Multiphore Model

Multiphore Model — drug molecule is composed of different parts

Pharmacophore — group of atoms responsible for binding to target (receptor, enzyme...)

Auxophore — rest of the molecule part we can modify

Metabophore — determines metabolic properties

Toxicophore — determines toxicologic properties

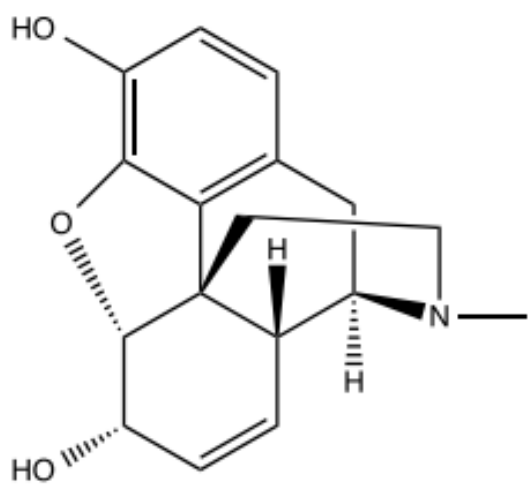
Morphine

isolated from opium poppies

opium = dried latex of seed pods

laudanum = 10% solution in alcohol

greater than 20 alkaloids including morphine + codeine



Morphine

☺ effective painkiller

☹ respiratory depression

dependence + tolerance

nausea

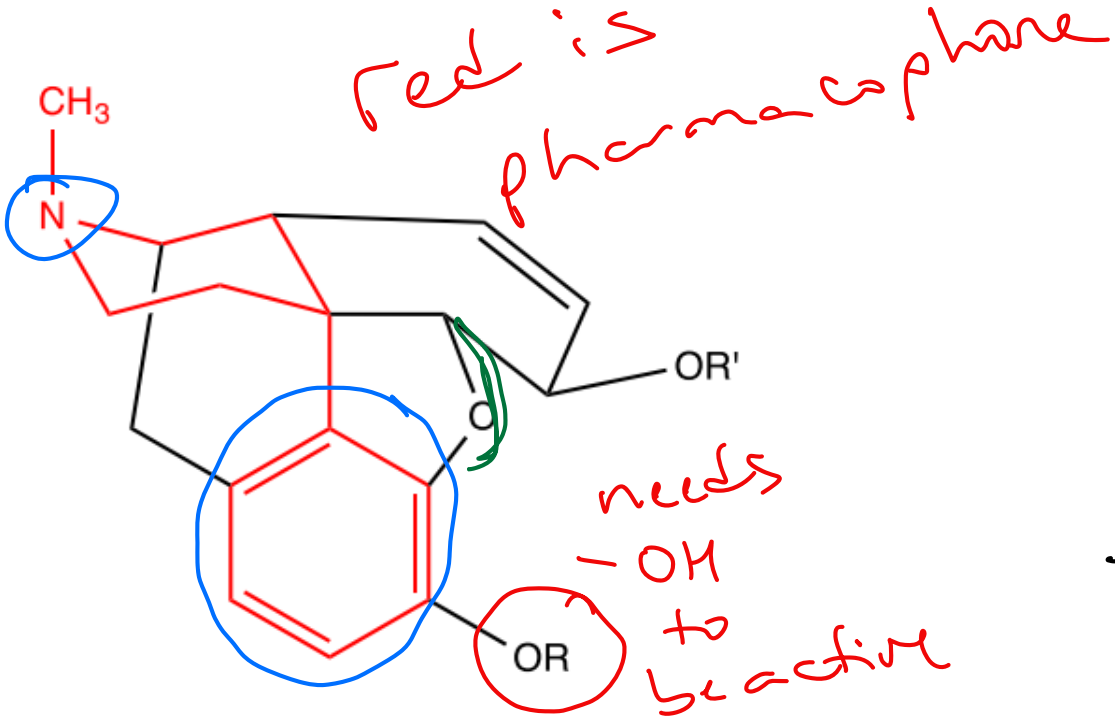
constipation

require increasing amts

