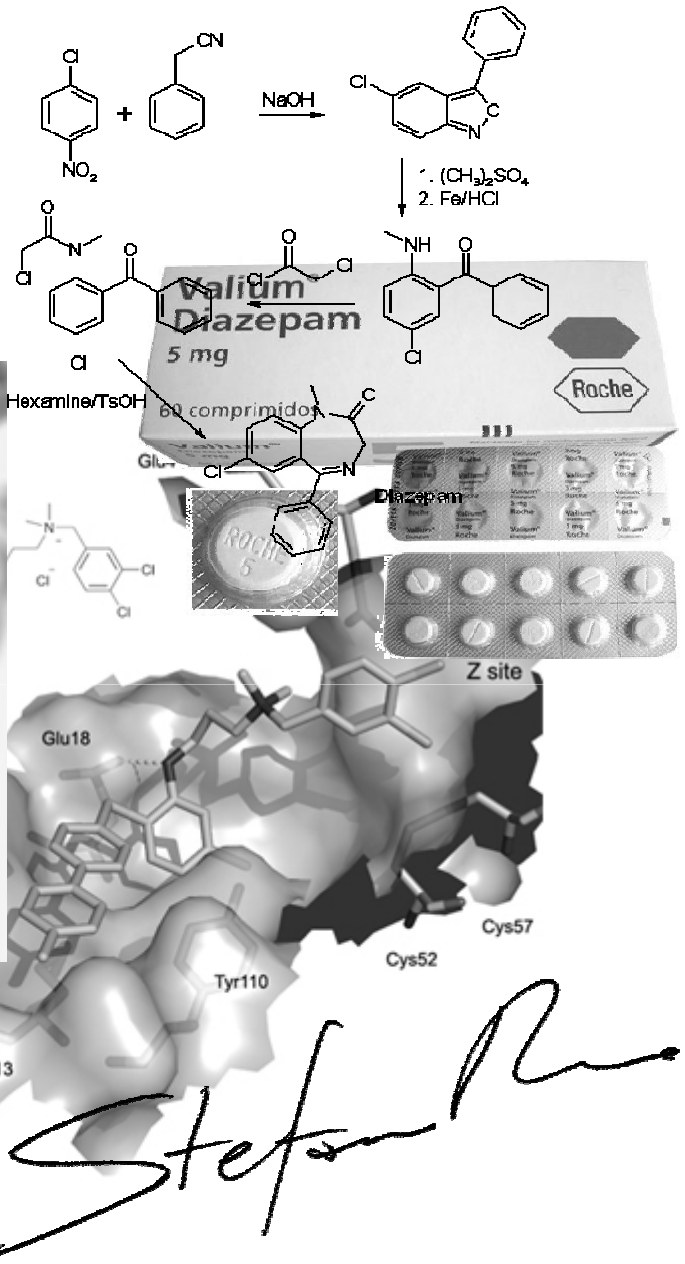
Chimica Farmaceutica e Tossicologica – Parte II



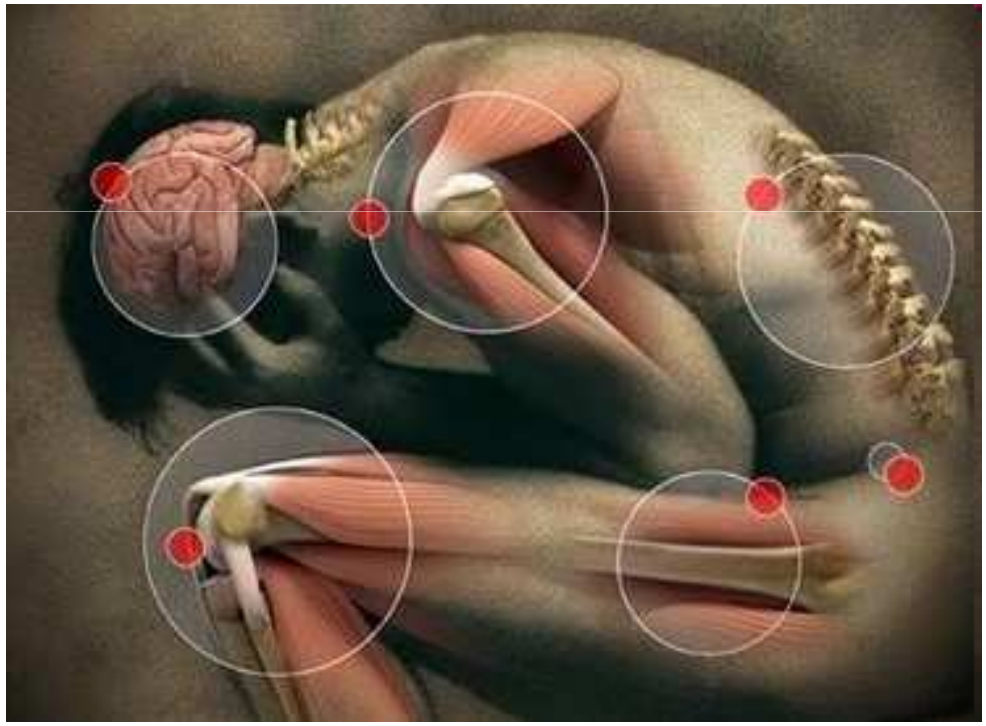
Pain and Narcotic Analgesics

Parte I

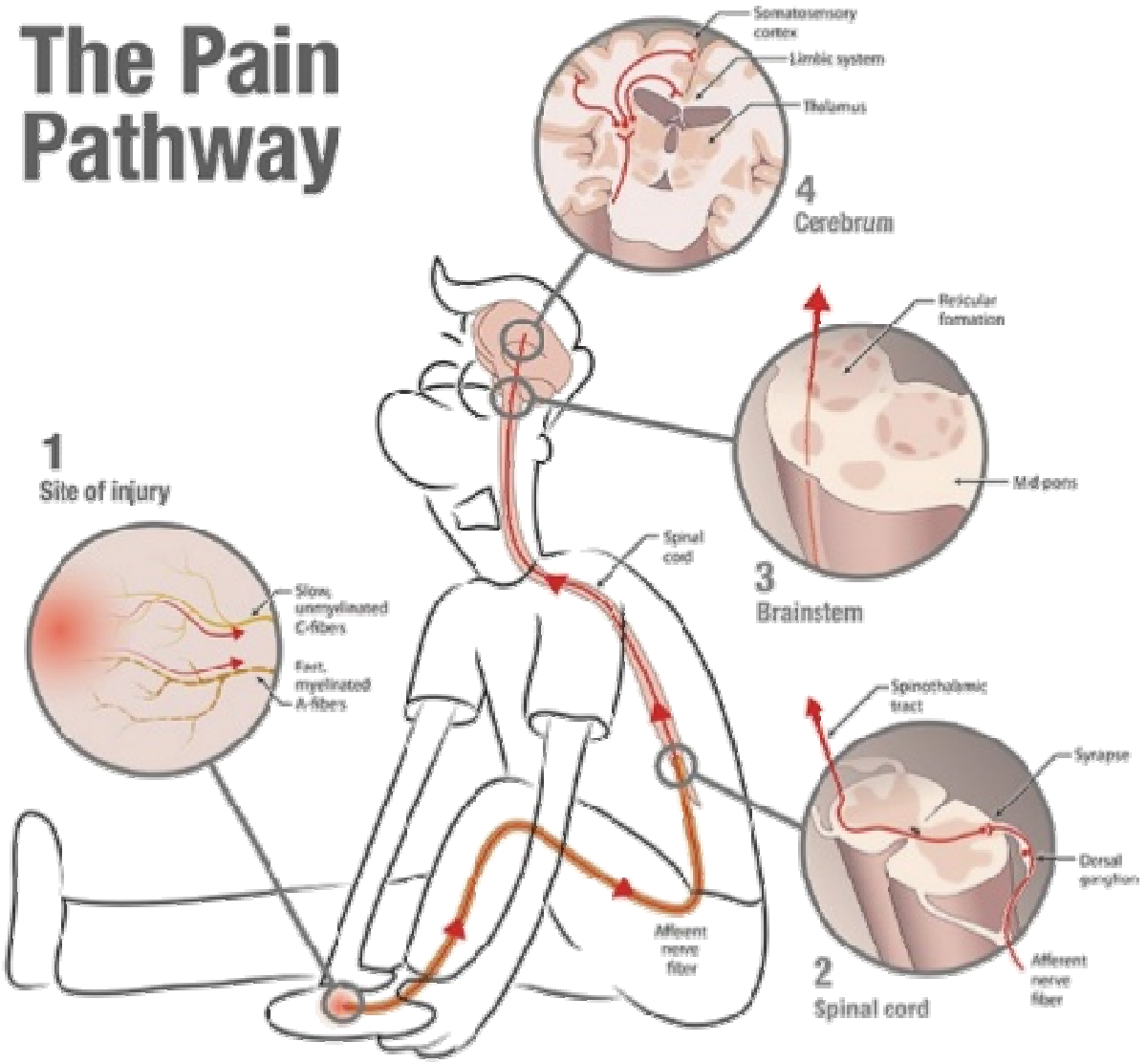
1. Pain and Narcotic Analgesics

Pain, the experience of hurting or soreness, is generally classified into four broad categories which are differentiated according to the source of pain. The categories include:

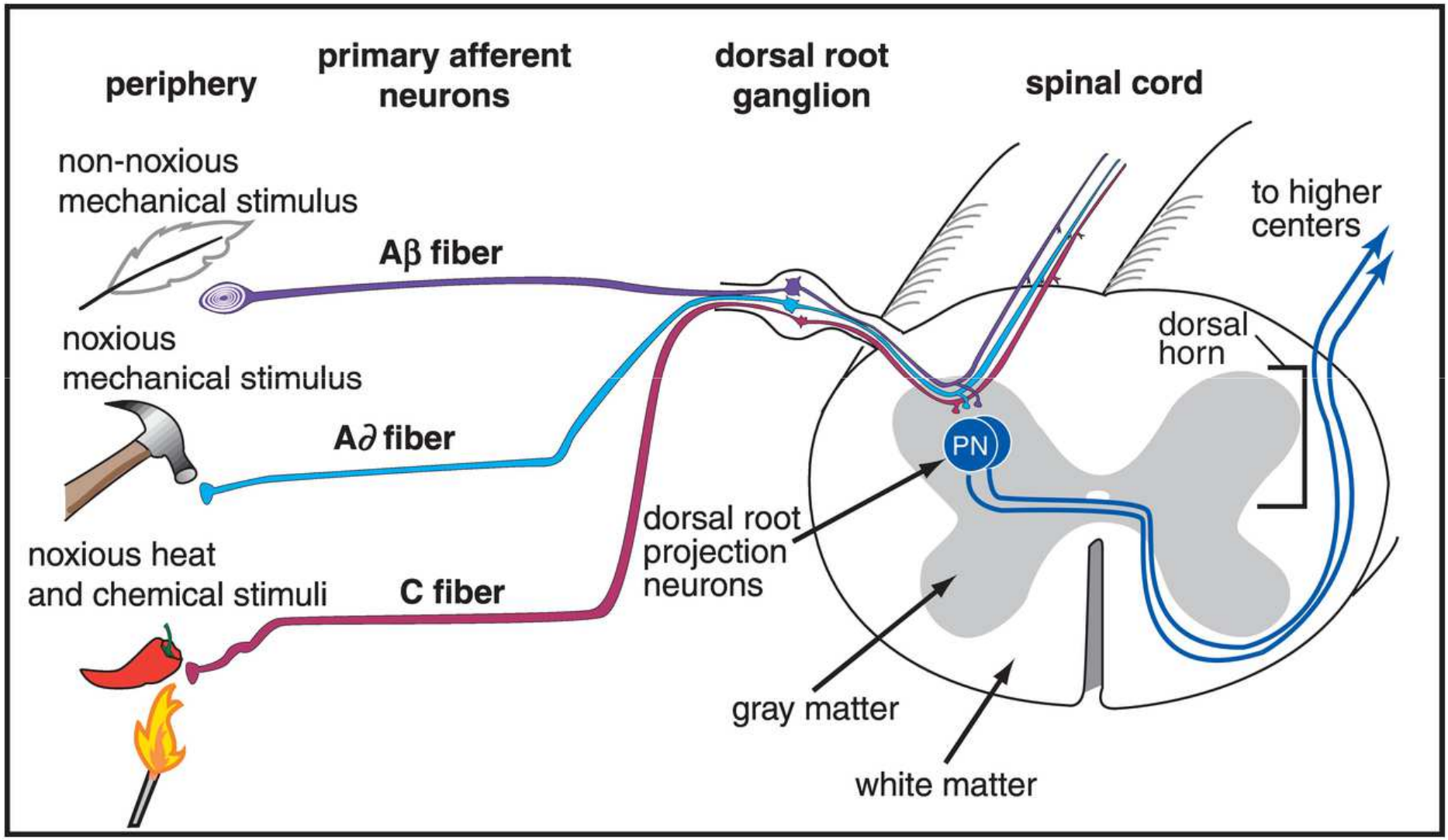
1. **nociceptive,**
2. **inflammatory,**
3. **neuropathic**
4. **functional pain.**



1. Pain and Narcotic Analgesics



1. Pain and Narcotic Analgesics

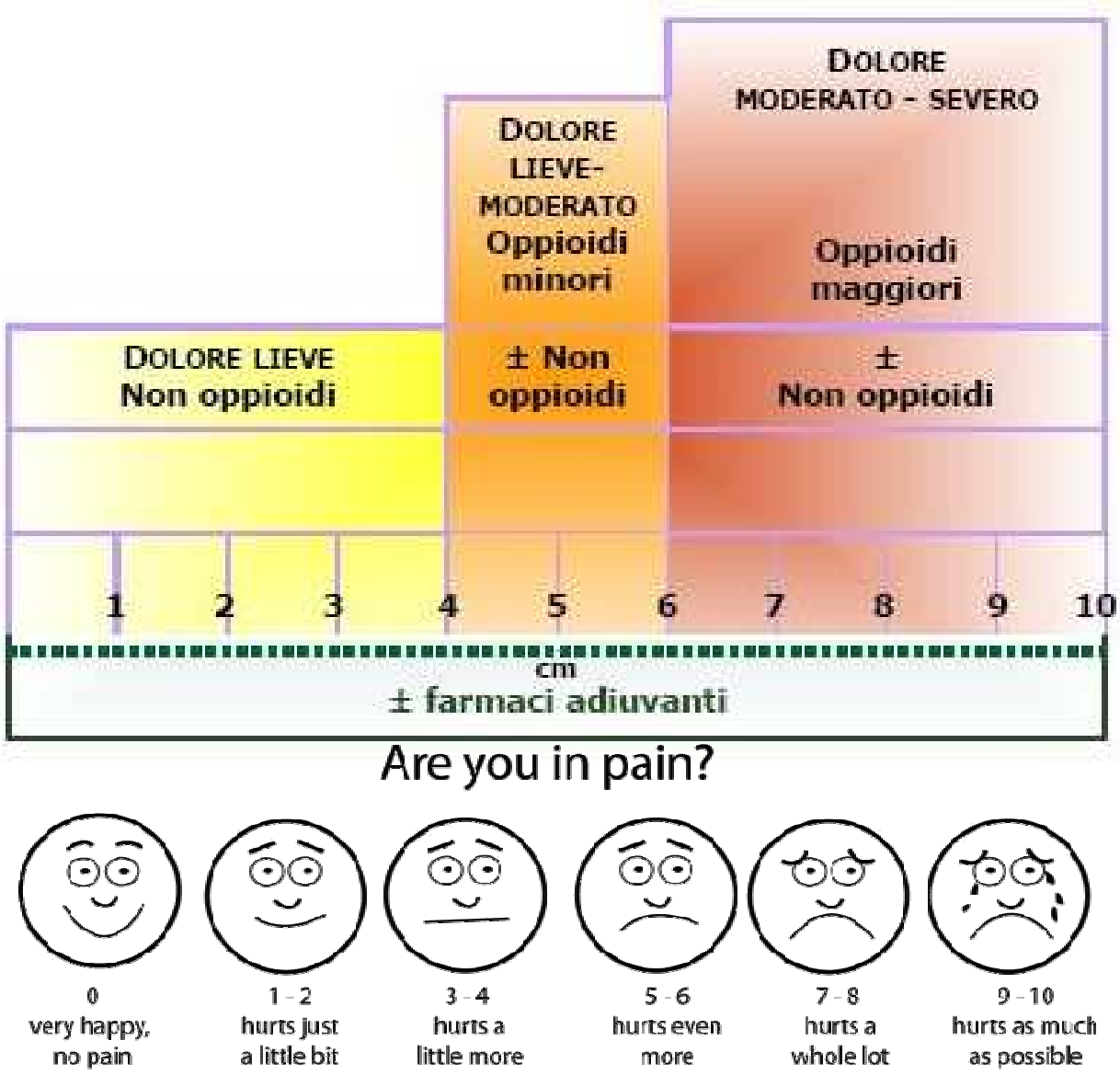


1. Pain and Narcotic Analgesics

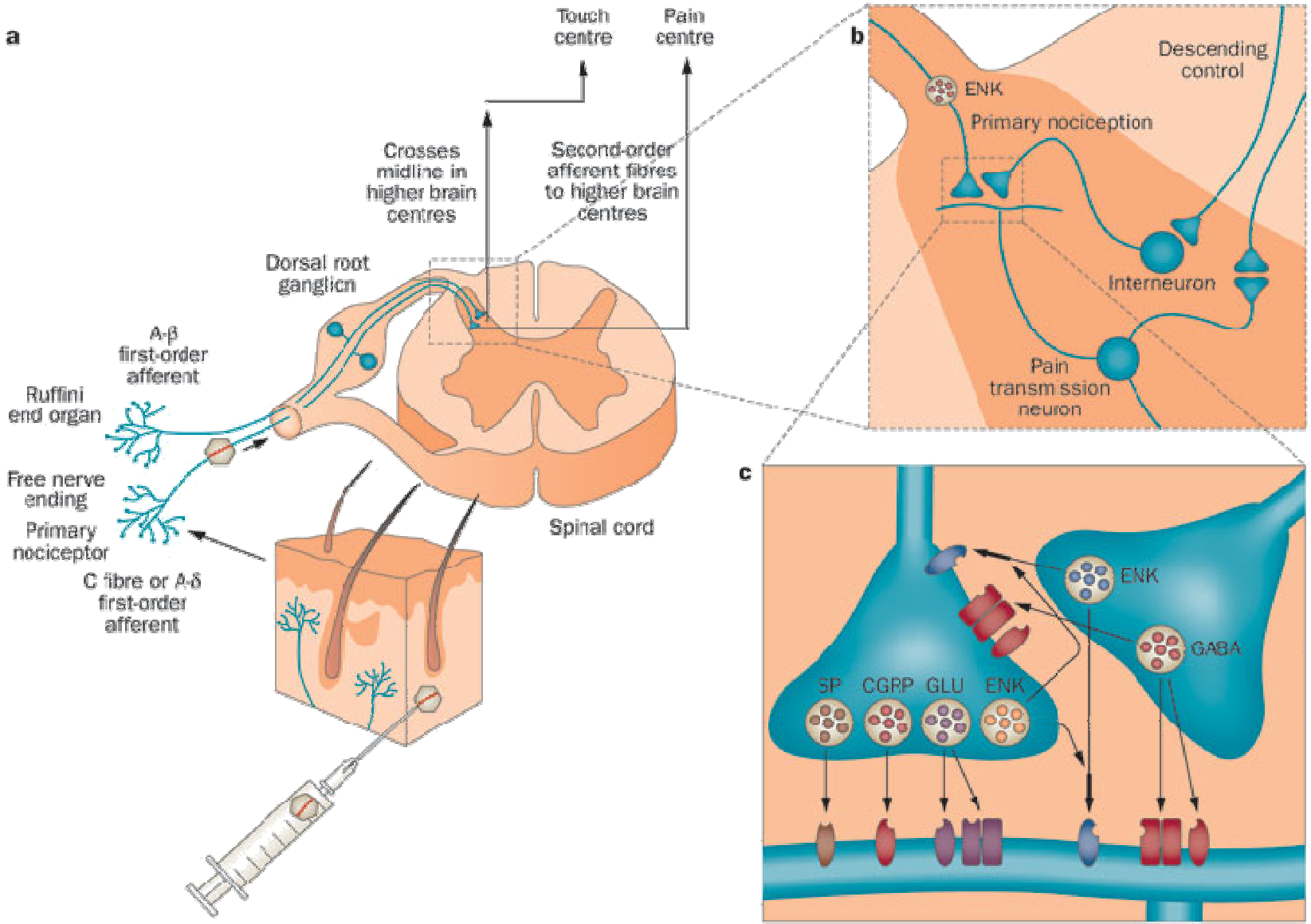
Classification of *neuropathic pain* by etiological and anatomical localization

Periphery	Spinal	Brain
Neuropathies	Multiple sclerosis	Syringobulbia
Traumatic nerve injury	Spinal injuries	Stroke
Plexus avulsion	Myelopathies	Multiple sclerosis
Amputation	Ischaemic lesions	Parkinson's disease
Neuralgia	Syringomyelia	
Compression (e.g. cancer)	Chordotomy	
HIV infections	Cancer compression	
Polyradicultis		

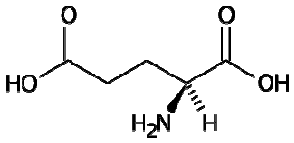
1. Pain and Narcotic Analgesics



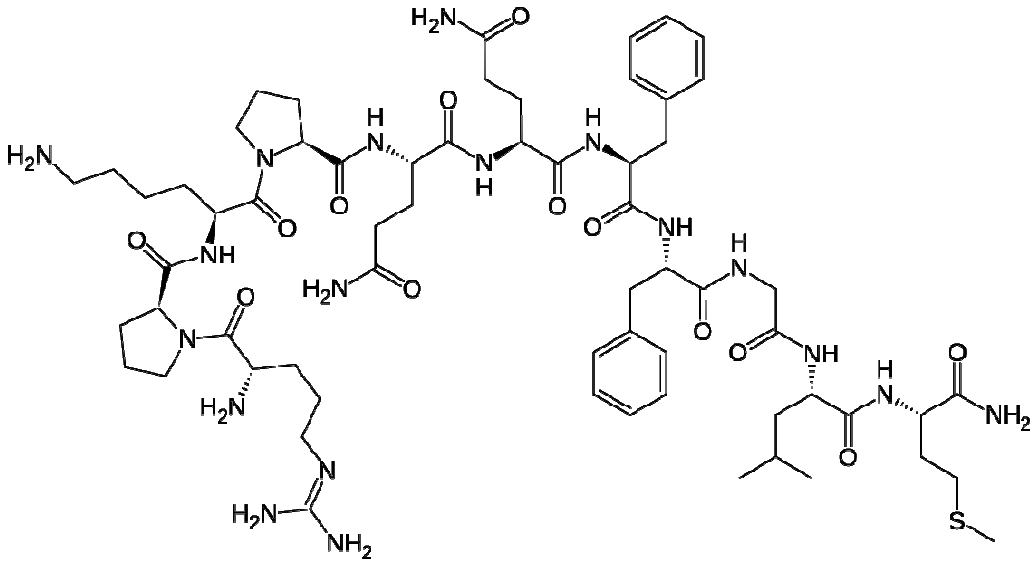
1. Pain and Narcotic Analgesics



1. Pain and Narcotic Analgesics



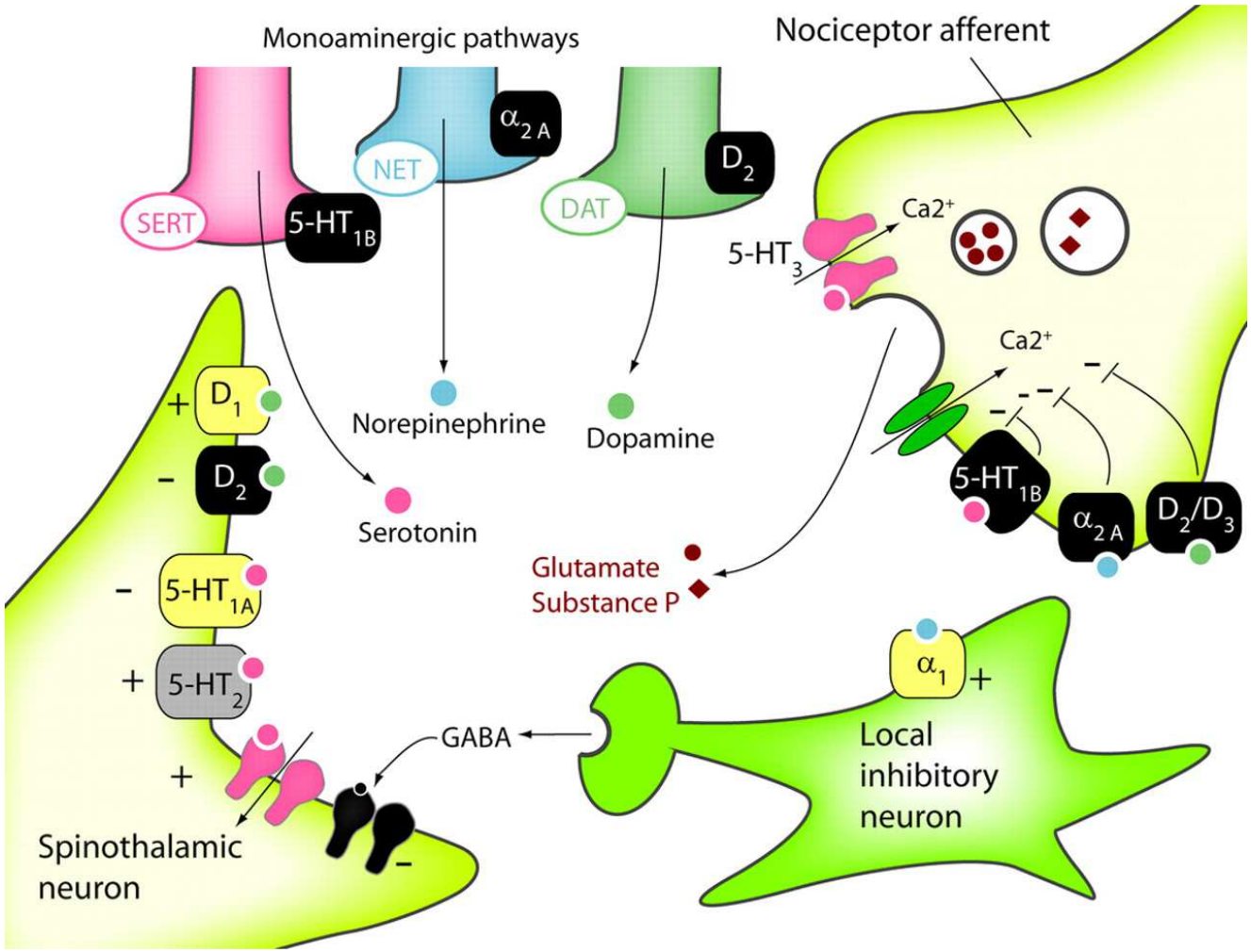
Glutammic acid



Substance P

1. Pain and Narcotic Analgesics

The importance of the descending monoamine system for the pain experience and its treatment:



1. Pain and Narcotic Analgesics

1.1 Endogenous Opioid Peptides

The ***Endogenous Opioid*** system includes a large number of opioid peptides that are ligands for the different types of opioid receptors.

Opioid peptides that are produced in the body include:

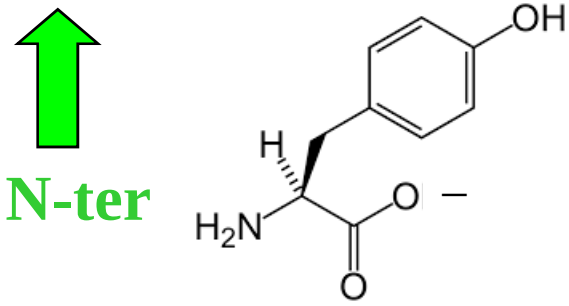
1. Endorphins
2. Enkephalins
3. Dynorphins
4. Endomorphins

Each family derives from a distinct *precursor protein* and has a characteristic anatomical distribution. Each precursor is subject to complex cleavages and post-translational modifications resulting in the synthesis of multiple active peptides.

1. Pain and Narcotic Analgesics

1.1 Endogenous Opioid Peptides

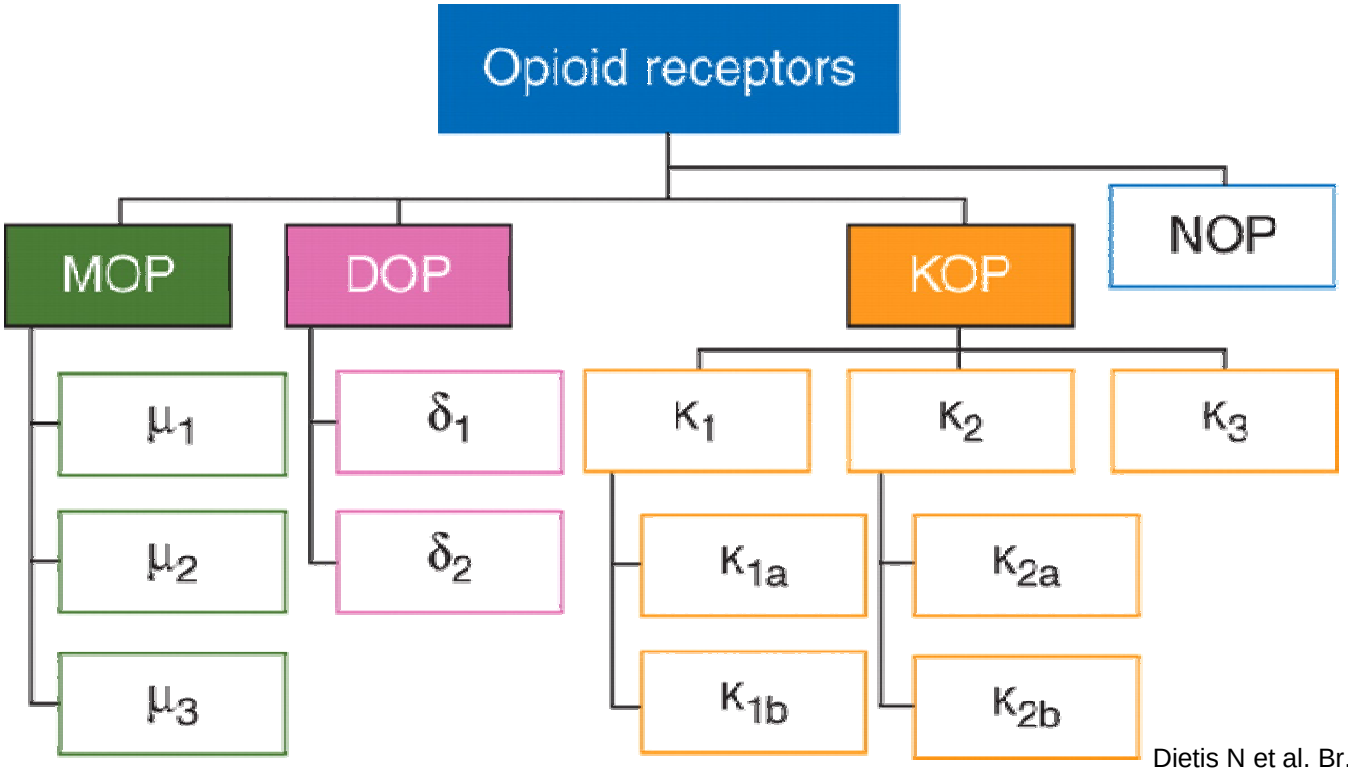
Dynorphin A 1-17	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Arg-Asn-Gln
γ-Endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser Gln-Thr-Pro-Leu-Val-Thr-Leu
Met-enkephalin	Tyr-Gly-Gly-Phe-Met
Leu-enkephalin	Tyr-Gly-Gly-Phe-Leu
Endomorphin 1	Tyr-Pro-Trp-Phe
Endomorphin 2	Tyr-Pro-Phe-Phe



