH2OCH3	
Remifentanil	—CO_2CH_3	—CO_2CH_3

Synthetic opioids: 4-Anilidopiperidine

Fentanyl:
50-100X more potent than morphine



R: -CH_2CH_2Ph **Fentanyl**

Rapid onset [lipophillic, 5 min]

Short duration [metabolism]

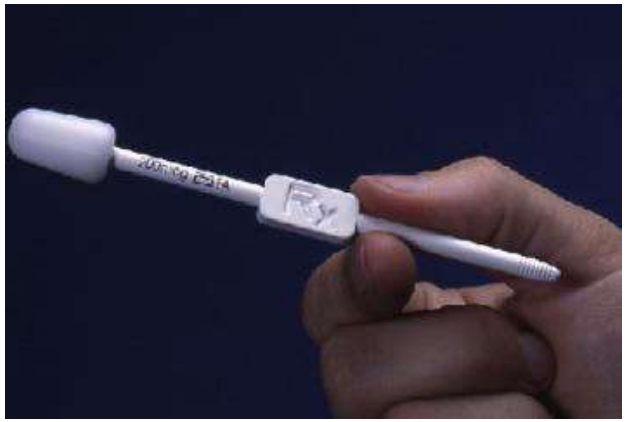
IV, sublingual, transdermal, buccal

Used as adjunct anesthetic

Lolipop for breakthrough pain in cancer patient, burns in children

No histamine release when given IV.

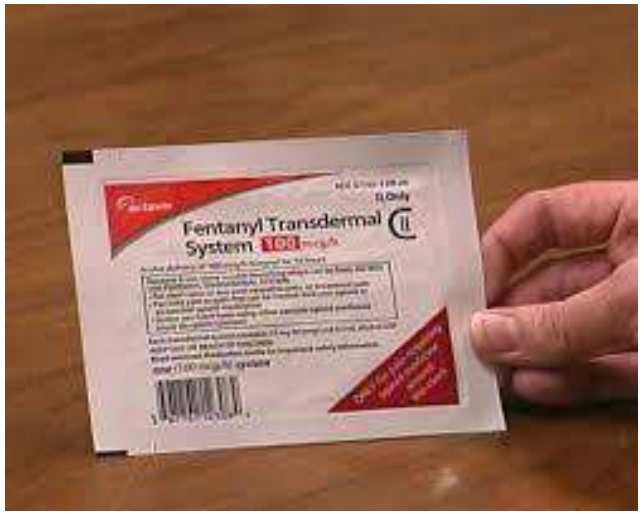
Side effect: Sudden respiratory depression




Abstral® 100 microgrammes
Comprimé sublingual
Fentanyl
10 comprimés
ProStrakan


SUBSYS®
fentanyl sublingual spray
600 mcg per spray
Dispense the enclosed Medication Guide to each patient.
IMPORTANT:


Sandoz Fentanyl
MST CONTINUS® 10 mg
30 Tablets
50 mcg/h


Fentanyl Transdermal System


28 Buccal Tablets
Rx only
FENTORA™
(fentanyl buccal tablet)
200 mcg
fentanyl base

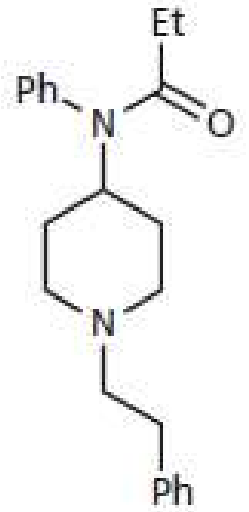
Synthetic opioids: 4-Anilidopiperidine

Sufentanil

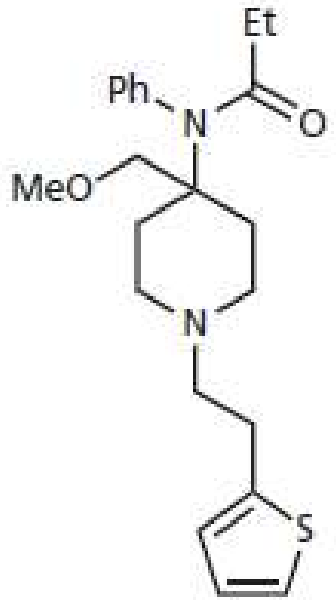
Sufentanil is 7 times more potent than fentanyl with an immediate onset of action and a similar recovery time compared with fentanyl.

Sufentanil: only injectable

An anesthetic adjunct.



Fentanyl



Sufentanil (Sufenta)

Synthetic opioids: 4-Anilidopiperidine

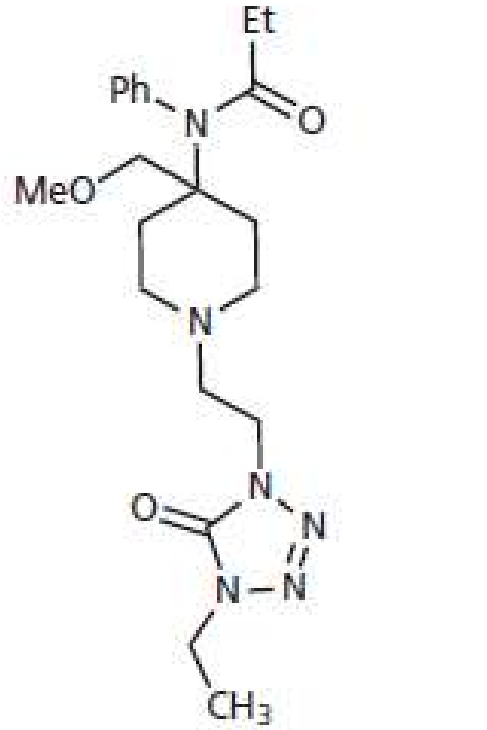
Alfentanil

Less Potent (1/4 X fentanyl)

It has a quicker onset of action, a shorter duration of action

Better, safety profile for use as an anesthetic adjunct.

IV



Alfentanil (Alfenta)

Piperidine amine has a pKa of 6.5 compared with fentanyl's pKa of 8.4.

Synthetic opioids: 4-Anilidopiperidine

Remifentanil

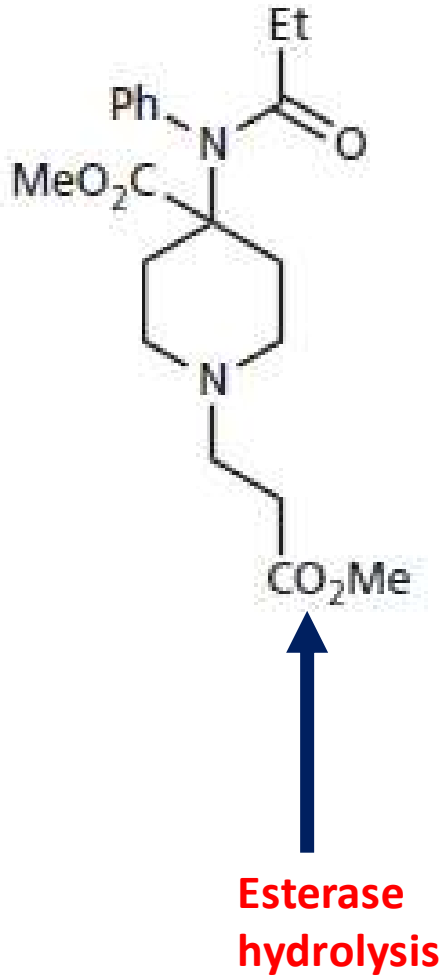
Short acting analgesic

Ester group instead of aromatic ethyl substituent at piperidine

Ester is metabolized by esterases in the blood and tissue to a weakly active metabolite (1:300–1:1,000 the potency of remifentanil

Rapid distribution across BBB (1 minute).
High Log P, pKa: 7.07

The ester hydrolysis leads to a quick recovery (5–10 minutes)



Synthetic opioids: 4-Anilidopiperidine

Rings C, D, and E are not essential for analgesic activity

Piperidines retain side effects, such as addiction and depression of the respiratory center, because they are agonists at the μ receptor

Piperidine analgesics are faster acting and have a shorter duration of action than morphine

The aromatic ring and basic nitrogen are essential to activity, but the phenol group is not

Piperidine analgesics appear to bind with analgesic receptors in a different manner to previous structural classes.

❑ Synthetic opioids:

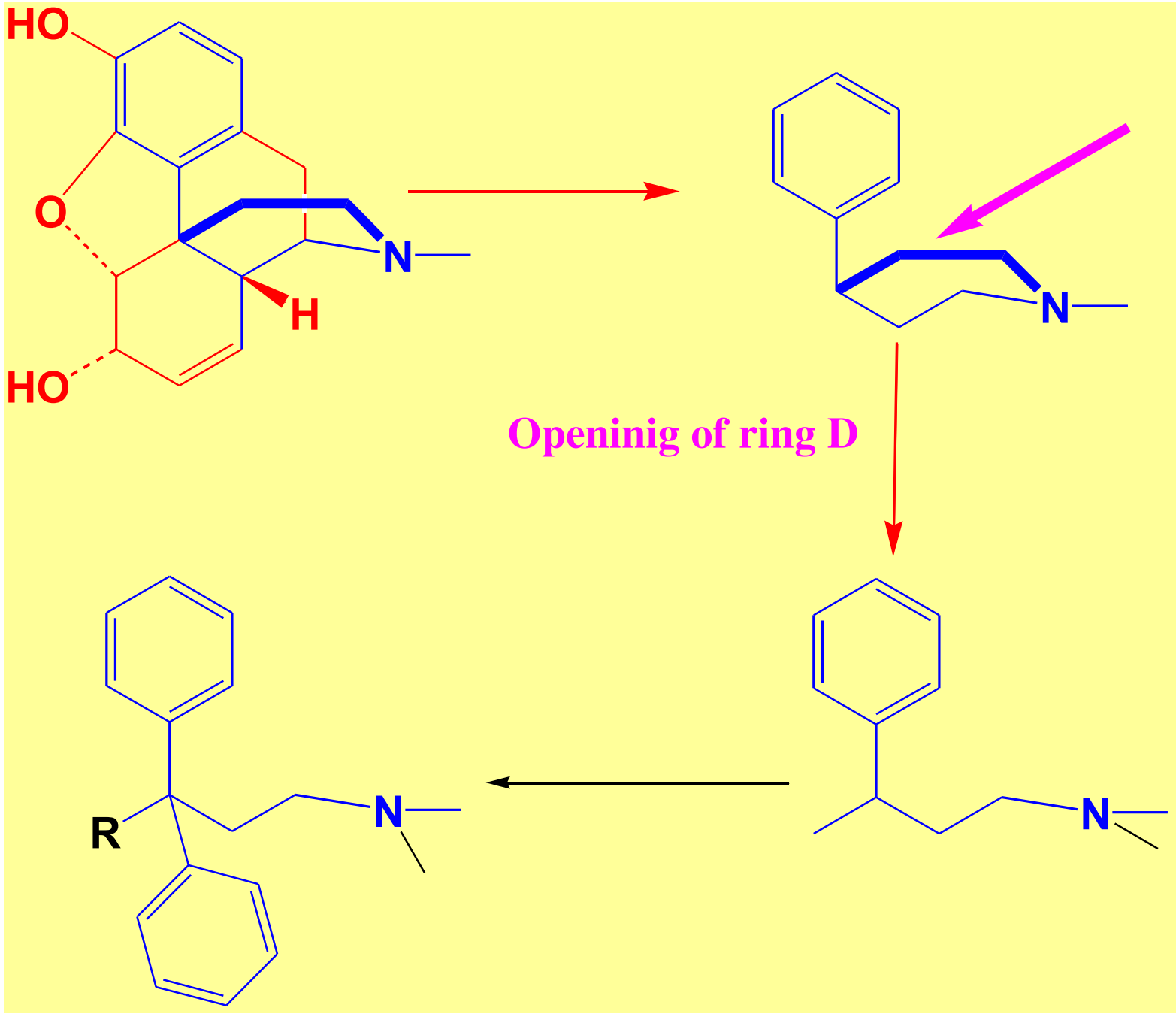
Diphenylheptane

Methadone

Levomethadone

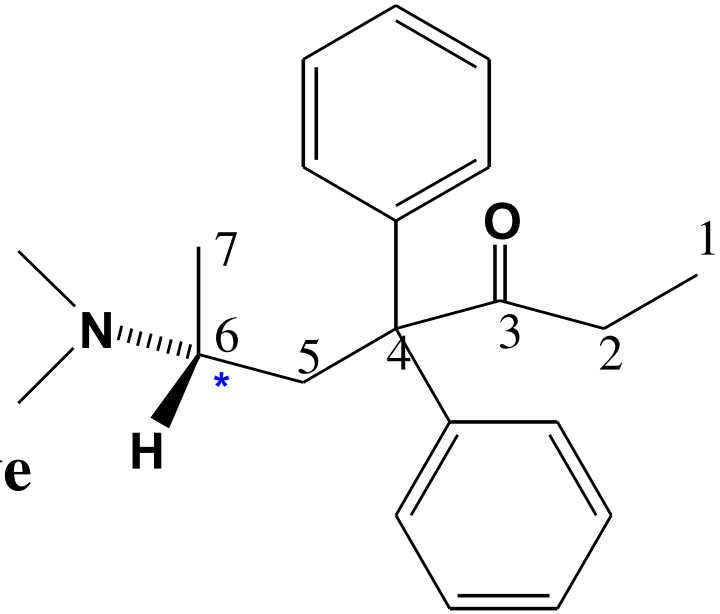
LAAM

Dextroprpoxyphene


HO
O
HO
H
N
Openinig of ring D
N
N
R
N

Synthetic opioid: Diphenylheptanes

Maintain ring A and open ring D



levomethadone

Absolute configuration R

Levorotatory

Open ring D of morphine ⟶ inactive compound

Diphenyl groups essential for activity

⇓

Phenyl group in the correct position related to 3^{o}-amine

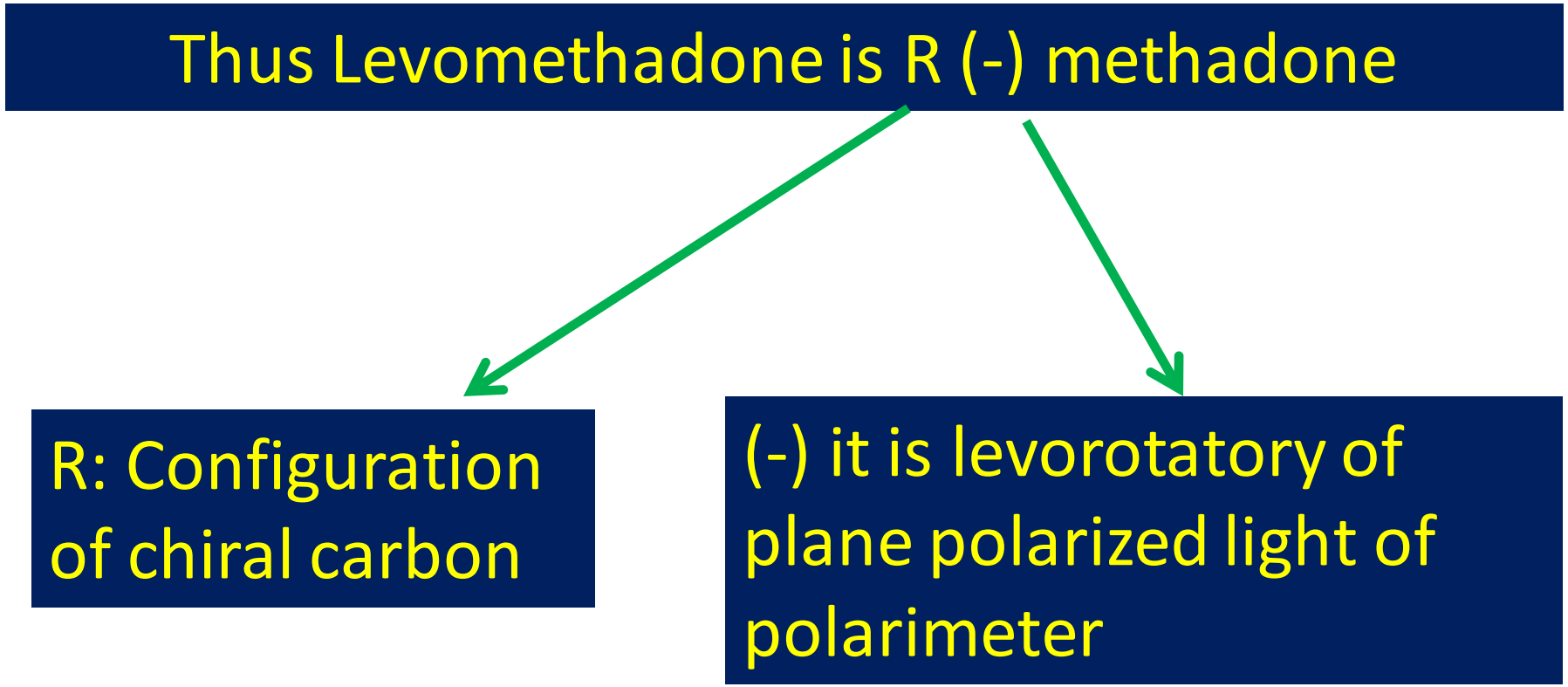
Synthetic opioid: Diphenylheptanes

There is a difference between R,S & (+) dextro, (-) levo

R,S is mentioned for Absolute configuration
Configuration is determined by priority of groups attached to chiral carbon

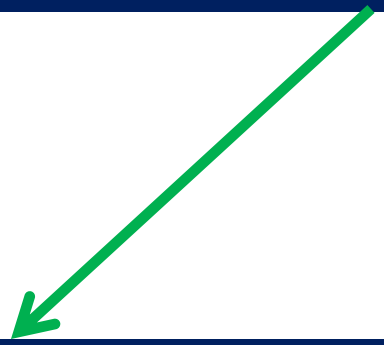
(+) dextro, & (-) levo are mentioned for optical activity of chiral compound which is measured by polarimeter

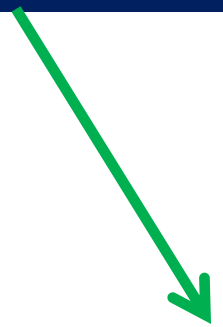
Synthetic opioid: Diphenylheptanes



Synthetic opioid: Diphenylheptanes

Thus Levomethadone IS NOT Methadone





Pure Enantiomer
R(-)-Methadone

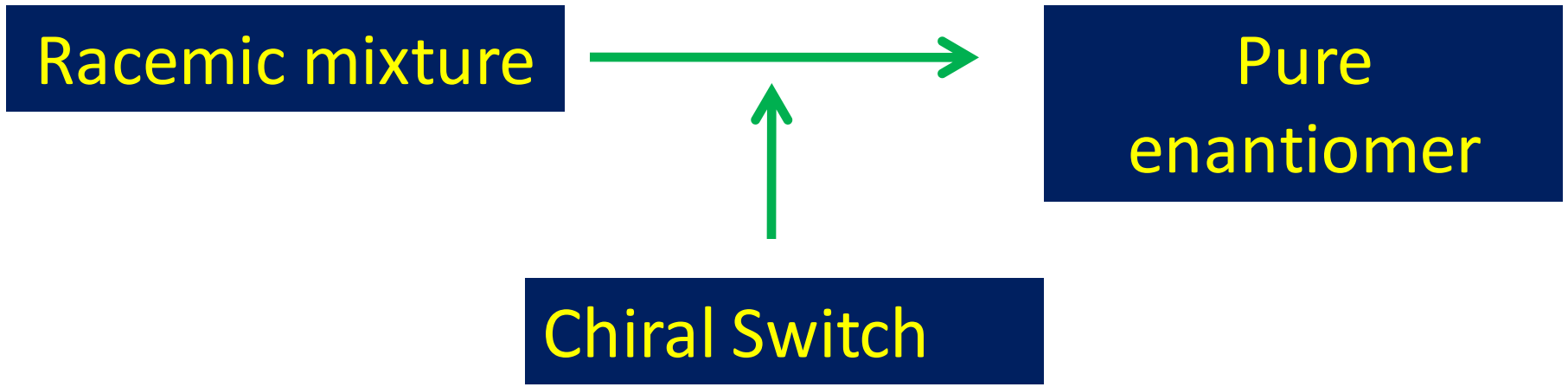
Racemic mixture
(±)-Methadone

Pure Enantiomer was choosen alone because it is the active enantiomer. It is only responsible for the effect ---------- Thus S(+) methadone is considered as impurity.

Synthetic opioid: Diphenylheptanes

Enantiomer responsible for activity is called Eutomer

Inactive enantiomer is called dystomer



Synthetic opioid: Diphenylheptanes

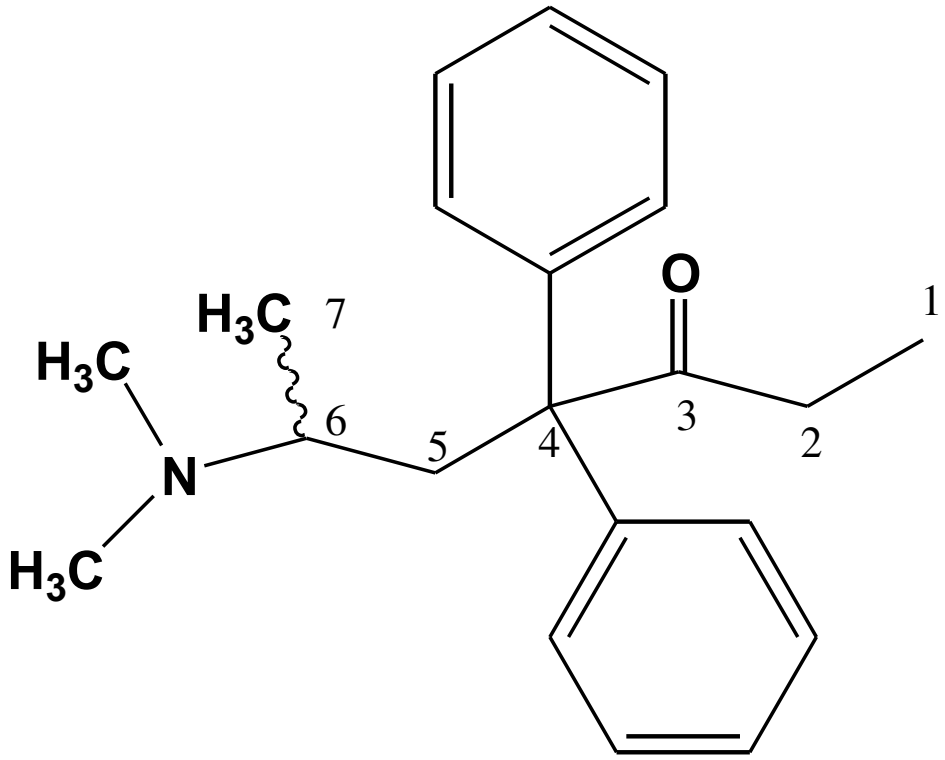
Levomethadone

Used as racemic mixture

Or pure enantiomer

R(-)-methadone is levomethadone is 7-50 times more active than S-(+)-enantiomer

R(-) is eutomer, S-(+) is dystomer



Methadone

Loss of rings B, C, E, open ring D
Phenyl bonded to quaternary C, then 2C bridge to 3°-amine

