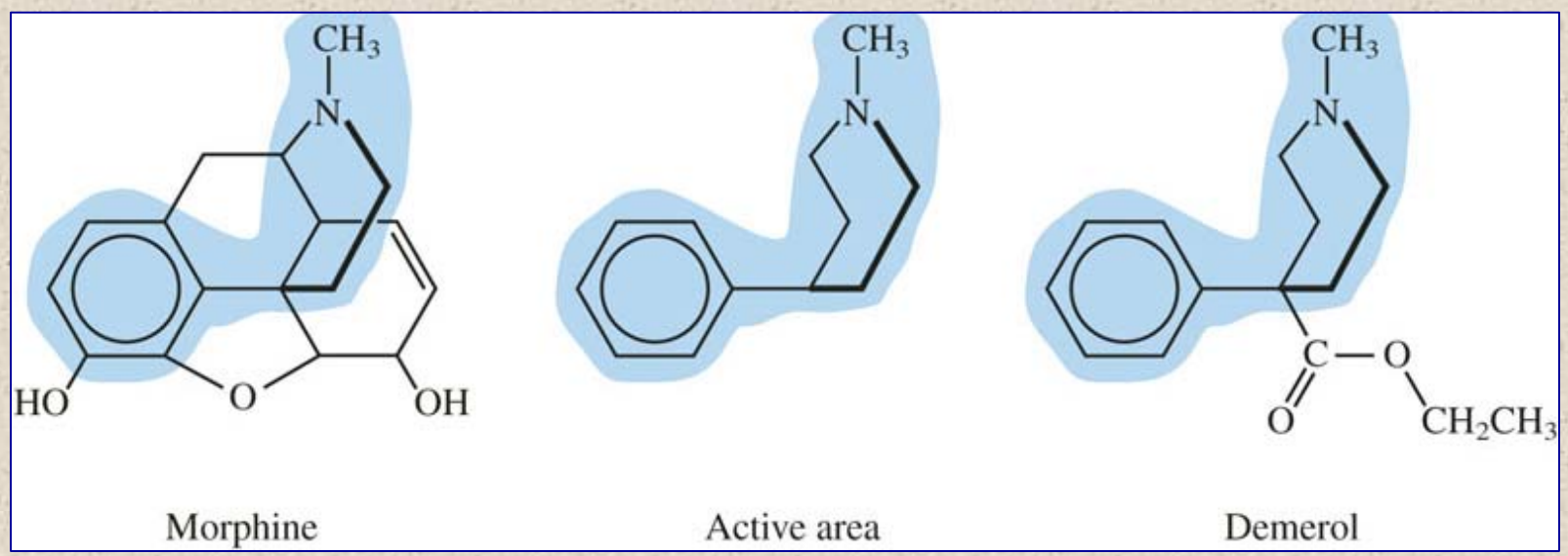
Receptor Sites and Drug Design

Case Study: Opiates use for Anesthesia & analgesia


PAIN

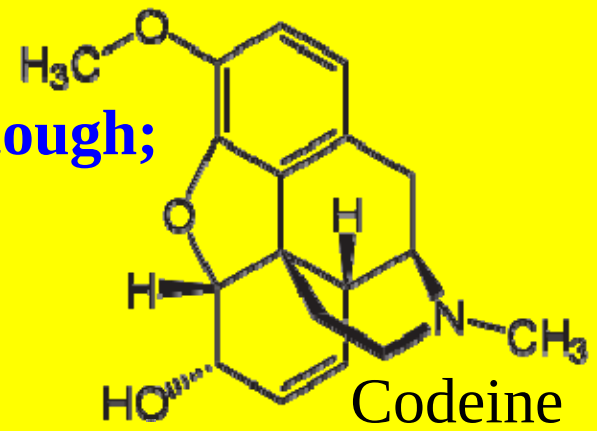
The **functional groups** and their placement in three-dimensional space determines to a large degree a molecule's biological activity.



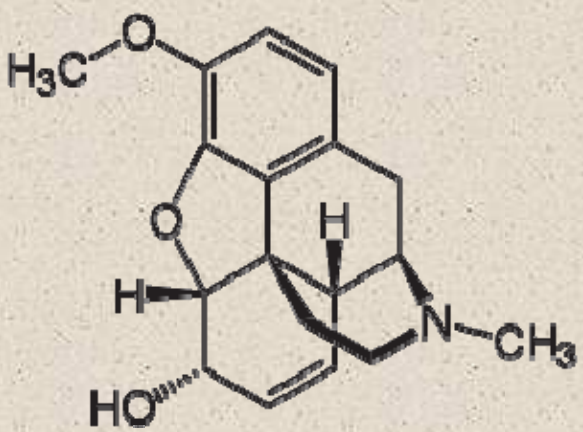
The portion of a molecule that determines the biological effects of a drug is called the pharmacophore.

Medicinal Uses for Morphine:

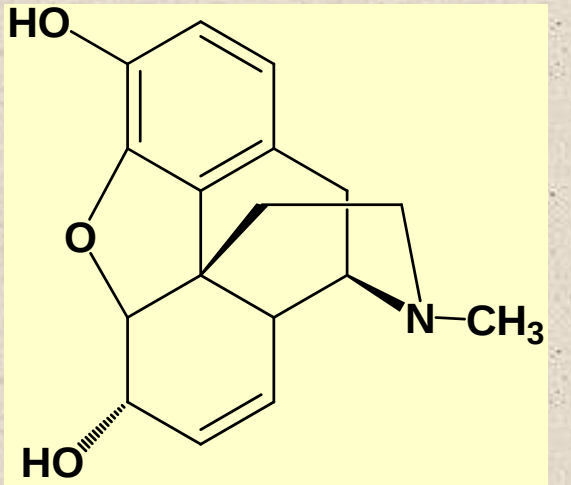
- as an adjunct to general anesthesia
- in epidural anesthesia or intrathecal analgesia
- for palliative care (i.e. to alleviate pain without curing the underlying reason for it, usually because the latter is found impossible)
- as an antitussive for severe cough; (Codeine is better)



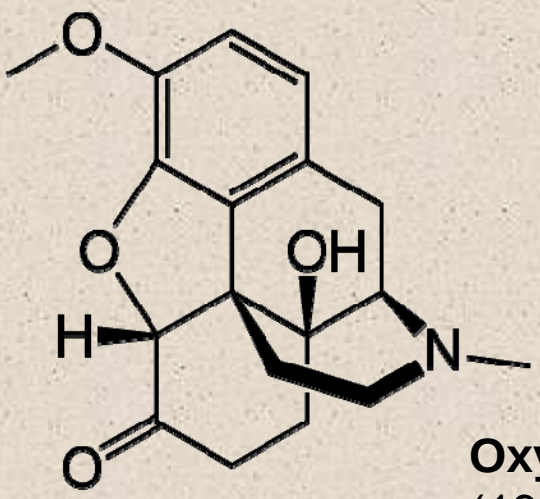
Codeine



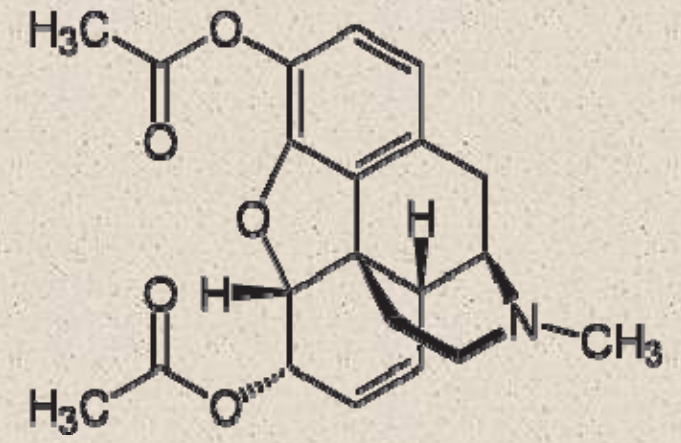
Codeine
(1832)



Morphine (~1805)



Oxycodone
(1916)

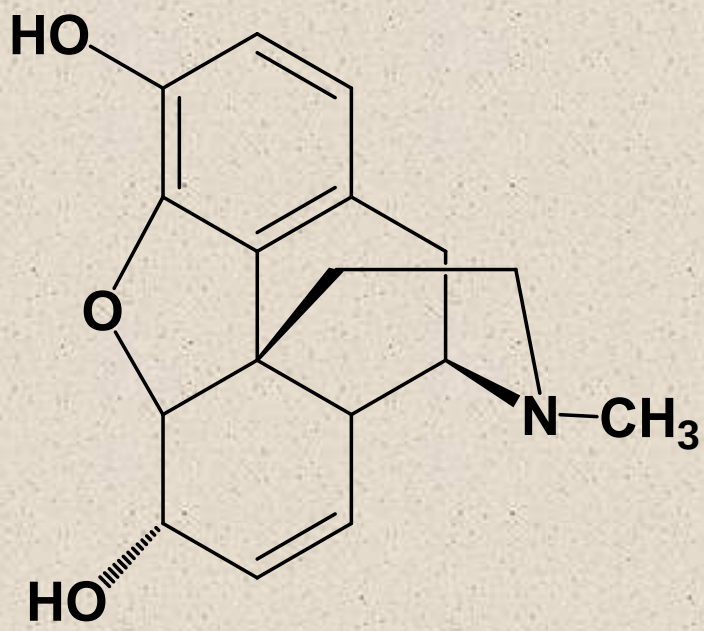


Heroin
(1874)