1. Pain and Narcotic Analgesics

1.3 Opioid Receptors: pharmacological classification:

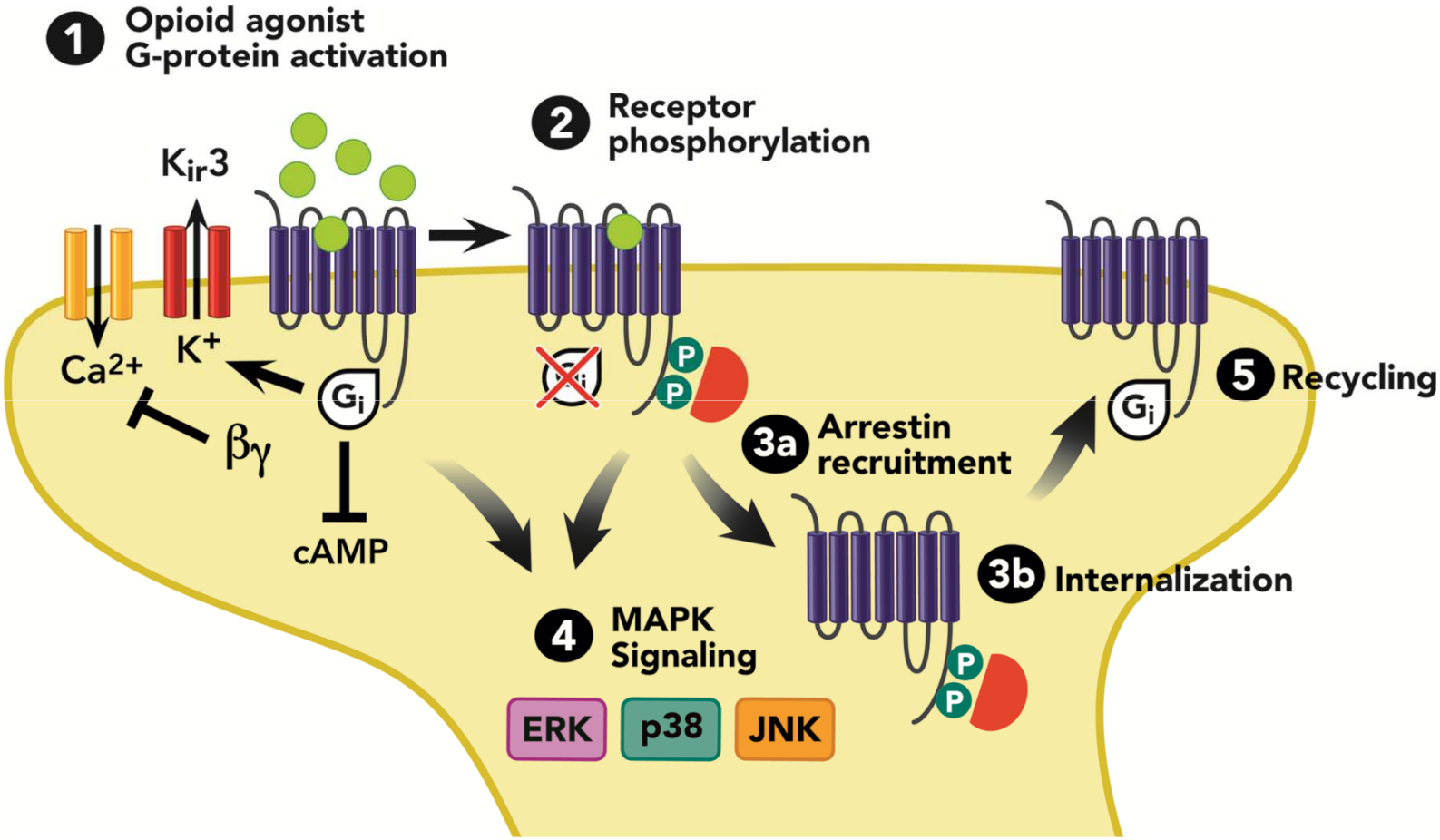
- **Three major classes of opioid receptors: Mu (m, MOR), Delta (d, DOR), and Kappa (k, KOR)**
- **They are all G protein-coupled and show significant amino acid sequence similarities.**



Dietis N et al. Br. J. Anaesth. 2011;107:8-18

1. Pain and Narcotic Analgesics

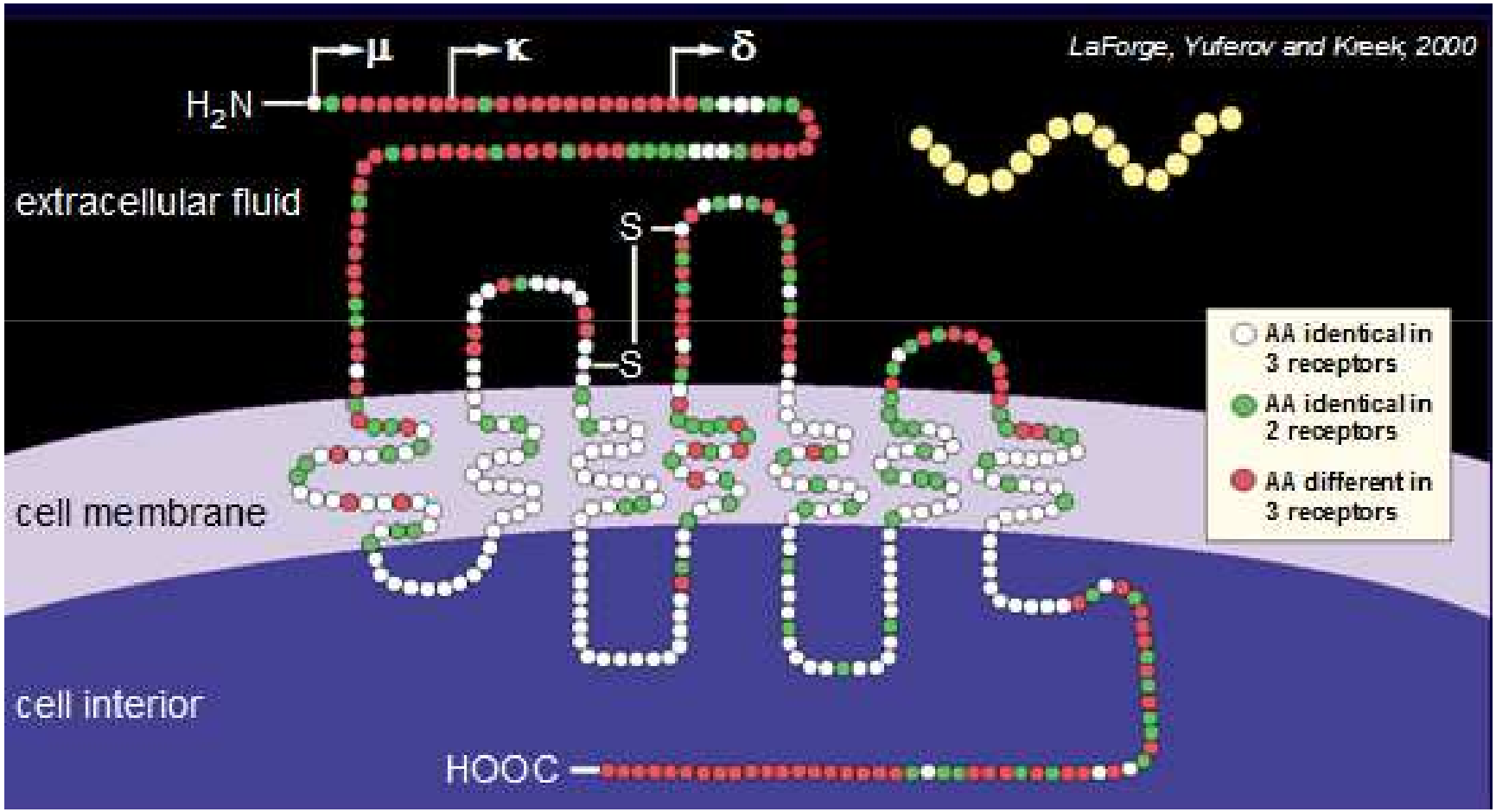
1.3 Opioid Receptors: pharmacological classification:



Dietis N et al. Br. J. Anaesth. 2011;107:8-18

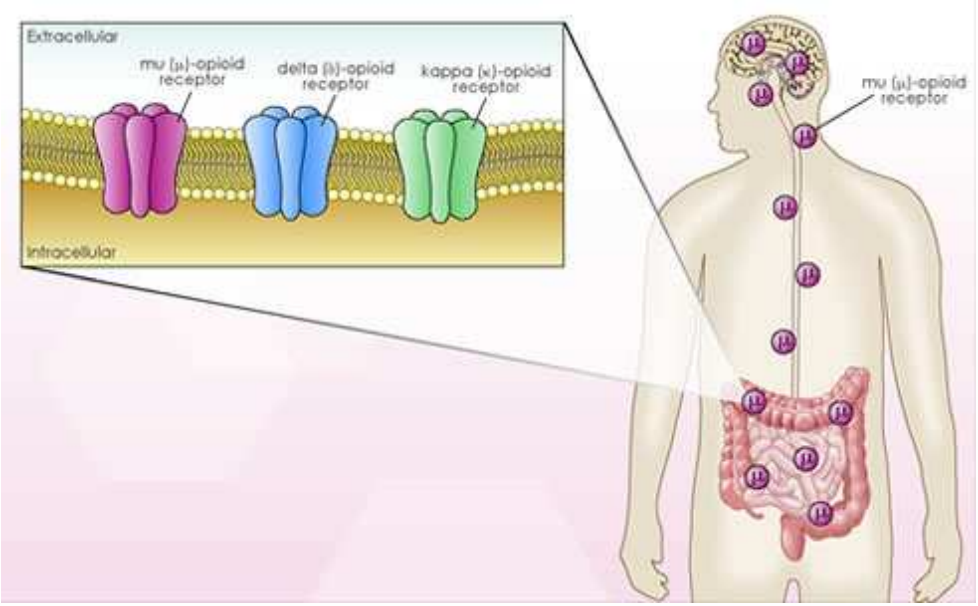
1. Pain and Narcotic Analgesics

1.3 Opioid receptors sequence similarity



1. Pain and Narcotic Analgesics

1.3 Opioid receptors distribution and site effects



Opioid use carries several side effects. These include drowsiness, nausea, slower breathing, and a general depression of the respiratory system. ***Further, opioids often cause constipation, or opioid-induced constipation (OIC).*** OIC is an uncomfortable side-effect that occurs in many patients who receive opioid treatments to relieve pain.

1. Pain and Narcotic Analgesics

1.3 Opioid Receptors: physiological effects

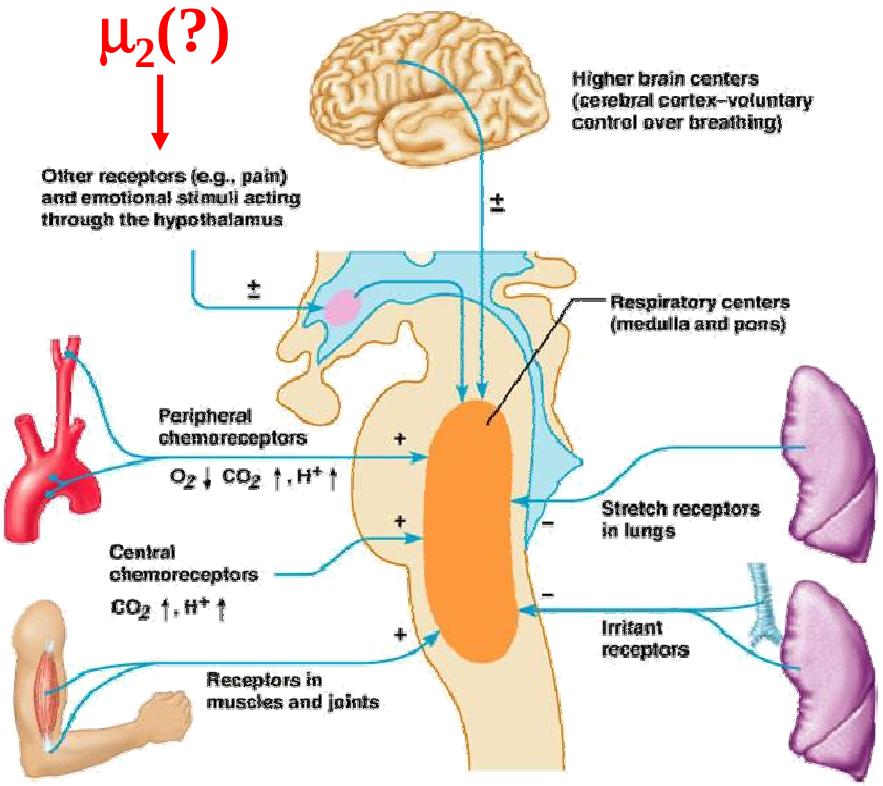
(1) Analgesia, euphoriant, respiratory depressant, and physical dependence properties of morphine result principally from actions at mu receptors (MOR). *Stimulation of mu_1-receptors blocks pain while stimulation of mu_2-receptor causes respiratory depression and constipation.*

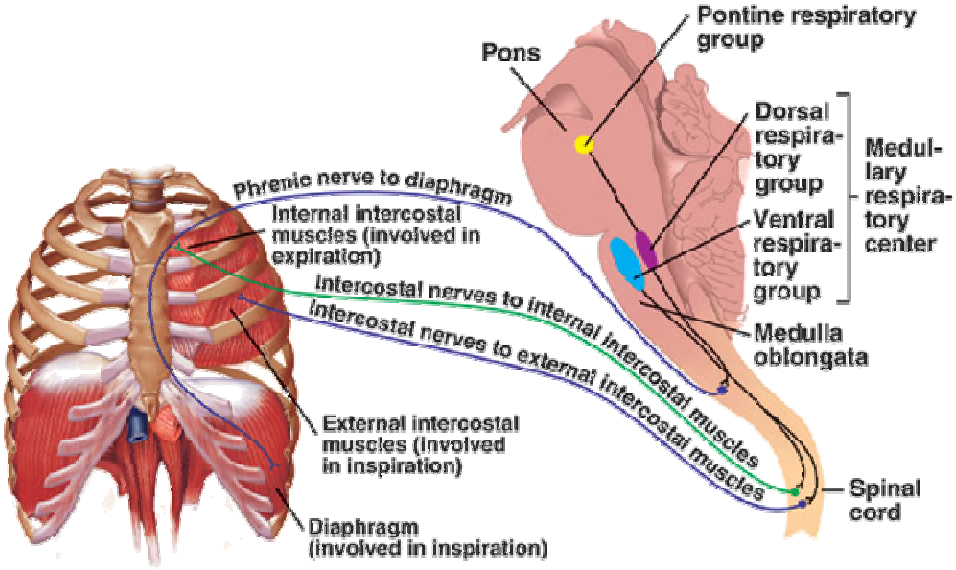
(2) Most of the currently available opioid analgesics act primarily at the mu receptor.

(3) Delta and kappa receptors can also contribute to analgesia.

1. Pain and Narcotic Analgesics

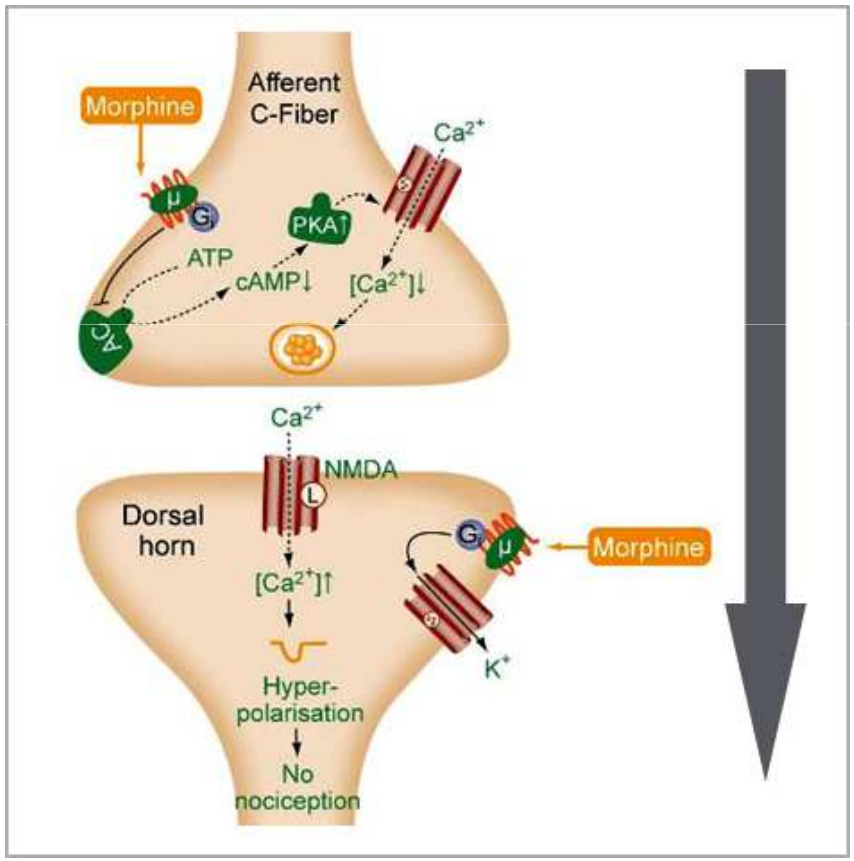
1.3 Opioid Receptors: control of ventilation





1. Pain and Narcotic Analgesics

1.3 Opioid Receptors: cellular actions



Opioids act at two sites:

1. They reduce pain signal transmission by activation pre-synaptic opioid receptors. This leads to reduced intracellular cAMP concentration, decreased calcium ion influx and thus inhibits the release of excitatory neurotransmitters (glutamate, substance P).

2. At the post-synaptic level, opioid-receptor binding evokes a hyperpolarisation of the neuronal membrane which decreases probability of the generation of an action potential.

1. Pain and Narcotic Analgesics

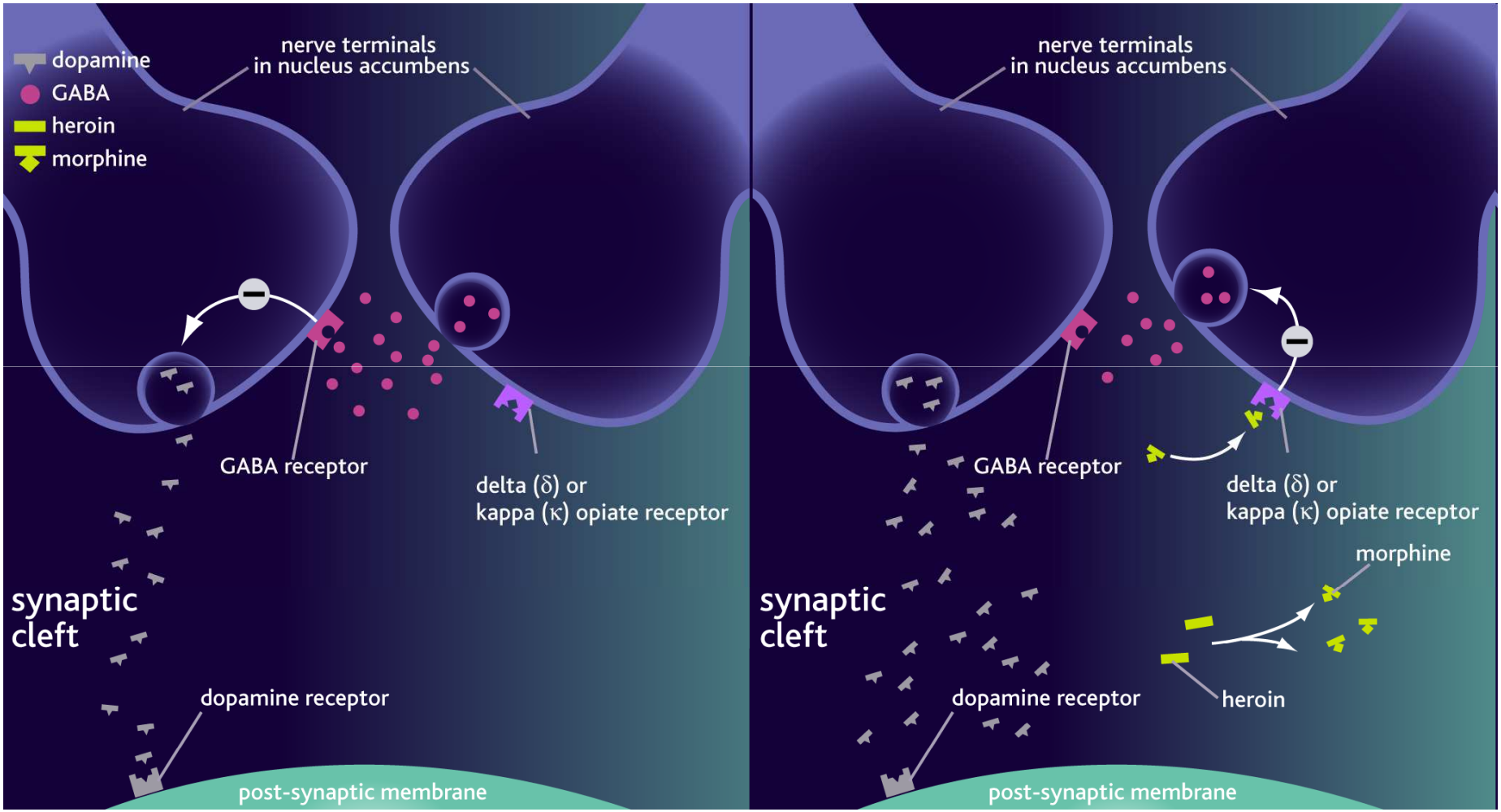
1.3 Opioid Receptors: Tolerance and physical dependence

(1) ***Tolerance***: with frequently repeated administration of therapeutic doses of morphine or its surrogates, there is a gradual loss in effectiveness. To reproduce the original response, a larger dose must be administered.

(2) ***Physical dependence***: when the drug is stopped or an antagonist is administered, a characteristic withdrawal or abstinence syndrome occurs.

1. Pain and Narcotic Analgesics

1.3 Opioid Receptors: euphoria effect



1. Pain and Narcotic Analgesics

1.4 Morphine

Opium is the dried latex obtained from opium poppies (*Papaver somniferum*).

Raw opium contains approximately 25 different alkaloids by weight, depending on the variety. The chief alkaloids are Morphine (4-21%), Codeine (0.8-2.5%), Thebaine (0.5-2%), Papaverine (0.5-2.5%), Noscapine (4-8%), Meconic Acid (3-5%).

Papaver somniferum

Morphine was the first pharmaceutical isolated from a natural product by 1820. Morphine sales began in 1827, by Heinrich Emanuel Merck of Darmstadt, and helped him expand his family pharmacy into the Merck KGaA pharmaceutical company.

1. Pain and Narcotic Analgesics

1.4 Opiates and Opioids: definitions

Opiates:

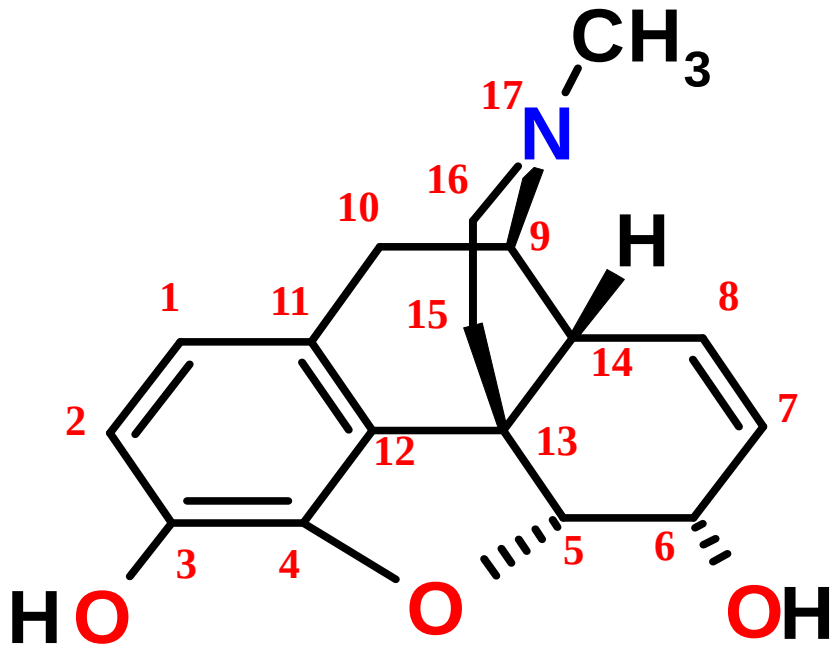
alkaloids derived from the opium poppy (Morphine, Codeine, Thebaine…)

Opioids:

Opiates plus
Semi Synthetics – derived from the alkaloids like Thebaine (Hydrocodone, Oxycodone, Heroin…)
Synthetics: Fentanyl, Methadone…

1. Pain and Narcotic Analgesics

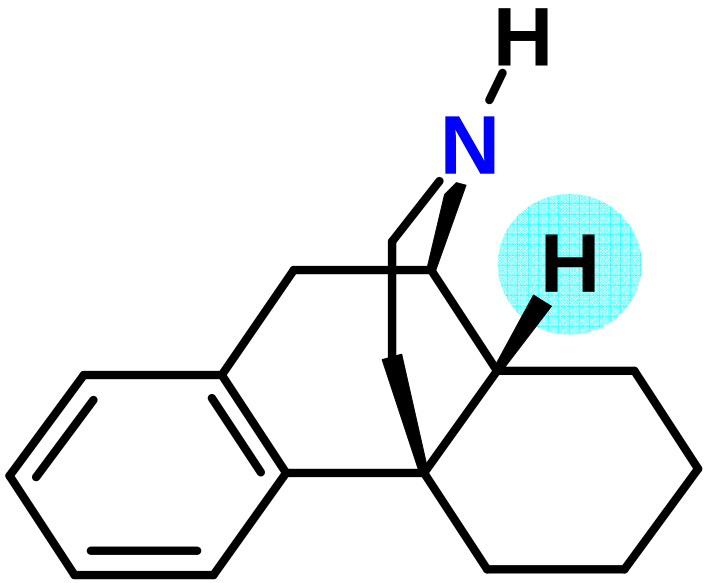
1.4 Morphine



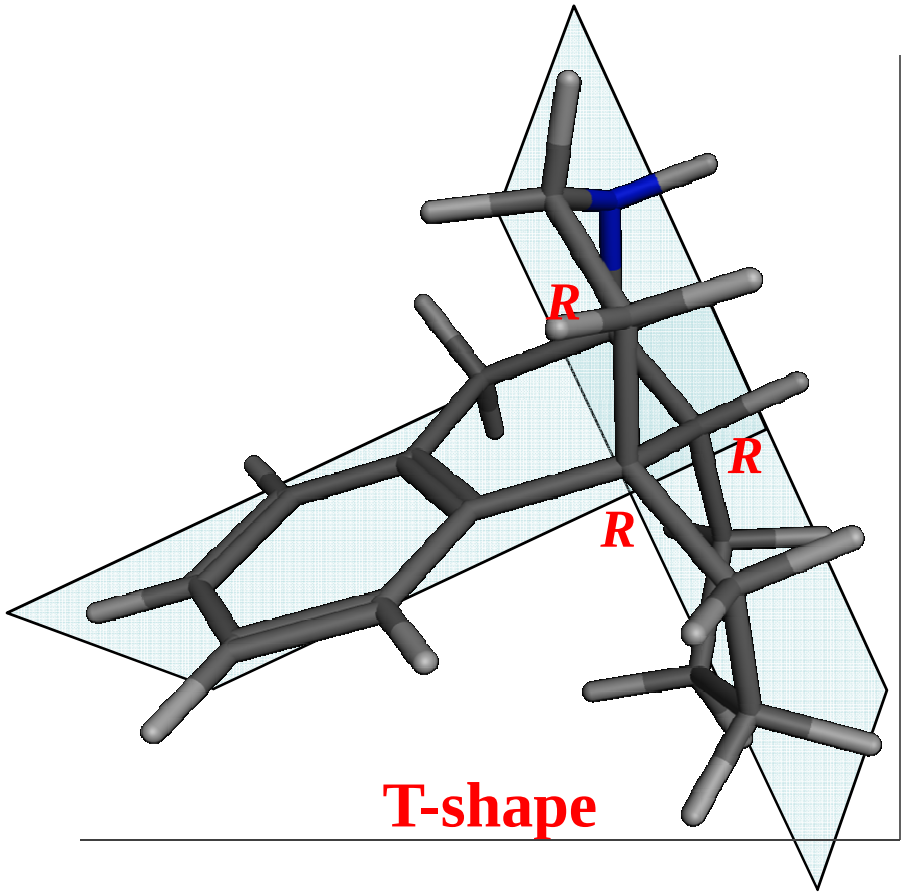
(5α,6α)-7,8-didehydro-
4,5-epoxy-17-methylmorphinan-3,6-diol

1. Pain and Narcotic Analgesics

1.4 Morphine: morphinan scaffold



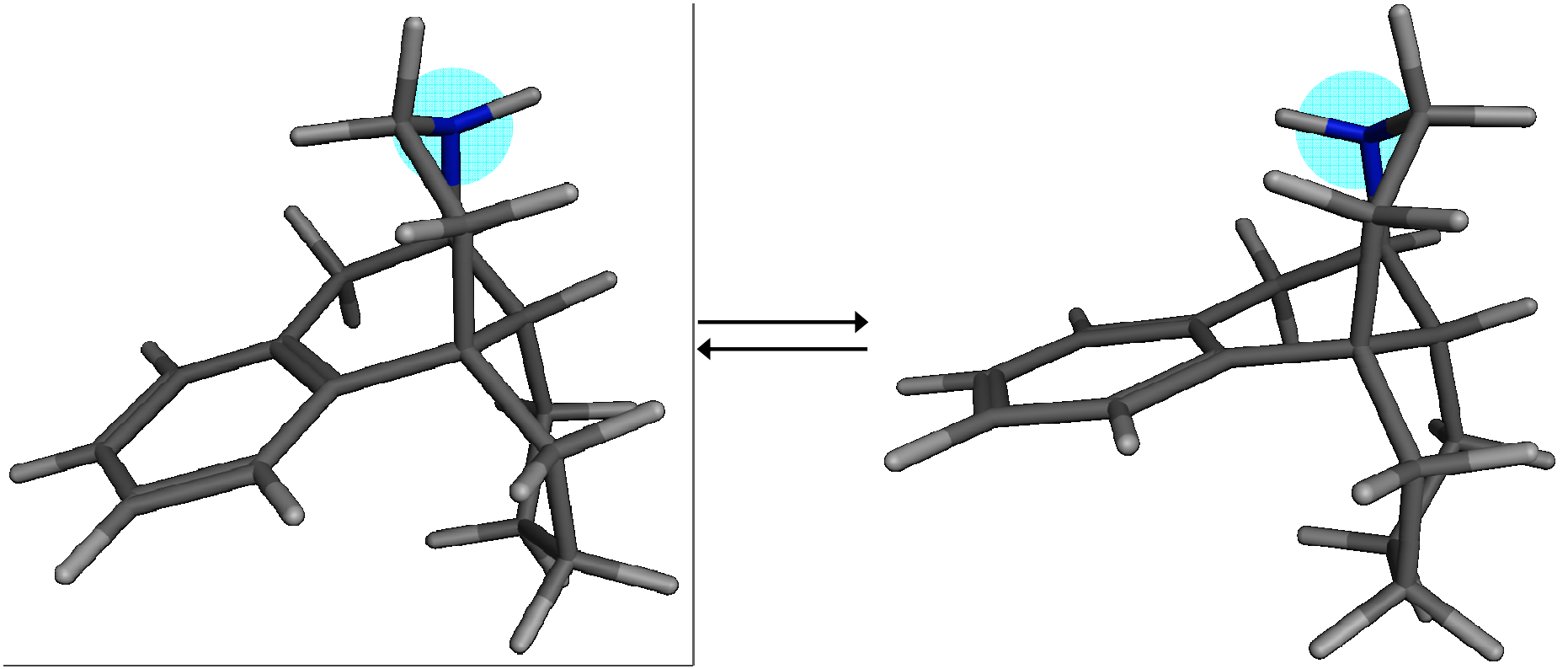
Morphinan



T-shape

1. Pain and Narcotic Analgesics

1.4 Morphine: morphinan equilibrium



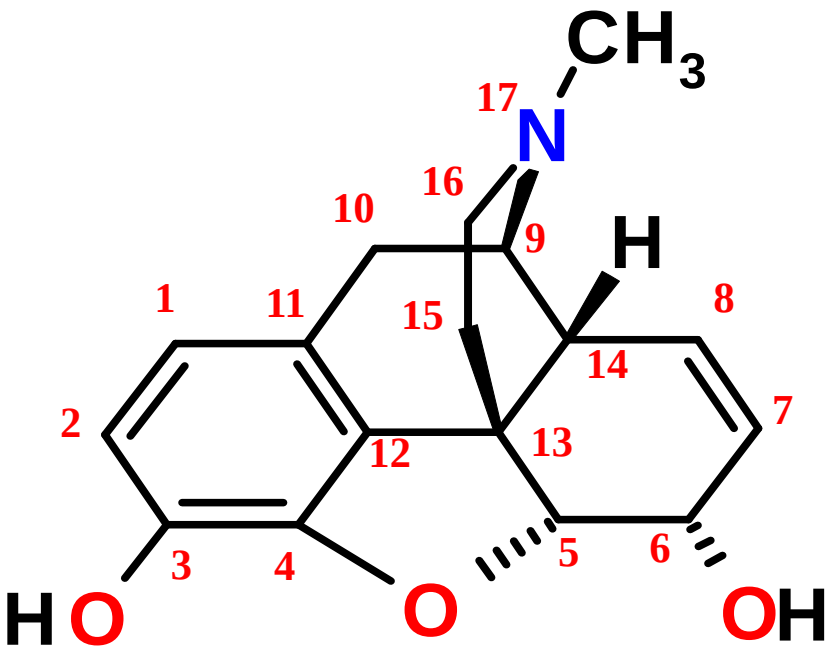
ΔH_{form} = 11. 8 kcal/mol

ΔH_{form} = 16. 2 kcal/mol

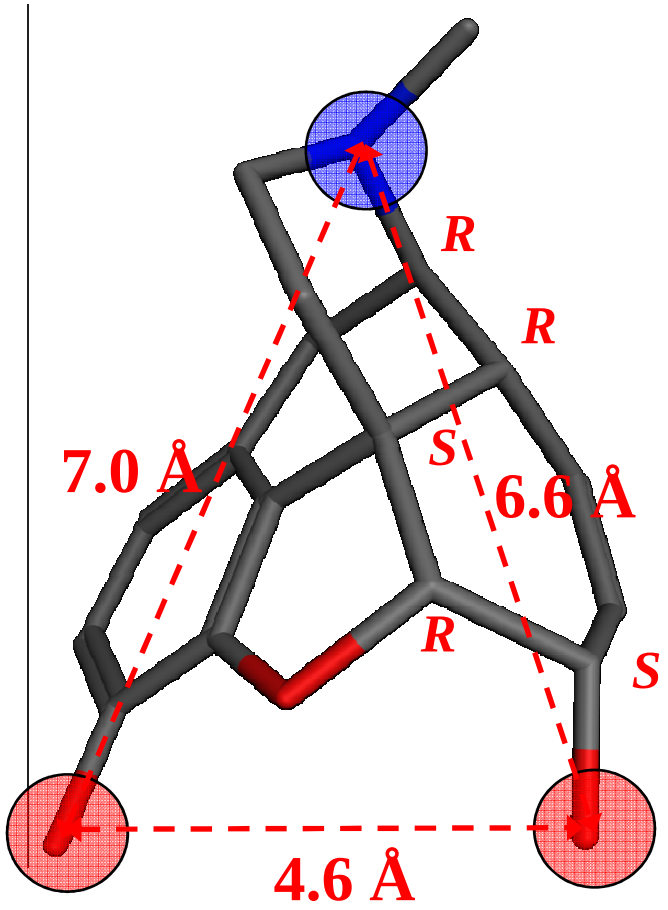
Can you remember this equilibrium, please?