Synthetic opioid: Diphenylheptanes

Methadone

Comparable in activity with morphine (±-Racemic mixture)

Similar Side effects. Less severe euphoria, sedation, constipation, emetic

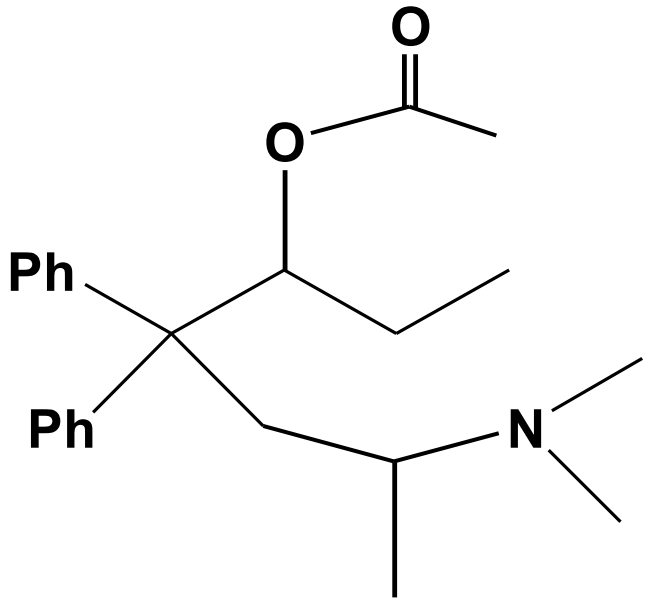
Orally active [$t_{1/2}$: 19h--------42h **depends on urine pH**]

long duration of action due to active metabolite

For treatment of opioid addiction [Once a day dose to suppress withdrawal symptoms]

Synthetic opioid: Diphenylheptanes

Modification of methadone: L-α-Acetylmethadol



L-alpha-Acetylmethadol [LAAM]

more potent than methadone

long duration (one dose every 3 days)

Synthetic opioid: Diphenylheptanes

Modification of methadone: Dextropropoxyphene

The analgesic effect is for the + isomer with (2S,3R) configuration

Analgesic effect is 1/8X that of methadone and 0.1 X potency of morphine

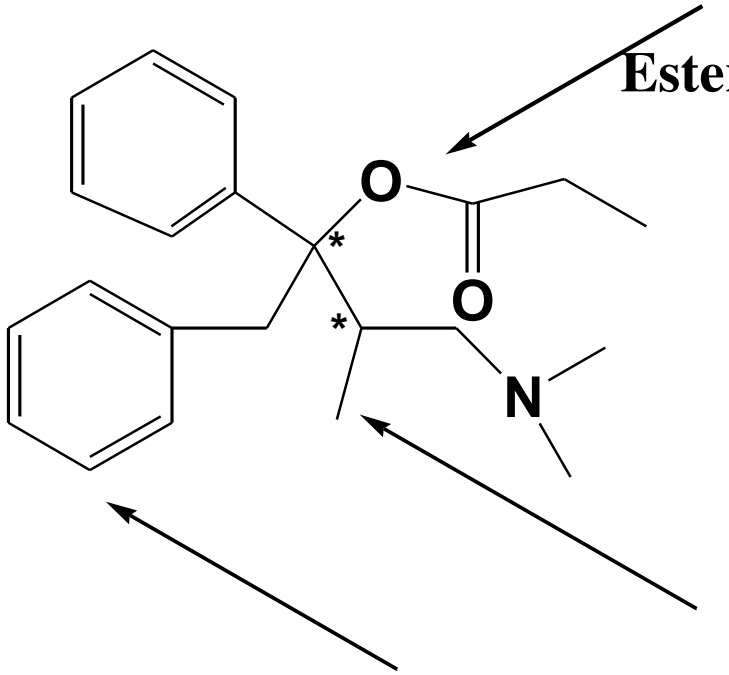
The (-) isomer with (2R,3S) configuration is a pure antitussive and lacks the characteristics of opioids.

Side effects: Cardiotoxicity [metabolite: Norpropoxyphene]

Propoxyphene HCl [Darvon®]
Propoxyphene napsylate [Darvon N®] not water soluble to avoid abuse

Synthetic opioid: Diphenylheptanes

Modification of methadone: Dextropropoxyphene



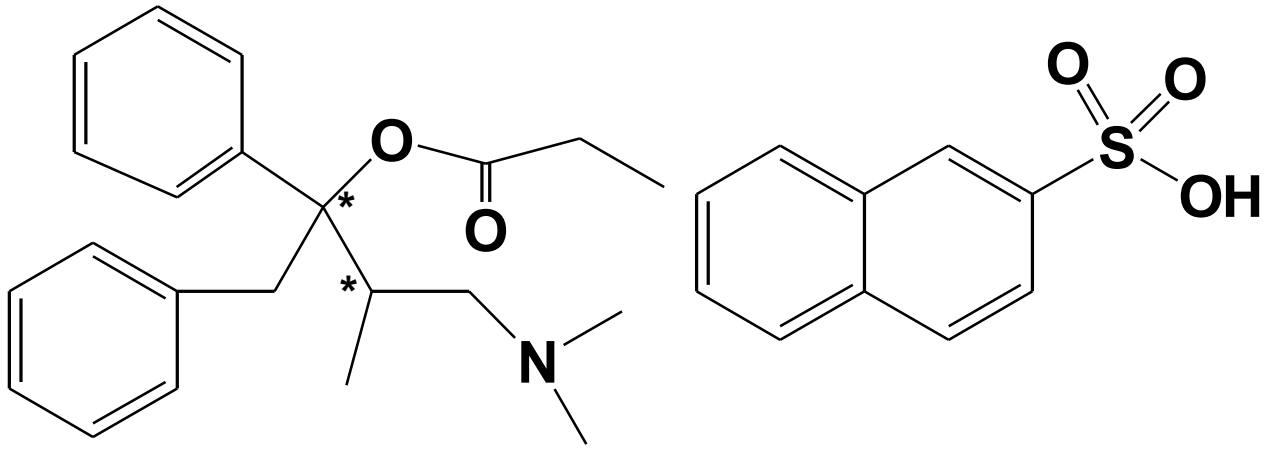
Ester replace ketone

CH3 is moved to beta position

Phenyl is replaced by benzyl

2S, 3R-(+)-Propoxyphene Analgesic
2R, 3S-(-)-Propoxyphene antitussive

Synthetic opioid: Diphenylheptanes



Propoxyphene napsylate

- Synthetic opioids:

phenylpropylamine

Tramadol

Tapendadol

Synthetic opioid: Phenylpropylamine

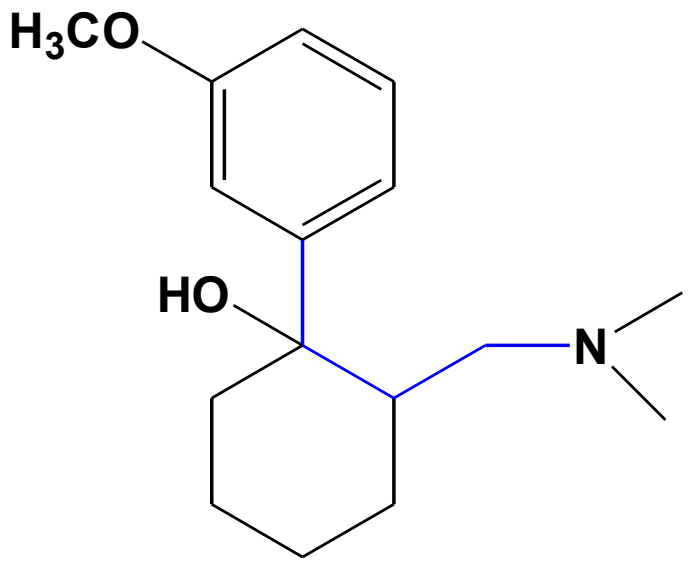
Tramadol:

Orally active analgesic

Potency 0.1X morphine

Two chiral centers

Hydrochloride salt

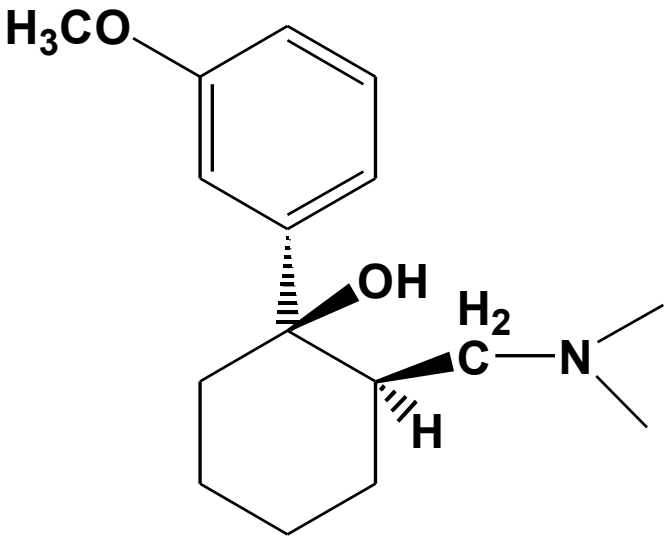


Tramadol

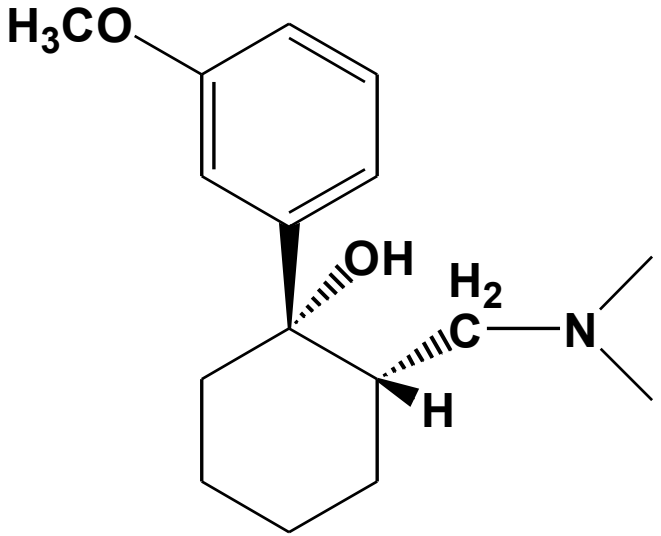
Marketed as Racemic mixture of **cis isomer**
[1R,2R-(+) and 1S,2S-(-)-isomers]

(+)-Eantiomer is 30 folds more potent than (-) enantiomer.