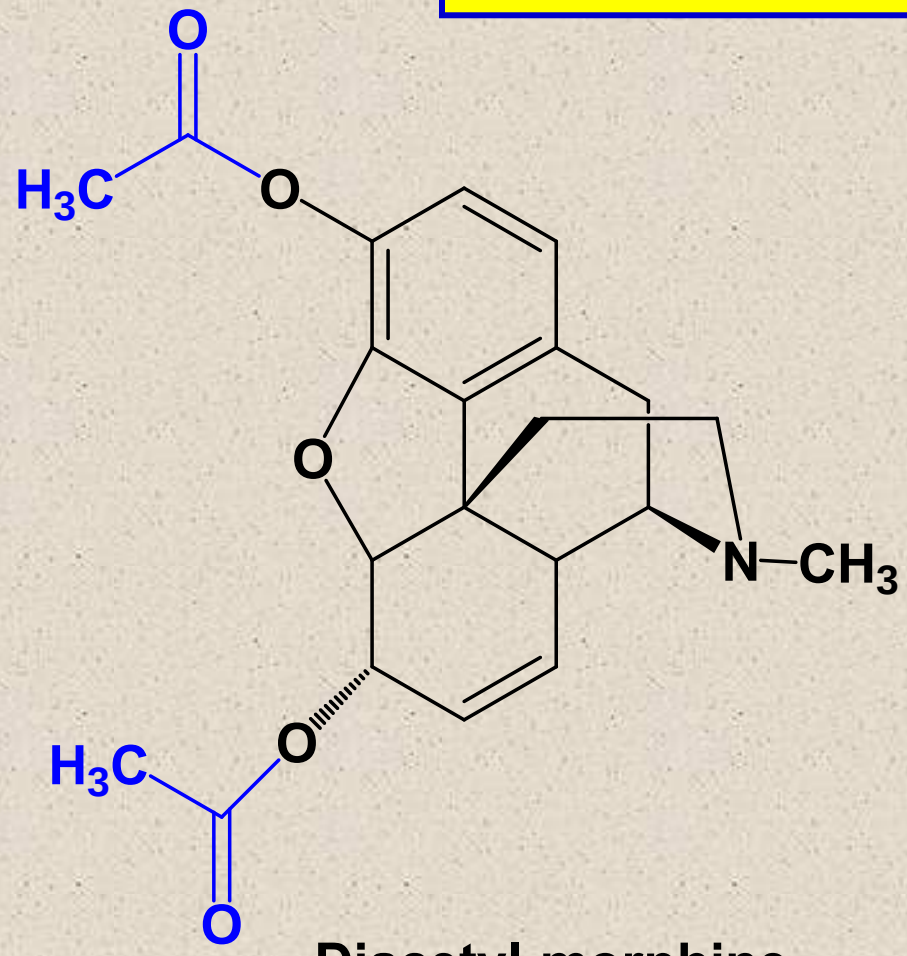
An **analgesic** (also known as a **painkiller**) is any member of the group of drugs used to relieve pain (achieve analgesia). The word *analgesic* derives from Greek *an-* ("without") and *algos* ("pain").

A **general anesthetic** is a drug that brings about a reversible loss or alteration of consciousness.

Local anesthesia is any technique to render part of the body insensitive to pain without affecting consciousness.



Morphine

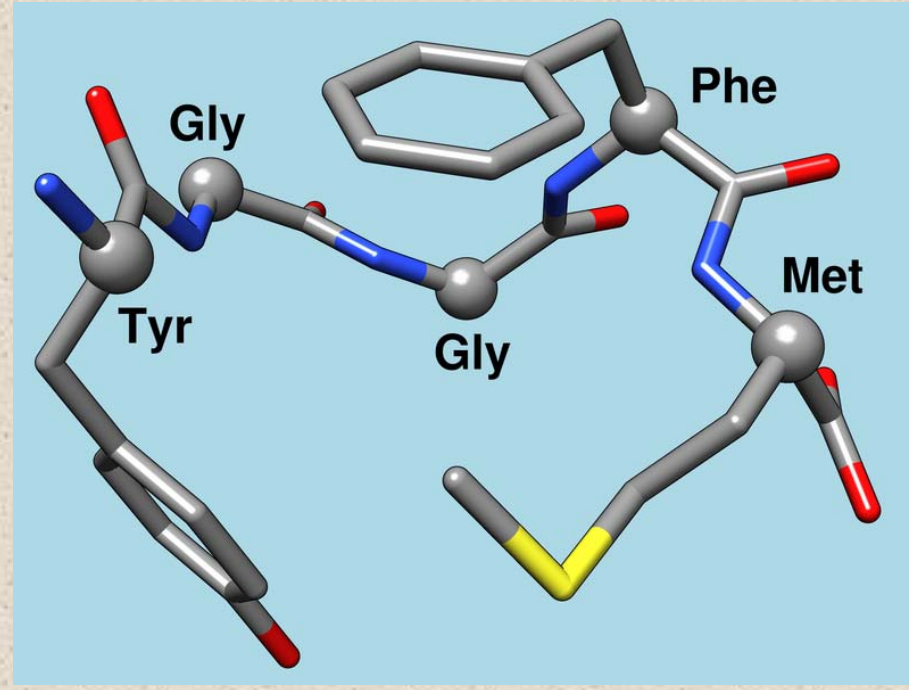


Diacetyl-morphine
(Heroin)

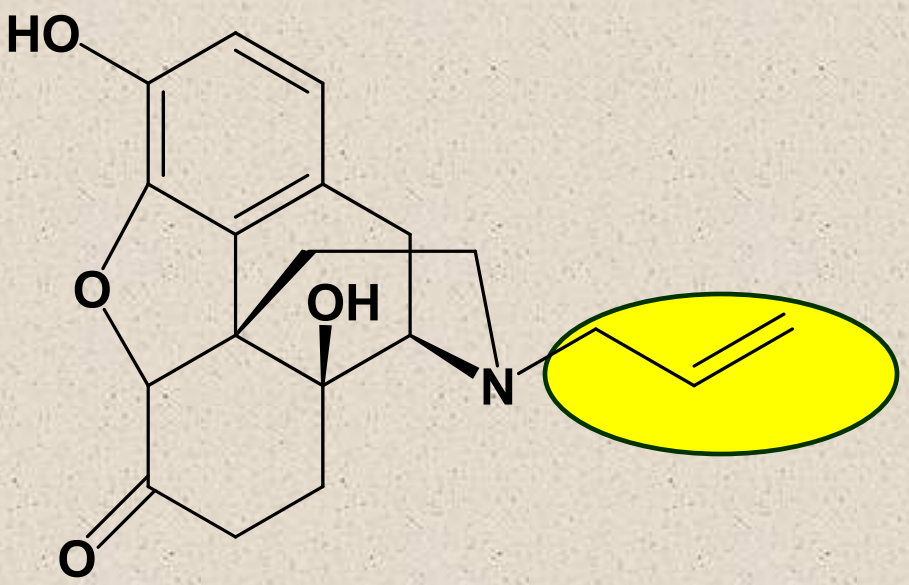
Why do humans have receptor sites for such a complex structure?

Endorphins ("**endo**genous mo**rphin**e") are endogenous opioid peptides (discovered in 1974)

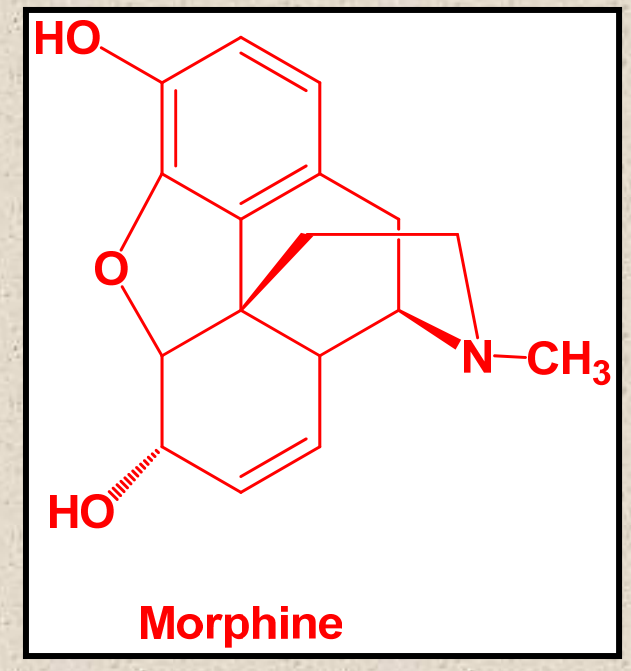
An **enkephalin** is a pentapeptide involved in regulating perception of pain in the body