1. Pain and Narcotic Analgesics

1.4 Morphine

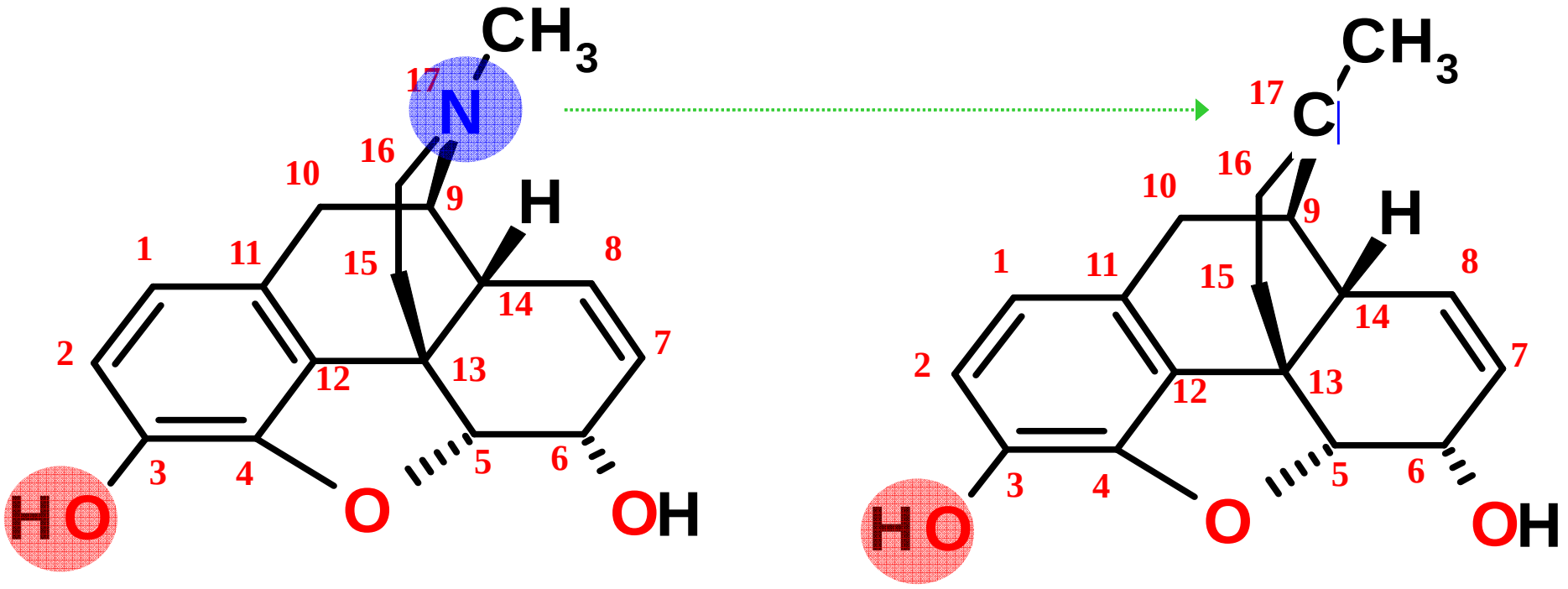


(5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol



1. Pain and Narcotic Analgesics

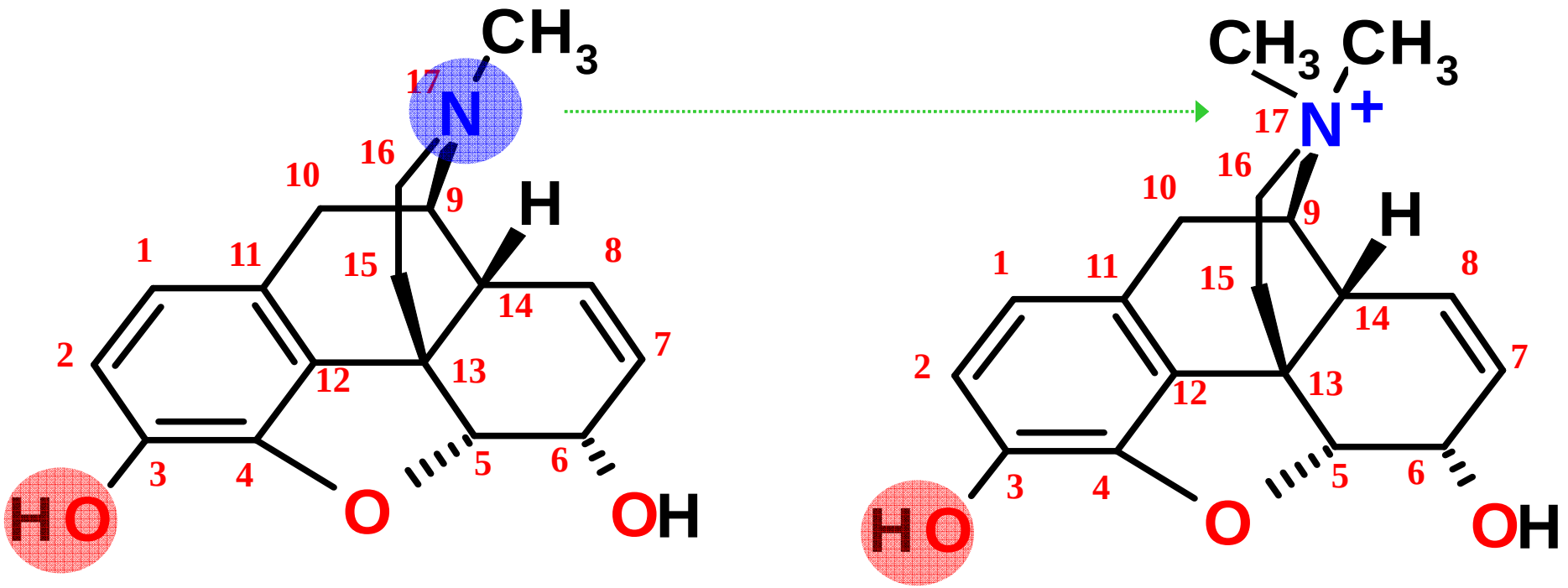
1.4 Morphine: 17-N is essential to receptor binding



No activity!!!

1. Pain and Narcotic Analgesics

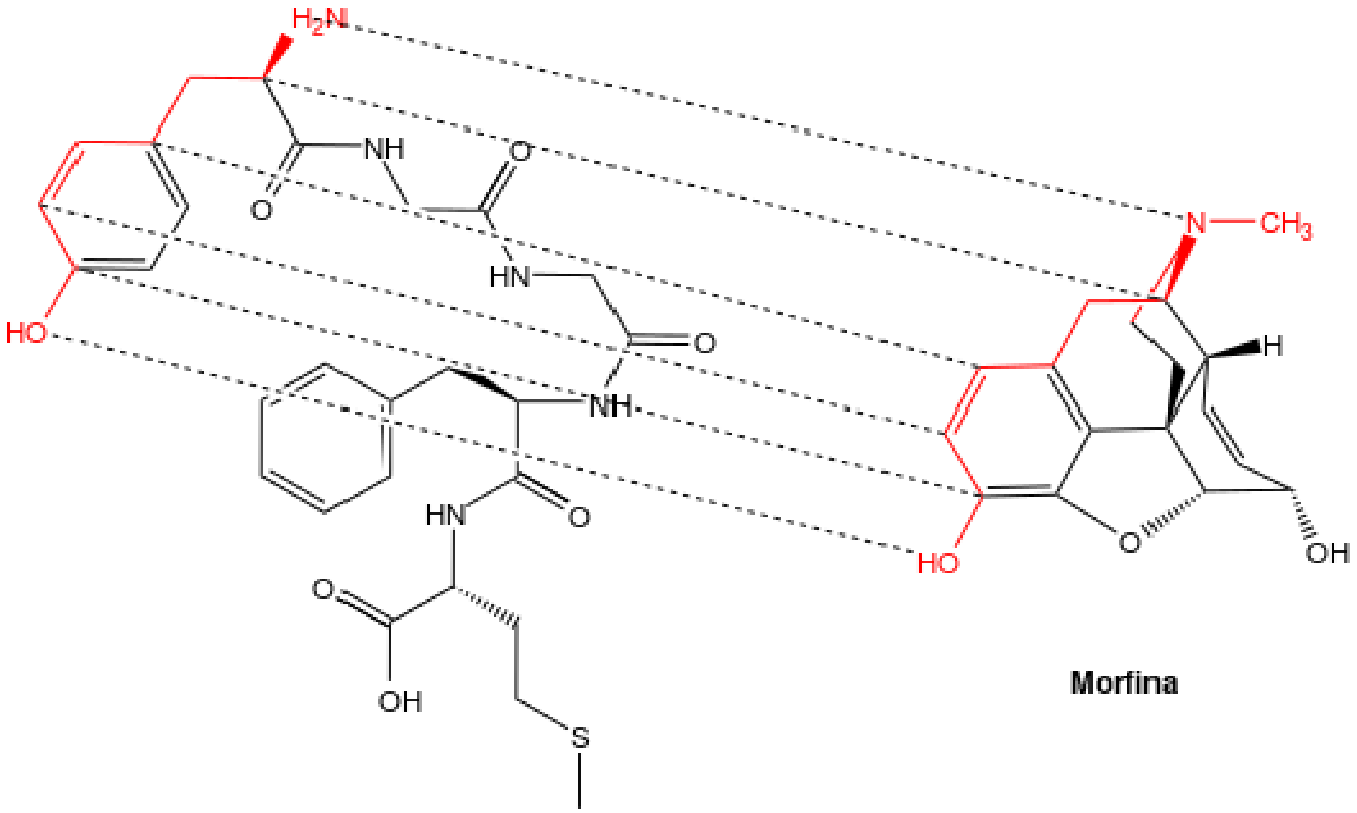
1.4 Morphine: 17-N is essential to receptor binding



No activity…
at least at SNC!!!

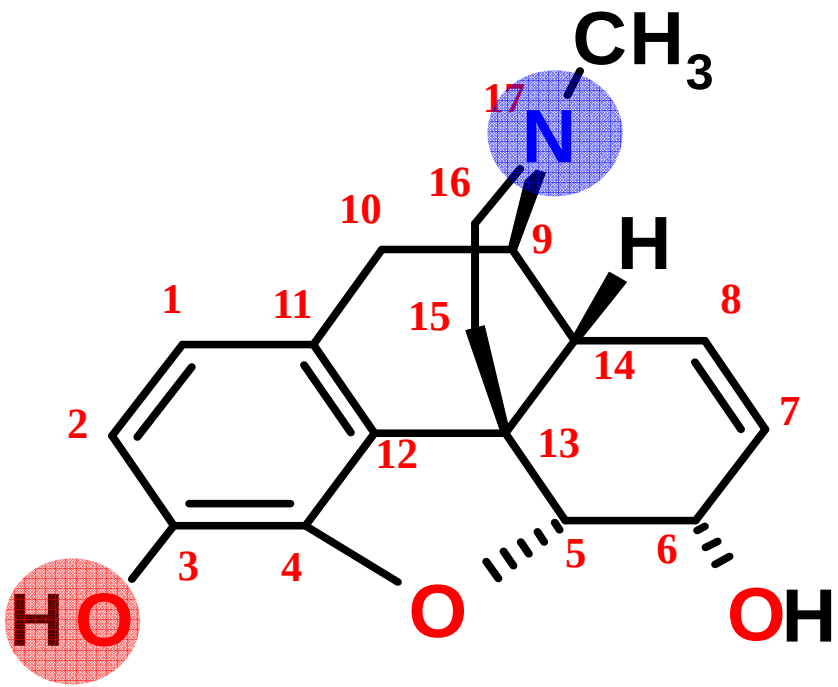
1. Pain and Narcotic Analgesics

1.4 Morphine: nice comparison…



1. Pain and Narcotic Analgesics

1.4 Morphine:



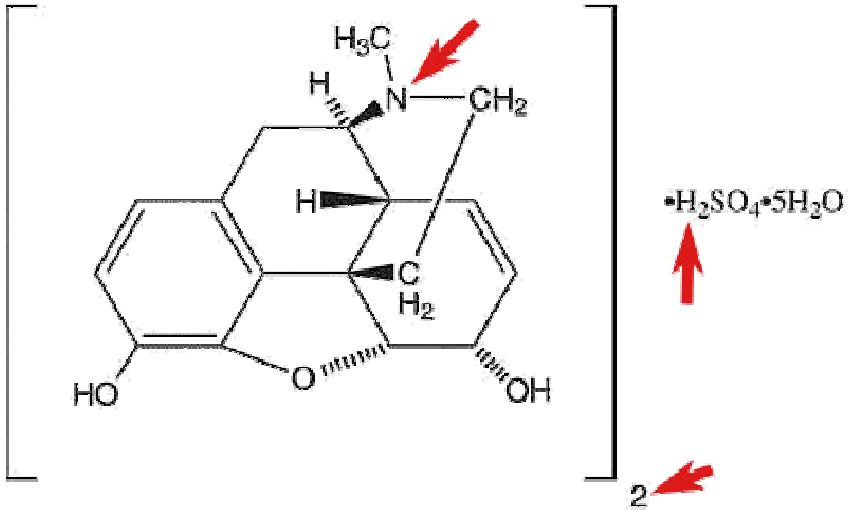
(5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol

Morphine presents difficulty in gaining access to the brain appears to be greatest with amphorteric agents (ie., drugs possessing both acidic [a phenolic hydroxyl at C3] and basic groups [the N17 amine]). Heroin and codeine traverse the B. B. B. more readily.

logP = 0.8

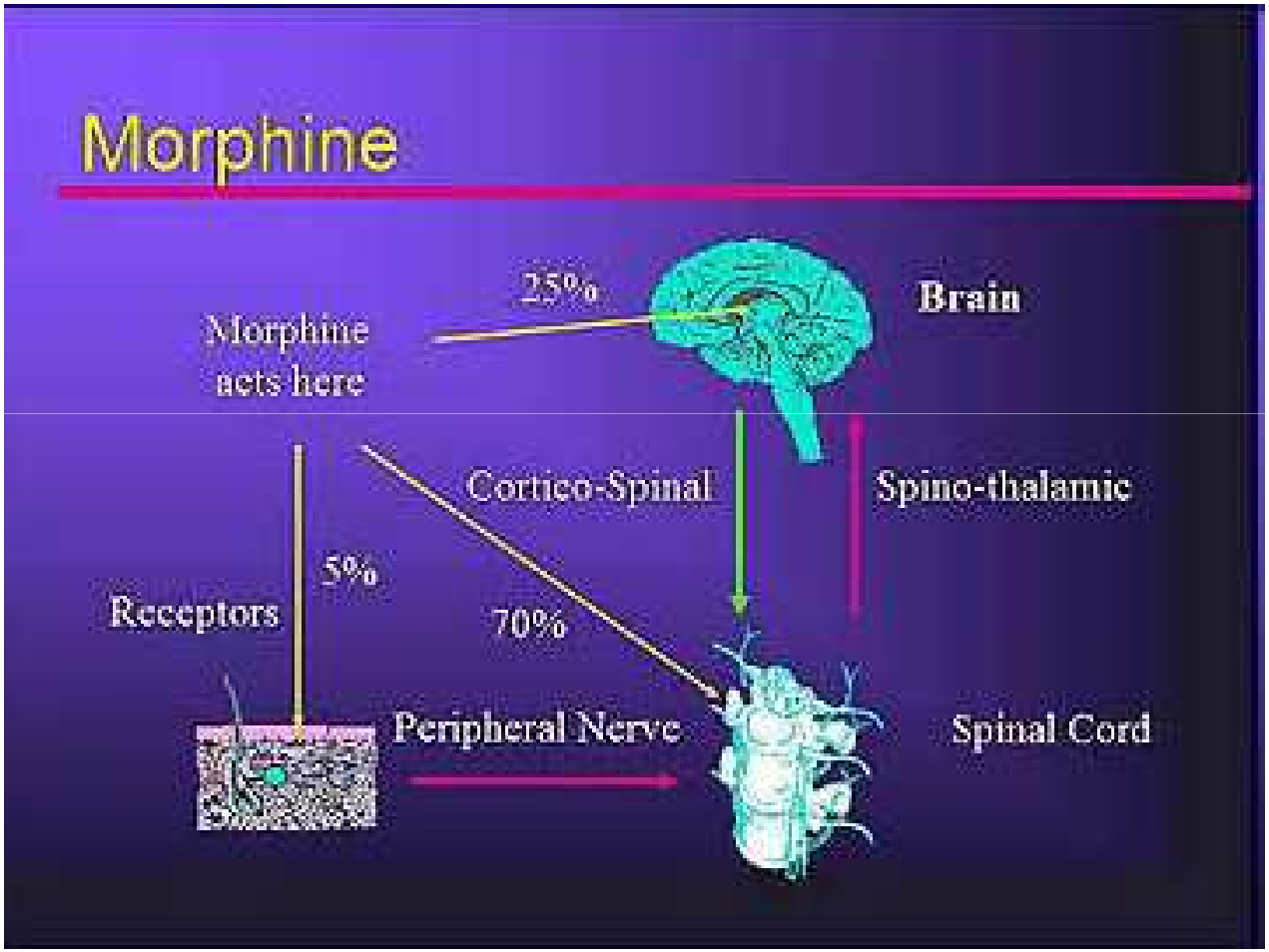
1. Pain and Narcotic Analgesics

1.4 Morphine: formulations… as sulfate!



1. Pain and Narcotic Analgesics

1.4 Morphine



1. Pain and Narcotic Analgesics

1.4 Morphine

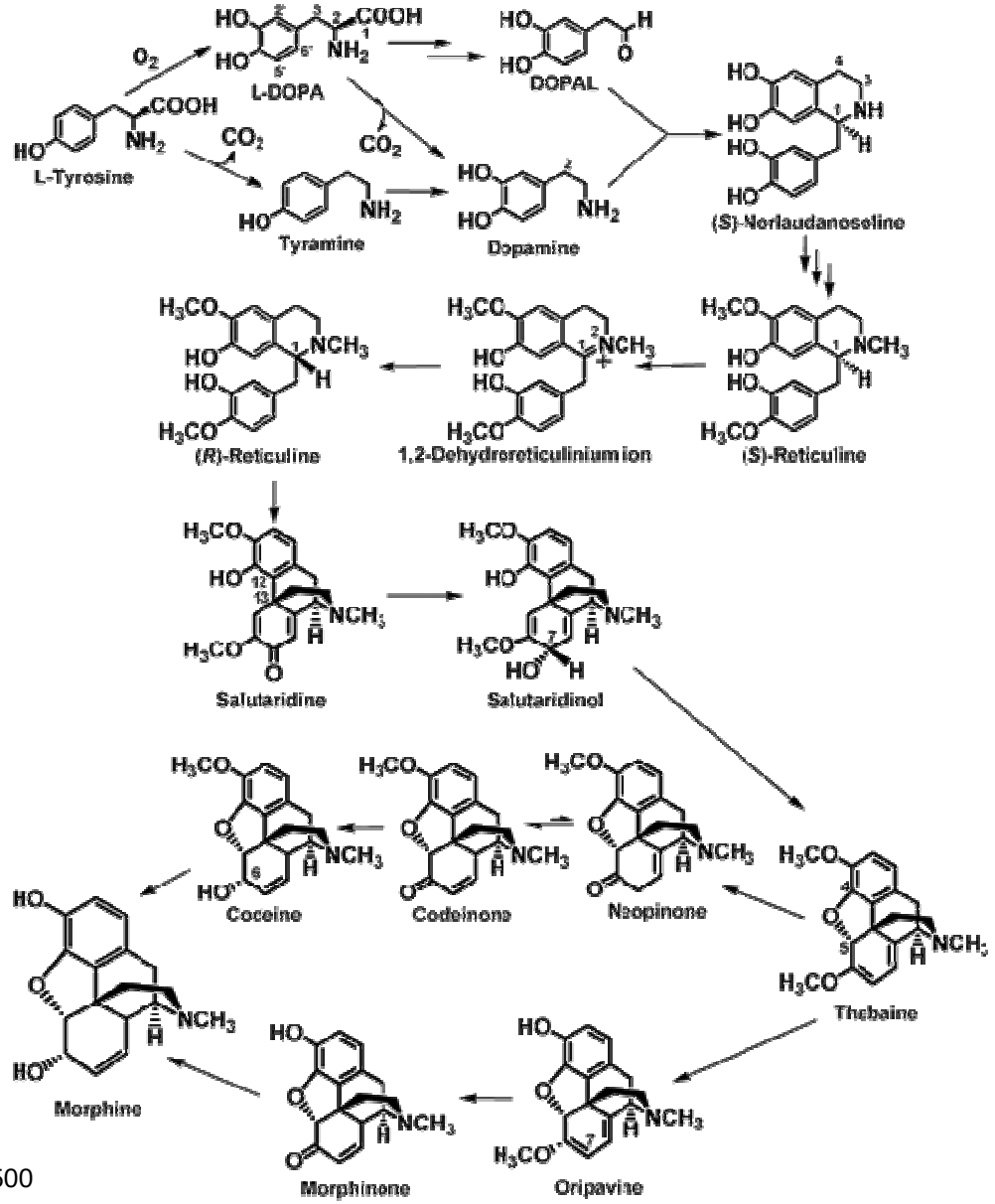
It has been unequivocally shown that human neuroblastoma cells are able to synthesize morphine.

The metabolic route starting from L-tyrosine involving at least 19 chemical steps shares remarkable similarities with the morphine biosynthesis in opium poppy.

In the future, the identification of the respective genes and enzymes in humans and animals will provide information on the evolution of this pathway in the animal kingdom. The function of endogenous morphine is still a matter of discussion. In contrast to plants, where morphine is a highly specific secondary metabolite providing protection against herbivores, presumptions indicate that morphine in animals and humans may play a role as a general regulator and/or transmitter. Once these functions are identified, the genes and enzymes of morphine biosynthesis may become attractive targets for the modulation of pain, immune response, cell death, and behavioural phenomena.

Boettcher C et al. PNAS 2005;102:8495-8500

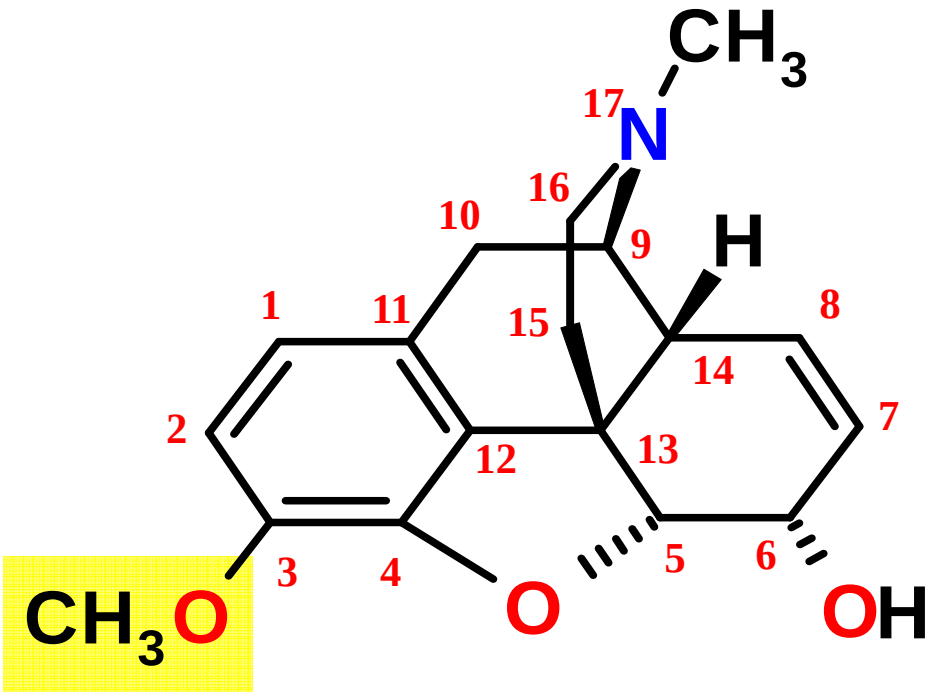
1. Pain and Narcotic Analgesics



Boettcher C et al. PNAS 2005;102:8495-8500

1. Pain and Narcotic Analgesics

1.5 Codeine



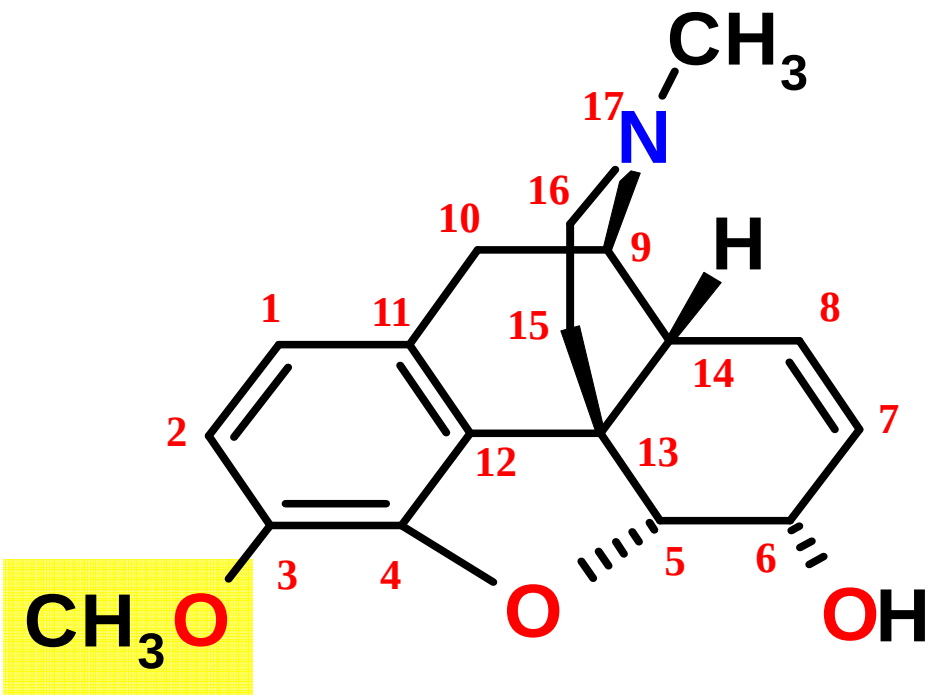
Codeine

(5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy -17-methylmorphinan-6-ol

Codeine, or methylmorphine, is a natural alkaloid found in opium poppy. Codeine was first isolated in 1832 in France by Pierre Robiquet, a French chemist and pharmacist already famous for the discovery of ***alizarin***, the most widespread red dye, while working on refined morphine extraction processes. Codeine is currently the most widely used opiate in the world, and probably the most commonly used drug overall.

1. Pain and Narcotic Analgesics

1.5 Codeine



Codeine

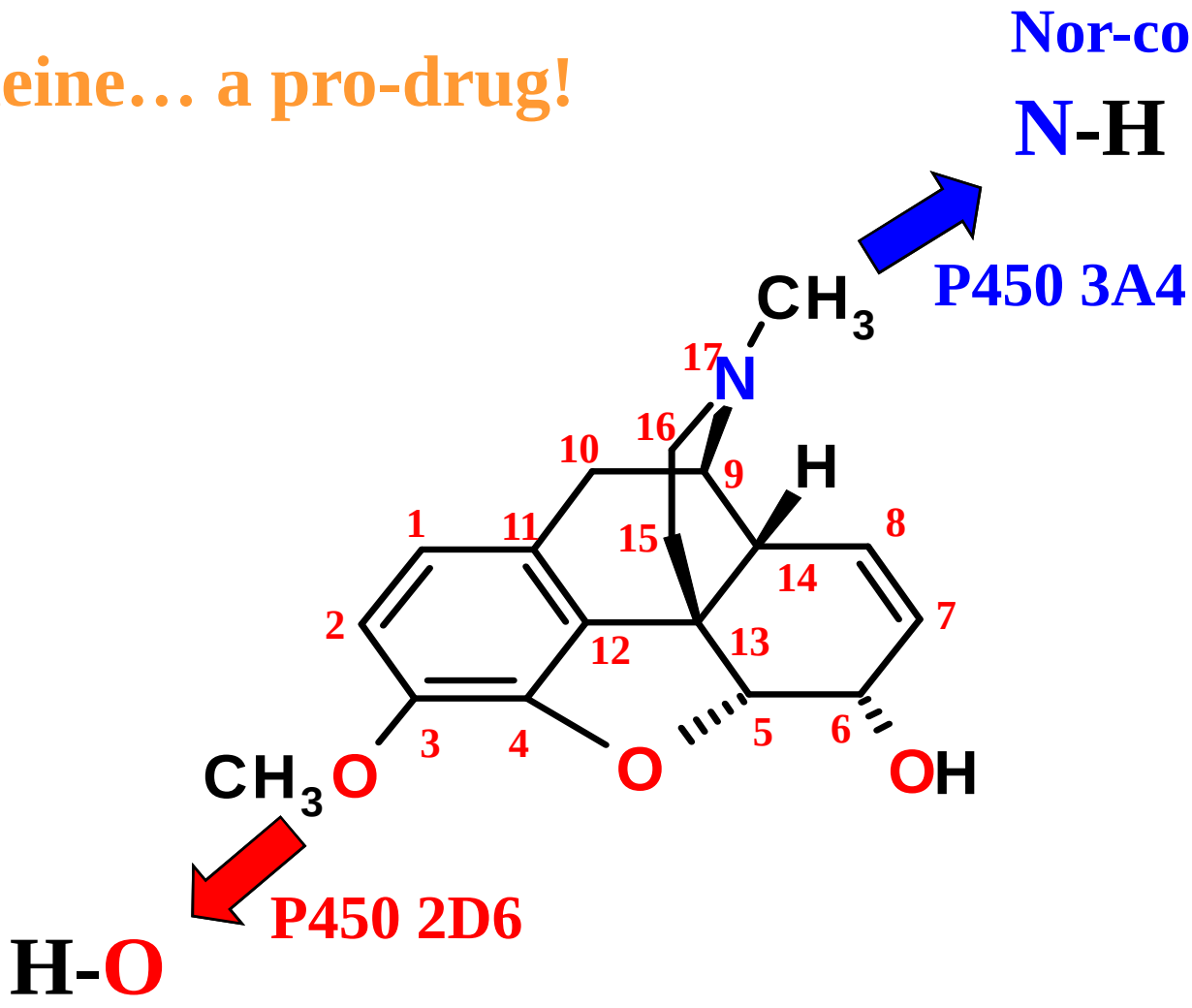
(5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy -17-methylmorphinan-6-ol

Codeine is partial agonist for mu and delta opioid receptors.
It is one of the most effective orally-administered opioid analgesics and has a wide safety margin. Its strength ranges from 8 to 12 percent of morphine in most people**.** Codeine is considered a prodrug, since it is metabolised *in vivo* to the primary active compounds morphine (5-10%) and codeine-6-glucuronide (≅ 70%).

logP = 1.2

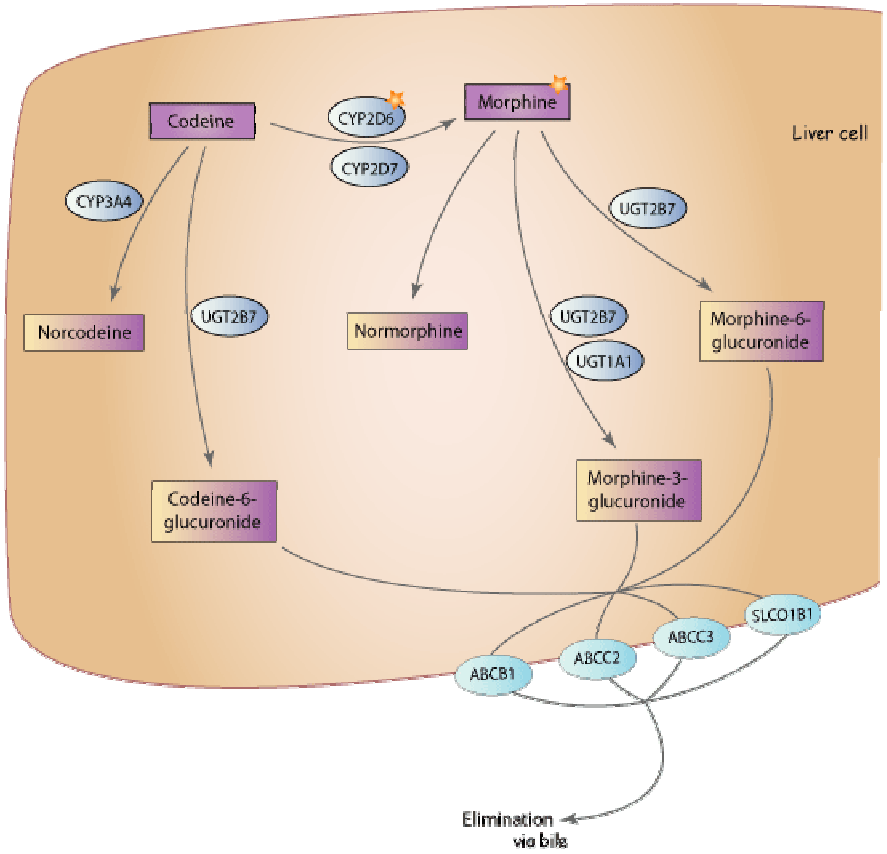
1. Pain and Narcotic Analgesics

1.5 Codeine… a pro-drug!



1. Pain and Narcotic Analgesics

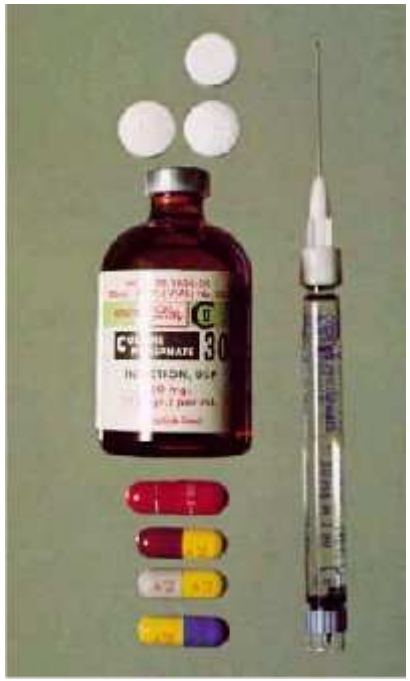
1.5 Codeine… and its metabolism!