Synthetic opioid: Phenylpropylamine



1R,2R-(+)-Tramadol



1S,2S-(-)Tramadol

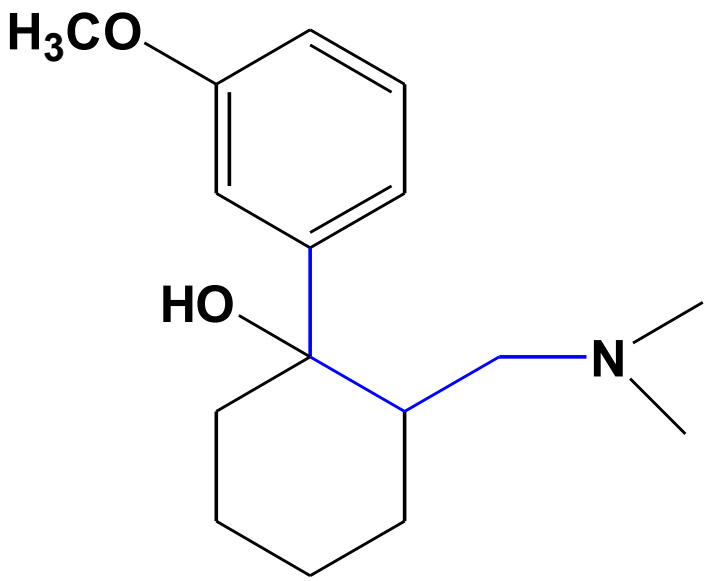
Cis isomer

Synthetic opioid: Phenylpropylamine

Tramadol: Metabolism

O-Dealkylation

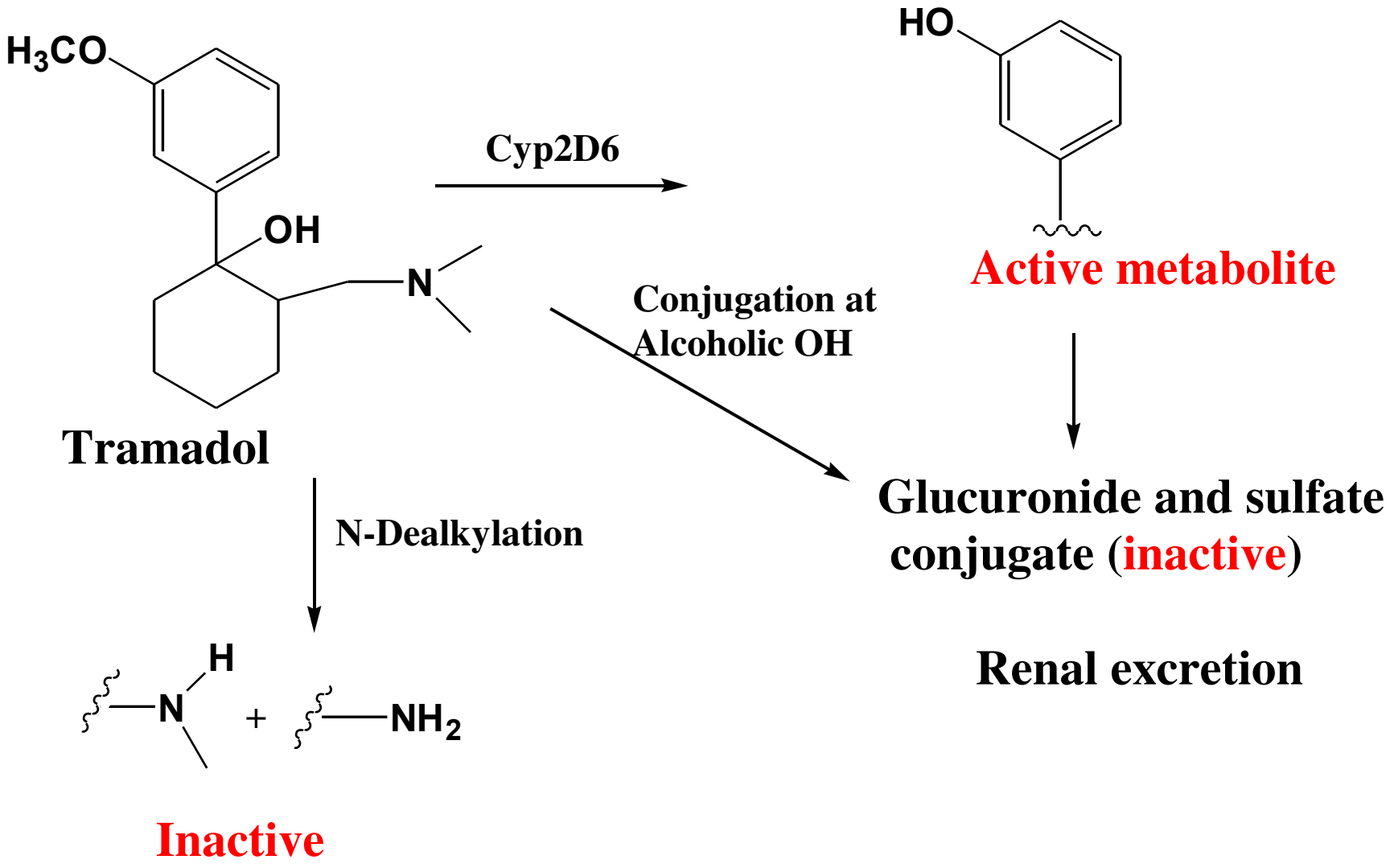
[**CYP2D6** like codeine] results in a **200 folds** more active metabolite than the parent drug.



Tramadol

Synthetic opioid: Phenylpropylamine

Metabolism: Tramadol



Synthetic opioid: Phenylpropylamine

Tramadol:

Dual mechanism of action: Stimulation of μ-receptor and inhibition of NE, 5-HT reuptake in CNS

Minimal effects on respiratory rate, blood pressure, heart rate, and GI transit times.

Drug–drug interactions [SSRIs, MAOIs, and tricyclic antidepressants, ⟶ CNS excitation and seizure

Tramadol has been associated with misuse and abuse

Both enantiomers of tramadol and the major *O*-demethylated metabolite are proconvulsive (**Risk of seizures**)

Synthetic opioid: Phenylpropylamine

Tapentadol

Dual mechanism of action

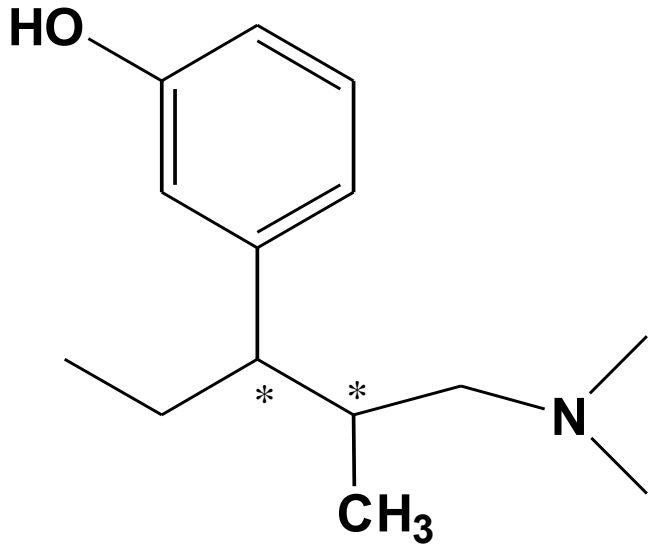
Marketed as pure one enantiomer
1R,2R-(-) isomer

Analgesic effect: 1/2X as potent as morphine

Metabolite mainly (55%) glucuronide conjugate
Or sulfate (15%) at phenolic OH

All metabolite are inactive.

Tolerable side effect profile



Tapentadol

Opioid Analgesics
Part 6

Dr. Mai Ramadan

Rigidification of morphine and opioid analgesic

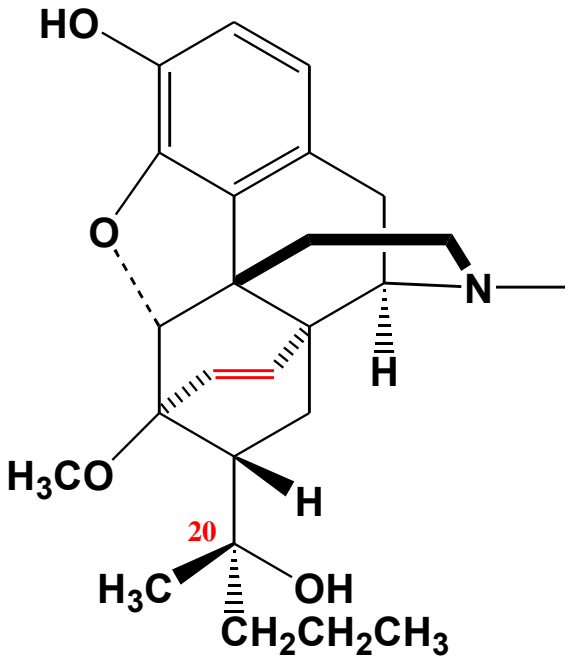
Synthetic opioid: Oripavine

Etorphine is a semisynthetic opioid analgesic [**Hexacyclic**]

Potency is **1000 times** that of morphine

Used in veterinary medicine as an immobilizer to permit safe capture or handling of zoo animals.

Study the structure!!!!!



Etorphine

Synthetic opioid: Oripavine

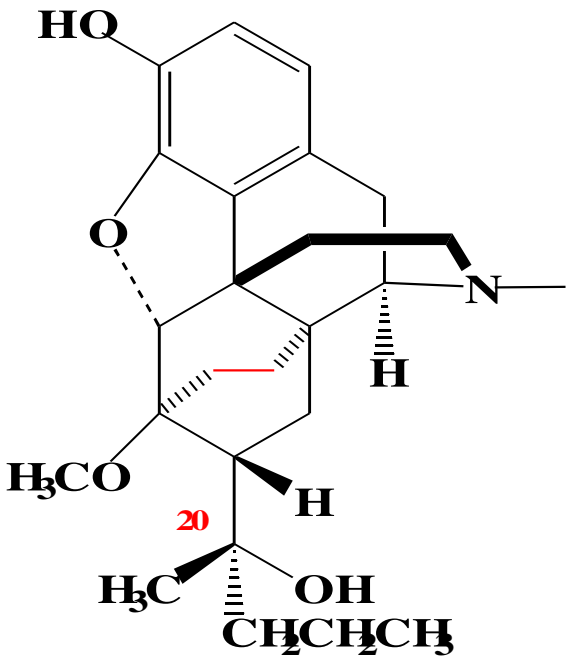
Dihydroetorphine

Dihydroetorphine is used in China as a strong analgesic and as a treatment for opioid addiction

Reducing the double bond of etorphine increases activity more than 10-fold

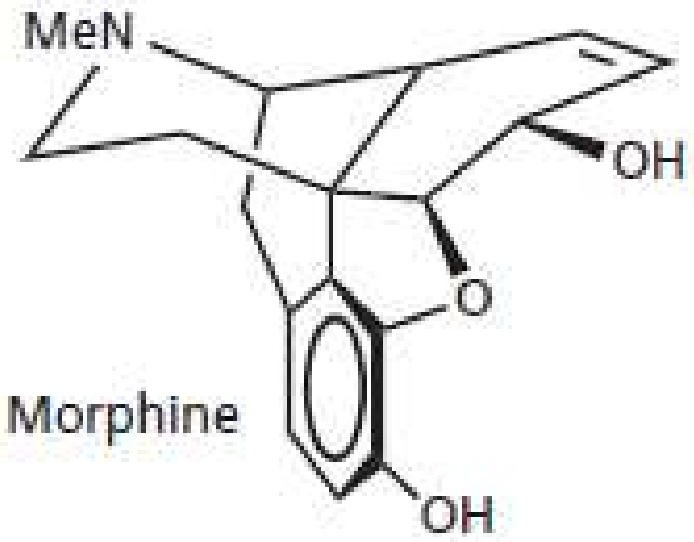
Potency is **10,000 times** that of morphine

Study the structure!!!!!