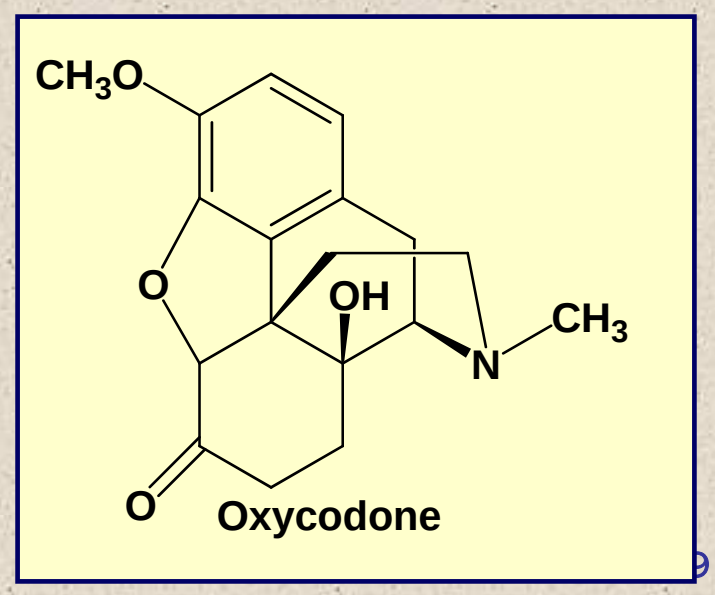
Opiate antagonist-reversal agent



Naloxone



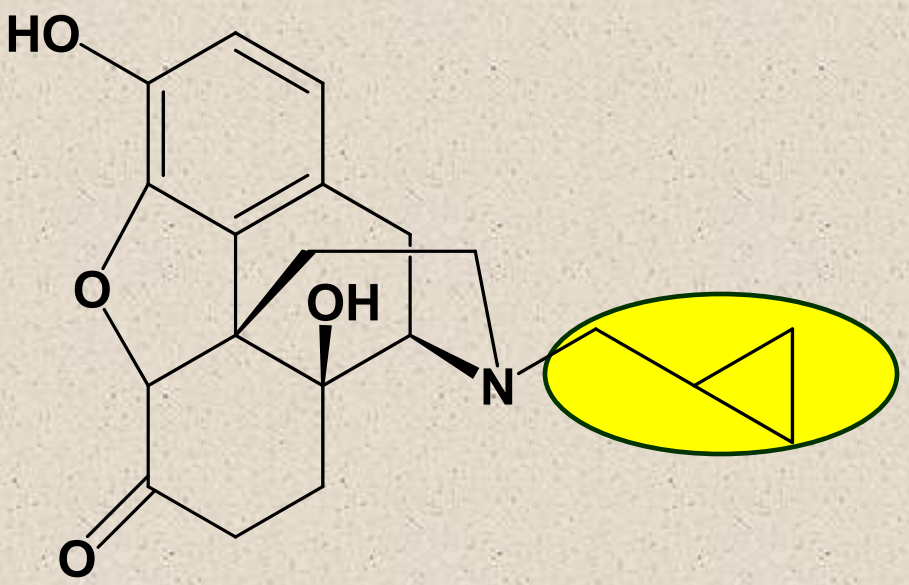
Morphine



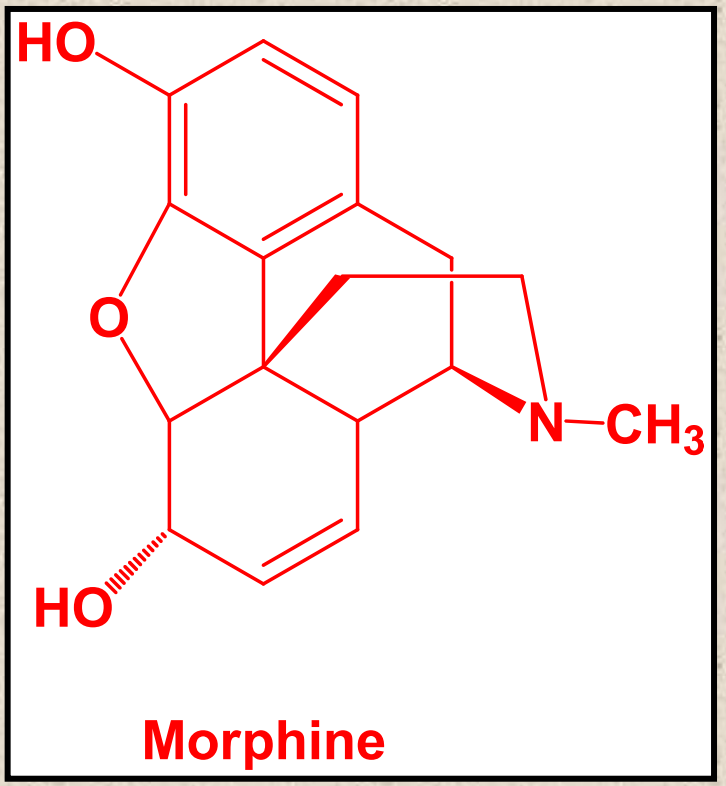
Oxycodone

Opiate reversal agent (competitive antagonist)
-high affinity for μ-receptor site