The metabolism rate is approximately 30 mg of codeine in an hour and about 90% of the drug will be excreted from the body within a day. **In most people, only about 10% of codeine is transformed into morphine.**

1. Pain and Narcotic Analgesics

1.5 Codeine: formulations.



Codeine in conjunction with anti-nausea medication promethazine in the form of the syrup has become one of the most abused codeine preparations. Although there are various forms of this syrup varying in strengths, the “purple” version is highly publicized and is the most sought after. In this form, 60 mg of codeine per liquid ounce is used which makes it the strongest of the codeine syrups. This “Purple Drank” is frequently referenced and praised in the southern rap and Houston-based hip-hop community where it is mixed with the soft drink Sprite.

1. Pain and Narcotic Analgesics

1.5 Codeine as antitussive?

Codeine for acute cough in children

QUESTION Owing to Health Canada's recent recommendations to avoid the use of over-the-counter cough and cold medications in preschool children, I was looking at other antitussive medications for acute cough. Codeine was recommended in the past for this indication. What is the evidence for its use and how effective and safe is it?

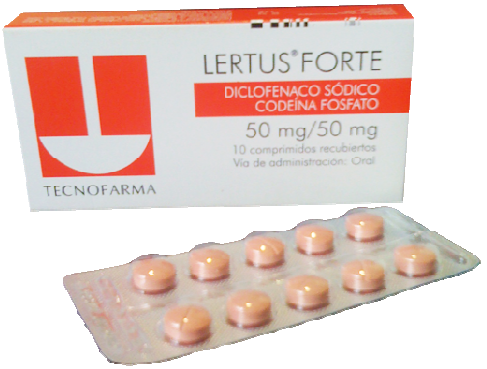
ANSWER Cough is one of the most common symptoms in children, and the opioid codeine has known antitussive qualities mediated by a central nervous system pathway. ***However, current evidence finds codeine to be no more effective than placebo for acute cough in children.*** Its safety profile and recent advances in understanding codeine's variable effectiveness prohibit recommending codeine for cough in children.

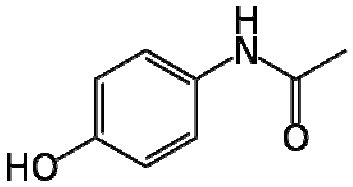
Goldman, RD "Codeine for acute cough in children". *Canadian Family Physician* 56 (12): 1293–4 (2010).

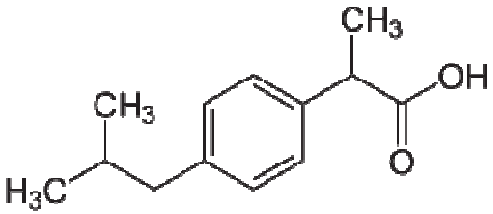
1. Pain and Narcotic Analgesics

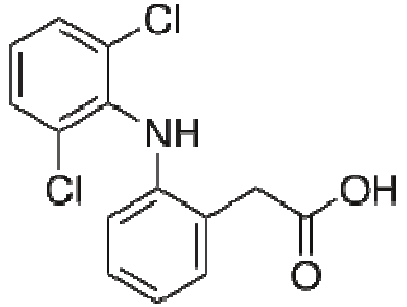
1.5 Codeine in combination with…

Codeine is marketed as both a single-ingredient drug and in combination preparations with **Paracetamol**, with **Aspirin**; with **Ibuprofen** or **Naproxen** or **Diclofenac** or **Indomethacin**. These combinations provide greater pain relief than either agent alone (*drug synergy*).



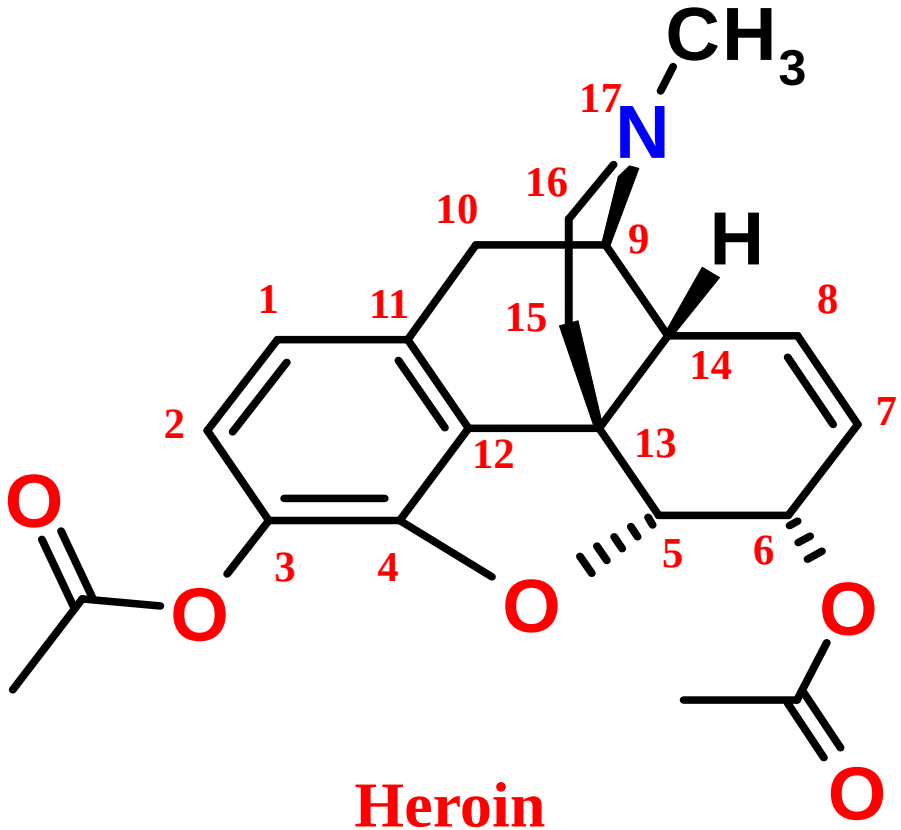






1. Pain and Narcotic Analgesics

1.5 Heroin



Heroin

(5α,6α)-7,8-didehydro- 4,5-epoxy-
17-methylmorphinan- 3,6-diol diacetate

logP = 1.6

Heroin, or **diacetylmorphine**, also known as **diamorphine**, is a semi-synthetic opioid drug synthesized from morphine.

The German drug company Bayer named its new over the counter drug "Heroin" in 1895. The name was derived from the German word "*heroisch*" (heroic) due to its perceived "heroic" effects upon a user. However it was chiefly developed as a morphine substitute for cough suppressants that did not have morphine's addictive side-effects; morphine at the time was a popular recreational drug so Bayer wanted to find a similar but non-addictive substitute to market. However, contrary to Bayer's advertising as a "non-addictive morphine substitute," heroin would soon have one of the highest rates of dependence amongst its users

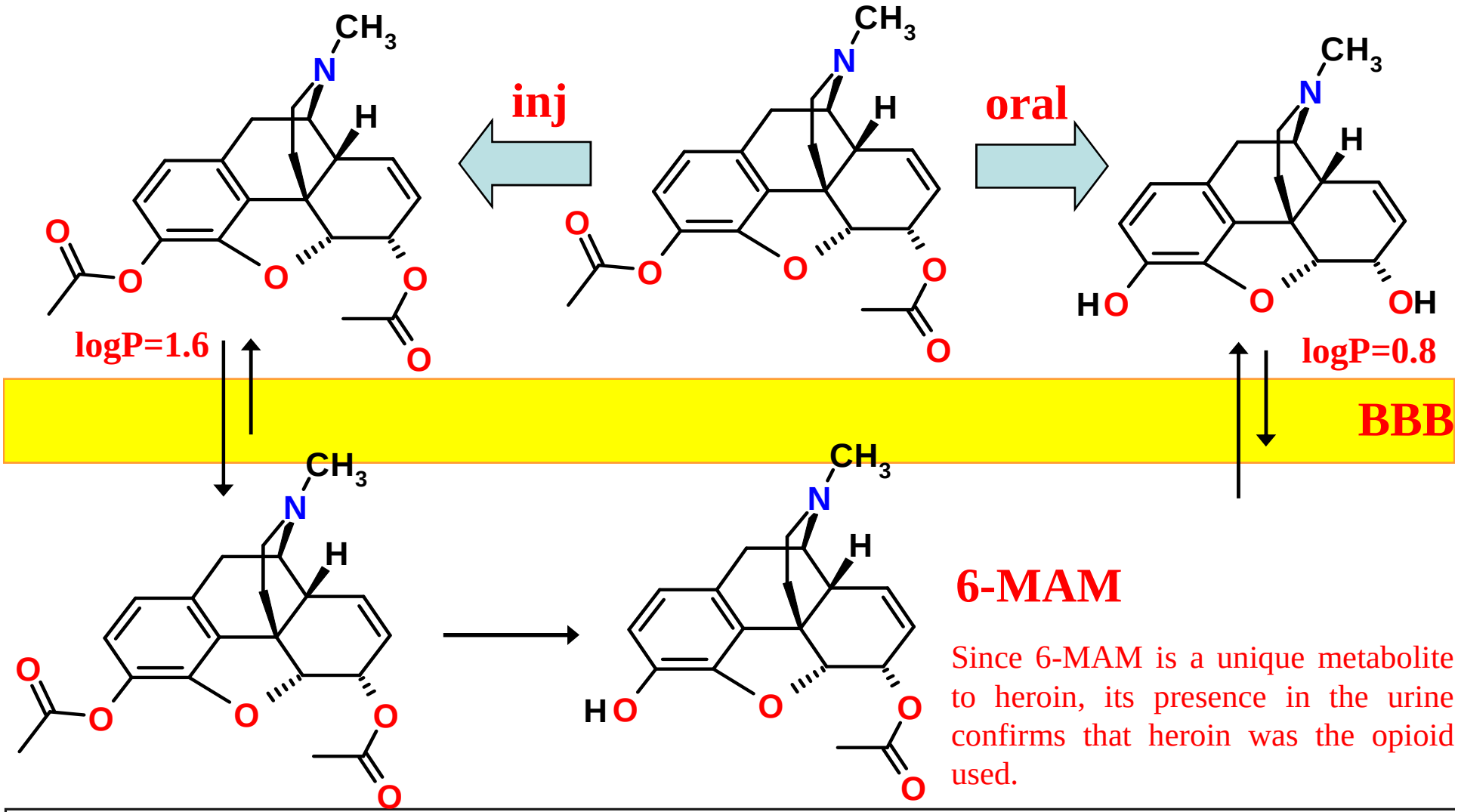
1. Pain and Narcotic Analgesics

1.5 Heroin

Heroin was originally marketed as a cough suppressant in 1898. It was, at the time, believed to be a non-addictive alternative to other opiate-containing cough syrups. This was quickly realized to be not true as heroin readily breaks down into morphine in the body. Morphine was already known to be addictive,.

1. Pain and Narcotic Analgesics

1.5 Heroin

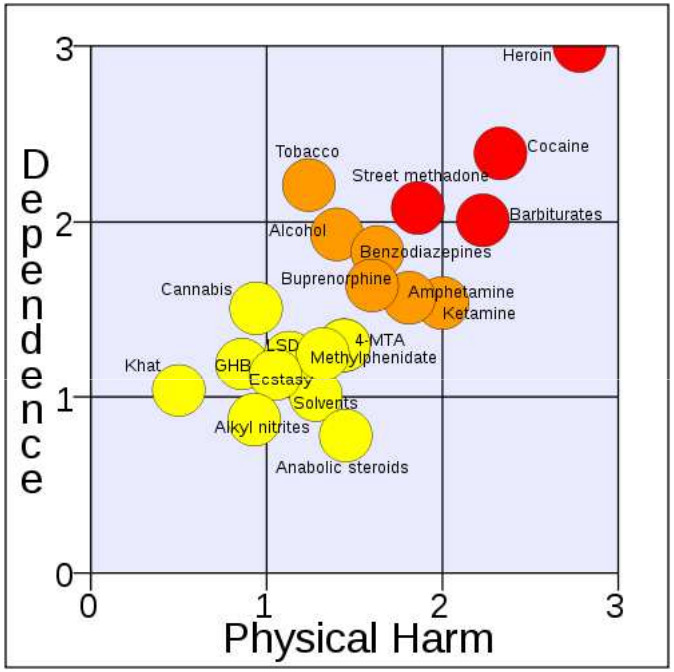


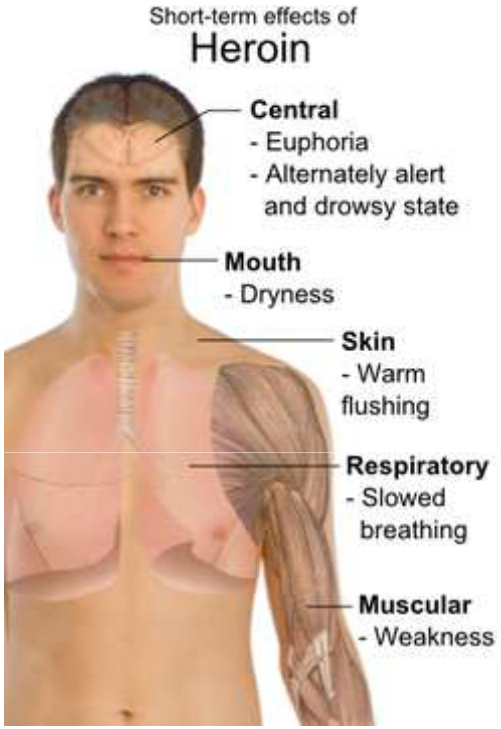
6-MAM

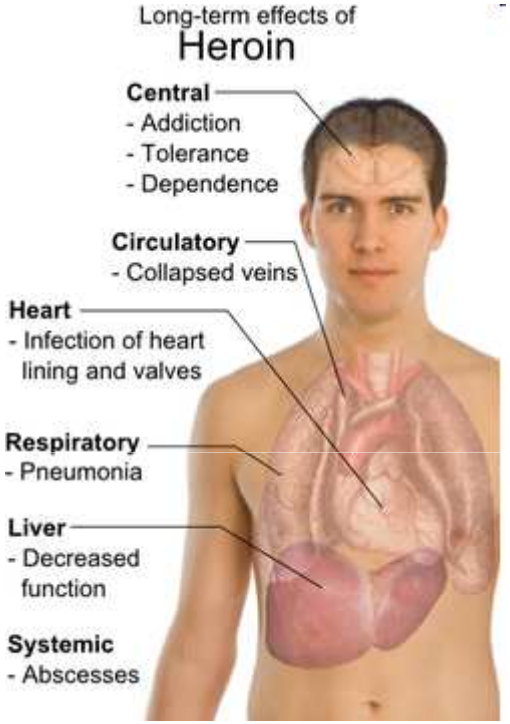
Since 6-MAM is a unique metabolite to heroin, its presence in the urine confirms that heroin was the opioid used.

1. Pain and Narcotic Analgesics

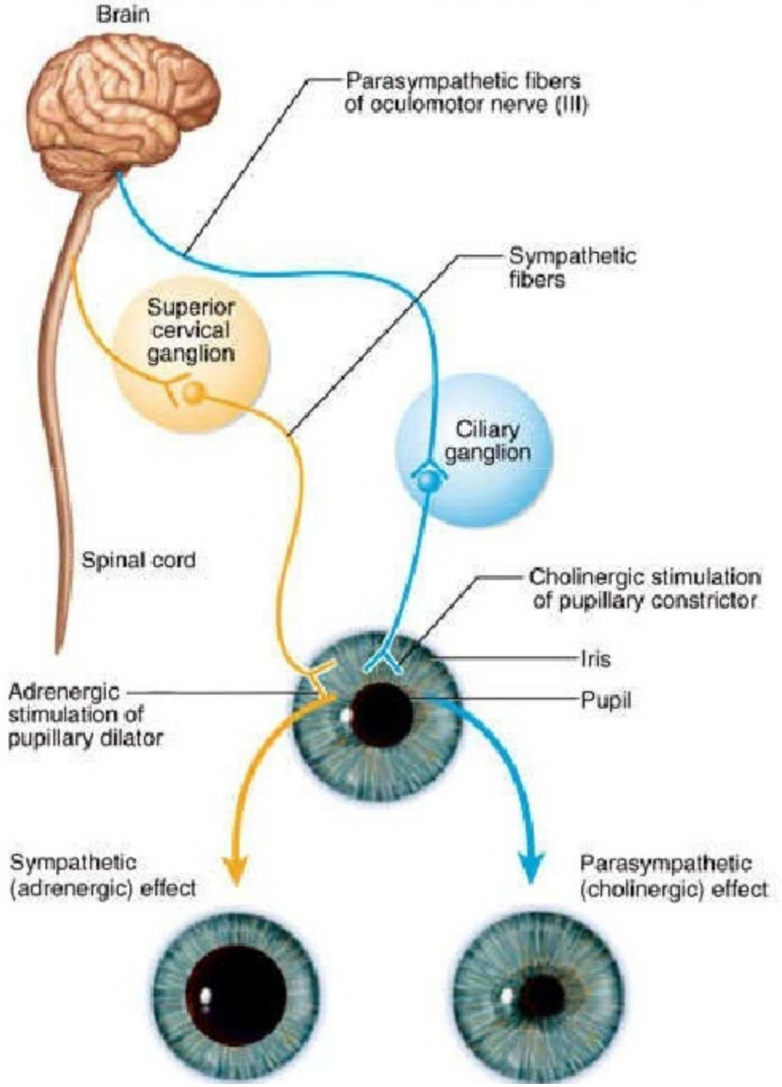
1.5 Heroin

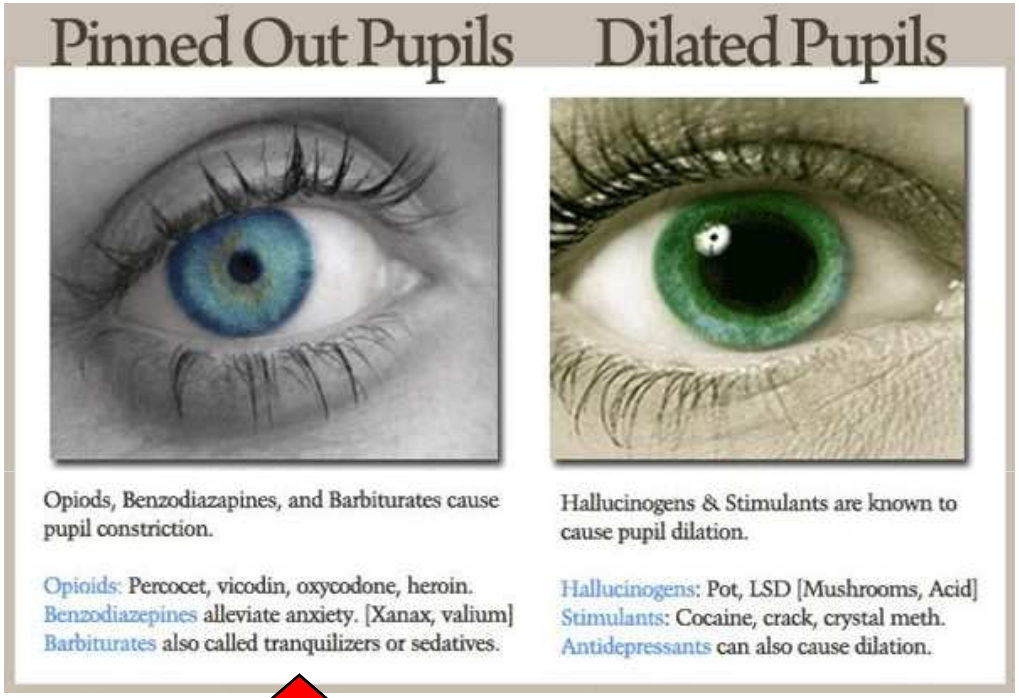


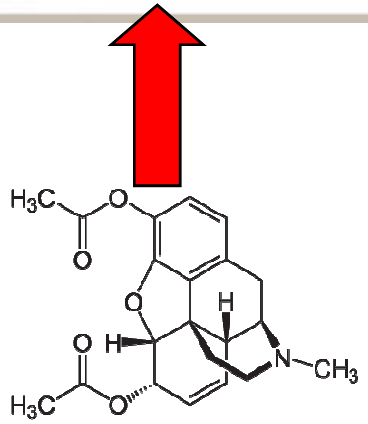




The eyes don't lie!!!

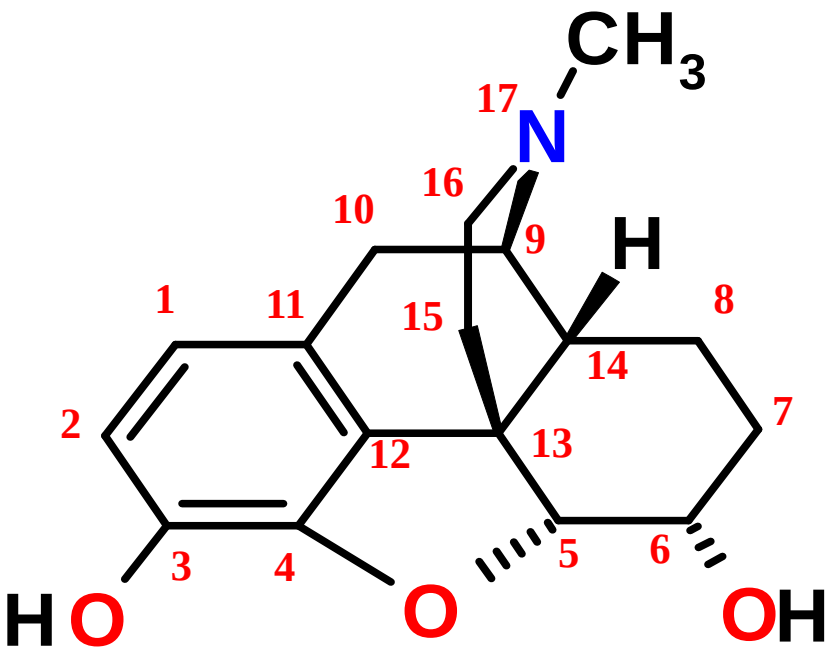






1. Pain and Narcotic Analgesics

1.6 Dihydromorphine



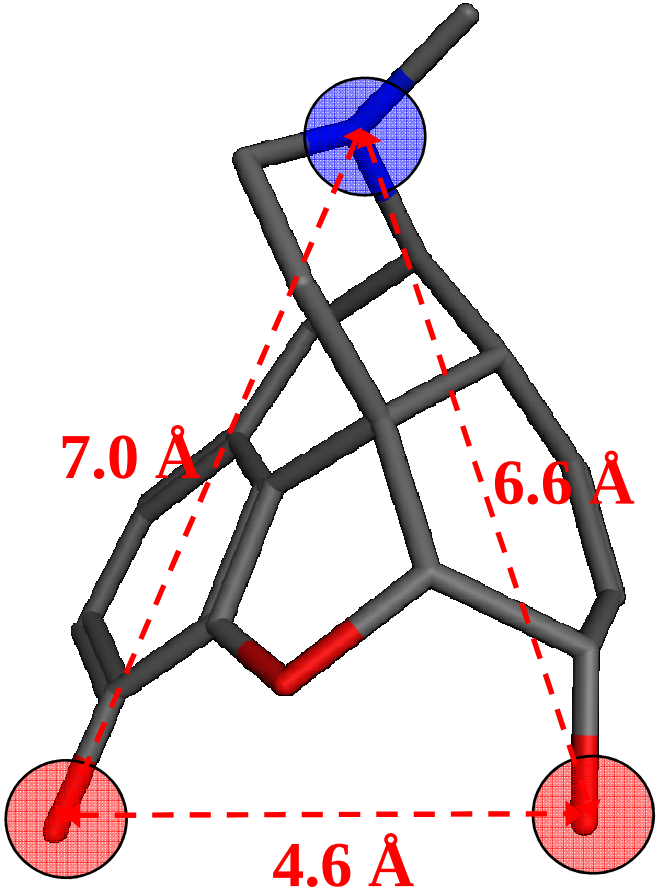
3,6-dihydroxy- (5α,6α)- 4,5-epoxy- 17-methylmorphinan

Dihydromorphine is a semi-synthetic opioid invented in Germany in 1900. In structure, it is very similar to morphine, the only difference being the reduction of the double bond between positions 7 and 8 in morphine to a single bond. Dihydromorphine can be made by several processes, including hydrogenating morphine.

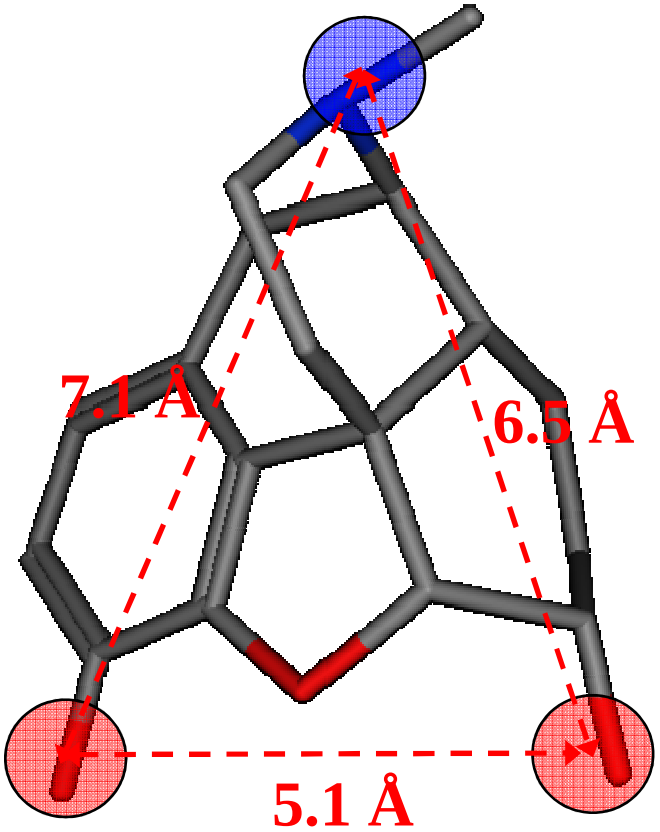
Dihydromorphine is slightly stronger than morphine as an analgesic with a similar side-effect profile.

1. Pain and Narcotic Analgesics

1.6 Dihydromorphine



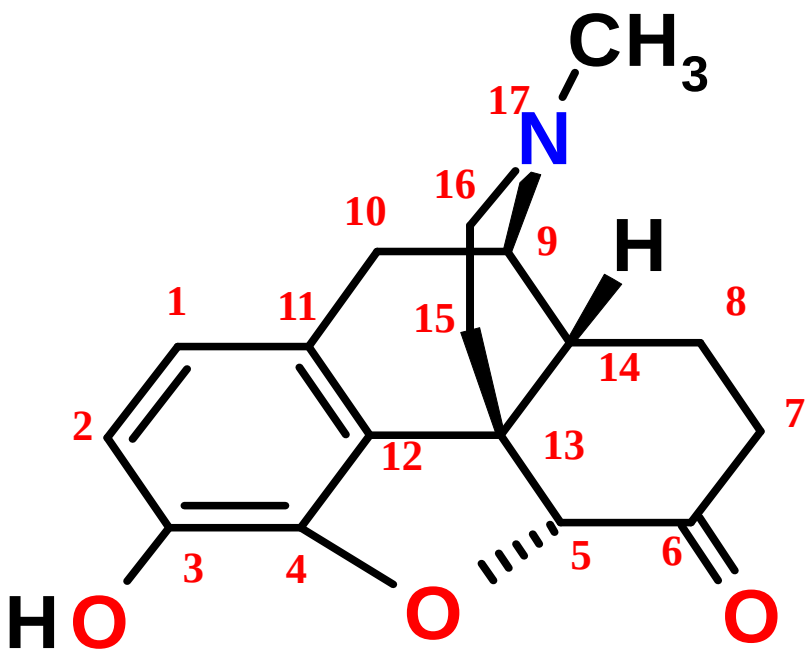
Morphine



Dihydromorphine

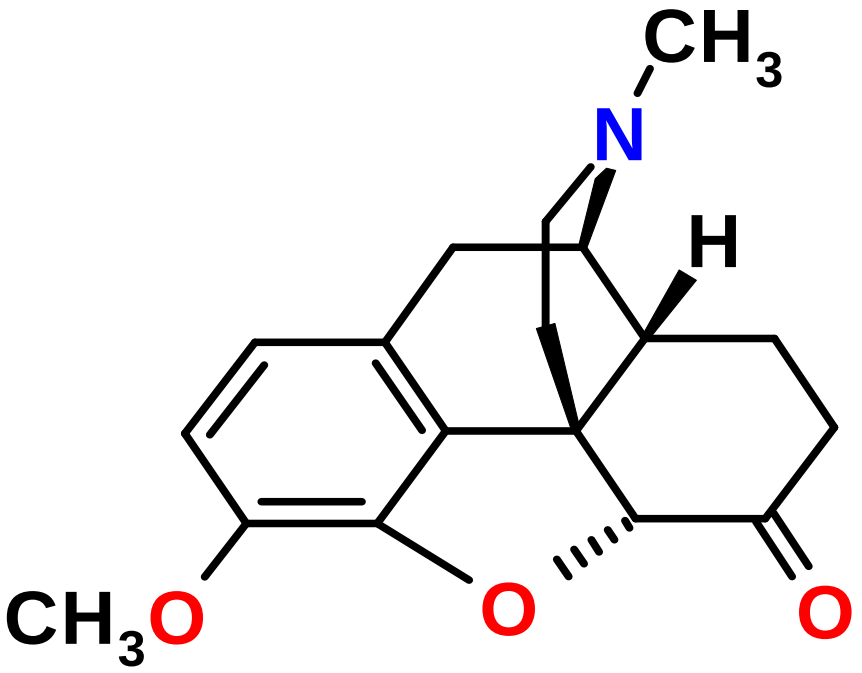
1. Pain and Narcotic Analgesics

1.7 Hydromorphone and Hydrocodone



Hydromorphone
(7X active than morphine)

logP = 0.9



Hydrocodone (Vicodin ®)
(10X active than morphine)

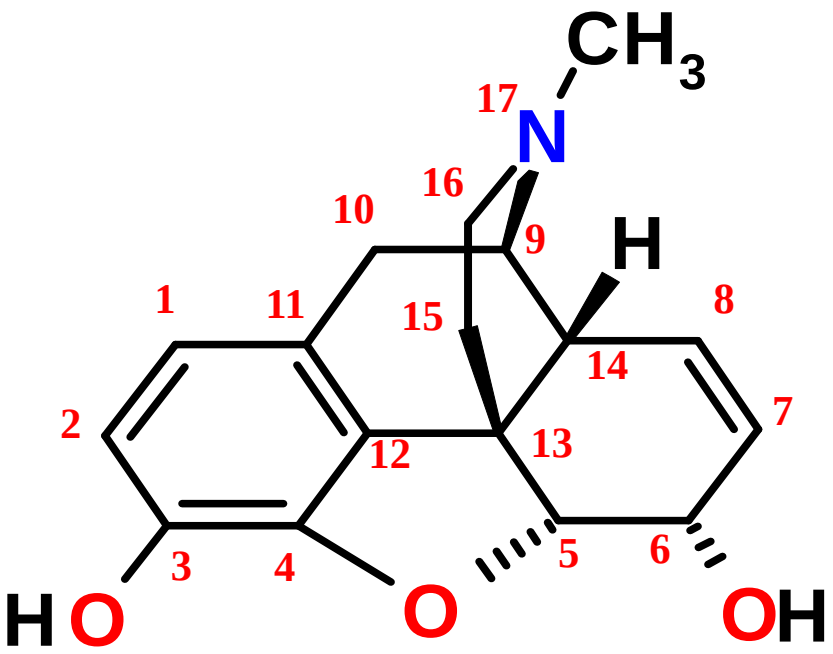
logP = 1.2

1. Pain and Narcotic Analgesics

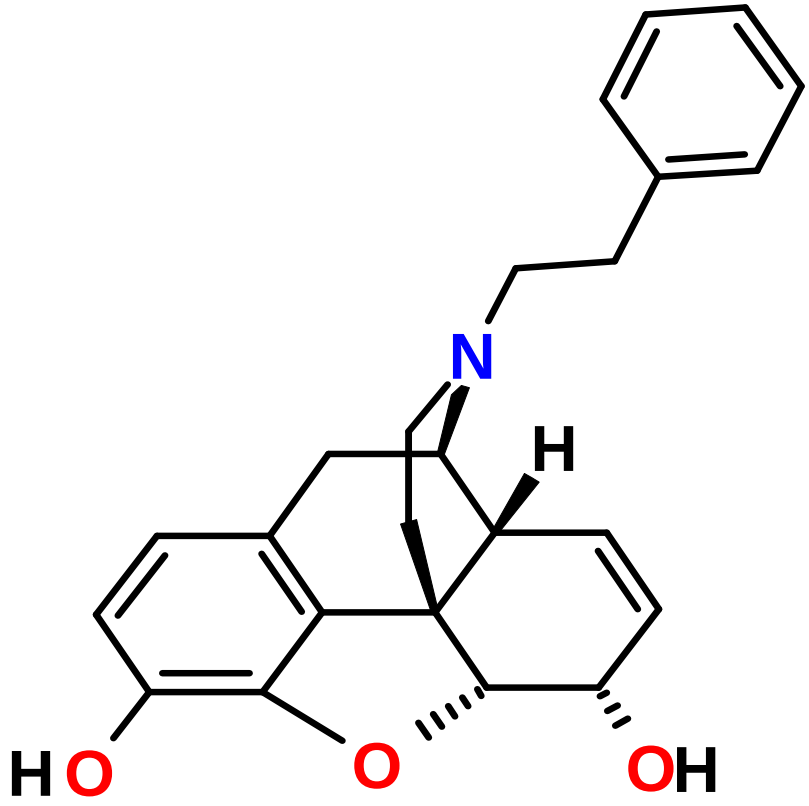
Oxycodone is one of the drugs commonly associated with overdose deaths in relation to prescription drug abuse, in particular in North America.