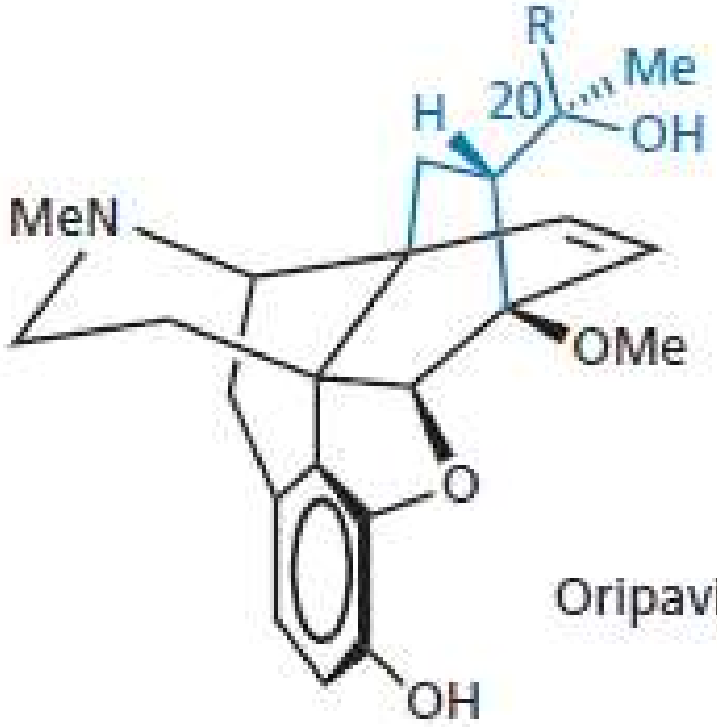


Dihydroetorphine

Synthetic opioid: Oripavine



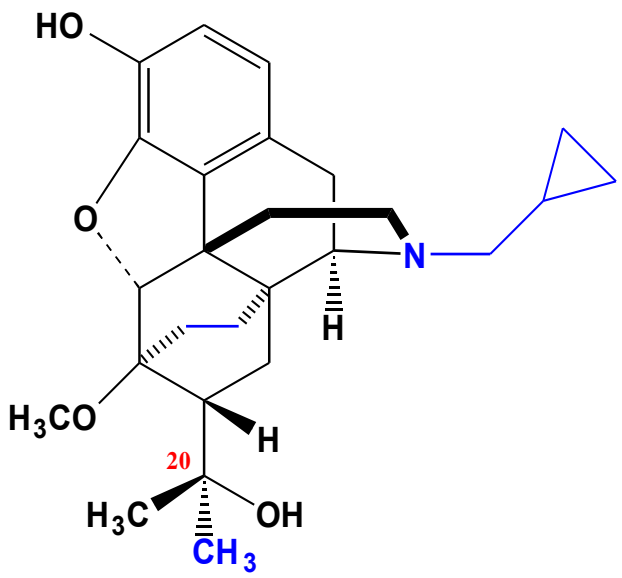
Morphine



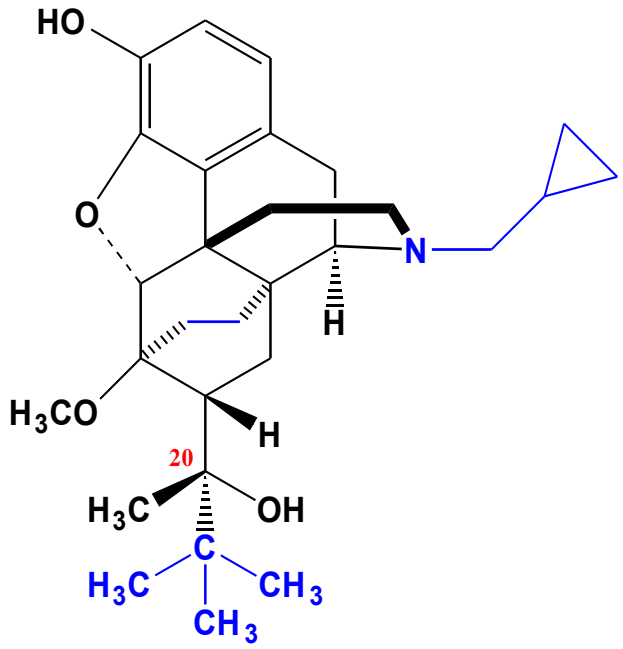
Oripavines

The presence of lipophilic groups at C20 is found to improve activity dramatically, indicating the existence of an extra hydrophobic binding region in the receptor binding site.
The group best able to interact with this region is a phenethyl substituent, and the product containing this group is even more active than etorphine.

Synthetic opioid: Oripavine



Diprenorphine



Buprenorphine

Diprenorphine:

A very powerful antagonist

100 times more potent than nalorphine

Reverse the immobilizing effect of etorphine. Used in veterinary medicine

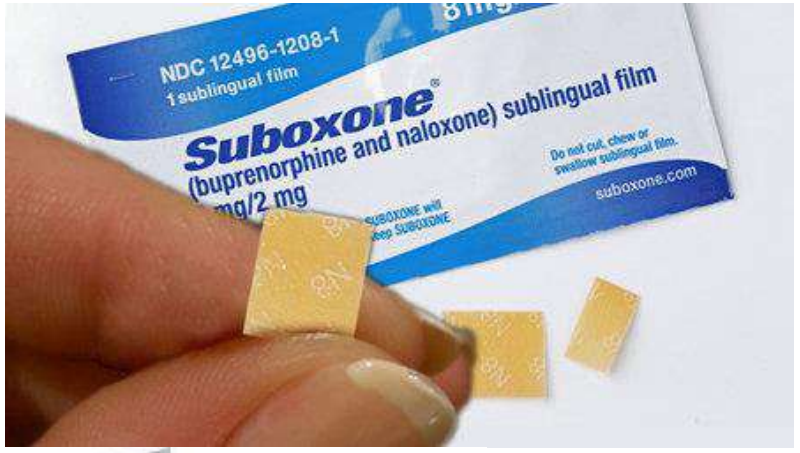
Diprenorphine has no analgesic activity.

Synthetic opioid: Oripavine

Mixed μ-agonist/antagonist (a partial agonist) and a weak –κ antagonist.

It has a high affinity for the –receptors (1,000 times greater than morphine) and a slow dissociation rate leading to its long duration of action (6–8 hours)

It has analgesic activity
Low risk of addiction
little effect on respiration
Used as an alternative to methadone for weaning addicts off heroin.



Synthetic opioid: Oripavine

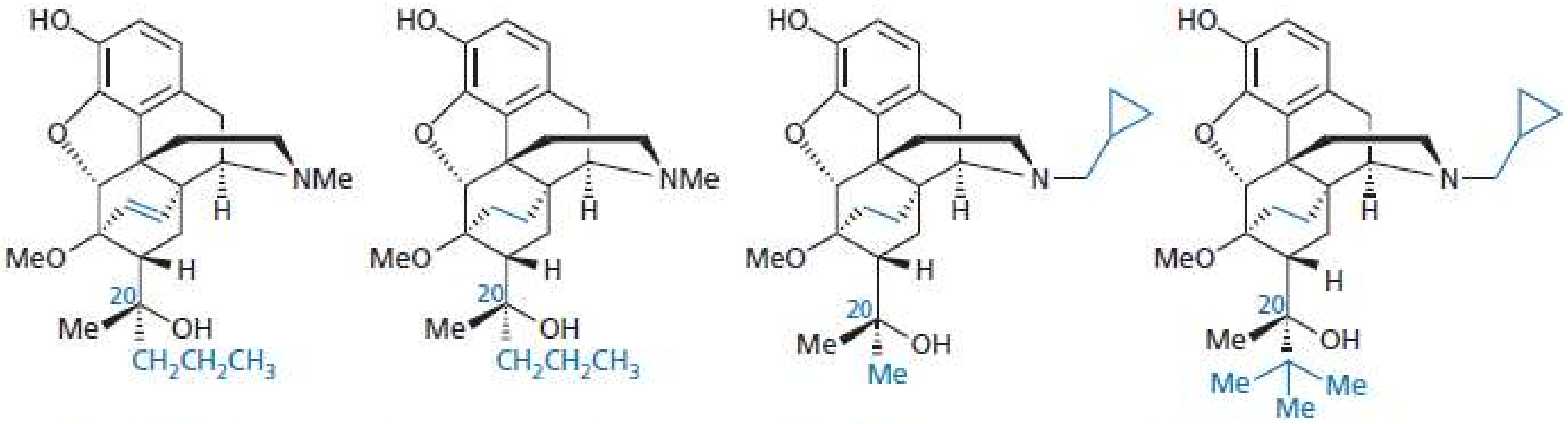


FIGURE 24.21 Etorphine and related structures.