Opiate antagonist-reversal agent

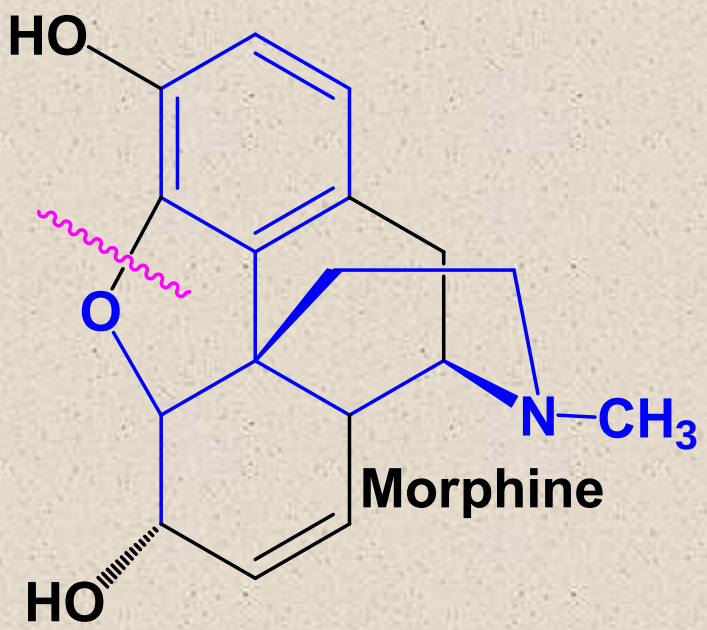


Naltrexone

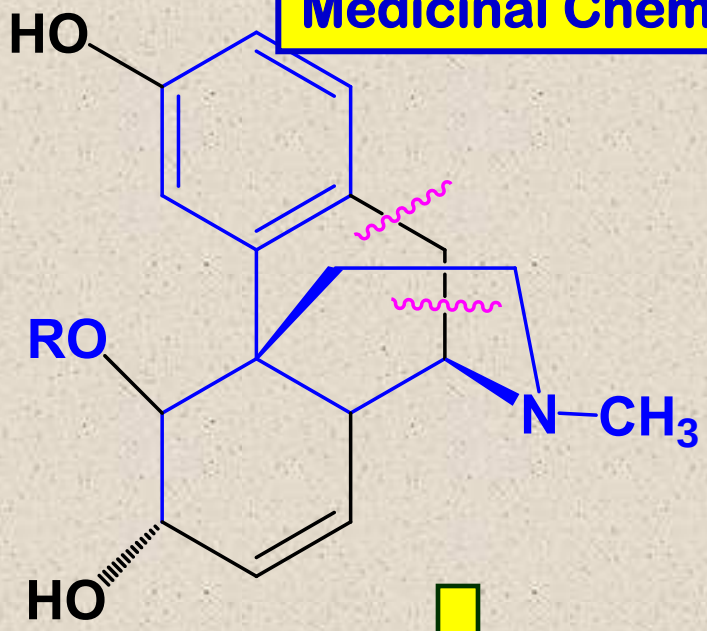


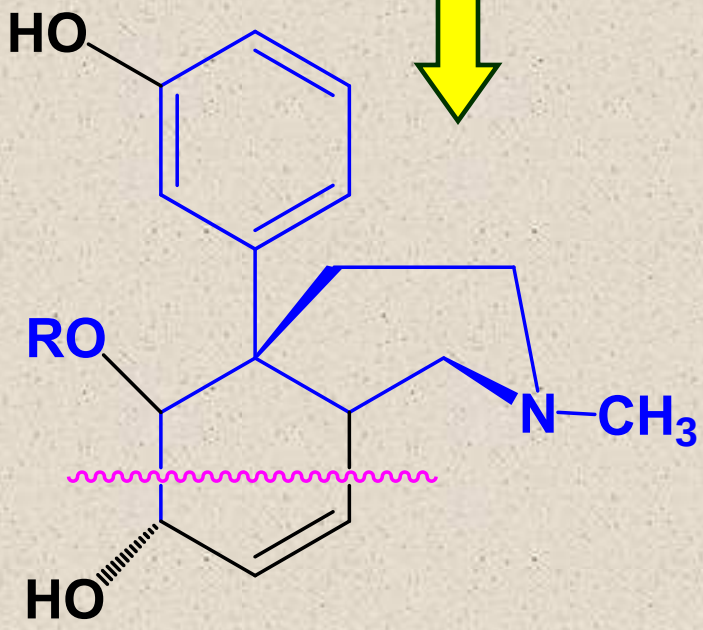
Morphine

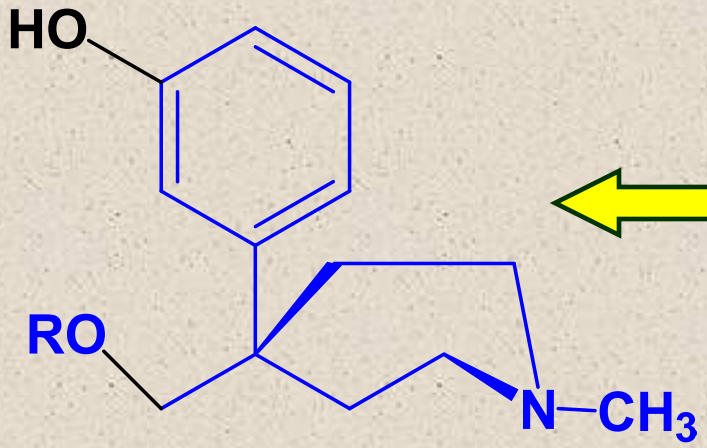
Opiate reversal agent (blocks “pleasure” centers)
-used for treatment of alcohol dependence (alcoholism)
& opiate addiction