1. Pain and Narcotic Analgesics

1.8 Changing substituents on nitrogen can either improve agonist activity or…



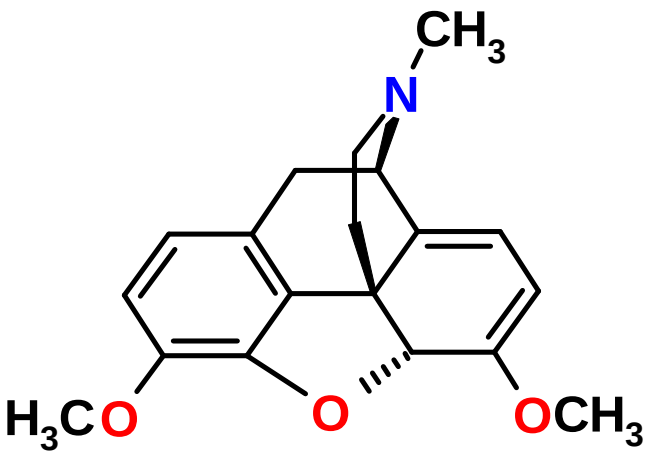
Morphine



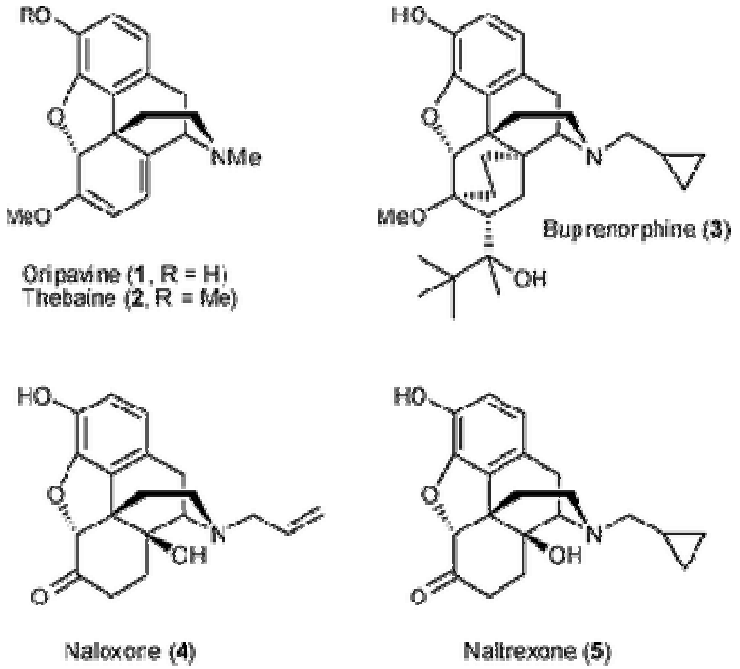
(more active than morphine)

1. Pain and Narcotic Analgesics

1.9 From Thebaine to …

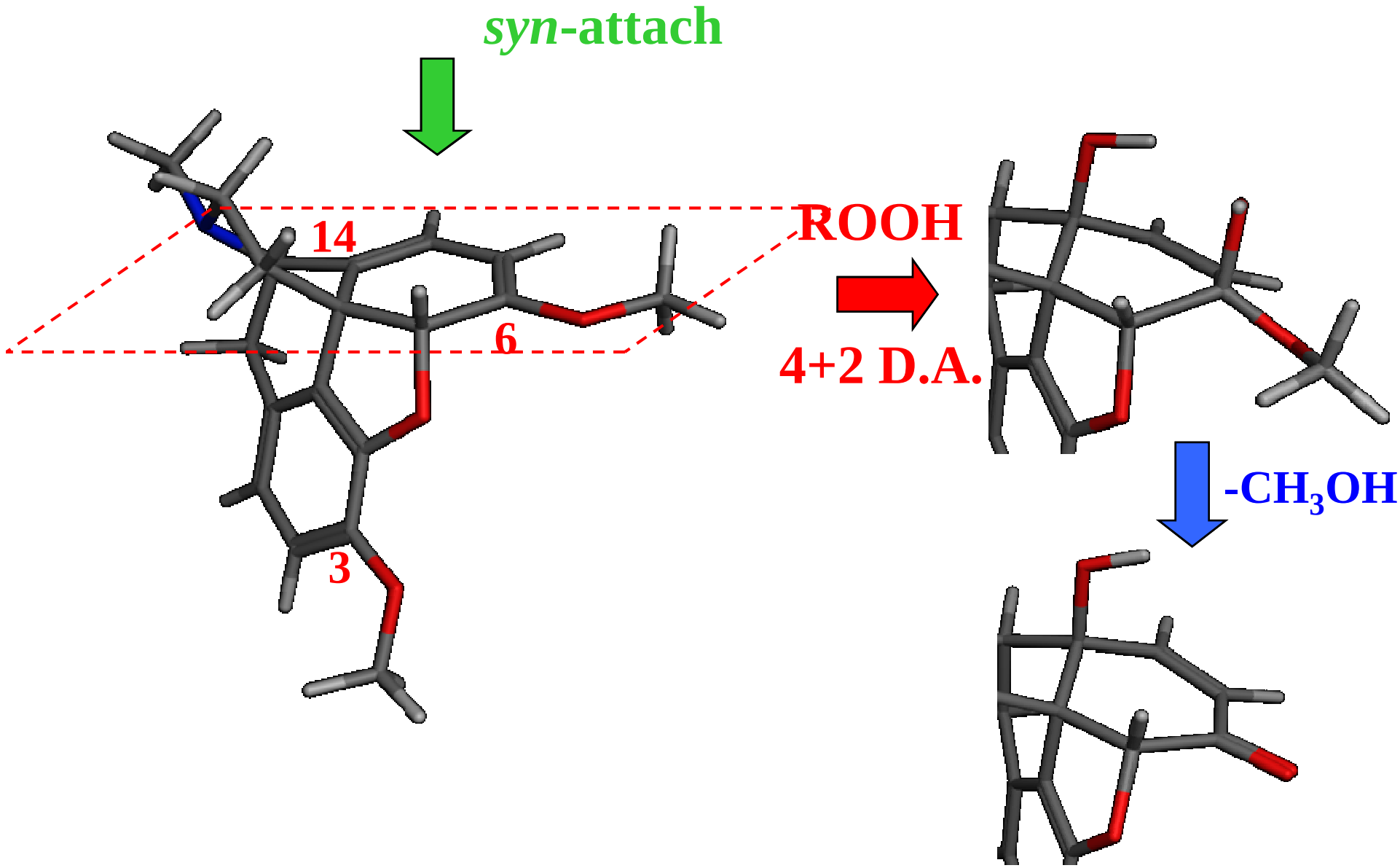


Thebaine



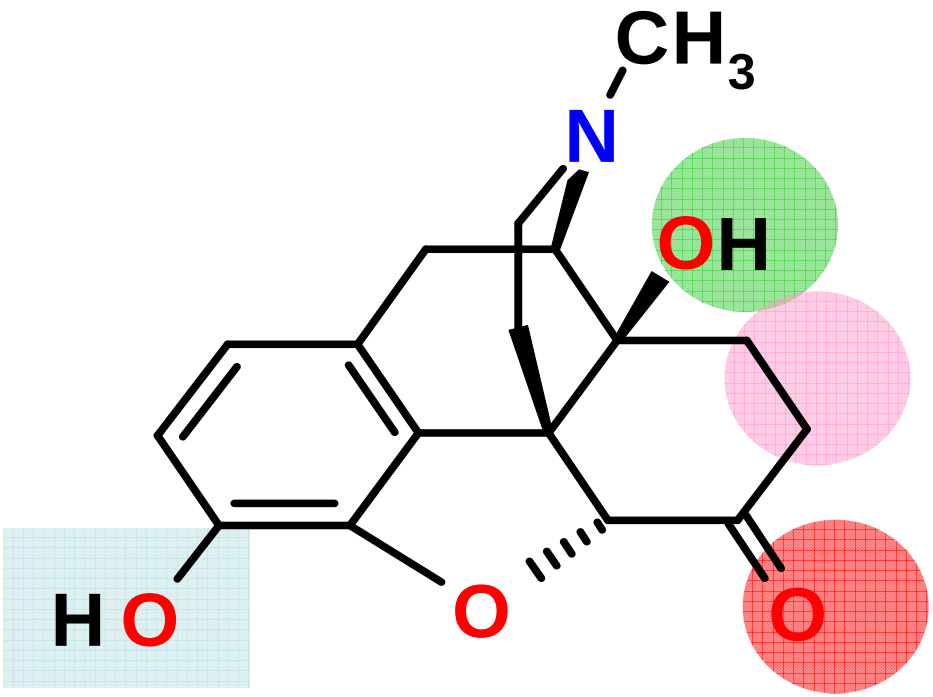
Thebaine is not used therapeutically, but as the main alkaloid extracted from *Papaver bracteatum* (Iranian poppy), it can be converted industrially into a variety of compounds including **Oxycodone**, **Oxymorphone**, **Nalbuphine**, **Naloxone**, **Naltrexone**, **Buprenorphine** and **Etorphine**.

Thebaine reactivity:

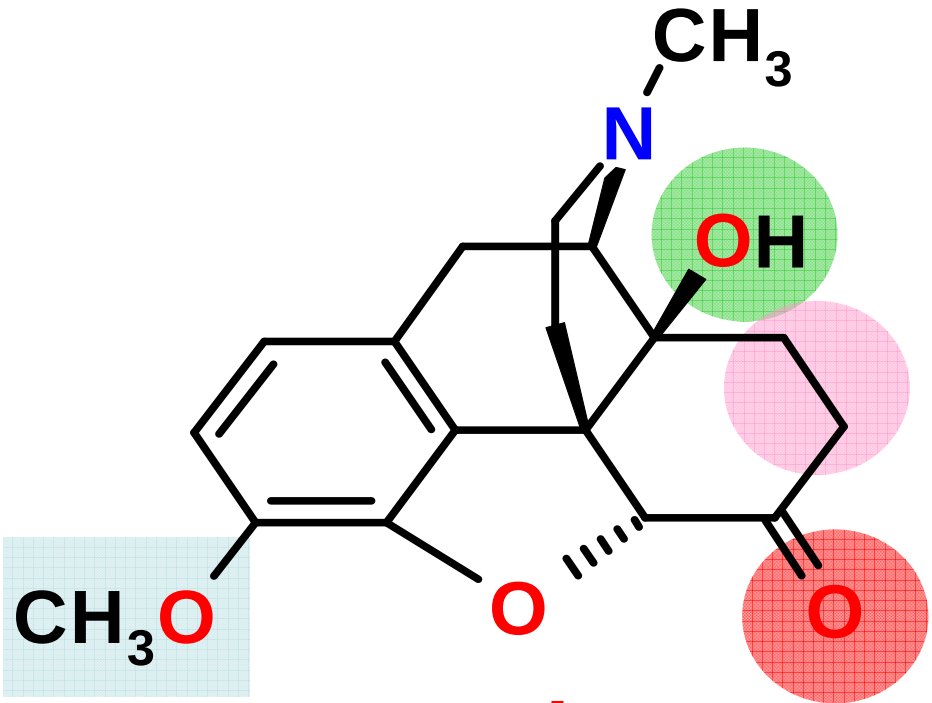


1. Pain and Narcotic Analgesics

1.9 Oxymorphone and Oxycodone



Oxymorphone
(8X active than morphine)

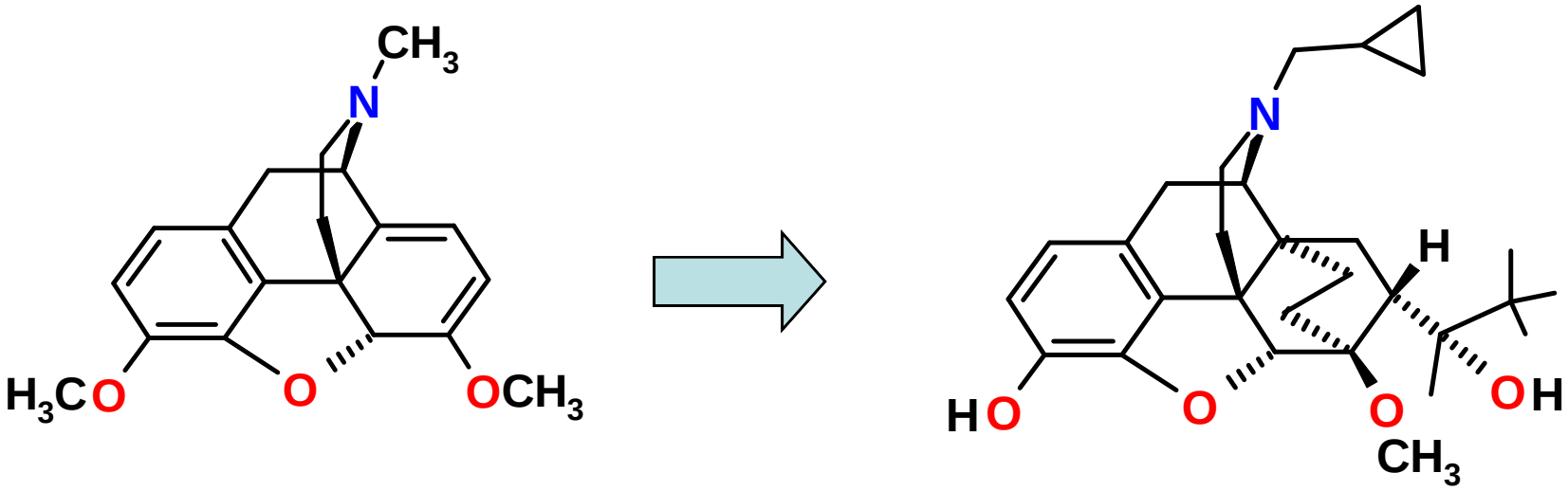


Oxycodone
(active as morphine)

Unlike morphine (the effect of which is mediated by μ-opioid receptors), **acts on κ-opioid receptors.**

1. Pain and Narcotic Analgesics

1.9 From Thebaine to Buprenorphine

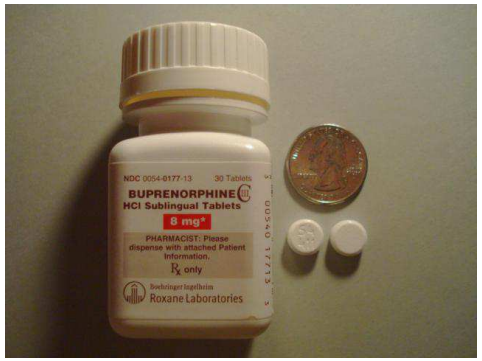


Thebaine **Buprenorphine**

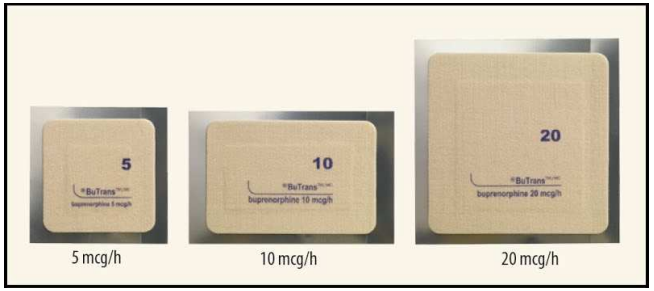
Buprenorphine is a derivative of the opioid alkaloid thebaine that is a more potent (25 – 40 times) and longer lasting analgesic than morphine. It appears to act as a ***partial agonist*** at mu and kappa opioid receptors and as an antagonist at delta receptors. The lack of delta-agonist activity has been suggested to account for the observation that buprenorphine tolerance may not develop with chronic use.

1. Pain and Narcotic Analgesics

1.9 Buprenorphine: formulations.



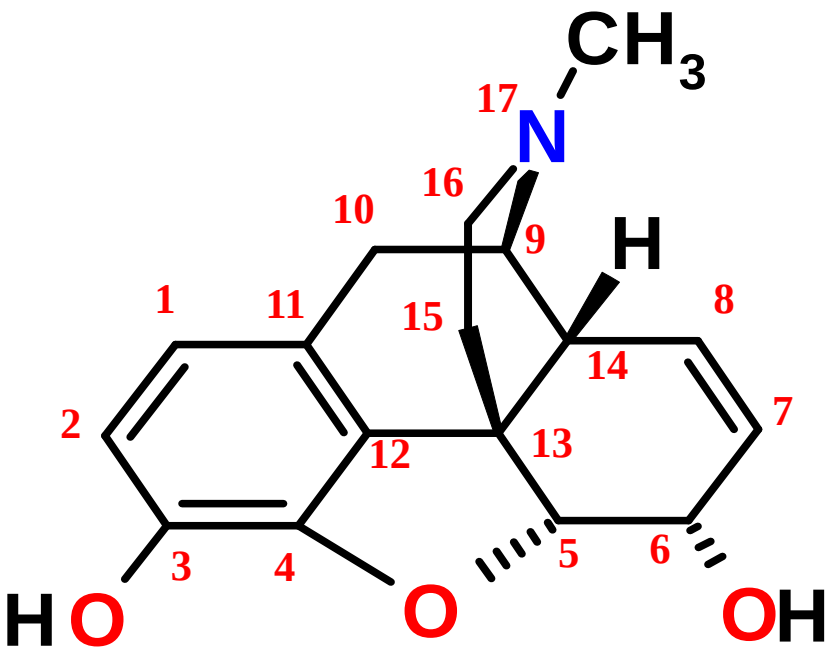
sublingual



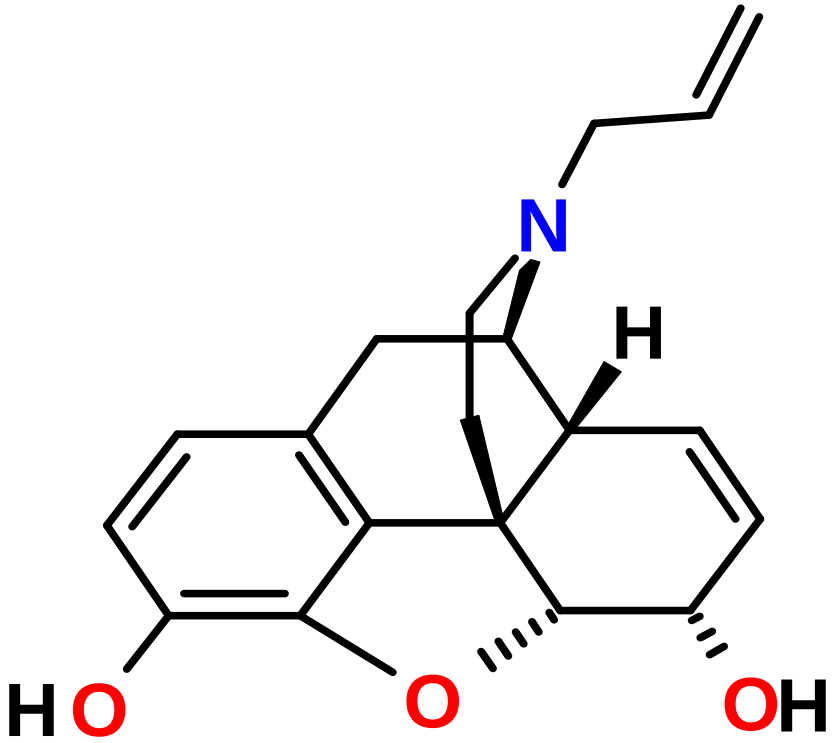
Transdermal patches

1. Pain and Narcotic Analgesics

1.9 or… create antagonists!!!



Morphine



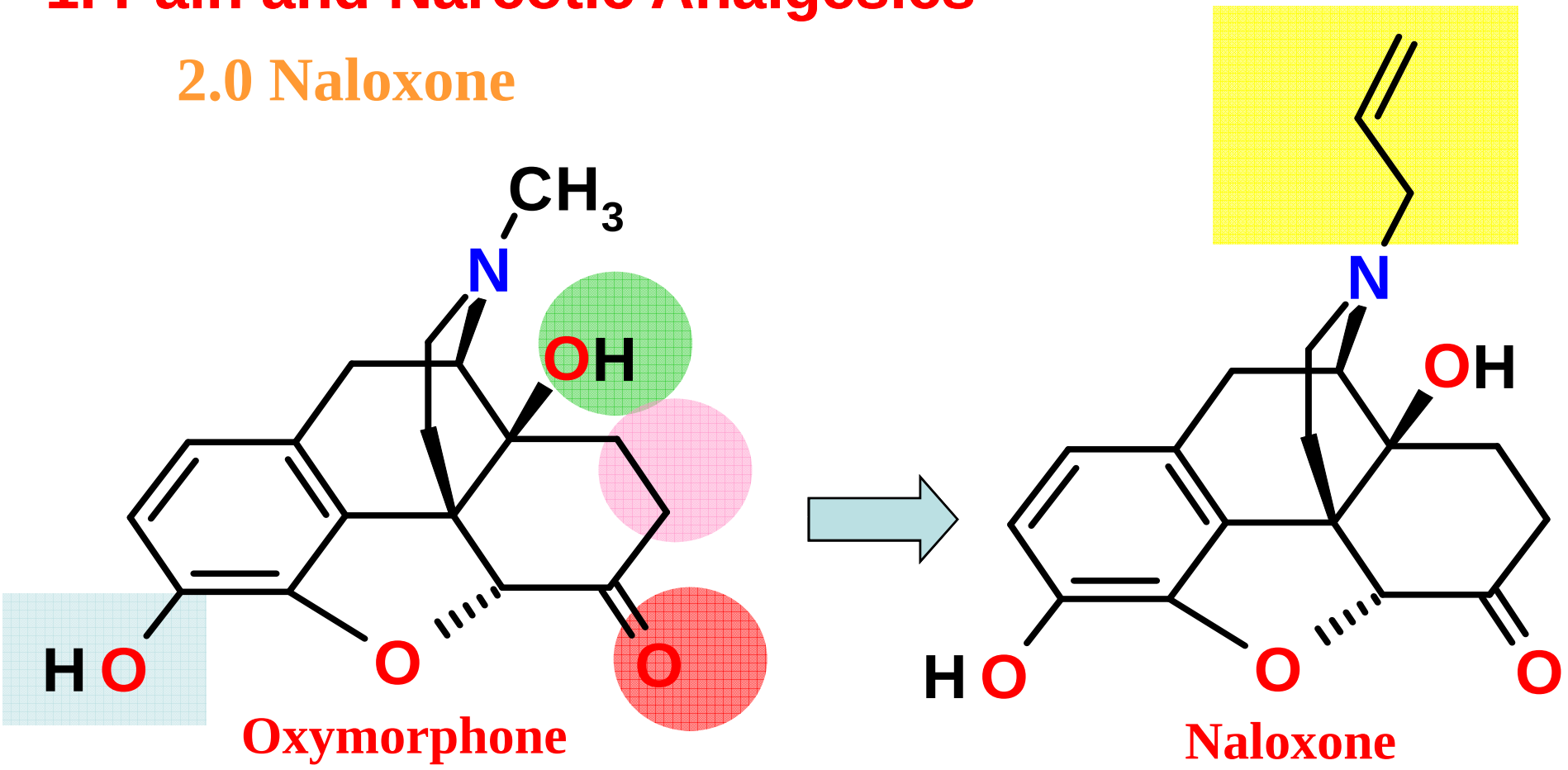
Nalorphine

(5α,6α)-17-allyl- 7,8-didehydro- 4,5-epoxymorphinan- 3,6-diol

mu-antagonist

1. Pain and Narcotic Analgesics

2.0 Naloxone



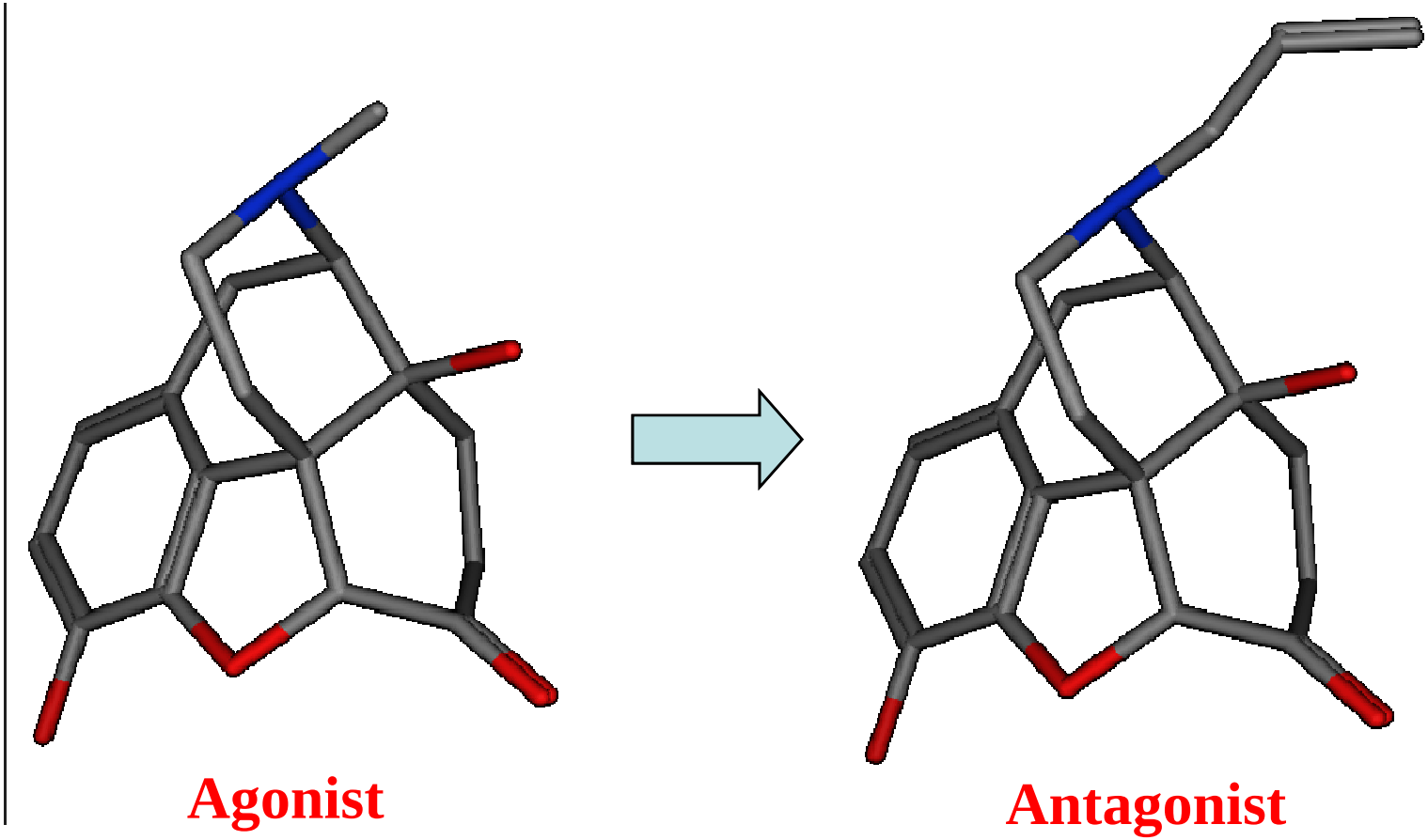
Naloxone is a drug used to counter the effects of opioid overdose, for example heroin or morphine overdose. Naloxone is specifically used to counteract life-threatening depression of the central nervous system and respiratory system. It is marketed under various trademarks including Narcan®.

1. Pain and Narcotic Analgesics

2.0 Naloxone: overdose awareness

1. Pain and Narcotic Analgesics

3.0 Naloxone



Agonist **Antagonist**

1. Pain and Narcotic Analgesics

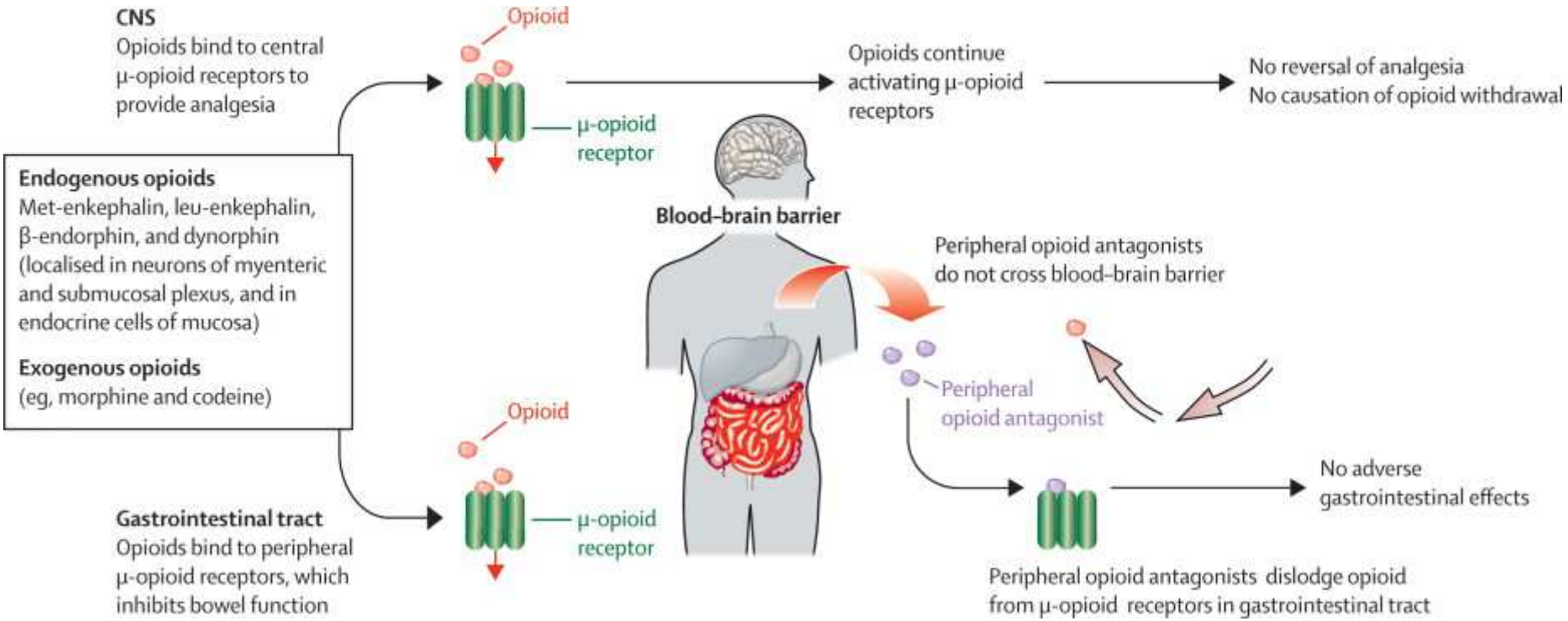
Agonists vs Antagonists

Why should small changes in structure (e.g. *N*-methyl to *N*-allyl) change an agonist to an antagonist at a specific receptor?