Morphine and related opioid

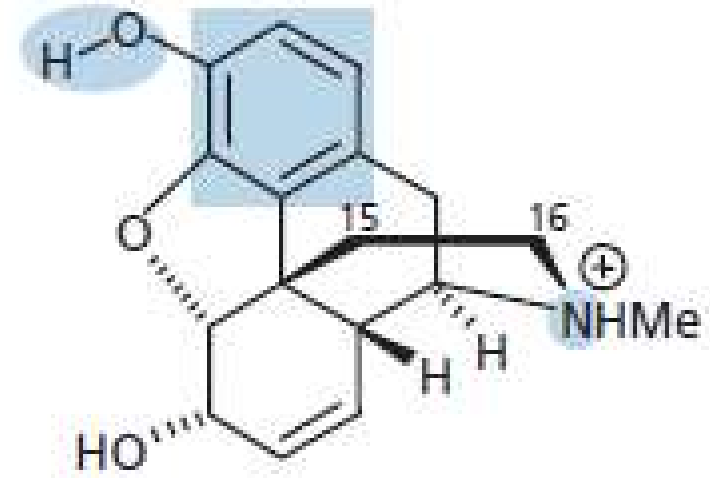
Pharmacophore is the relevant groups on a molecule that interact with a receptor and are responsible for the biological activity

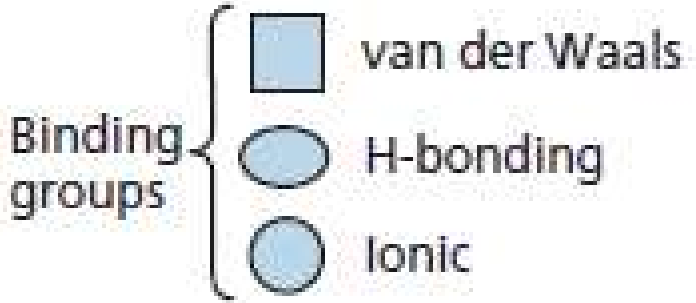
Important elements for activity

Phenolic OH: H bonding

Aromatic ring: van der Waals

3°-amine: Ionic





Endogenous opioid peptide

Precursor	Endogenous peptide	Receptor Binding
Pro-opiomelanocortin	β-Endorphin	μ and δ
Pro-enkephalin	[Met]enkephalin [Leu]enkephalin	δ
Pro-dynorphin	Dynorphin A Dynorphin A(1-8) Dynorphin B	κ μ and δ
Pro-nociceptin / OFQ	Nociceptin	ORL-1
Pro-endomorphin (?)	Endomorphin-1 Endomorphin-2	μ

Endogenous opioid peptide

Characteristics:

Peptides (5-31aa) synthesized by peptidase activity from a protein precursor

All have **identical N-terminal** (H_2N-Tyr-Gly-Gly-Phe-) except endomorphin

Neurotransmitters or neurohormones, operate as the body's natural painkillers

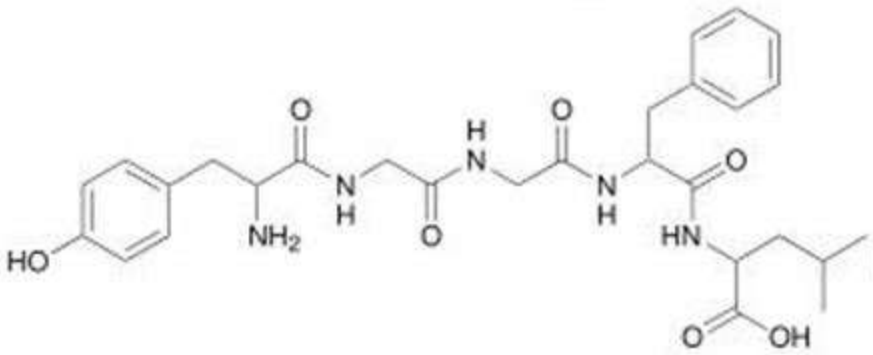
High affinity to opioid receptors

Effect antagonize by Naloxone

Endogenous opioid peptide

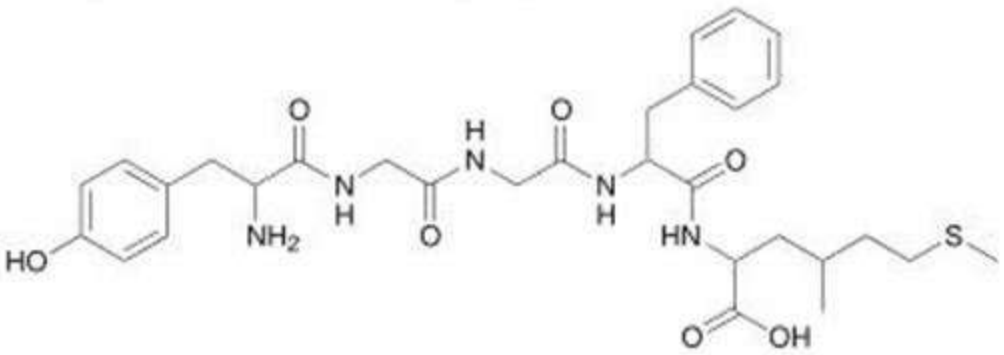
Characteristics:

Leu-Enkephalein, Met-Enkephalein [Pentapeptide]



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

Leu-enkephalin

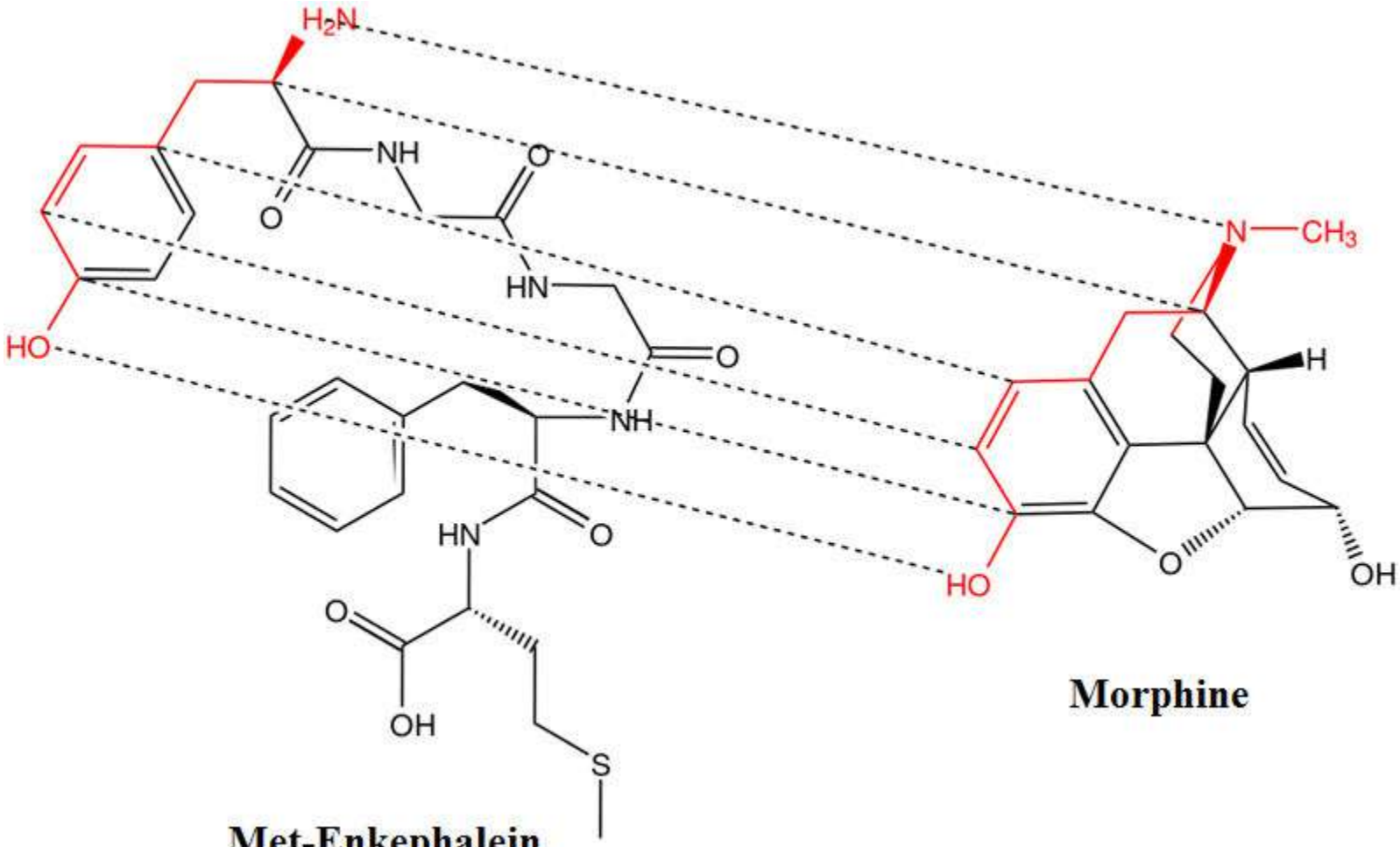


H_2N-Tyr-Gly-Gly-Phe-Met-COOH

Met-enkephalin

Endogenous opioid peptide

Met-Enkephalein AND morphine Similarities



Met-Enkephalein

Morphine

Regarding endogenous opioid

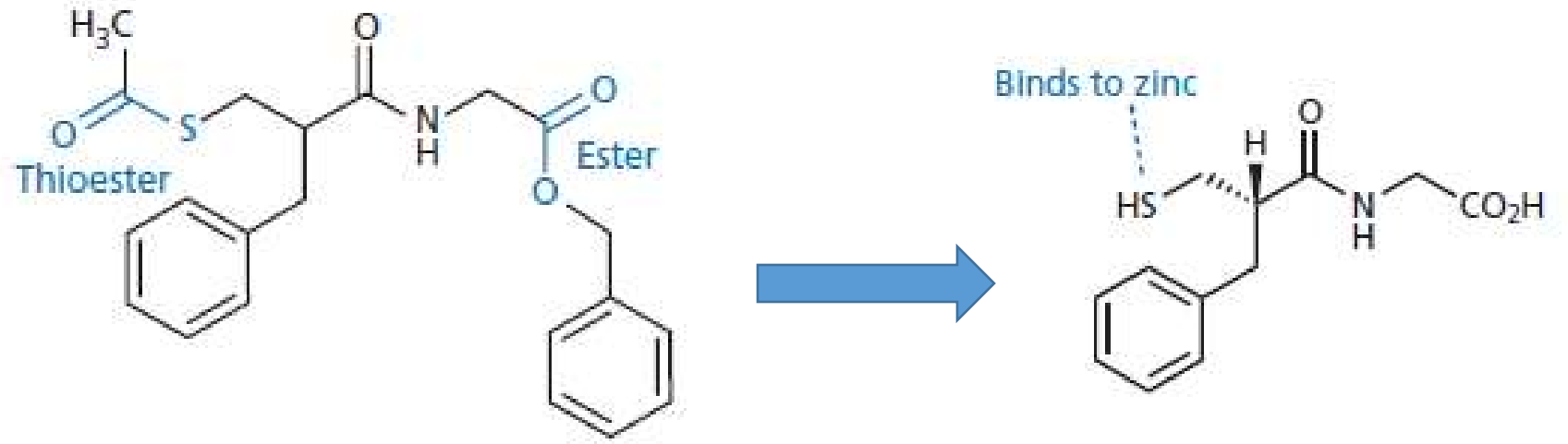
- ❑ Design of analgesic opioid based on their structure
- ❑ Inhibition of their metabolism

Enkephalinase inhibitors

Acetorphan (**racecadotril)** is a prodrug of thiorphan

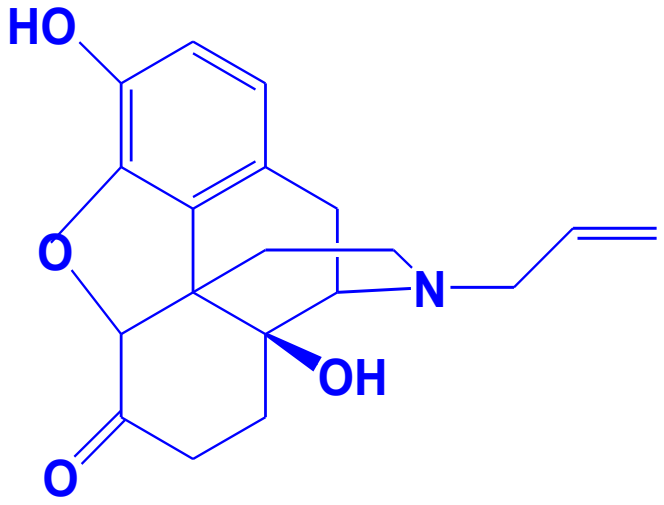
For treatment of diarrhea

The free thio group binds tightly to **Zinc** in active site of enkephalinase and inhibit its proteolytic effect.