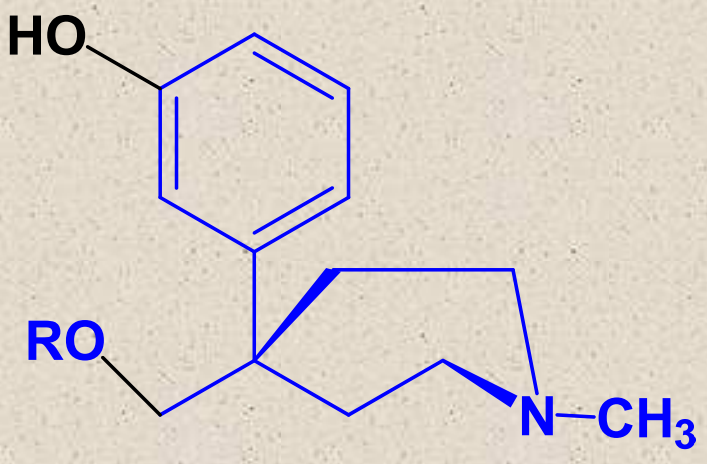


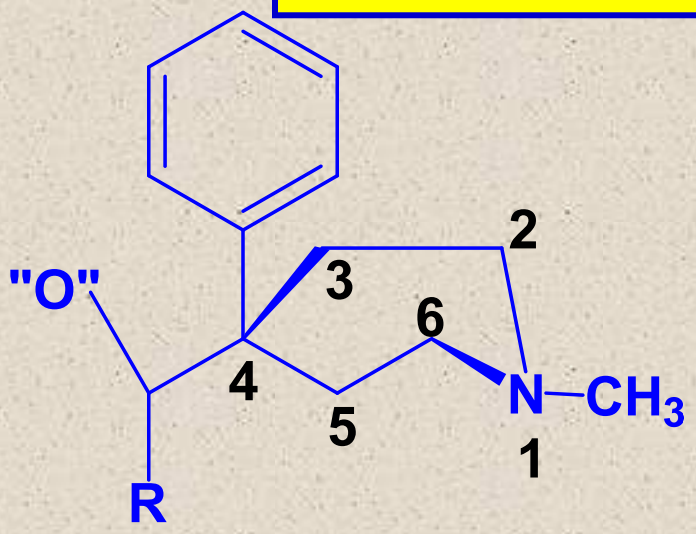
Morphine

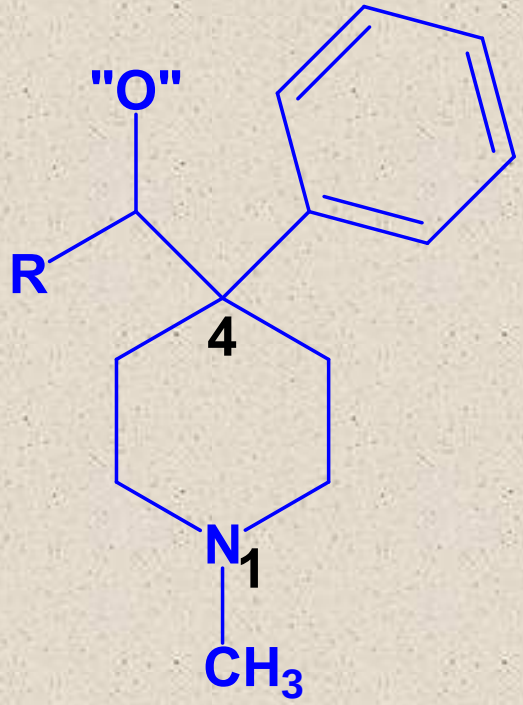


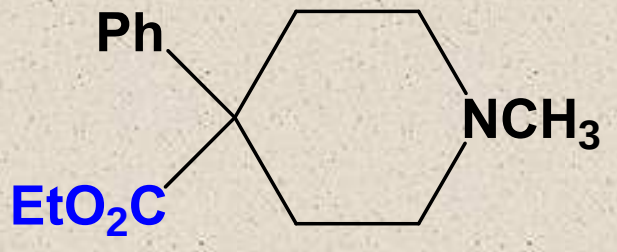





HO
RO
N
CH3


"O"
R
2
3
4
5
6
N
1
CH3

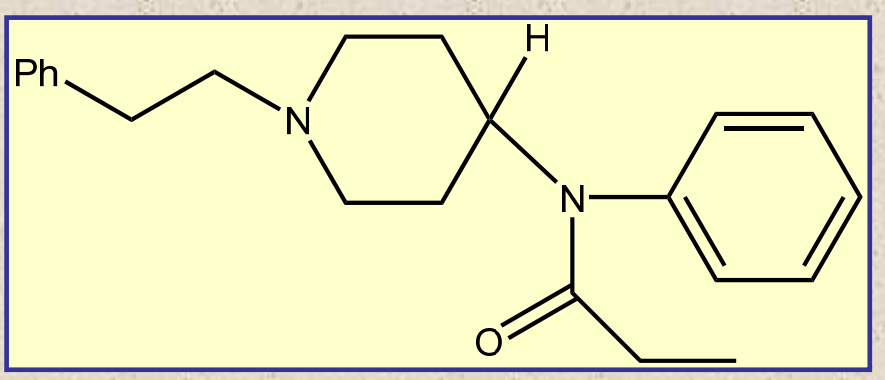

"O"
R
4
N
1
CH3



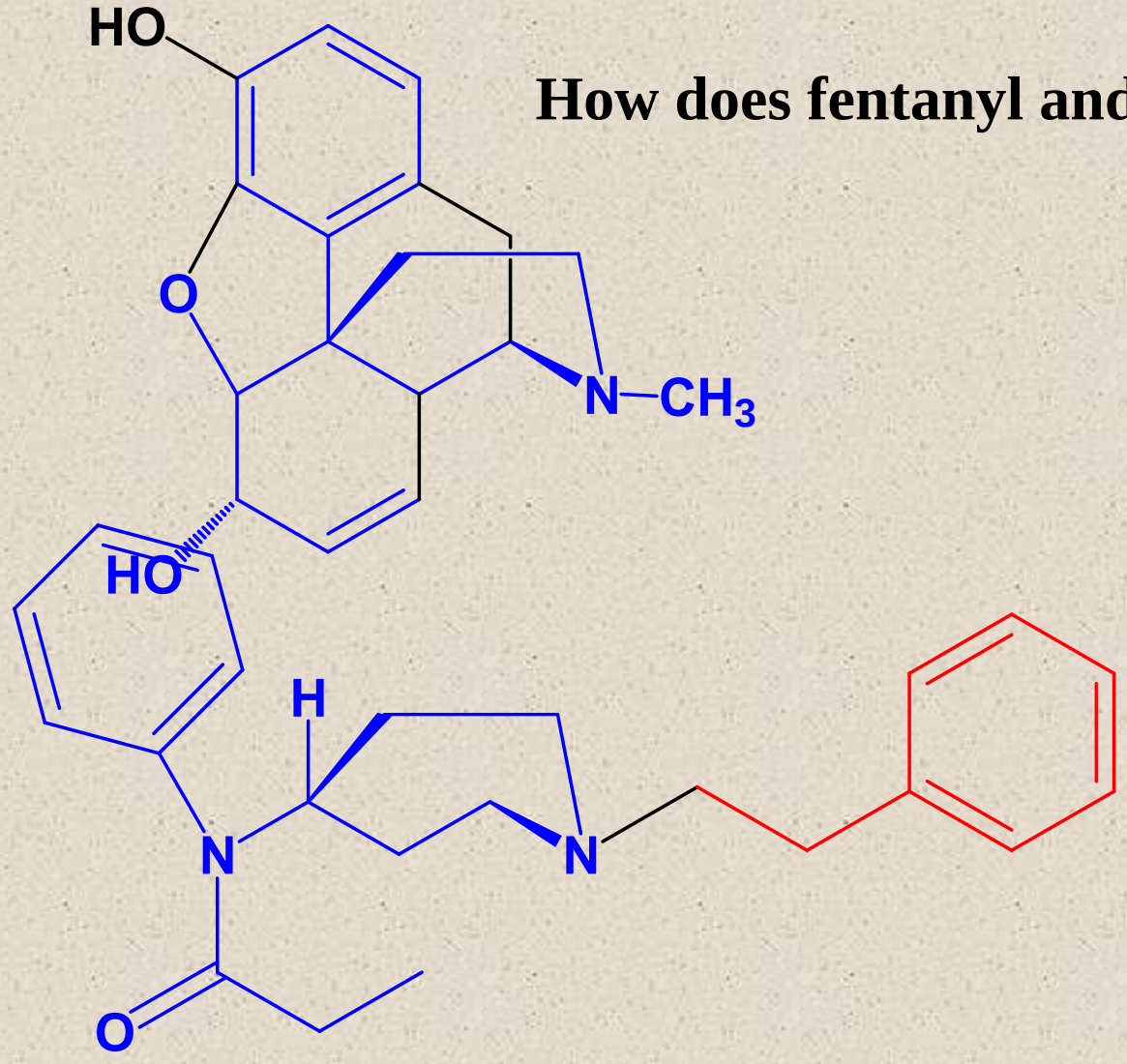
Meperidine

Demerol ®

1960-a new opiate, which was based on the piperidine structure was introduced:

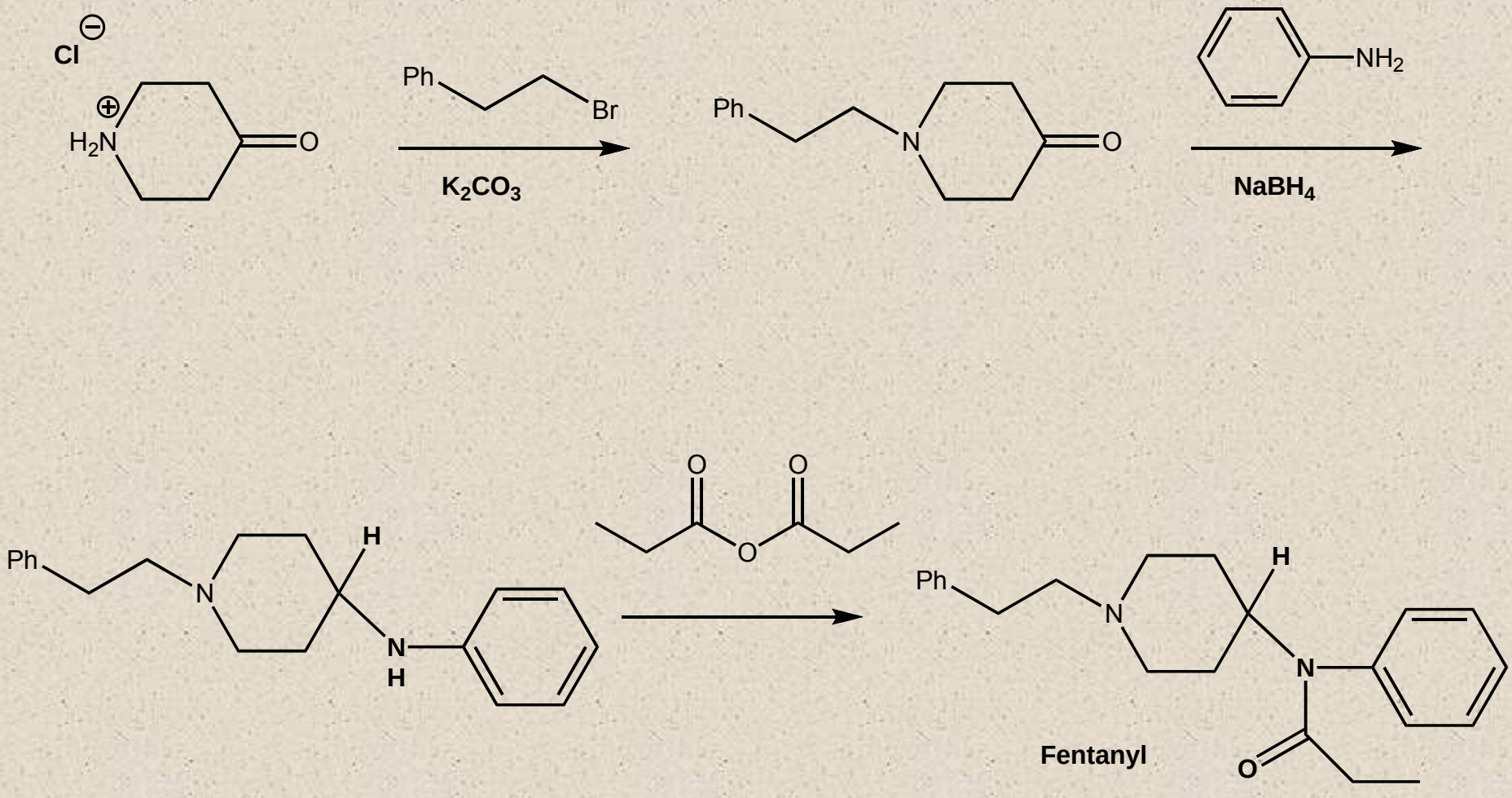


Fentanyl is about 100 X the potency of morphine

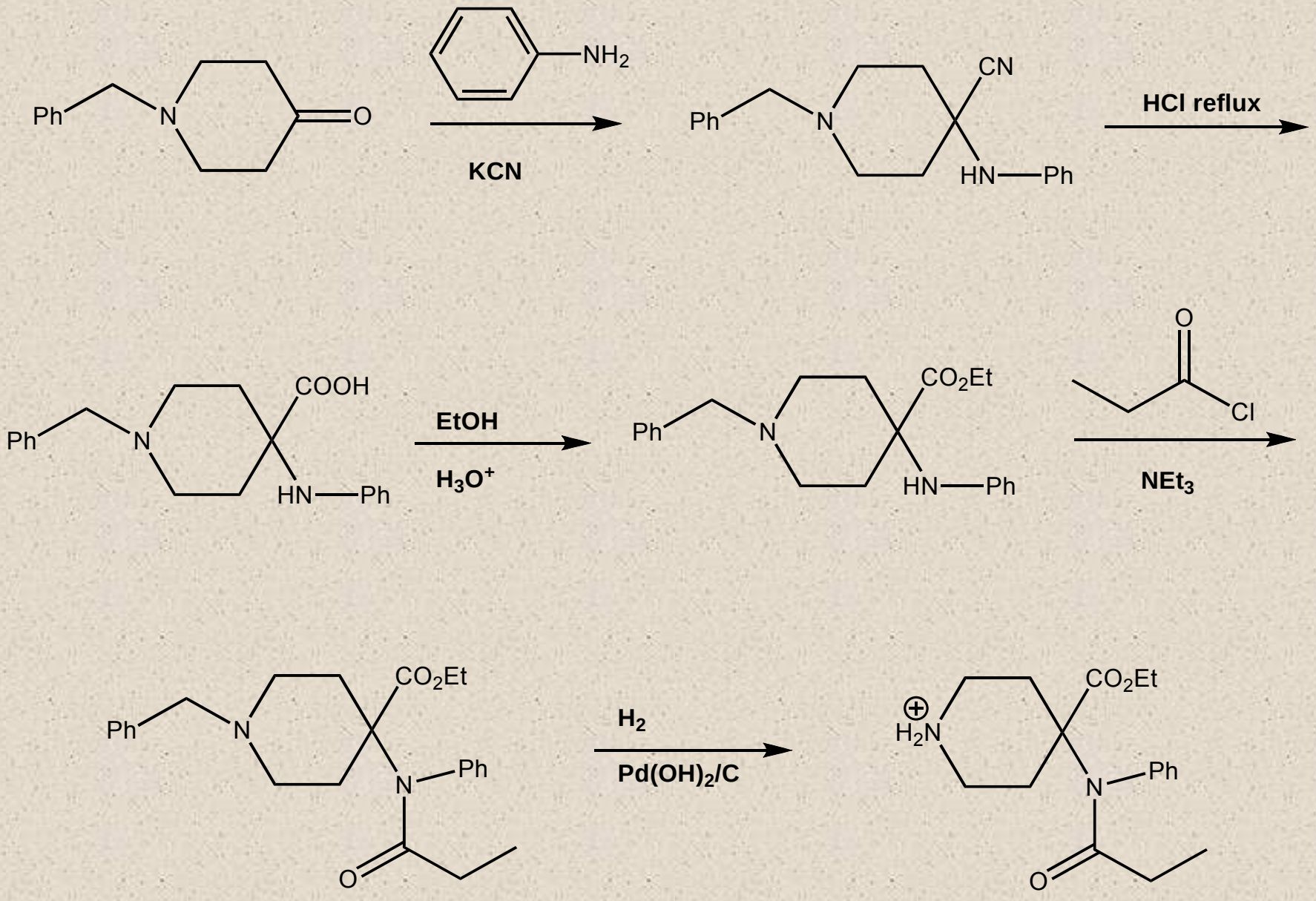


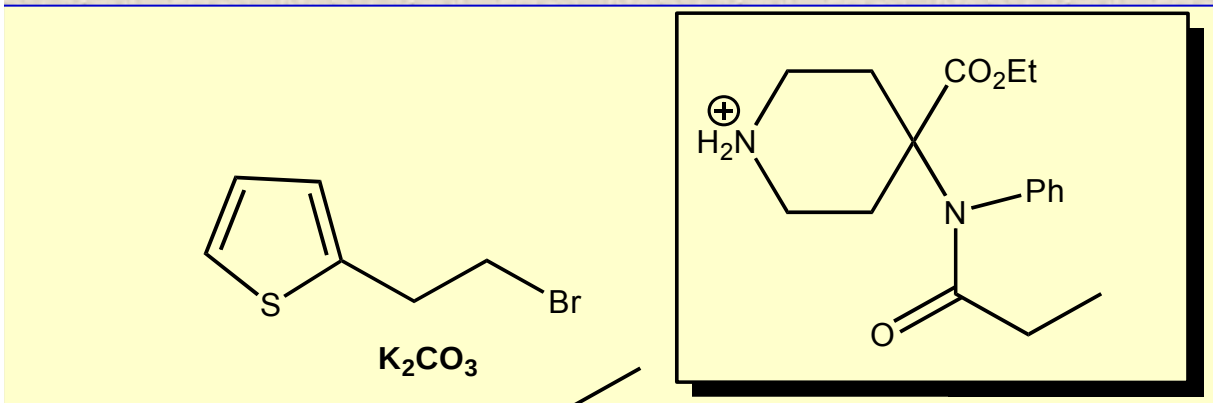
How does fentanyl and morphine compare?

Commercial Synthesis of Fentanyl



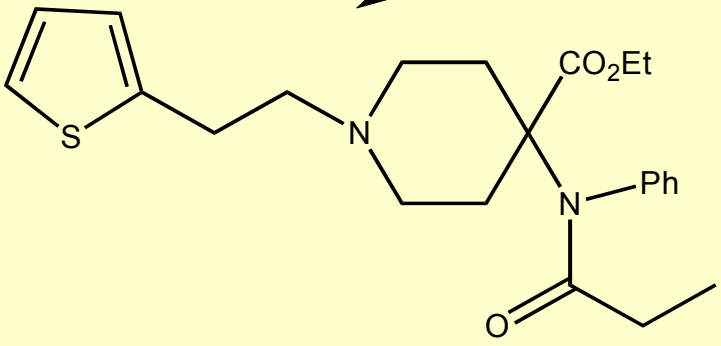
Anaquest Approach to 4,4-Disubstituted Piperdines:



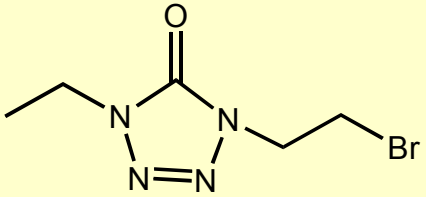


K_2CO_3

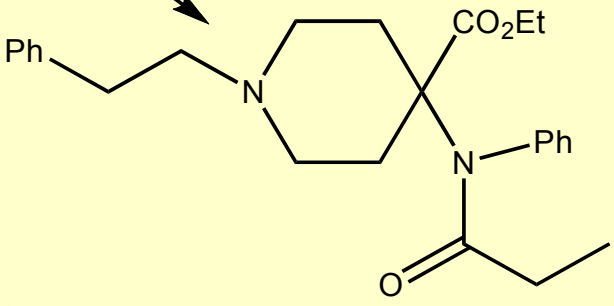
K_2CO_3



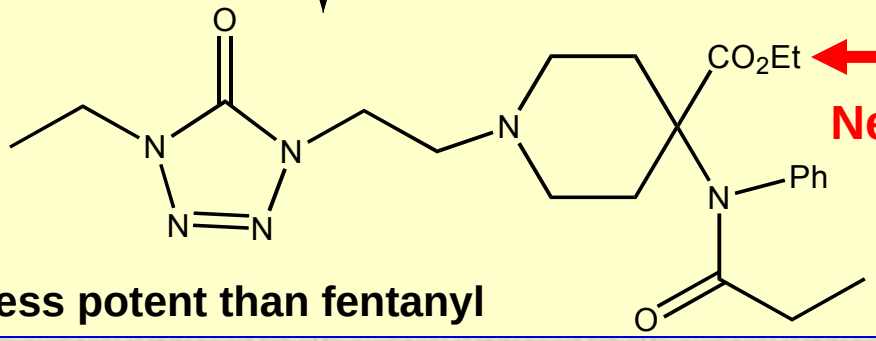
5-10X more potent than fentanyl



K_2CO_3



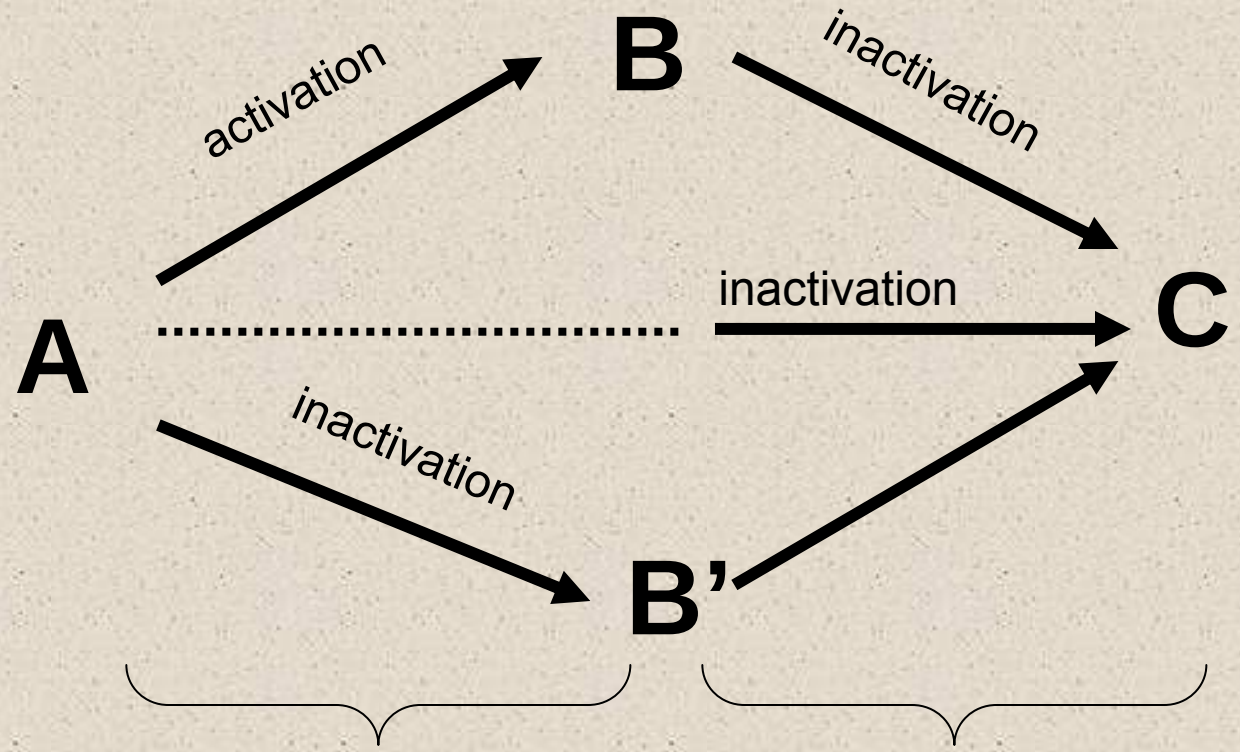
10,000 X more potent than morphine



Modify ester- New class of drugs?