It has been proposed that opioid receptors have additional hydrophobic binding regions which lead to agonist or antagonist activity:

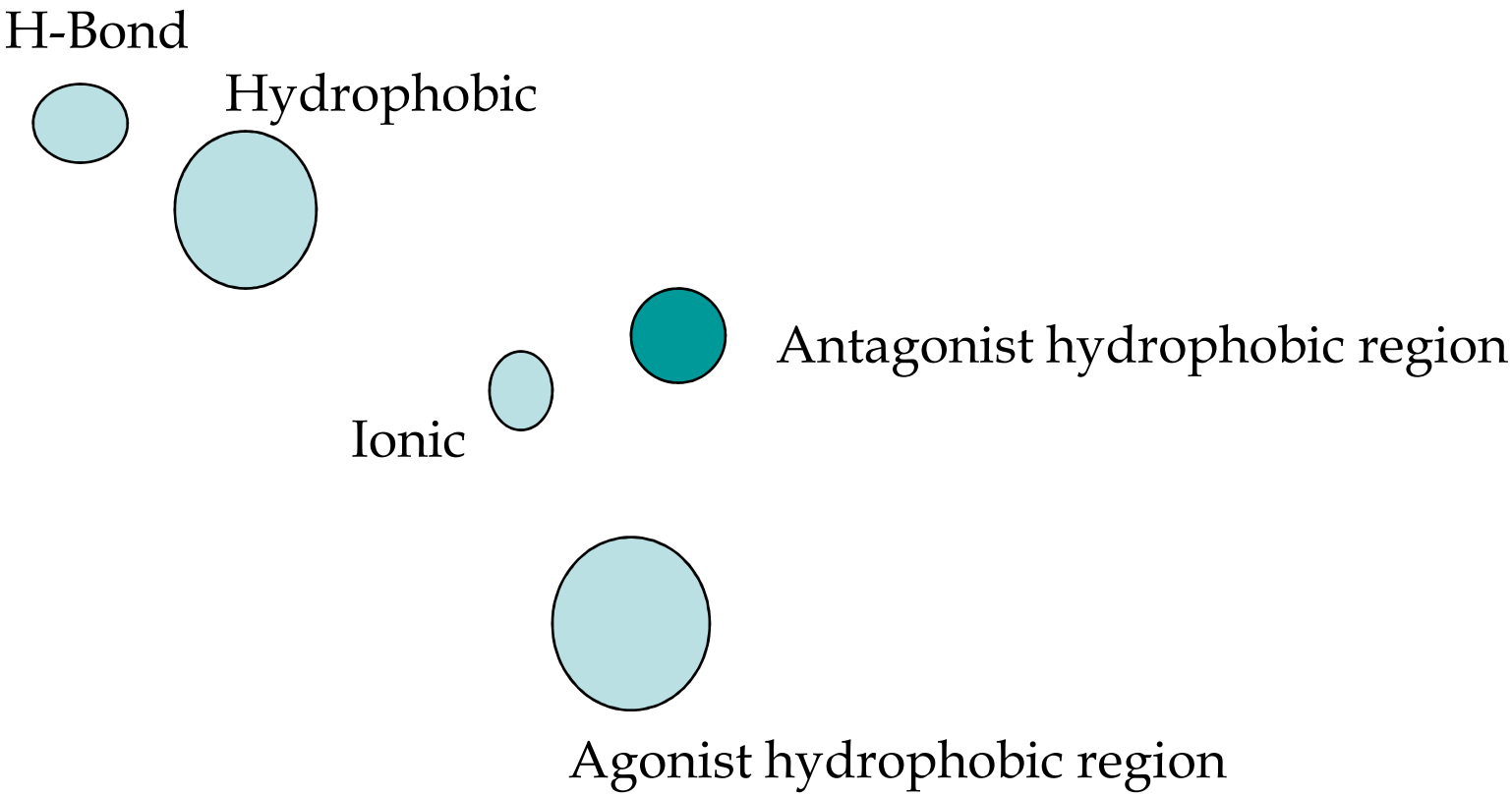
1. Pain and Narcotic Analgesics

Antagonists… as peripheral therapeutic agents?



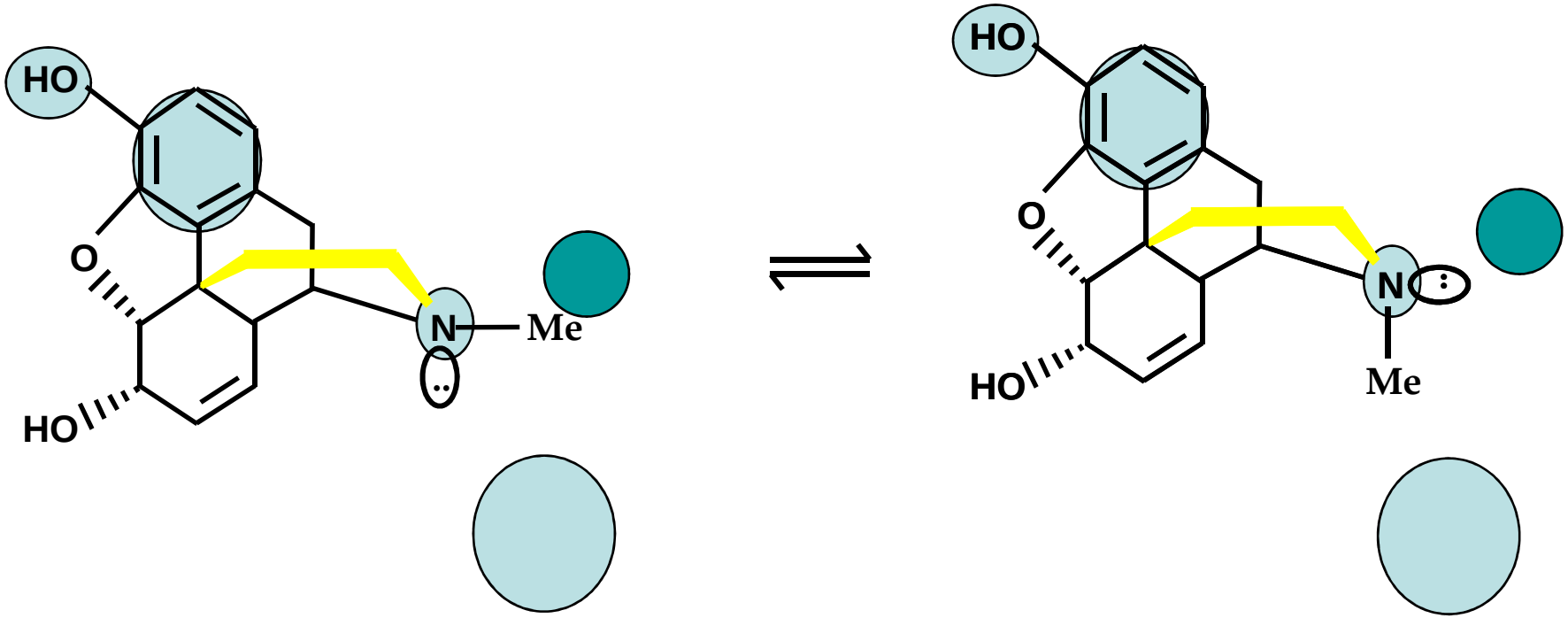
1. Pain and Narcotic Analgesics

TM Binding Regions



1. Pain and Narcotic Analgesics

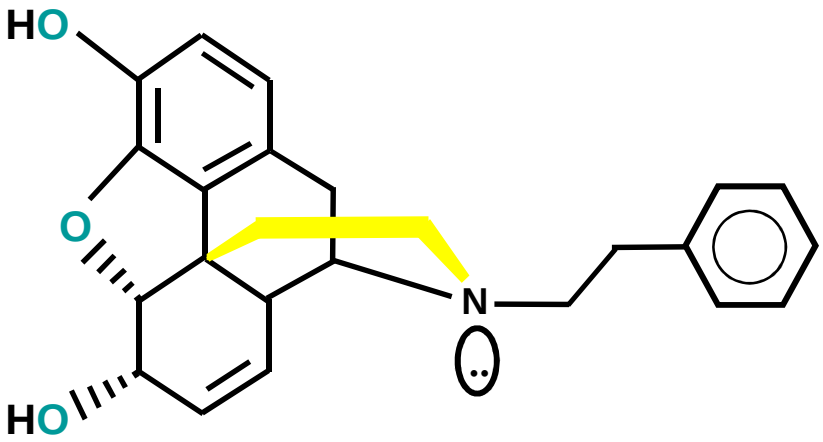
Binding Modes for Morphine



Morphine incapable of reaching either of the extra hydrophobic regions

1. Pain and Narcotic Analgesics

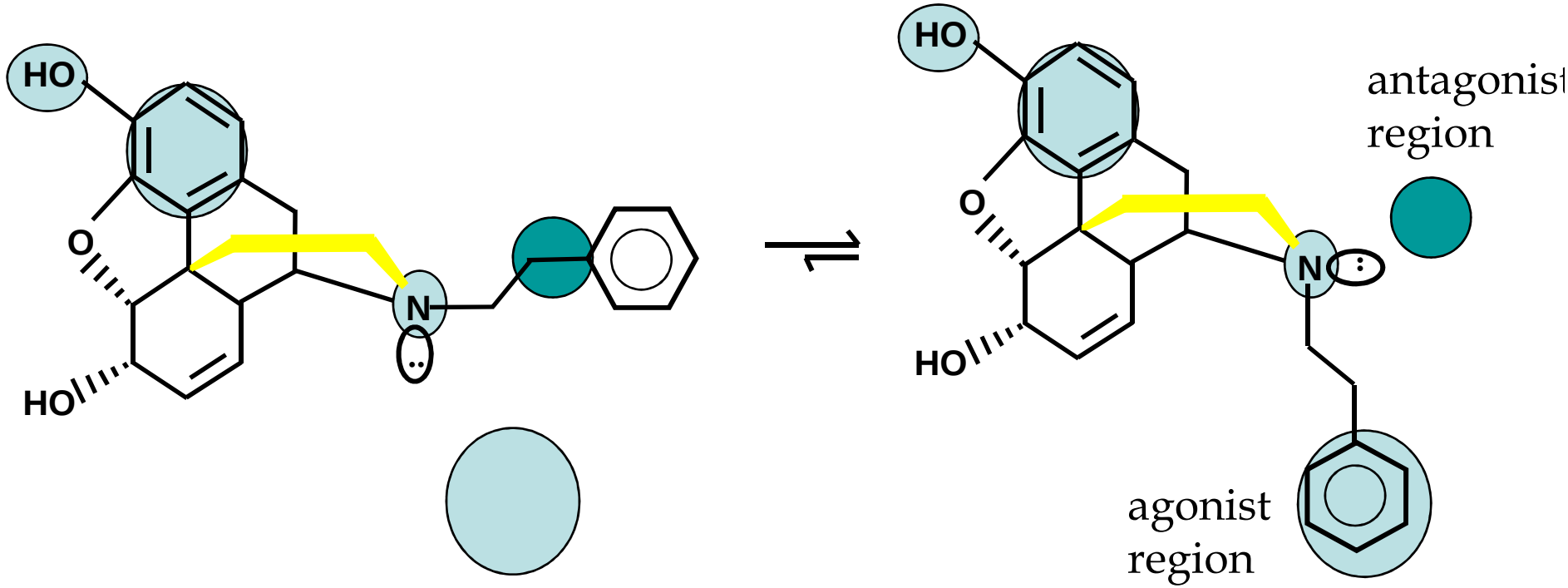
Binding Modes for *N*-Phenethylmorphine



Pure agonist with enhanced activity

1. Pain and Narcotic Analgesics

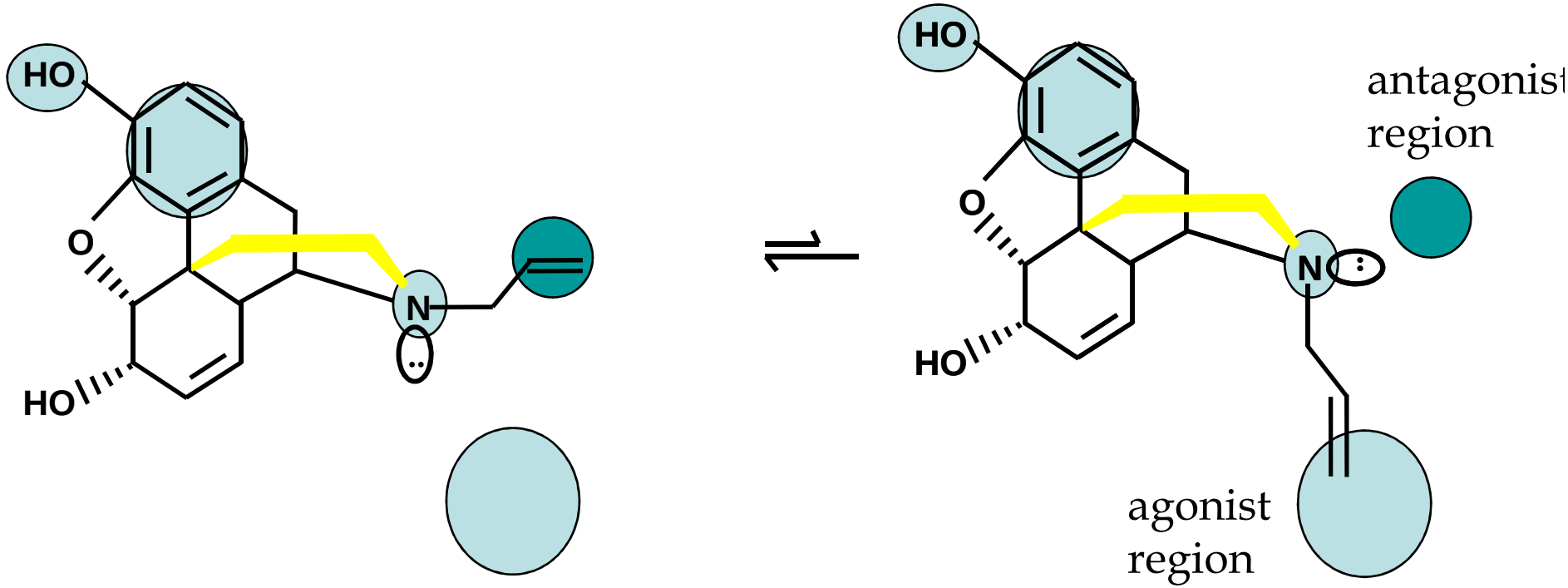
Binding Modes for *N*-Phenethylmorphine



- Aromatic ring pushed beyond antagonist region
- Correct distance to bind to agonist region

1. Pain and Narcotic Analgesics

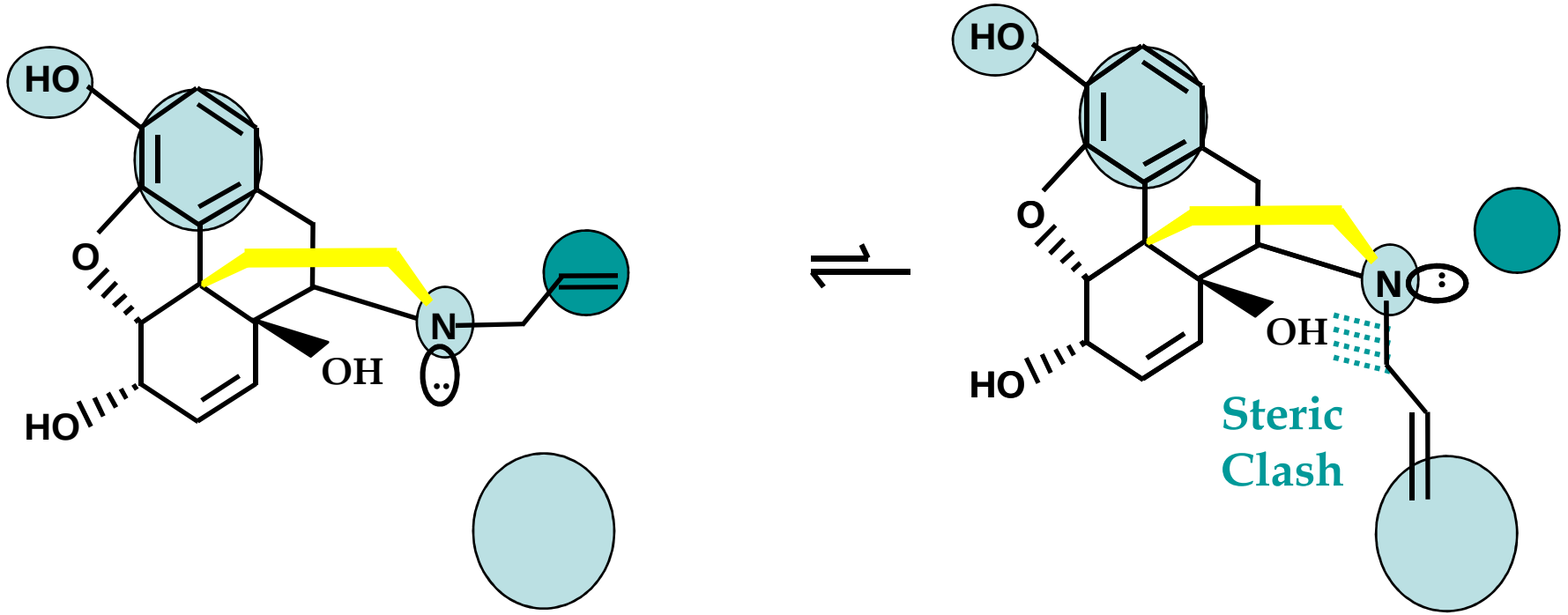
Binding Modes for *N*-Allylmorphine



- Allyl group binds well to the antagonist region
- Allyl group forms a weak interaction with the agonist region
- Antagonist with weak agonist properties

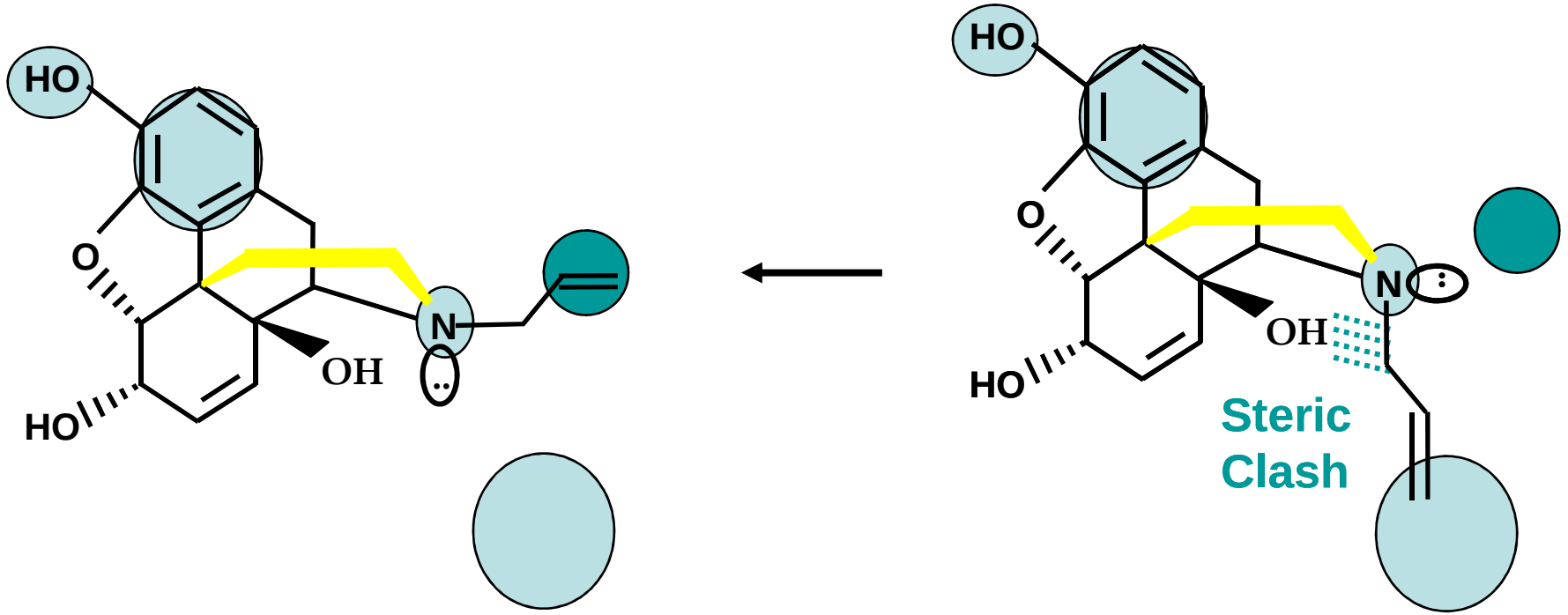
1. Pain and Narcotic Analgesics

Influence of a 14-OH Group



1. Pain and Narcotic Analgesics

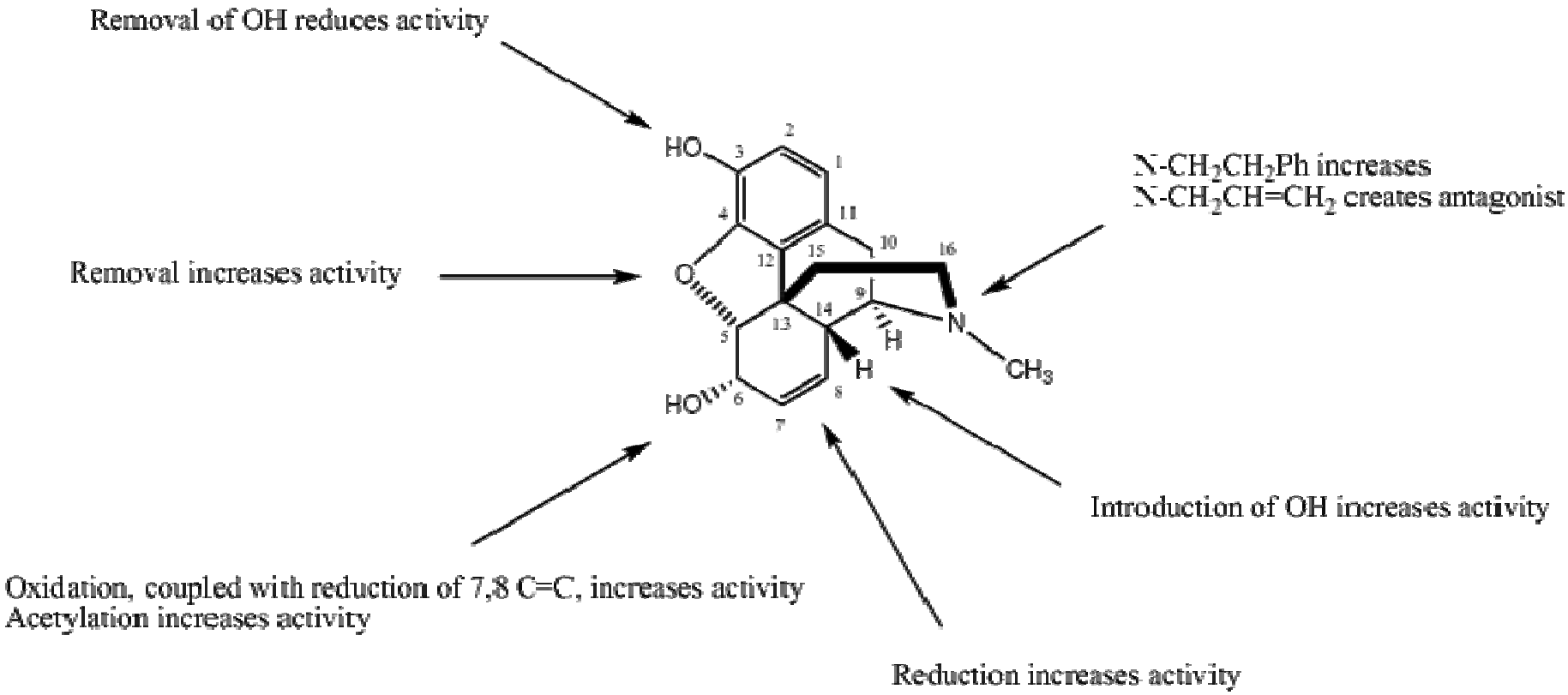
Influence of 14-OH Group



Pure antagonist

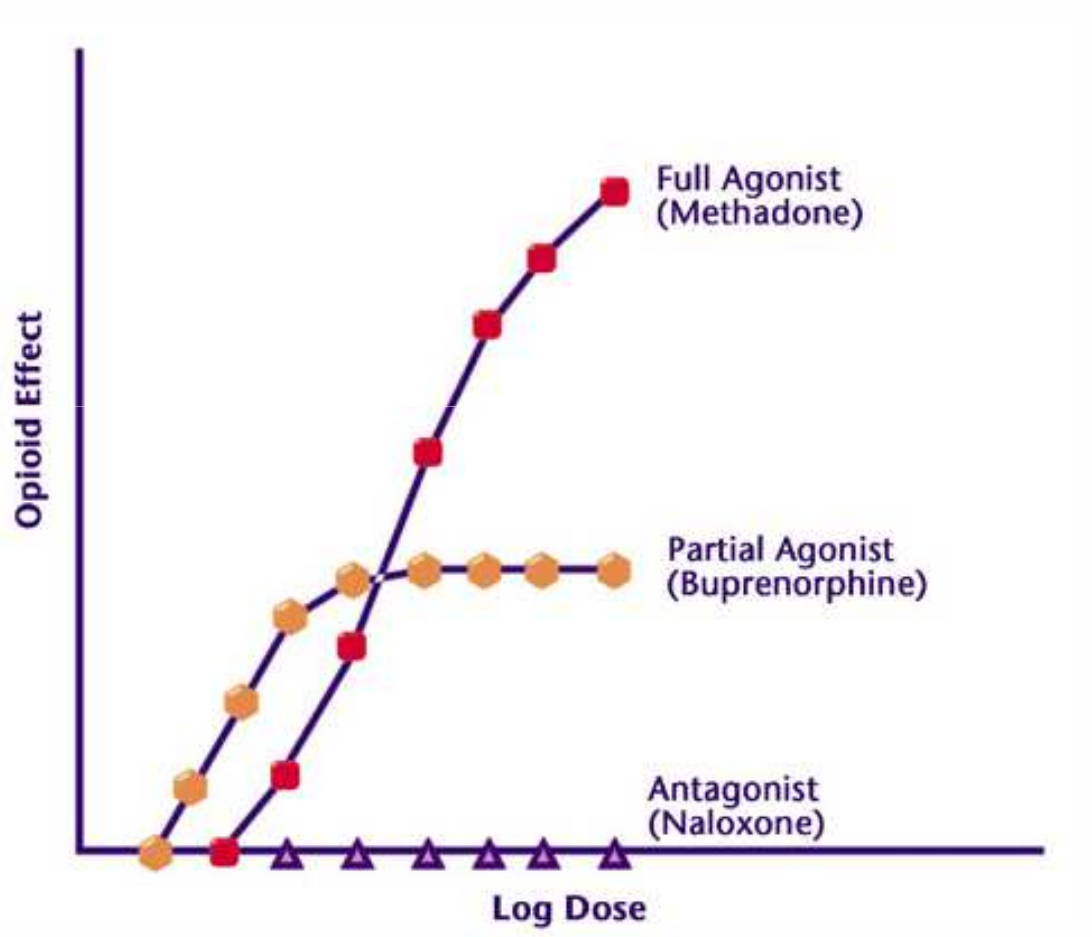
1. Pain and Narcotic Analgesics

Summary of structure-activity relationship:



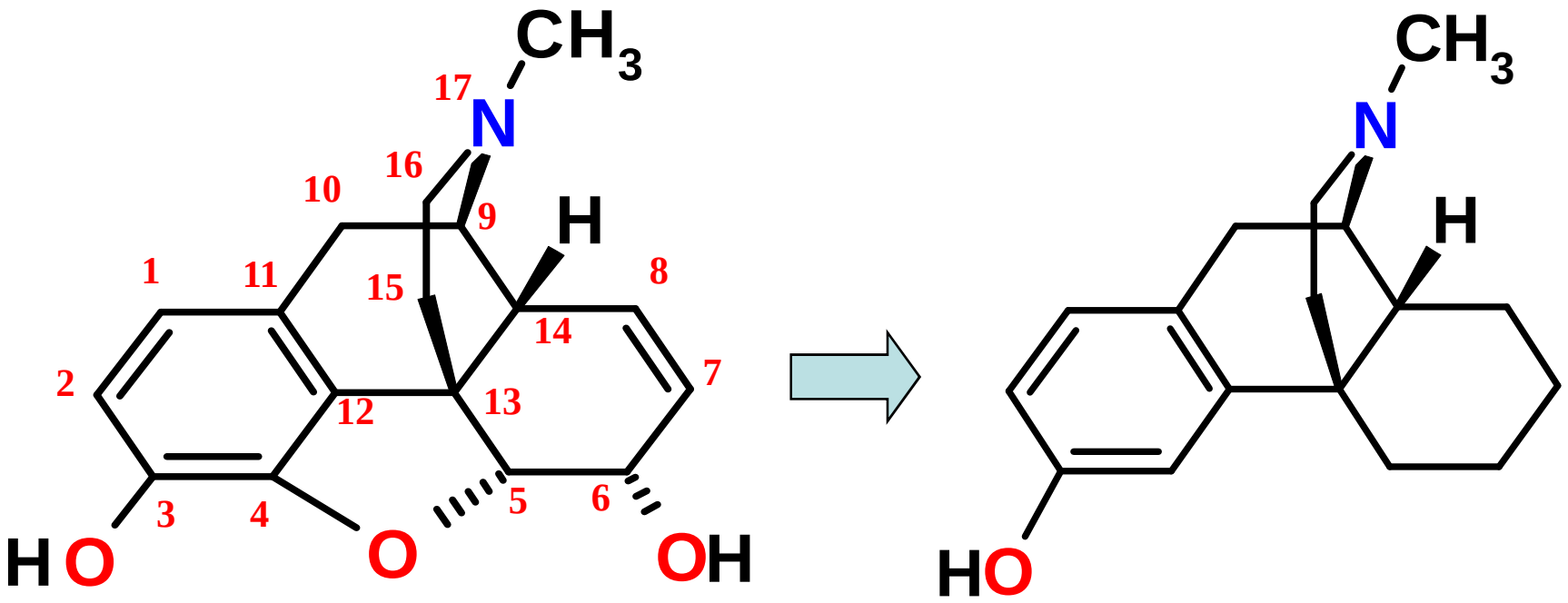
1. Pain and Narcotic Analgesics

From agonist to antogonist:



1. Pain and Narcotic Analgesics

2.0 Synthetic Opioids: simplification approach

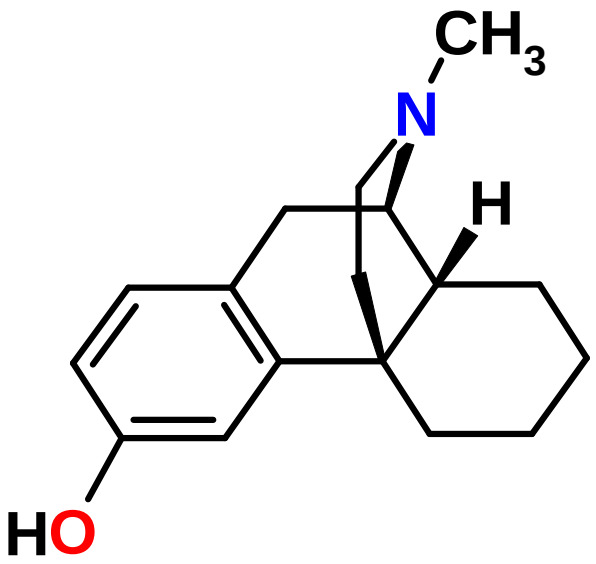


5 rings

4 rings (morphynan)

1. Pain and Narcotic Analgesics

2.1 Levorphanol



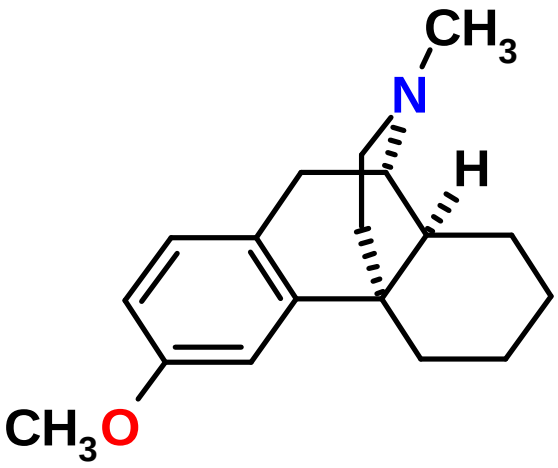
(-)-17-methylmorphinan-3-ol

logP = 3.1
pKa = 9.6

Levorphanol is an opioid medication used to treat severe pain.
Levorphanol has the same properties as morphine with respect to the potential for habituation, tolerance, physical dependence and withdrawal syndrome. It is 4 to 8 times as potent as morphine and has a longer half-life.
Levorphanol has affinity to μ, κ, and δ opioid receptors.