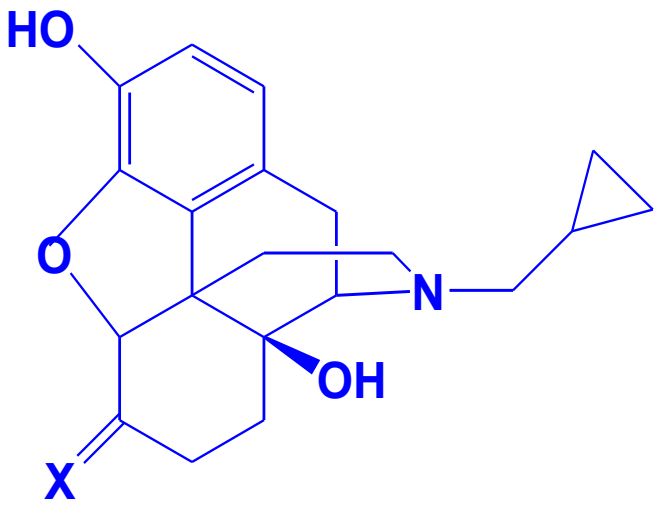


Acetorphan **Thiorphan**

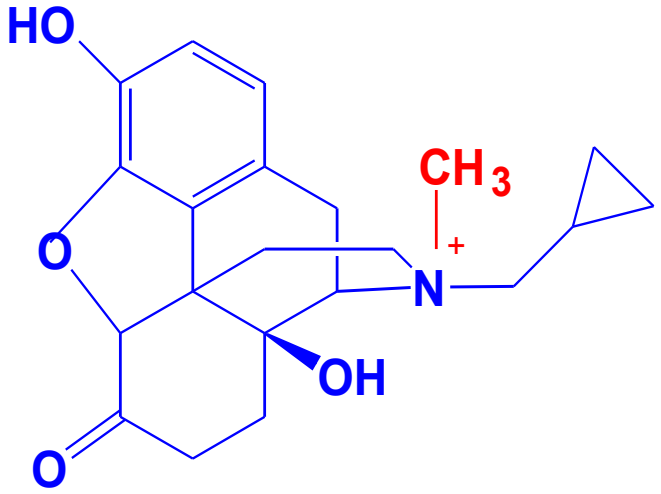
Opioid Antagonsit



Naloxone



X: O Naltrexone
X: C Nalmefene



Methylnaltrexone

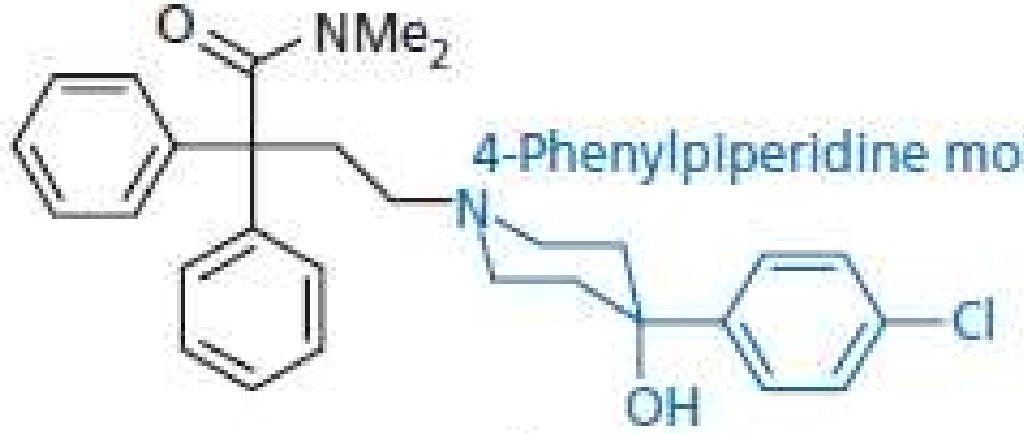
Not Cross BBB ??

Use???????????