Fast acting-less potent than fentanyl

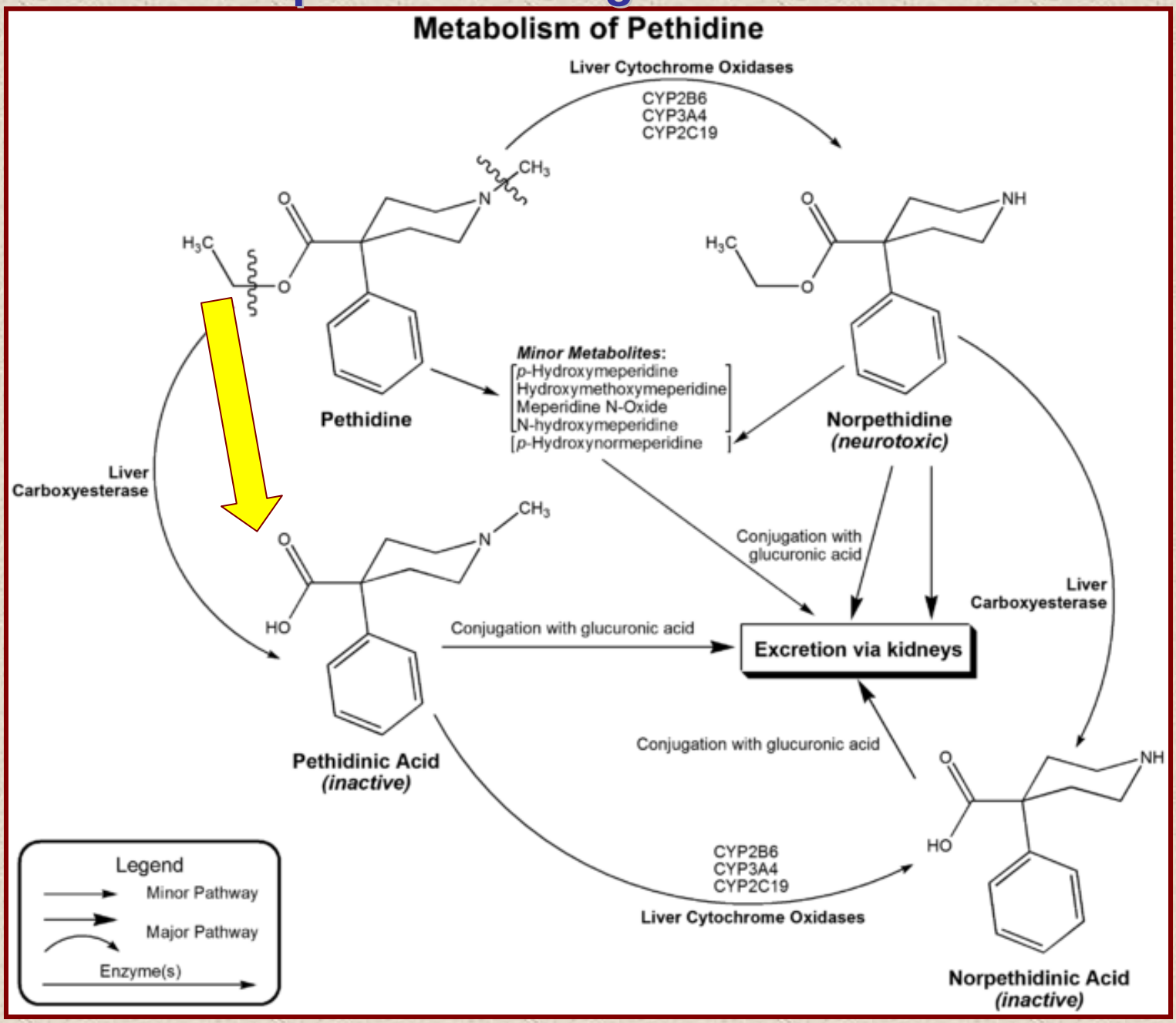
Organic compounds are transformed to molecules of increasing polarity, then excreted by the kidneys:

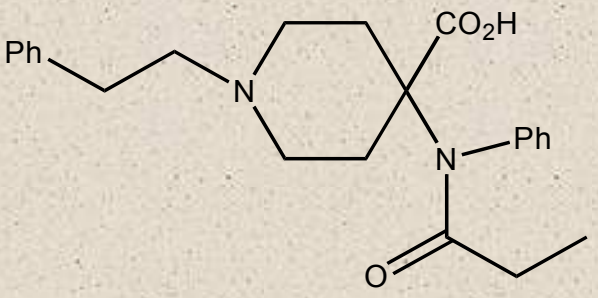


Phase I:
Oxidation-reduction
Hydrolysis
Demethylation

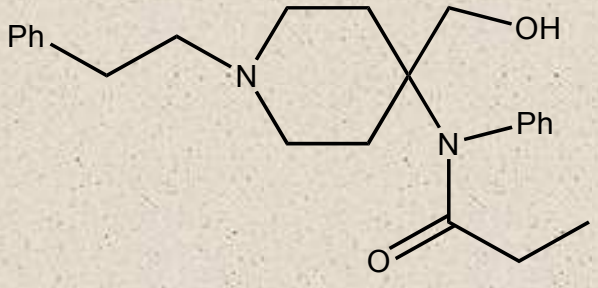
Phase II:
Synthesis (acylation, methylation etc.)
Conjugation-covalent bonding with carbohydrates, AA or sulfates