1. Pain and Narcotic Analgesics

2.1 Dextromethorphan



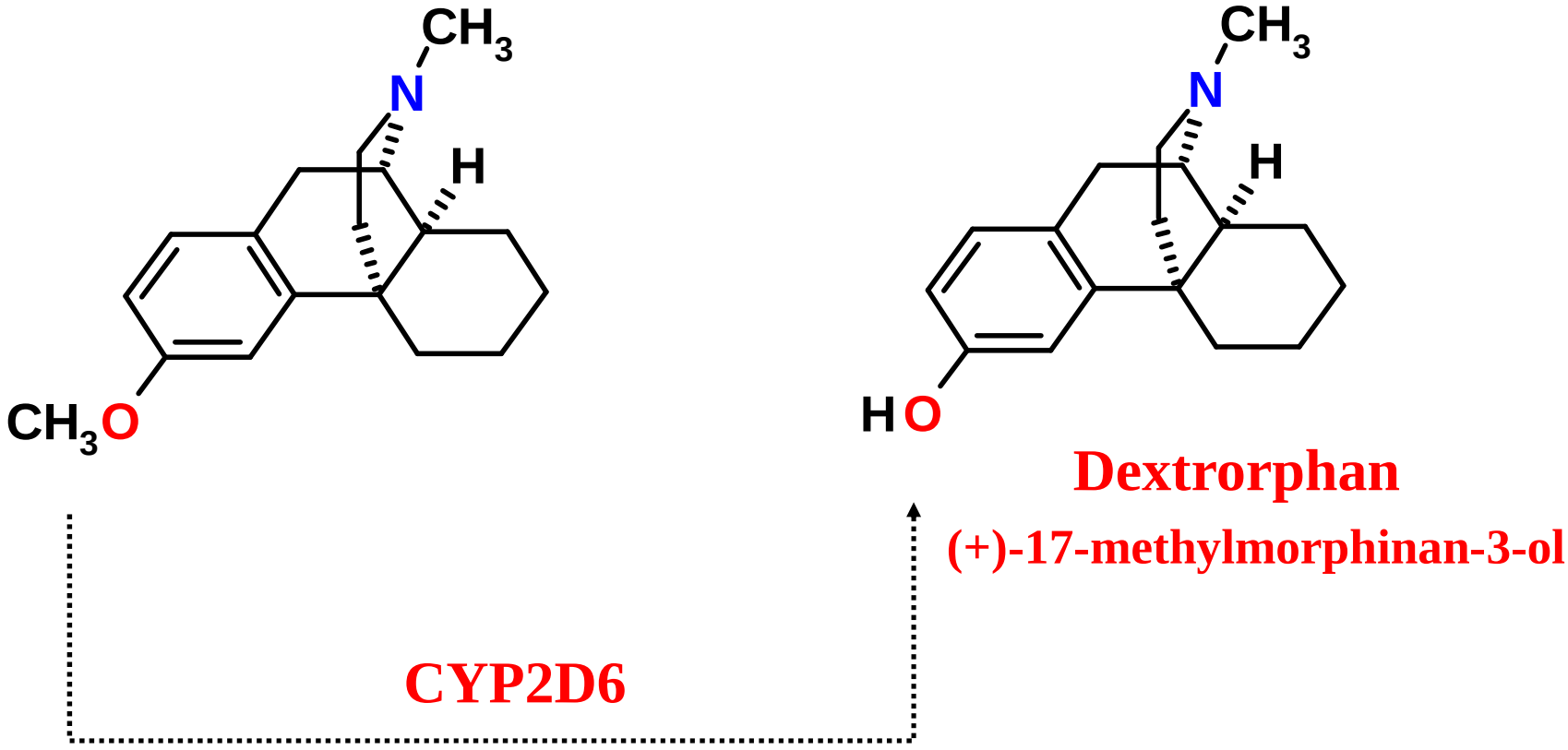
(+) 17-methylmorphinan-3-methoxy

logP = 3.6
pKa = 9.7

Dextromethorphan is the dextrorotatory enantiomer of **Levomethorphan**, which is the methyl ether of **Levorphanol**, both opioid analgesics. Dextromethorphan is an **antitussive** (cough suppressant) drug**.** It shows high affinity binding to several regions of the brain, including the medullary cough center. It is one of the widely used antitussives.

1. Pain and Narcotic Analgesics

2.1 Dextromethorphan… as a pro-drug, again!



1. Pain and Narcotic Analgesics

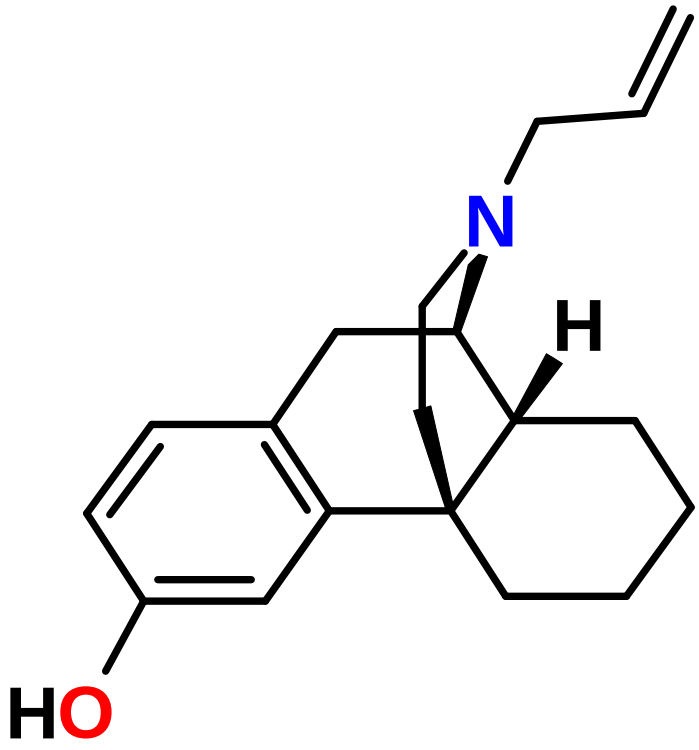
1.5 Dextromethorphan/Dextrophan as antitussive?

A 2004 studies conducted by the American Academy of Pediatrics show that dextromethorphan is NOT superior to a placebo in providing nocturnal symptom relief for children with cough and sleep difficulty due to upper respiratory infections.

Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, Dilworth DA, Berlin CM (2004). "Effect of Dextromethorphan, Diphenhydramine, and Placebo on Nocturnal Cough and Sleep Quality for Coughing Children and Their Parents". *Pediatrics* 114 (1): e85–90.

1. Pain and Narcotic Analgesics

2.2 Levallorphan



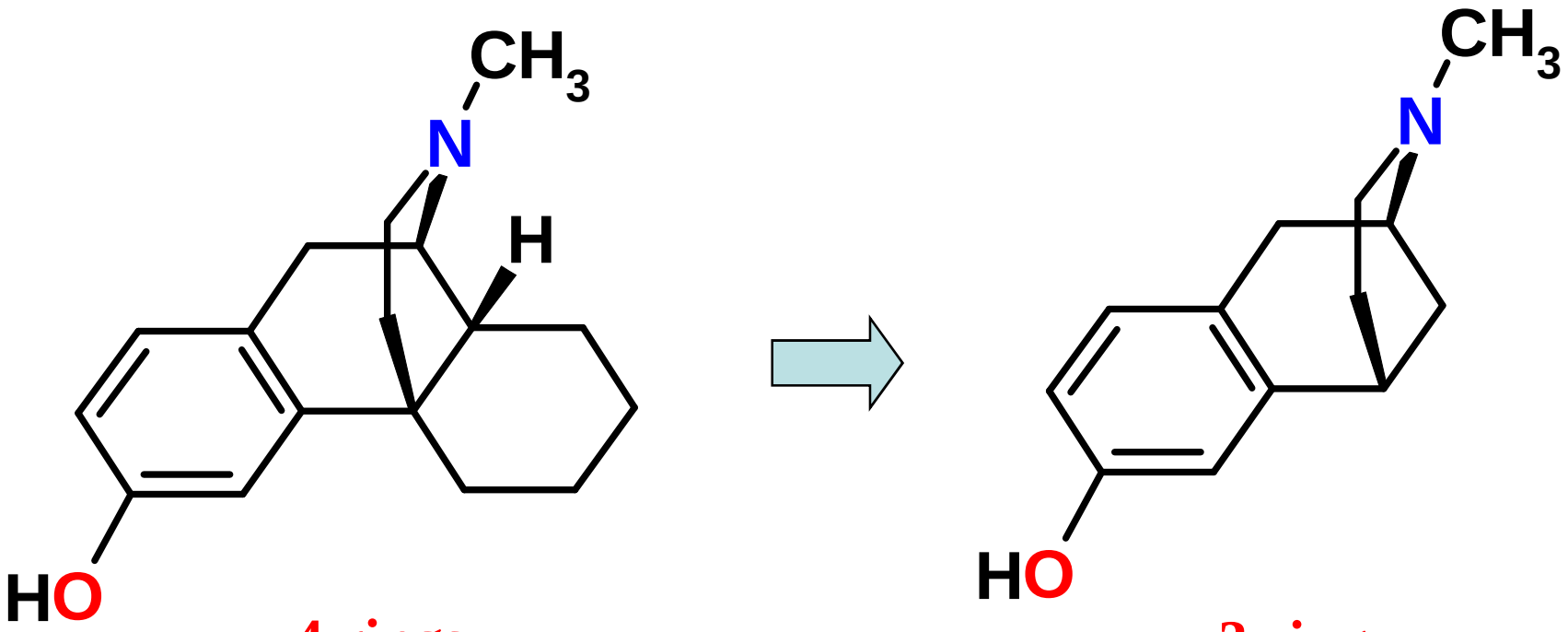
(-)-17-allylmorphinan-3-ol

Levallorphan is a drug of the morphinan family which is used as an opioid antidote or antagonist. It acts as a μ-opioid receptor weak partial agonist, and as a result, blocks the effects of stronger agents with greater intrinsic activity such as morphine or endogenous β-endorphin.

Levallorphan was formerly widely used in general anesthesia, mainly to reverse the respiratory depression produced by the opioid analgesics and barbiturates which are used for induction of surgical anaesthesia, although it is now less common as the newer drug naloxone tends to be used instead.

1. Pain and Narcotic Analgesics

2.3 Synthetic Opioids: simplification approach

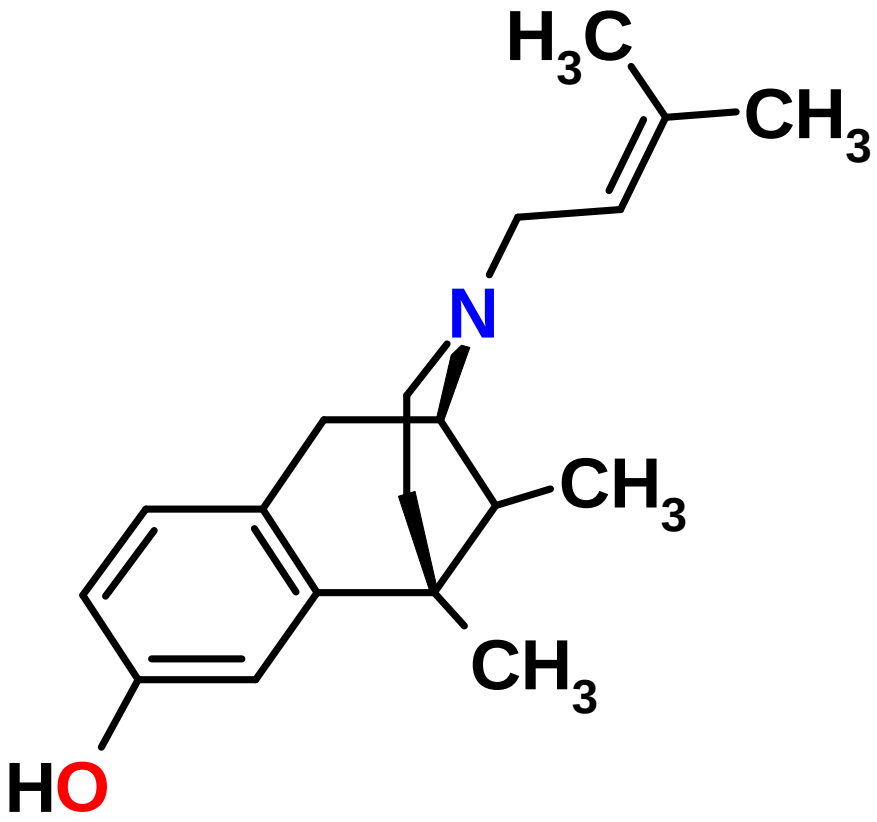


4 rings (morphynan)

3 rings (benzomorphan)

1. Pain and Narcotic Analgesics

2.4 Pentazocine



2-dimethylallyl-5,9-dimethyl-2'-hydroxybenzomorphan

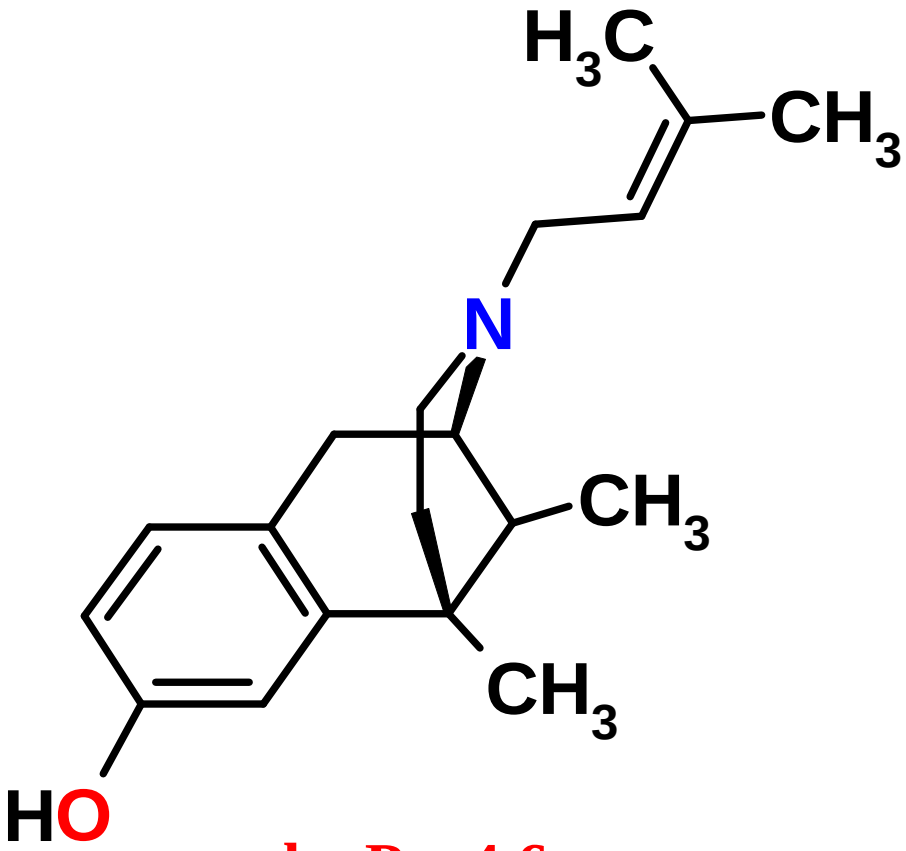
Pentazocine is a synthetically-prepared prototypical mixed agonist-antagonist narcotic (opioid analgesic) drug of the benzomorphan class of opioids used to treat mild to moderately severe pain.

It exists in two stereoisomers designated (+) and (-) that have radically different effects on opioid receptors. (-)-pentazocine is a kappa-opioid receptor agonist; (+)-pentazocine is a non-opioid sigma receptor agonist but is not an agonist at the kappa receptor. The (+)-pentazocine stereoisomer partially blocks the analgesic effects of morphine ostensibly at the mu receptor.

The kappa receptor agonism of the (-) isomer is analgesic.

1. Pain and Narcotic Analgesics

2.4 Pentazocine

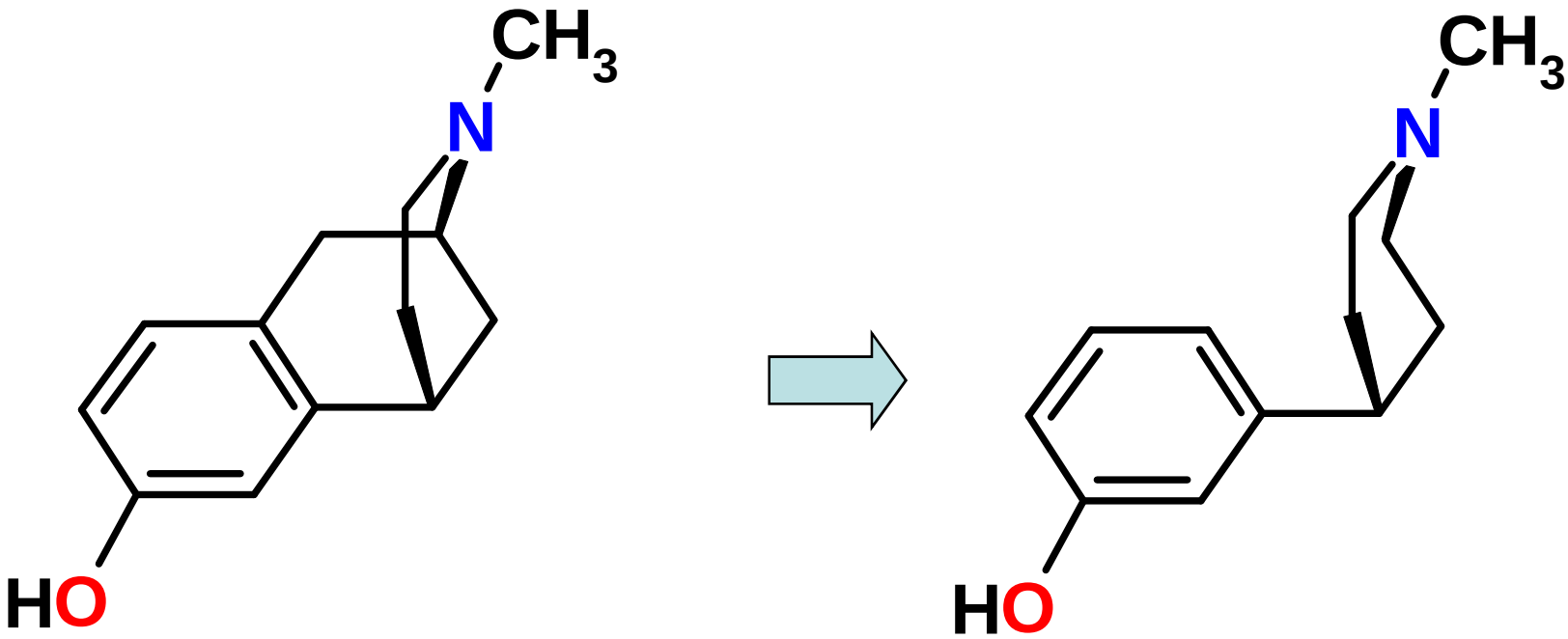


logP = 4.6

pKa = 8.9

1. Pain and Narcotic Analgesics

2.5 Synthetic Opioids: simplification approach

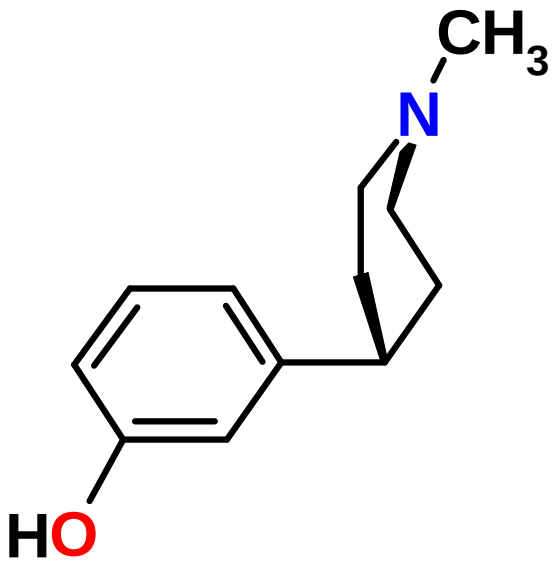


3 rings (benzomorphan)

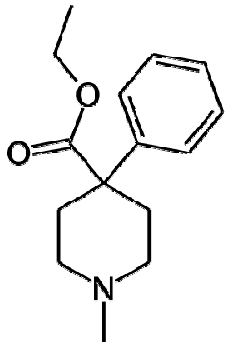
2 rings (phenylpiperidine)

1. Pain and Narcotic Analgesics

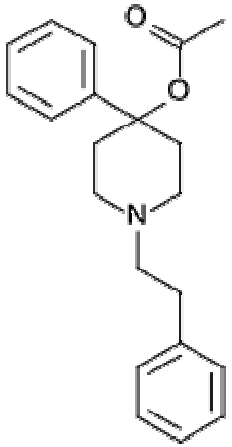
2.5 Synthetic Opioids: simplification approach



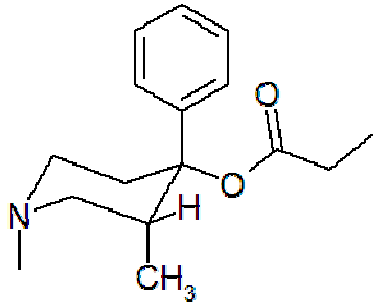
PhenylPiPeridines (PPPs)



Meperidina

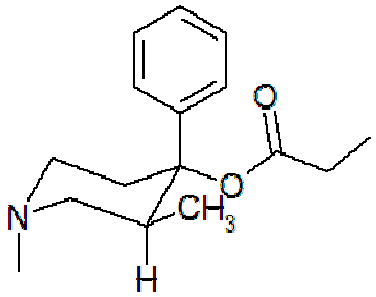


PEPAP



Alphaprodine

1-2x potency of morphine



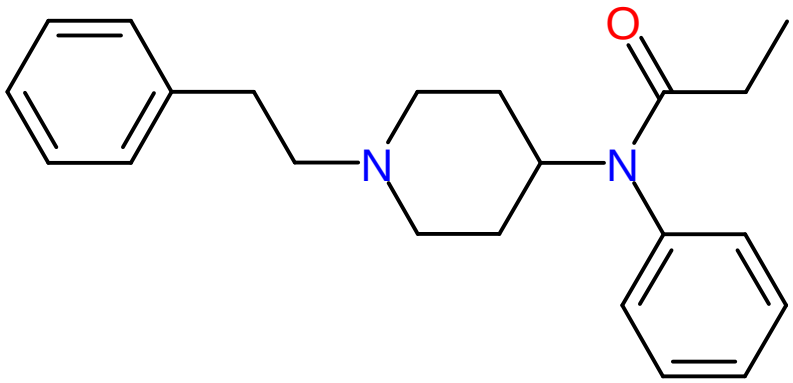
Betaprodine

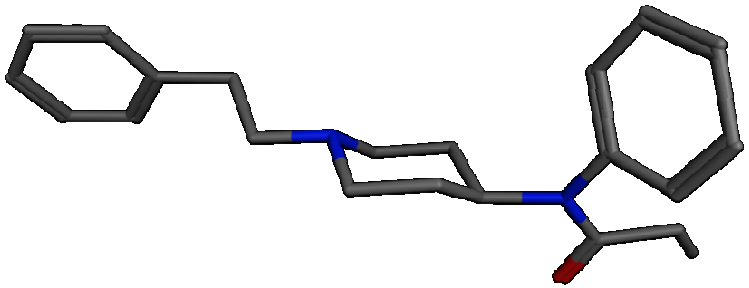
5-9x potency of morphine

Prodine

1. Pain and Narcotic Analgesics

2.6 Fentanyl





logP = 4.1

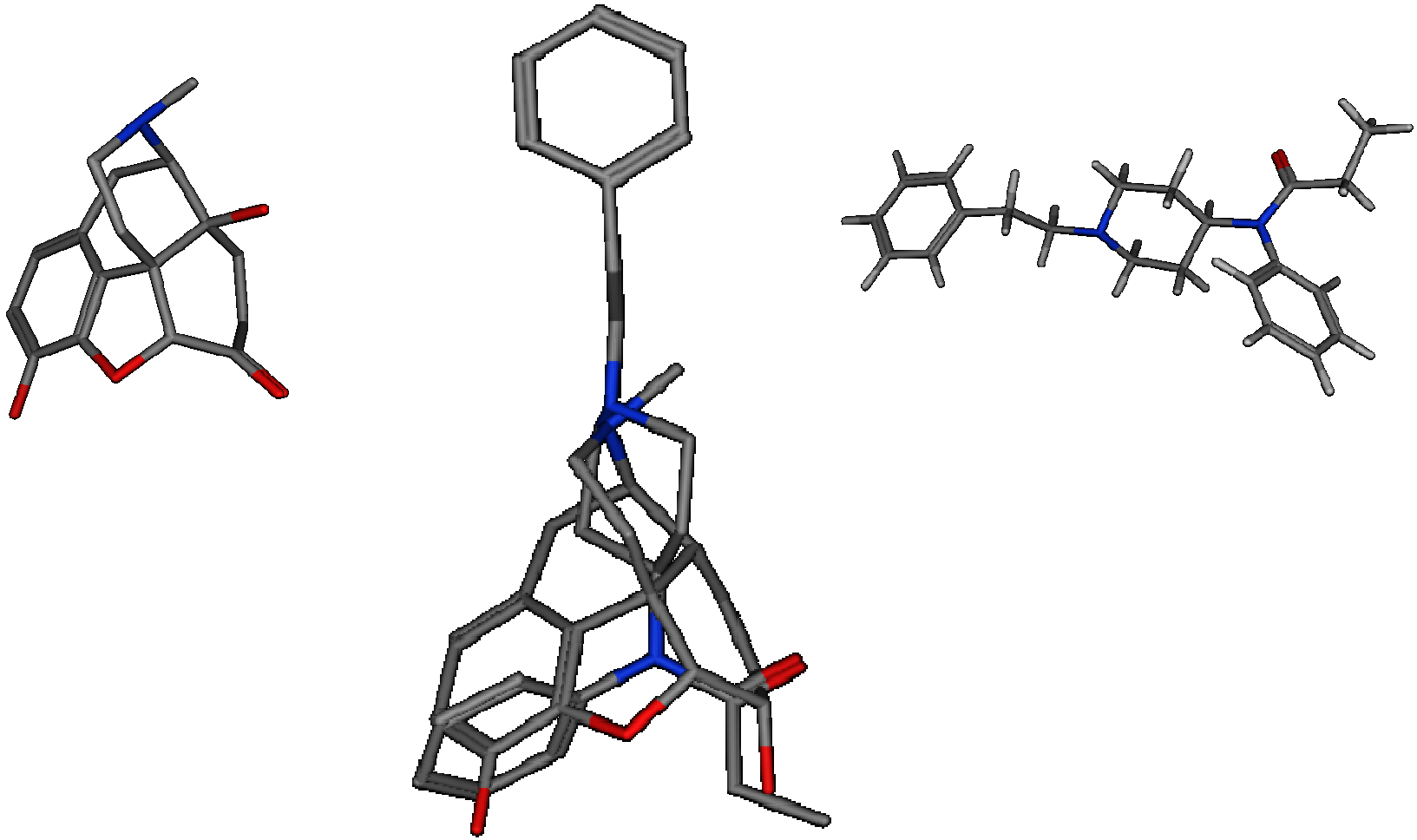
N-(1-(2-phenylethyl)-4-piperidinyl) -N-phenyl-propanamide

Fentanyl is a synthetic primary μ-opioid agonist and a potent narcotic analgesic with a rapid onset and short duration of action. **Fentanyl is approximately 100 times more potent than morphine.**

Fentanyl was first synthesized by Paul Janssen under the label of his relatively newly formed Janssen Pharmaceutica in 1959.