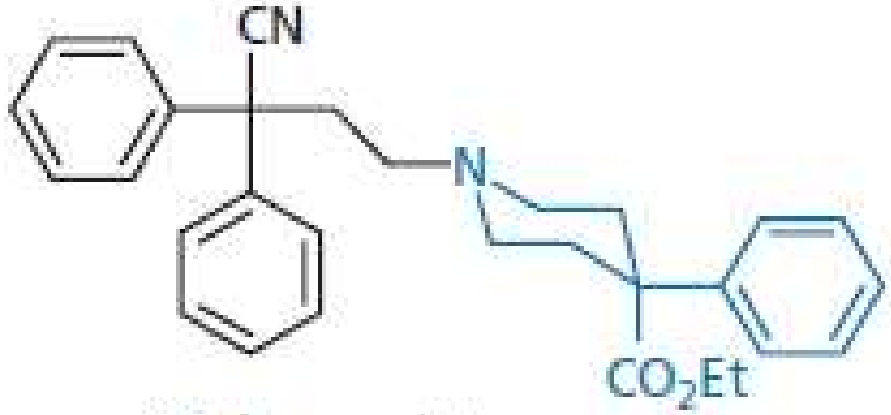
Opioid antagonist

Opioid as antidiarrheal drug

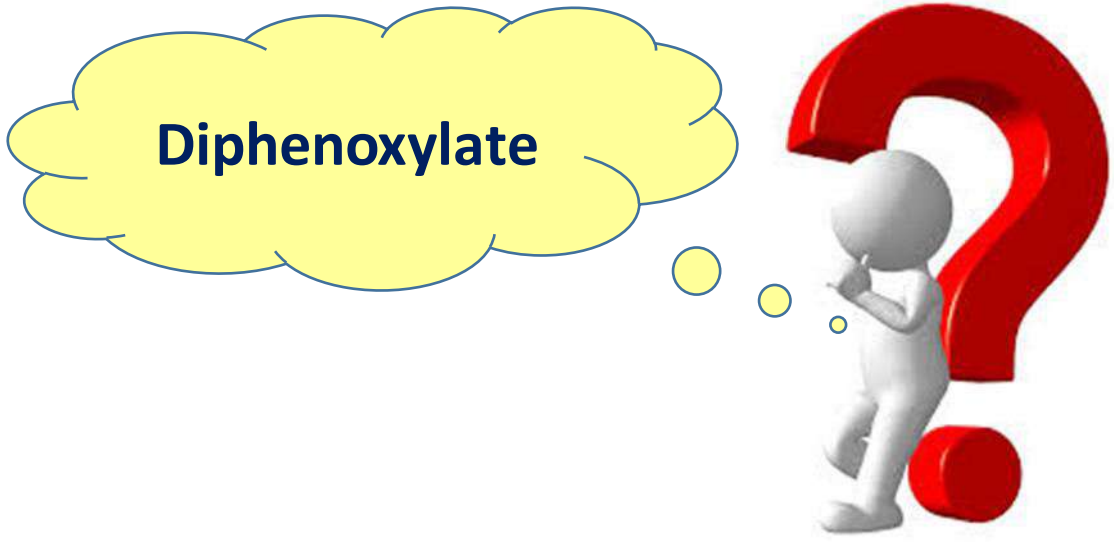
Methadone-like skeleton



Loperamide



Diphenoxylate



Opioid Analgesics
Part 7

Summary of SAR

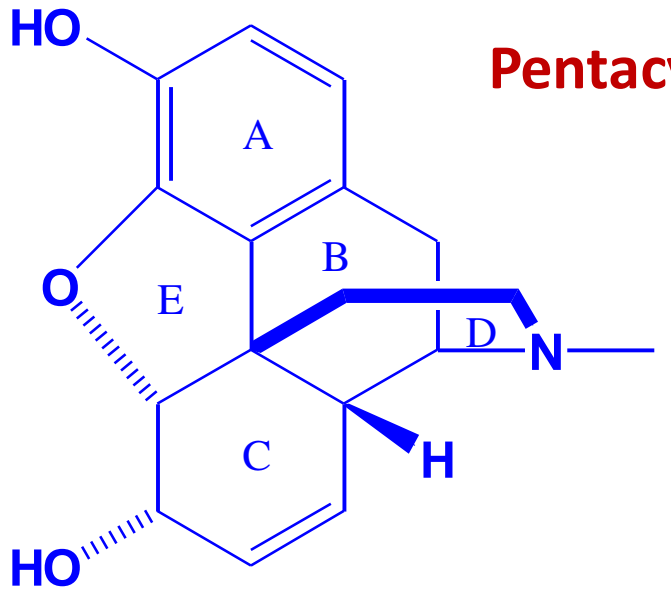
Dr. Mai Ramadan

Summarize the modification in synthetic opioid

Opioids

4,5-α-Epoxymorphinan

Pentacyclic system

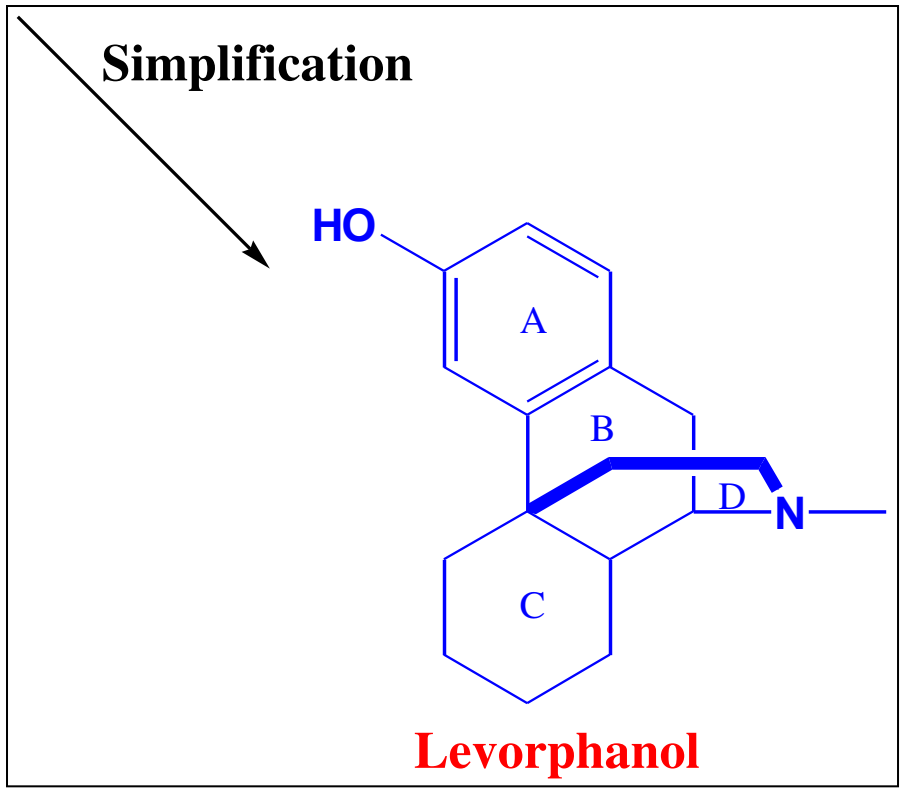


Morphine

Rigidification

Simplification

Opioids



Morphinan
Tetracyclic system

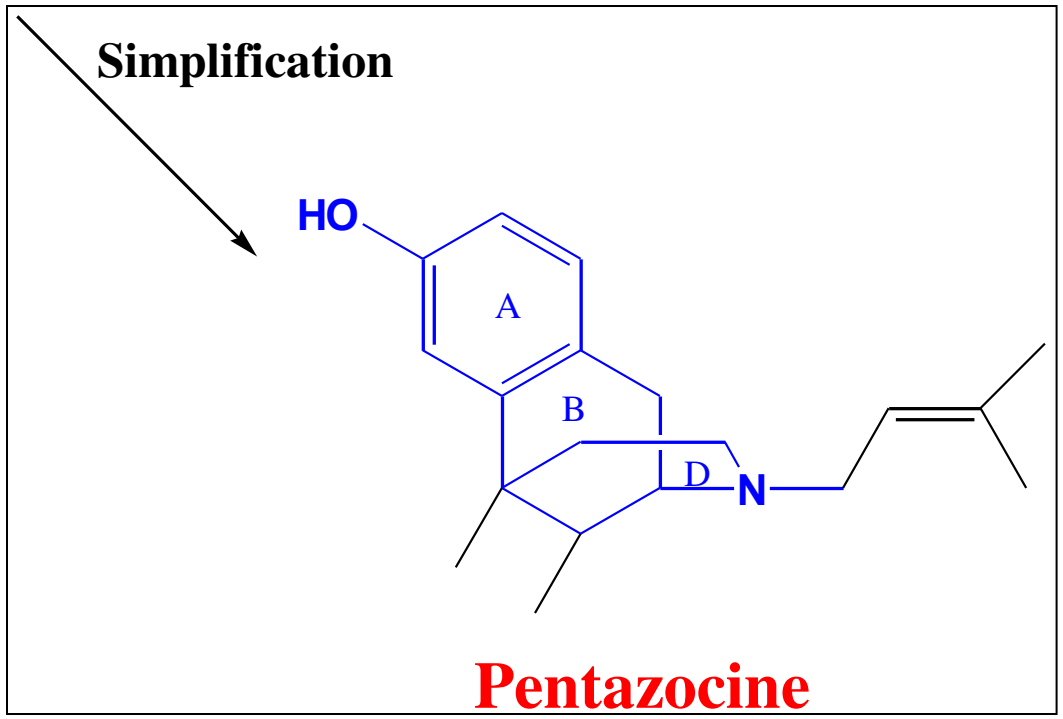
Ring E is not essential

Morphinans are more potent and longer-acting than their morphine counterparts, but have higher toxicity

SAR of morphinan is similar to that of morphine. They bind with receptor in the same way.

Morphinans are easier to synthesize

Opioids



Benzomorphan

Tricyclic system

rings C and E are not essential to analgesic activity

Analgesia and addiction are not necessarily co-existent

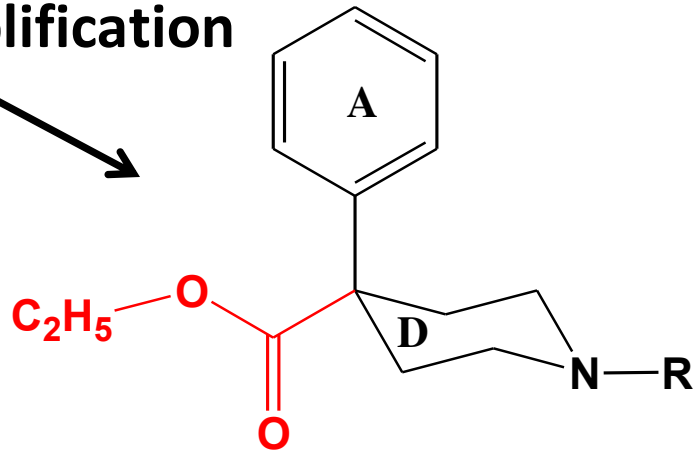
Reasonable analgesic activity, less addictive liability, less tolerance

Benzomorphans are simpler to synthesize than morphine and morphinans

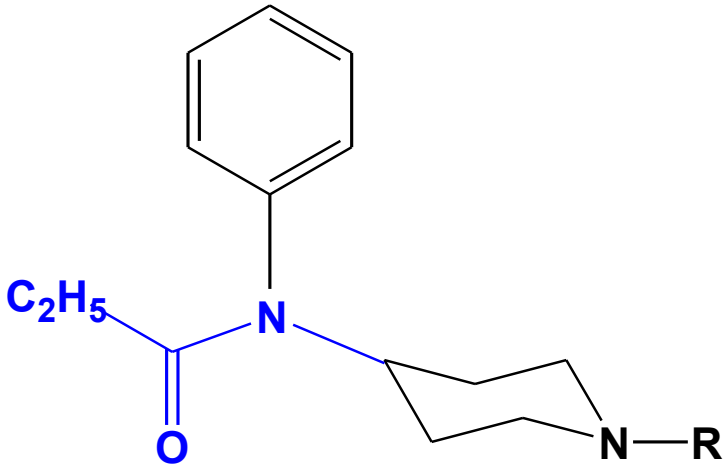
Benzomorphans bind to opioid receptors in the same manner as morphine and morphinans

Opioids

Simplification



R: CH3 Meperidine



R: -CH_2CH_2Ph Fentanyl

4-phenylpiperidine
4-Anilidopiperidine

Rings E,B,C are not essential for analgesic effect

Faster acting short duration of action

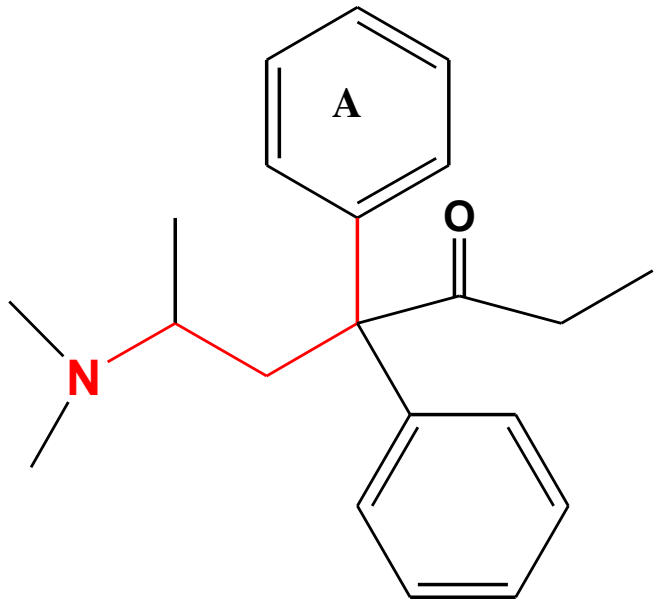
Retain side effect: addiction, respiratory system depression

Aromatic ring and basic nitrogen are essential to activity, but the phenol group is not

piperidine analgesics appear to bind with receptors in a different manner to previous structural classes.

Opioids

Simplification



Methadone

Diphenylheptane

Loss of rings B, C, E, open ring D

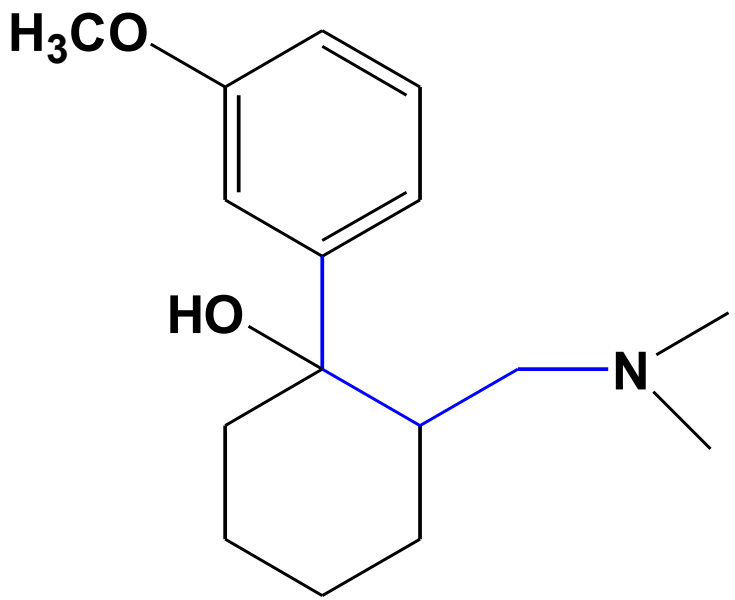
Comparable in activity to morphine

Less severe sedation, euphoria, withdrawal symptoms, emetic, constipation

Orally active

Opioids

Simplification



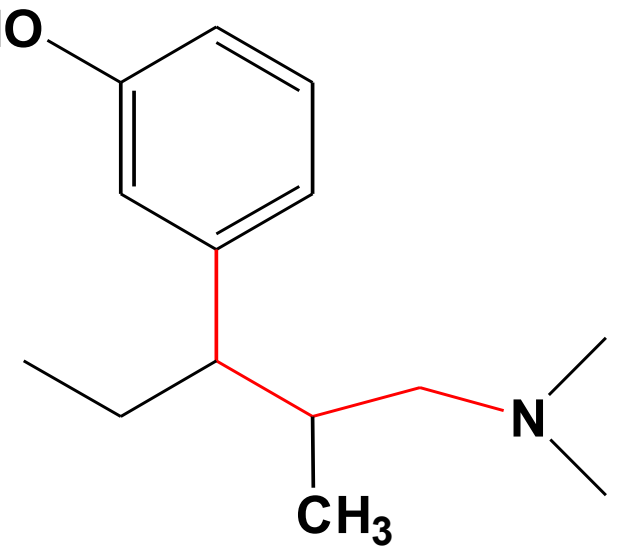
Tramadol

Phenylpropylamine

Phenyl group

3-amine group

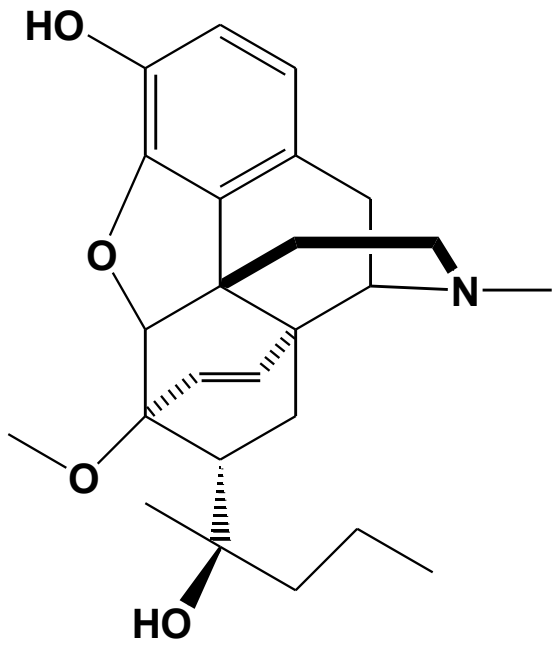
Inbetween 3C bridge



Tapentadol

Opioids

Rigidification



Etorphine

Oripavine
Hexacyclic system

Increase selectivity for receptors

Rigidification maintain the active conformation required for binding with receptors

End of opioid analgesics

Next subject

NSAIDs