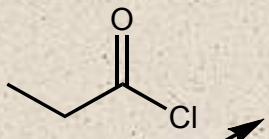
Metabolism of Piperidine Analgetics



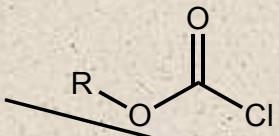


LAH

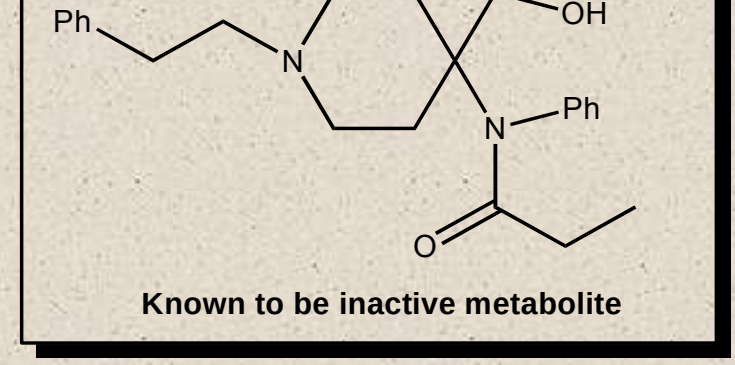




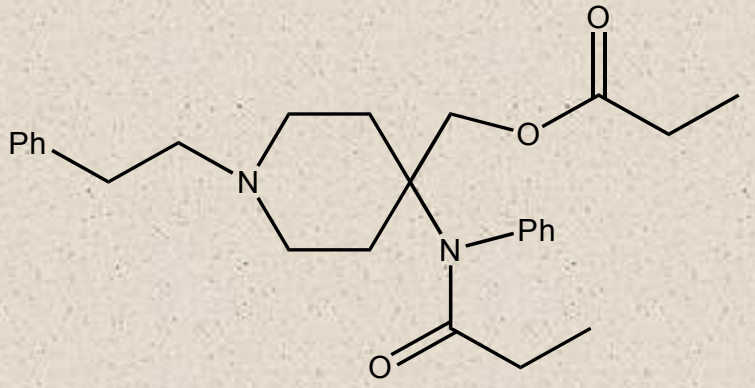
NEt_3

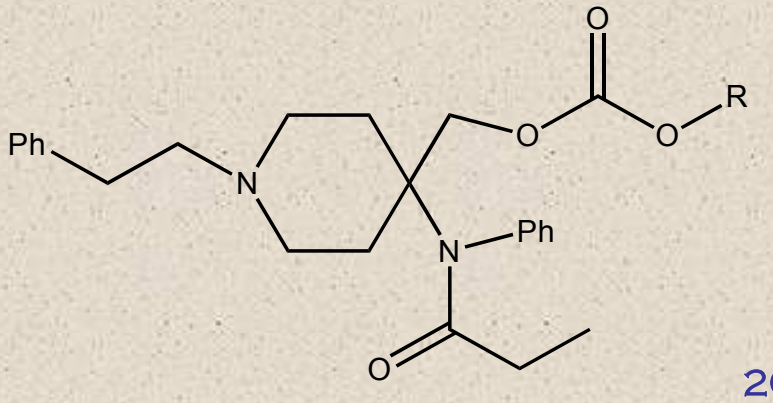


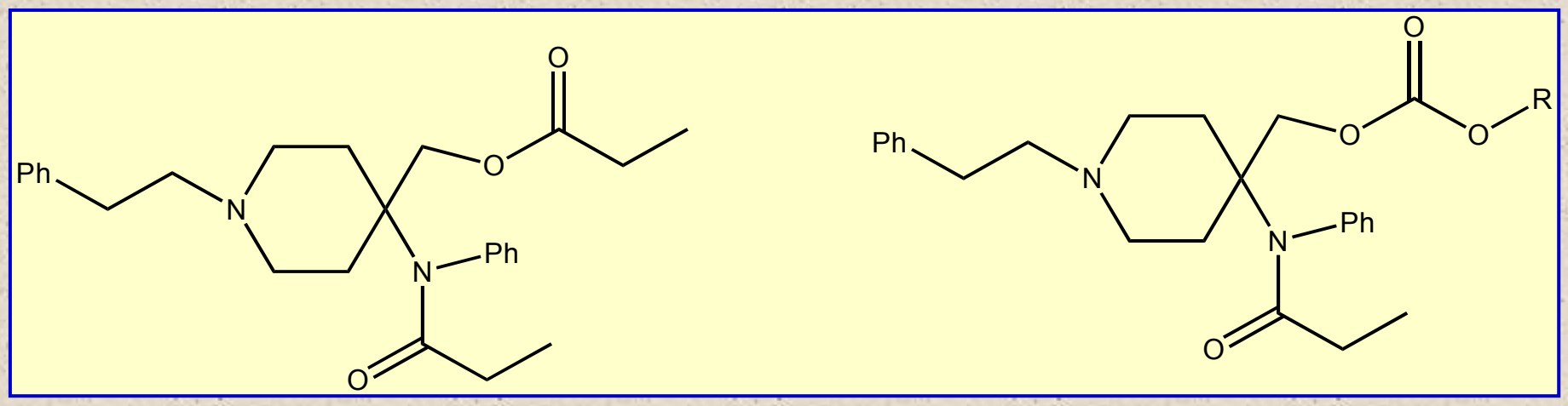
NEt_3



Known to be inactive metabolite

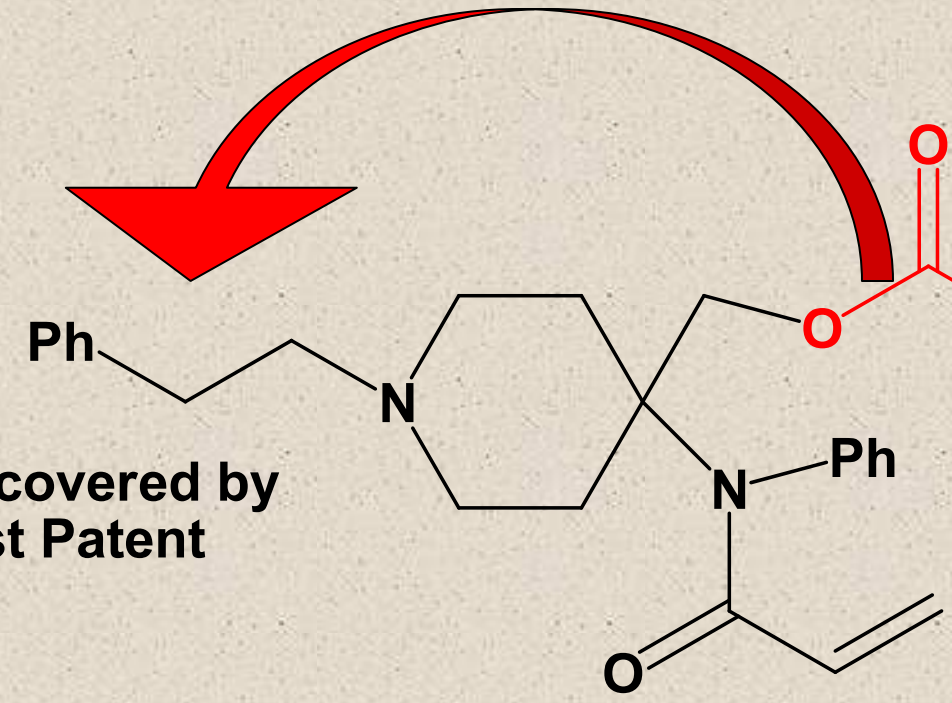






Pharmacological Profile:

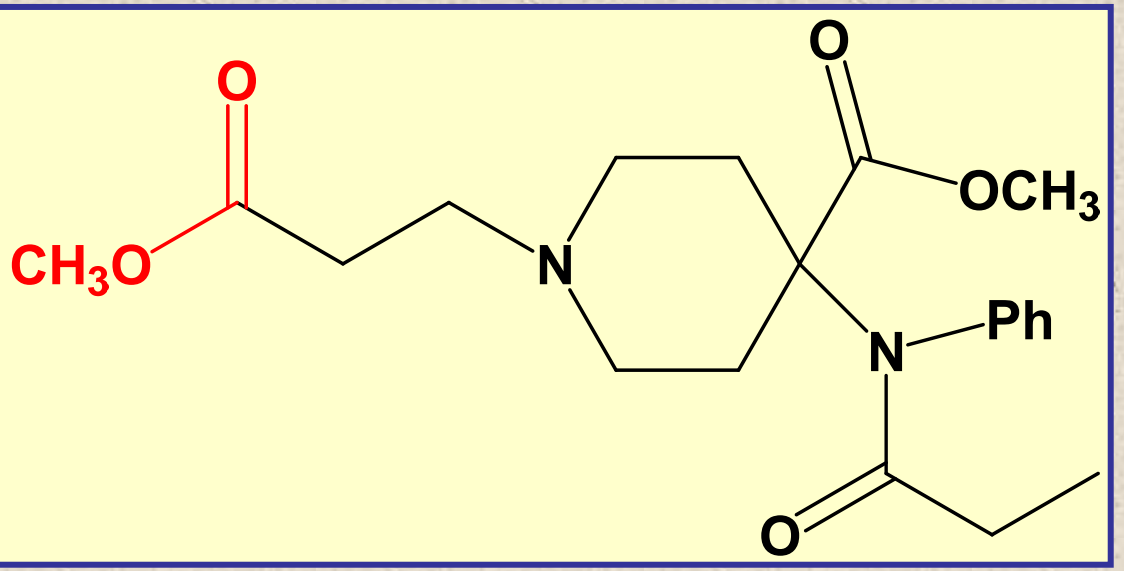
- MHP: ED_{50}=0.06 potent analgetic
- MHP: >15 min—long acting analgetic
- K_i = 3-9 (strength of μ receptor binding)
- Anesthesia—2-3 Minutes-short acting



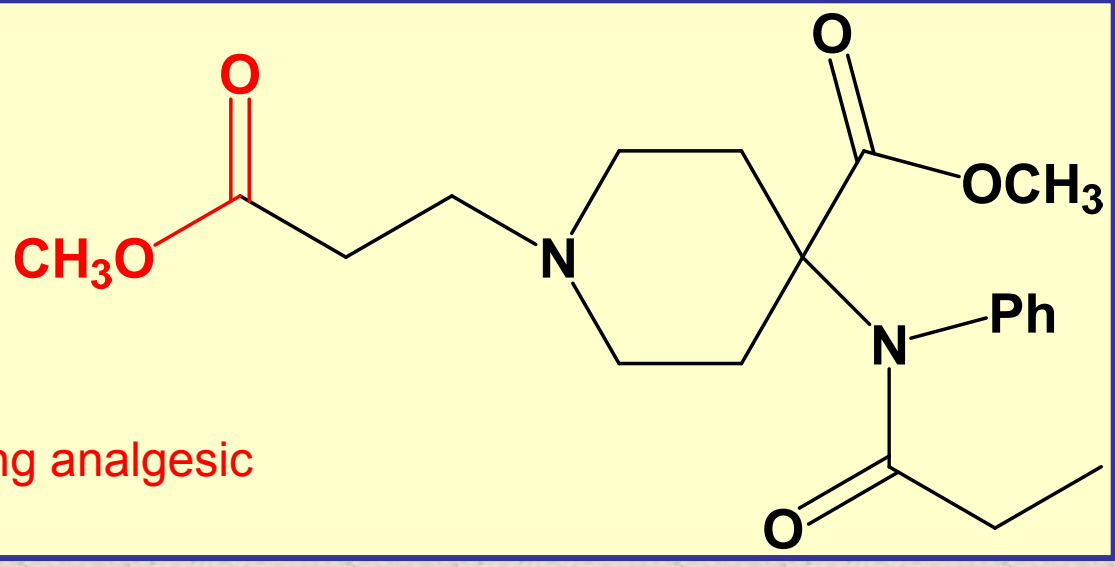
Esters & Carbonates

Already covered by Anaquest Patent

Remifentanil (Glaxo-Smith Kline & Abbott)



Remifentanil (Glaxo-Smith Kline & Abbott)



Ultra short acting analgesic

Remifentanil is a specific μ-receptor agonist.
It is potent & short acting- (1/2 life~4 min)

- a reduction in sympathetic nervous system tone,
- Slight respiratory depression and analgesia.
- dose-dependent decrease in heart rate arterial pressure
- respiratory rate and tidal volume near normal