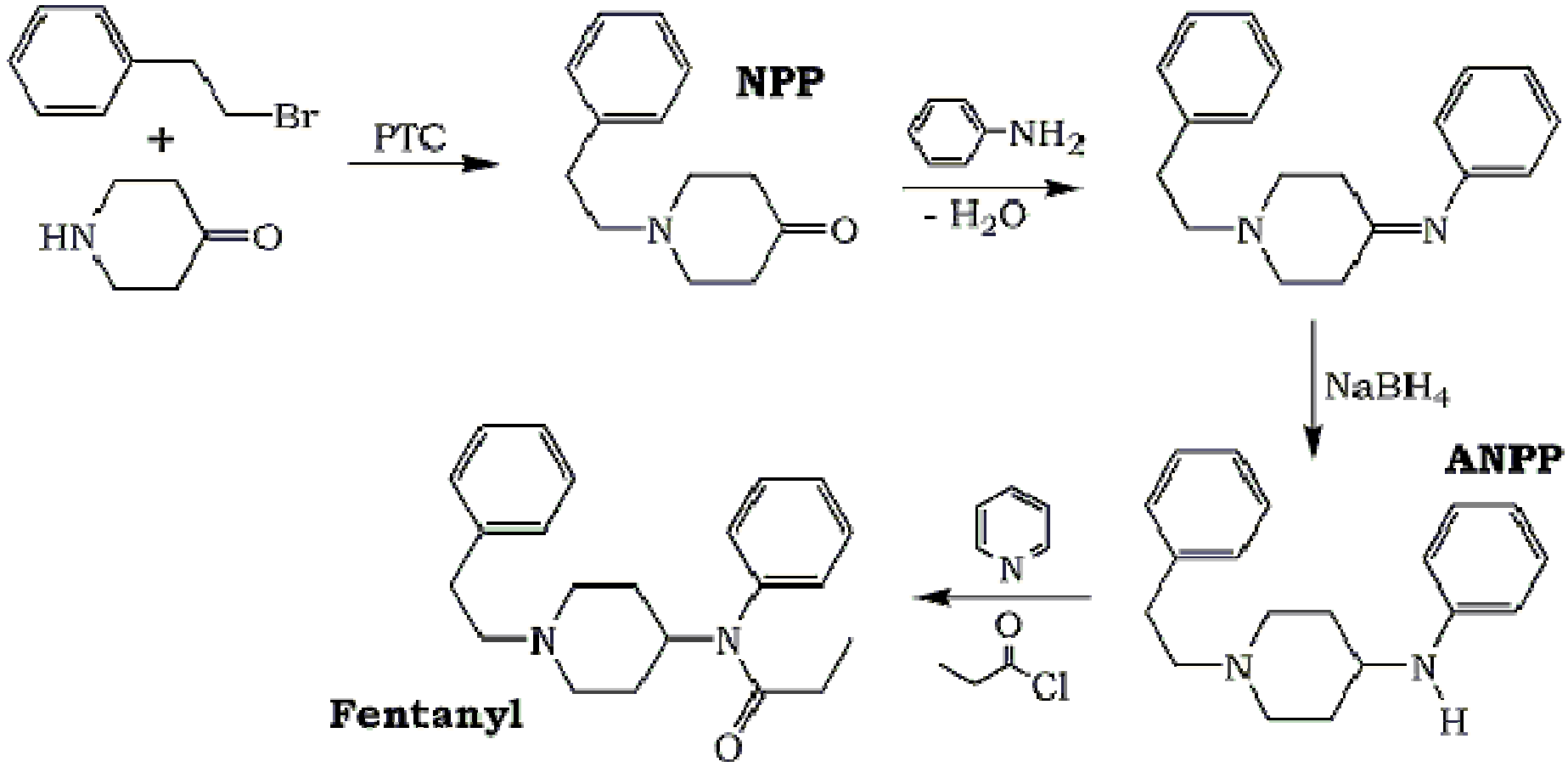
1. Pain and Narcotic Analgesics

2.6 Fentanyl



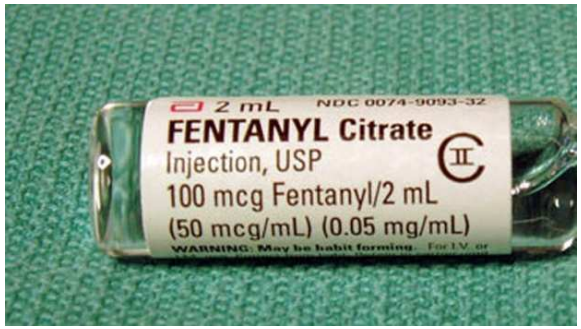
1. Pain and Narcotic Analgesics

2.6 Fentanyl

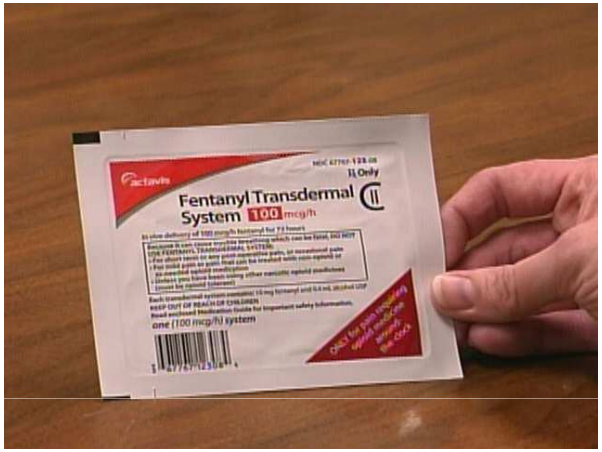


1. Pain and Narcotic Analgesics

2.6 Fentanyl: formulations.



Sublingual spray

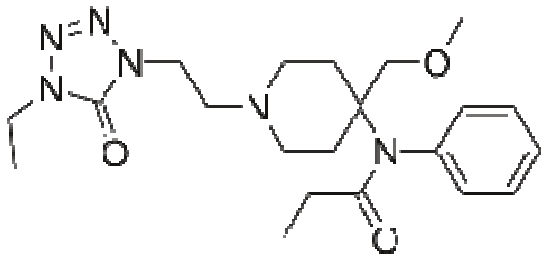


Transdermal patches

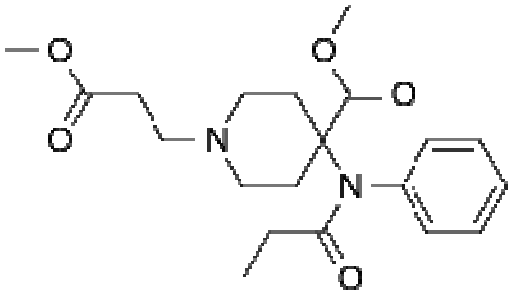
1. Pain and Narcotic Analgesics

2.6 Fentanyl analogs:

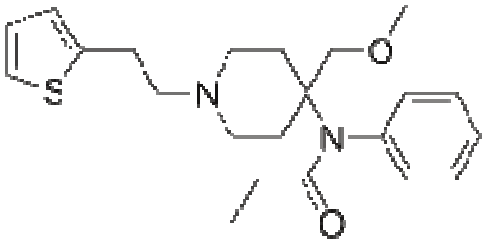
Alfentanyl



Remifentanyl

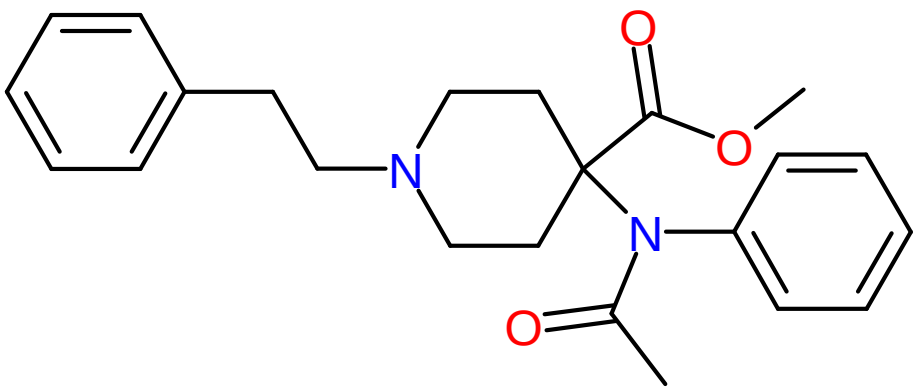


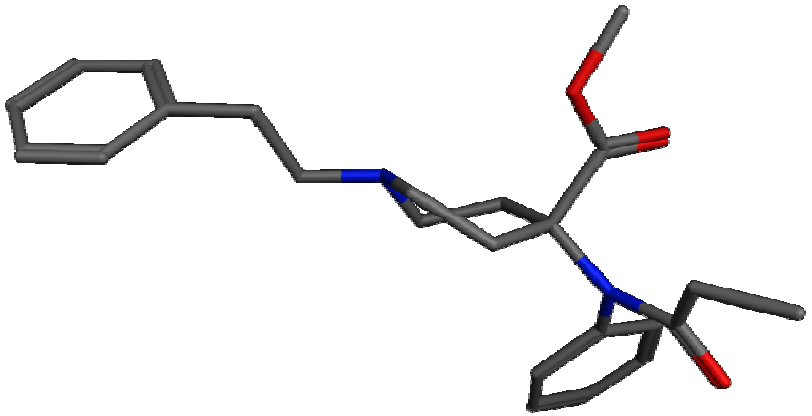
Sufentanyl



1. Pain and Narcotic Analgesics

2.7 Carfentanil





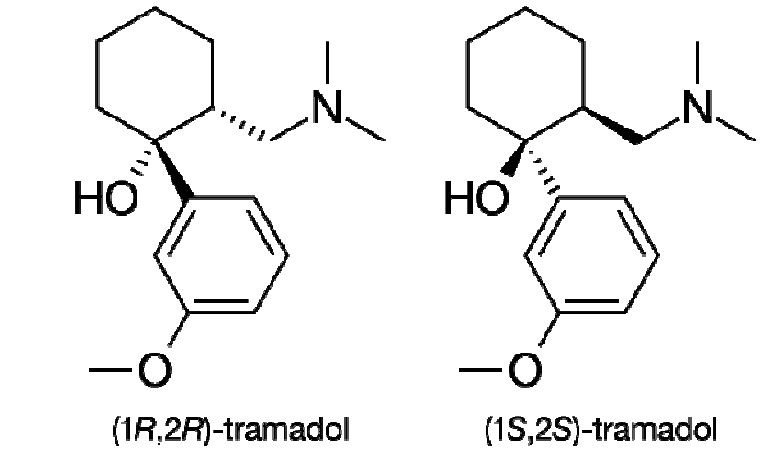
logP = 4.0

4-((1-oxopropyl)-phenylamino)- 1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester

Carfentanil is an analogue of the popular synthetic opioid analgesic fentanyl, and is one of the most potent opioids known (also the most potent opioid used commercially). Carfentanil was discovered in 1976 by Janssen Pharmaceutica. It has a quantitative potency approximately 10,000 times that of morphine and 100 times that of fentanyl. It is marketed under the trade name Wildnil as a tranquilizer for large animals.

1. Pain and Narcotic Analgesics

2.8 Tramadol



Tramadol, a centrally-acting analgesic, exists as a racemic mixture of the *trans* isomer, with important differences in binding, activity, and metabolism associated with the two enantiomers. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Opiate antagonist naloxone only partially antagonized tramadol-induced analgesia.

logP = 2.4

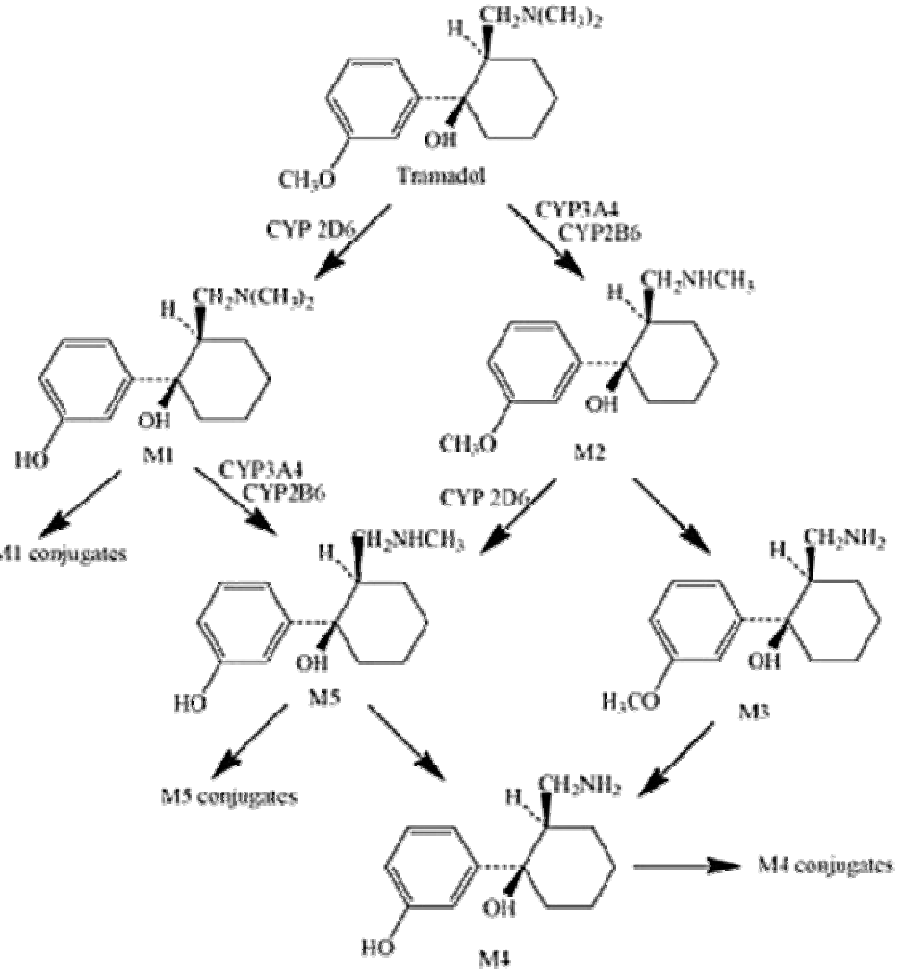
pKa = 9.4

(+)-trans-2-(Dimethylaminomethyl)-1-(m-methoxyphenyl)cyclohexanol

1. Pain and Narcotic Analgesics

2.8 Tramadol: methabolism

Hepatic. The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyltramadol, denoted M1) is pharmacologically active in animal models. CYP3A4 and CYP2B6 facilitates the biotransformation of tramadol to N-desmethyl-tramadol. CYP2D6 facilitates the biotransformation of tramadol to O-desmethyl-tramadol.



Binding Affinities at MOR (μM)

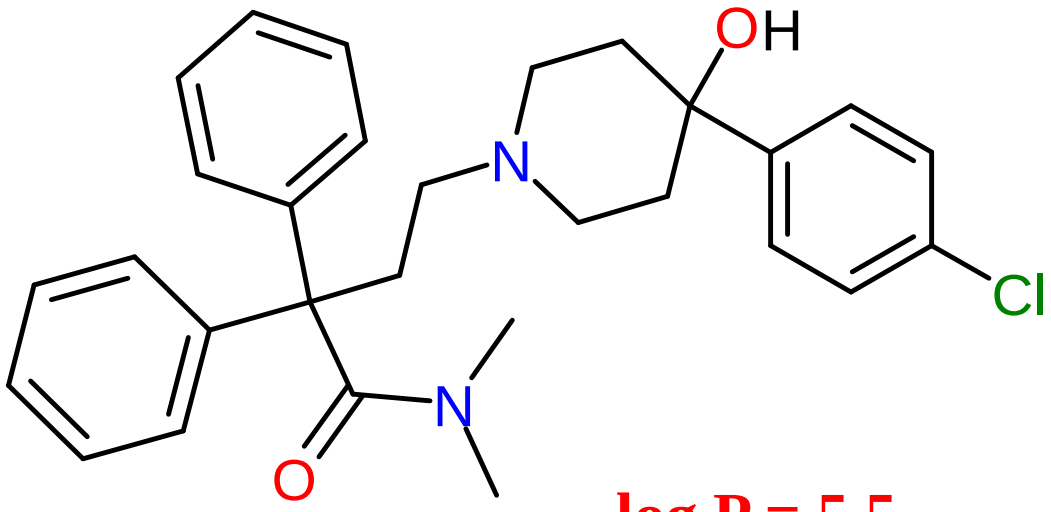
(1*R*,2*R*)-Tramadol:	5,1
(1*S*,2*S*)-Tramadol:	120
(1*R*,2*R*)-Nortramadol:	**0,02**
(1*S*,2*S*)-Nortramadol:	1,8

1. Pain and Narcotic Analgesics

2.8 Tramadol: formulations

1. Pain and Narcotic Analgesics

2.9 Loperamide:

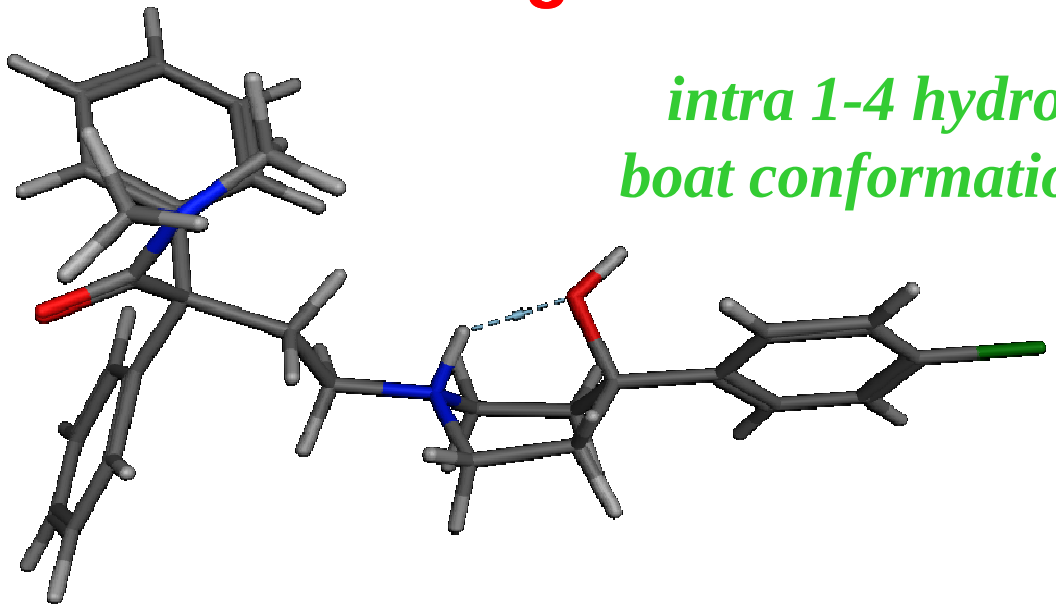


log P = 5.5

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide

Loperamide is an opioid receptor agonist and acts on the mu opioid receptors in the *myenteric plexus* large intestines; **it does NOT affect the central nervous system like other opioids.** It works specifically by decreasing the activity of the myenteric plexus which decreases the motility of the circular and longitudinal smooth muscles of the intestinal wall.

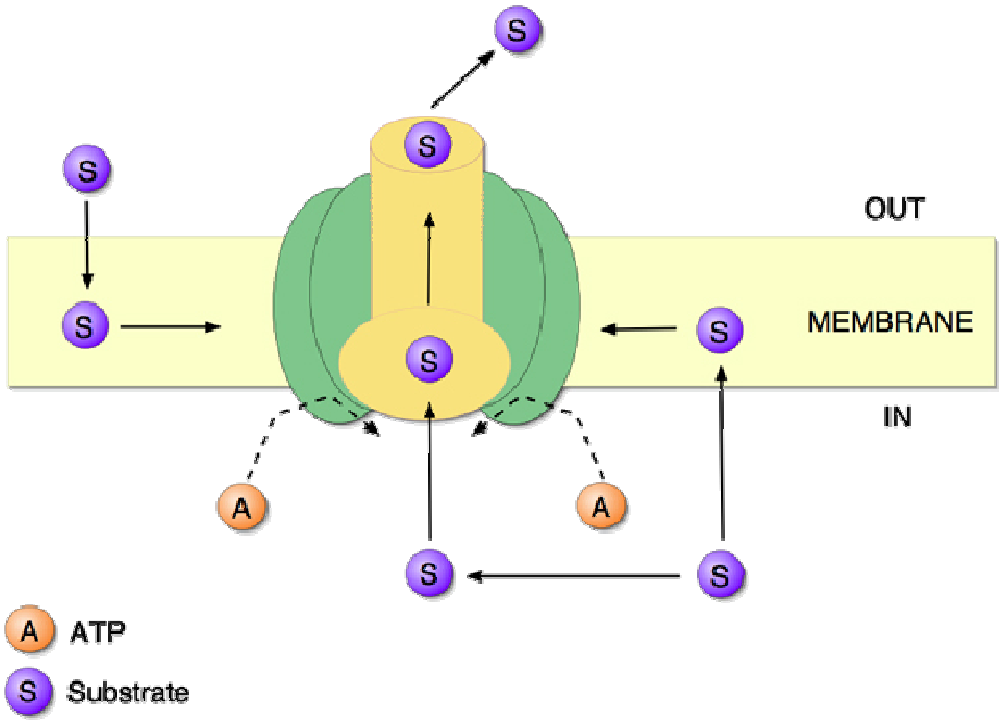
1. Pain and Narcotic Analgesics



intra 1-4 hydrogen bond
boat conformation selection

Loperamide is one of the long-acting synthetic **antidiarrheals**; it is not significantly absorbed from the gut, and has no effect on the adrenergic system or central nervous system. In fact, Loperamide is a **substrate of P-glycoprotein (P-gp)**, therefore the concentration of Loperamide will increase when given with a P-Glycoprotein inhibitor. Common P-Glycoprotein inhibitors include *quinidine*, *ritonavir*, and *ketoconazole*, among others. Loperamide is also capable of decreasing the concentration of other P-Glycoprotein substrates. As an example, when *saquinavir* concentrations can decrease by half when given with loperamide.

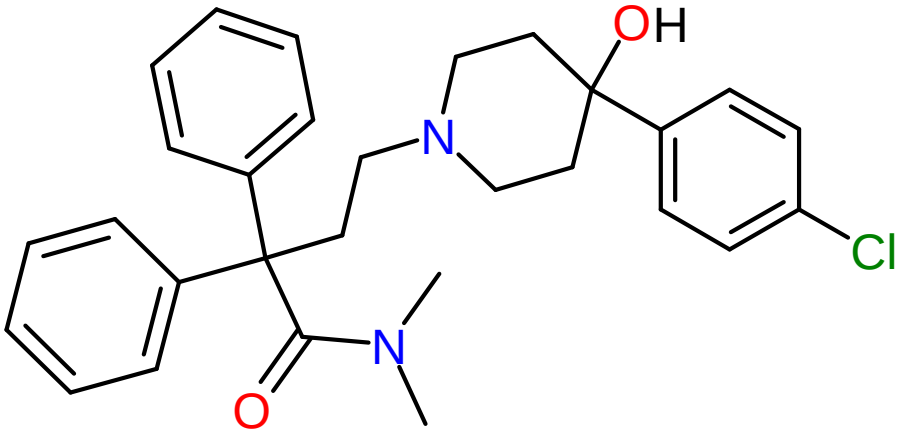
1. Pain and Narcotic Analgesics



P-gp is extensively distributed and expressed in the *intestinal epithelium* where it pumps xenobiotics (such as toxins or drugs) back into the intestinal lumen, in *liver cells* where it pumps them into bile ducts, in the cells of the *proximal tubule of the kidney* where it pumps them into urine-conducting ducts, and in the *capillary endothelial cells* composing the blood–brain barrier and *blood-testis barrier*, where it pumps them back into the capillaries.

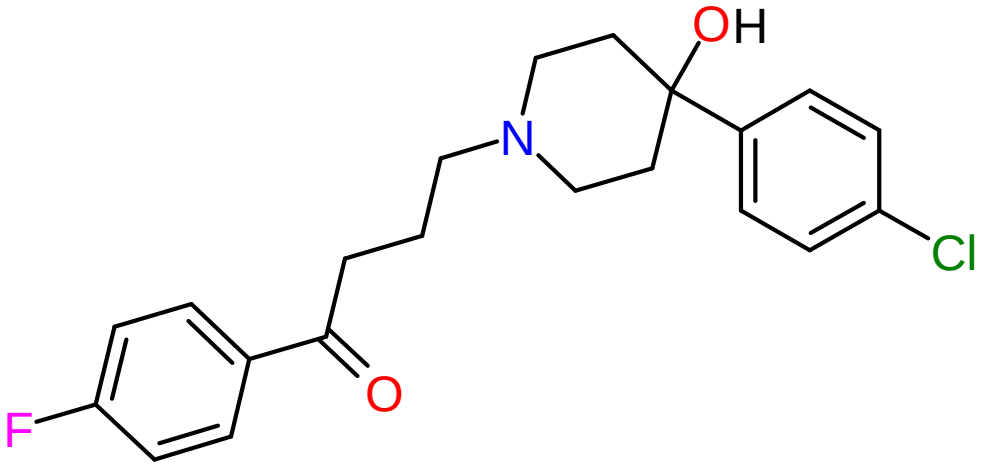
1. Pain and Narcotic Analgesics

Loperamide:



Opioid Receptor Agonist

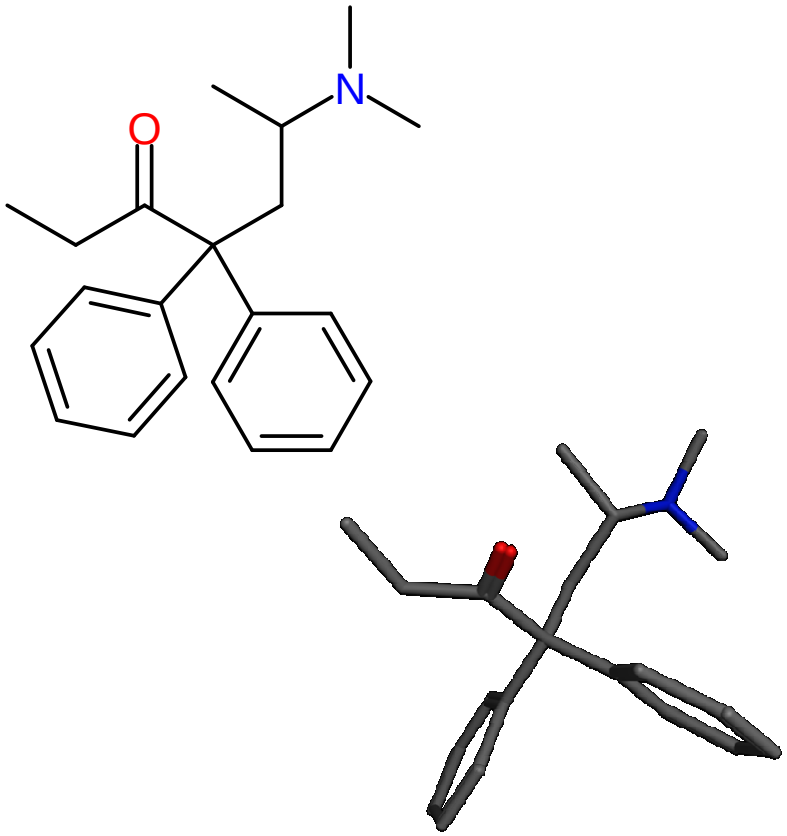
Haloperidol:



Dopamine D2 Receptor Inverse Agonist

1. Pain and Narcotic Analgesics

3.0 Methadone



Methadone is a synthetic opioid, used medically as an analgesic, antitussive and **a maintenance anti-addictive for use in patients on opioids**. It was developed in Germany in 1937. Methadone is a full μ-opioid agonist. Although chemically unlike morphine or heroin, methadone also acts on the opioid receptors and thus produces many of the same effects. Methadone is also used in managing chronic pain owing to its long duration of action and very low cost.

There are two methadone isomers. The racemic mixture is more common as it is cheaper to produce.

logP = 3.9

pKa = 8.9

(RS)-6-(Dimethylamino)-4,4-diphenylheptan-3-one

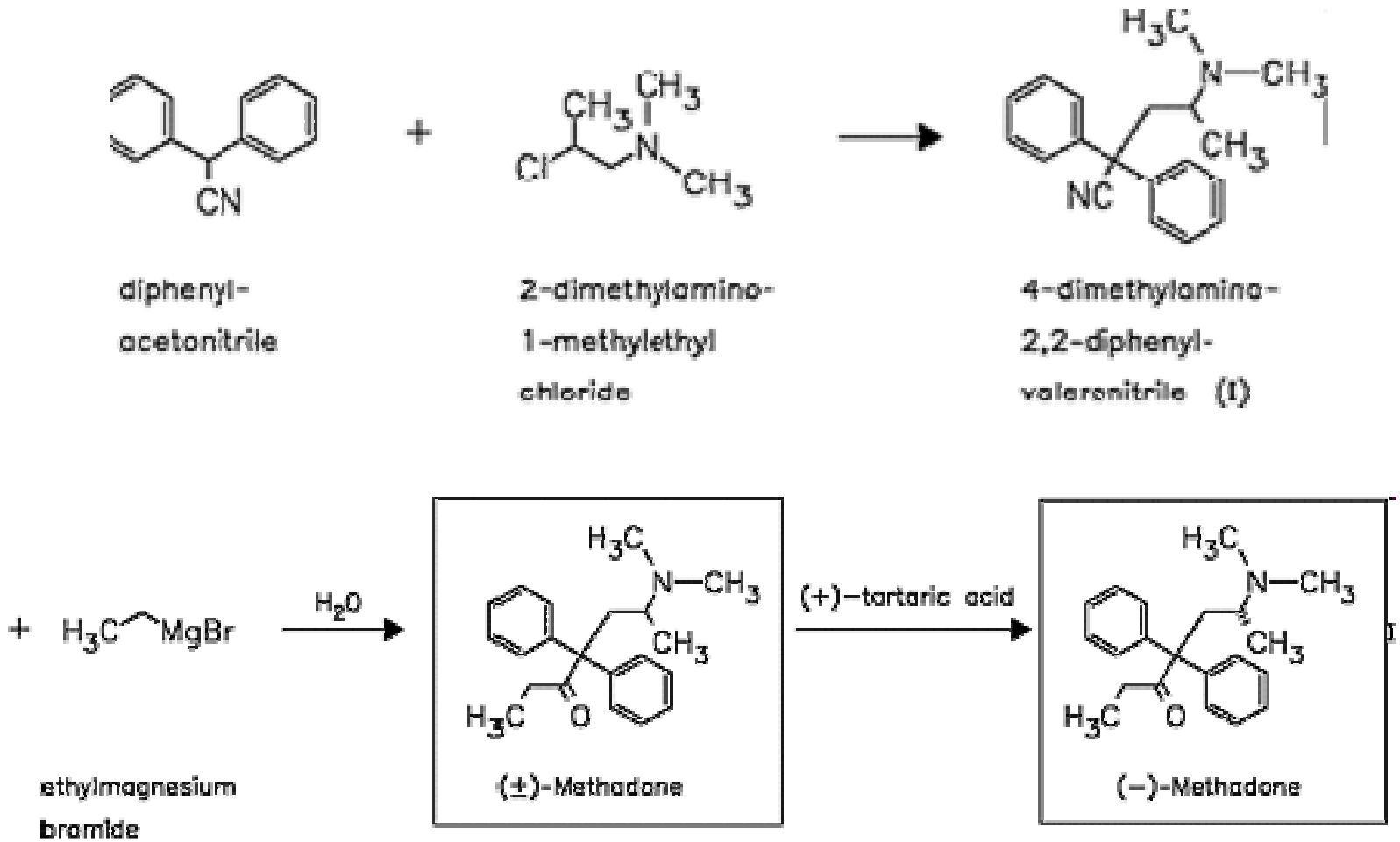
1. Pain and Narcotic Analgesics

3.0 Methadone: formulations

Oral solution

1. Pain and Narcotic Analgesics

3.0 Methadone



1. Pain and Narcotic Analgesics

Equianalgesia

Equianalgesia (morphine)				
Analgesic	**Strength** (relative)	**Equivalent dose** (10 mg)	**Bioavailability**	**Half-life of active metabolites** (hours)
Aspirin (non-opioid)	1/360	no equivalent dose	total	3.1–9
Diflunisal (NSAID, non-opioid)	1/160	1600 mg	80–90%	8–12
Acetaminophen IV (non-opioid) [7]	1/25	250 mg	100%	
Dextropropoxyphene[8]	1/13 to 1/20	130–200 mg		
Codeine	1/10	100 mg	≈90%	2.5–3 (C6G 1.94;[9] morphine 2–3)
Tramadol	1/10	100 mg	68–72%	5.5–7 (≈9)[clarification needed]
Dihydrocodeine	1/5	50 mg	20%	4
Tapentadol	1/10	100 mg	95%	
Anileridine[10]	1/4	40 mg		
Alphaprodine	1/4–1/6	40–60 mg		
Pethidine (meperidine hydrochloride)	1/3	28 mg	50–60%	3–5
Hydrocodone	1	10 mg	≥80%	3.8–6
Metopon	1	10 mg		
Pentazocine lactate (IV) [11]	1	10 mg (6.7–13.3 mg)		
Morphine (oral)	(1)	(10 mg)	≈25%	

1. Pain and Narcotic Analgesics

Equianalgesia (morphine)				
Analgesic	Strength (relative)	Equivalent dose (10 mg)	Bioavailability	Half-life of active metabolites (hours)
Morphine (oral)	(1)	(10 mg)	≈25%	
Oxycodone	1.5–2.0	5.0–6.7 mg	≤87%	3–4.5
Morphine (IV/IM)	3	3.33 mg	100%	2–3 mg
Clonitazene	3	3.33 mg		
Methadone (acute) [12][13]	3–4	2.5–3.33 mg	40–90%	15–60
Diamorphine (Heroin; IV/IM)[14]	4–5	2–2.5 mg	100%	<0.6
Hydromorphone[15]	5	2 mg	30–35%	2–3
Oxymorphone	7	1.4 mg	10%	7.25–9.43
Methadone (chronic) [13]	7.5	1.35 mg	40–90%	15–60
Levorphanol[16]	8	1.3 mg	70%	11–16
7-Hydroxymitragynine	17	≈.6 mg		
Buprenorphine[8][*dead link*]	40	0.25 mg	35–40% (sublingual)	20–70, mean 37
Fentanyl	50–100	0.1–0.2 mg	33% (oral); 92% (transdermal)	0.04 (IV); 7 (transdermal)
Sufentanil	500–1,000	10–20 µg		4.4
Bromadol [notes 1]	504	≈ 20 µg		
Etorphine [notes 1]	1,000–3,000	3.3–10 µg		
Etonitazene	2,000	5.0 µg		
Dihydroetorphine [notes 1]	1,000–12,000	20–40 µg		
Carfentanil [notes 1][16]	10,000–100,000	0.1–1.0 µg		7.7

Table 31–1. Common opioid analgesics.

Generic Name	Product Name	Approximate Dose (mg)	Oral:Parenteral Potency Ratio	Duration of Analgesia (hours)	Maximum Efficacy	Addiction/Abuse Liability
Morphine		10	Low	4–5	High	High
Hydromorphone	Dilaudid	1.5	Low	4–5	High	High
Oxymorphone	Numorphan	1.5	Low	3–4	High	High
Methadone	Dolophine	10	High	4–6	High	High
Meperidine	Demerol	60–100	Medium	2–4	High	High
Fentanyl	Sublimaze	0.1	Parenteral only	1–1.5	High	High
Sufentanil	Sufenta	0.02	Parenteral only	1–1.5	High	High
Alfentanil	Alfenta	Titrated	Parenteral only	0.25–0.75	High	High
Levorphanol	Levo-Dromoran	2–3	High	4–5	High	High
Codeine		30–60[2]	High	3–4	Low	Medium
Oxycodone[1]	Percodan	4.5[2]	Medium	3–4	Moderate	Medium
Dihydrocodeine[1]	Drocode	16[2]	Medium	3–4	Moderate	Medium
Propoxyphene	Darvon	60–120[2]	Oral only	4–5	Very low	Low
Pentazocine	Talwin	30–50[2]	Medium	3–4	Moderate	Low
Nalbuphine	Nubain	10	Parenteral only	3–6	High	Low
Buprenorphine	Buprenex	0.3	Parenteral only	4–8	High	Low
Butorphanol	Stadol	2	Parenteral only	3–4	High	Low

[1]Available in tablets containing aspirin, etc.
[2]Analgesic efficacy at this dose not equivalent to 10 mg of morphine. See text for explanation.


TITLE
"CHIMICA FARMACEUTICA E TOSSICOLOGICA II"
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Stefano Moro
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DATE
SCENE
TAKE

1. Pain and Narcotic Analgesics

The mechanism of action of heroin at the delta (δ) and kappa (κ) opiate receptors

Heroin modifies the action of dopamine in the nucleus accumbens and the ventral tegemental area of the brain – these areas form part of the brain's 'reward pathway'. Once crossing the blood-brain barrier, heroin is converted to morphine, which acts as a weak agonist at the delta and kappa opioid receptors subtypes. This binding inhibits the release of GABA from the nerve terminal, reducing the inhibitory effect of GABA on dopaminergic neurons. The increased activation of dopaminergic neurons 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. Morphine is a powerful agonist at the opioid mu receptor subtype and activation of these receptors has a strong activating effect on the dopaminergic reward pathway.