withdrawal

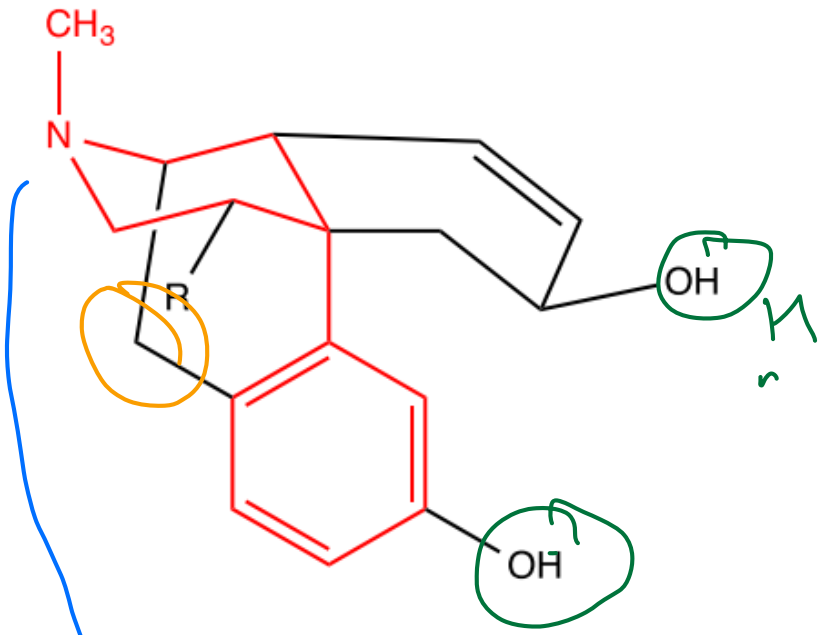
chills sweat

tremor



R	R'	
H	H	morphine 1
CH_3	H	codeine 0.2
$-\overset{O}{\overset{\|\|}{C}}CH_3$	$-\overset{O}{\overset{\|\|}{C}}CH_3$	heroin 2
$-\overset{O}{\overset{\|\|}{C}}CH_3$	$-H$	3-acetyl morphine
$-H$	$-\overset{O}{\overset{\|\|}{C}}CH_3$	6-acetyl

We can remove rings



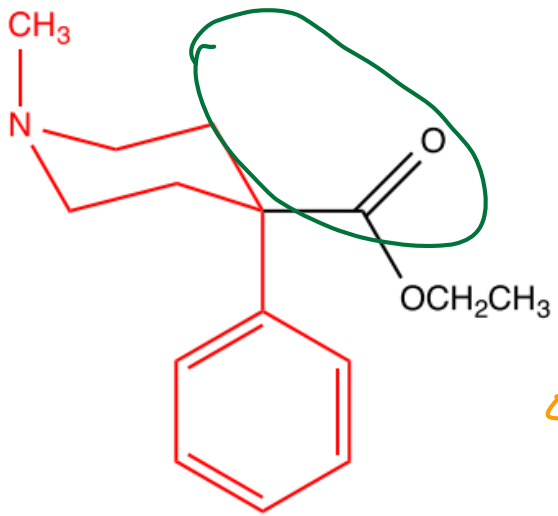
morphinans

= levorphanol

- 3-4x more analgesic than morphine
- still addictive

the N-phenylethyl derivative is ~20x more potent

Remove another ring



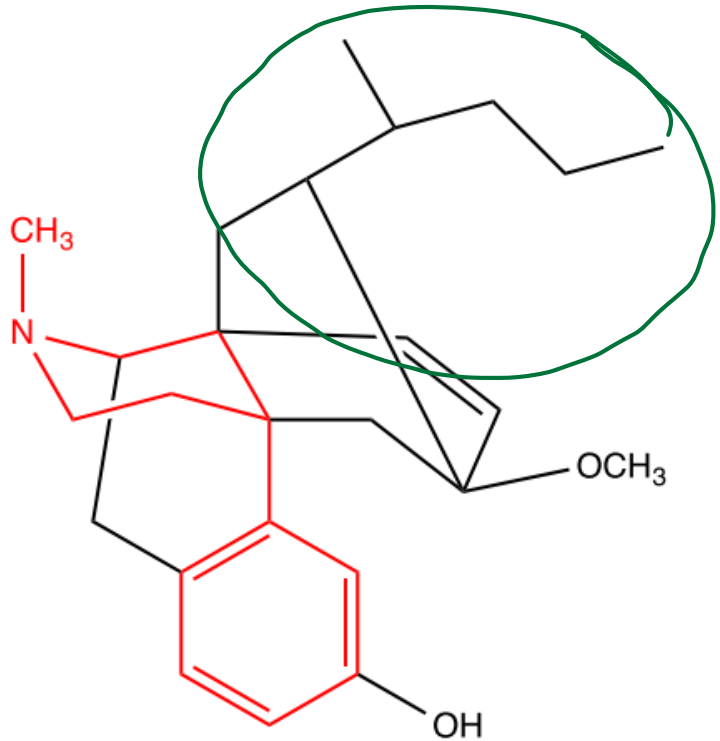
piperidine derivatives

meperidine (Demerol)

- rapid onset
- shorter duration of action
- 10-12% morphine

now it is too floppy

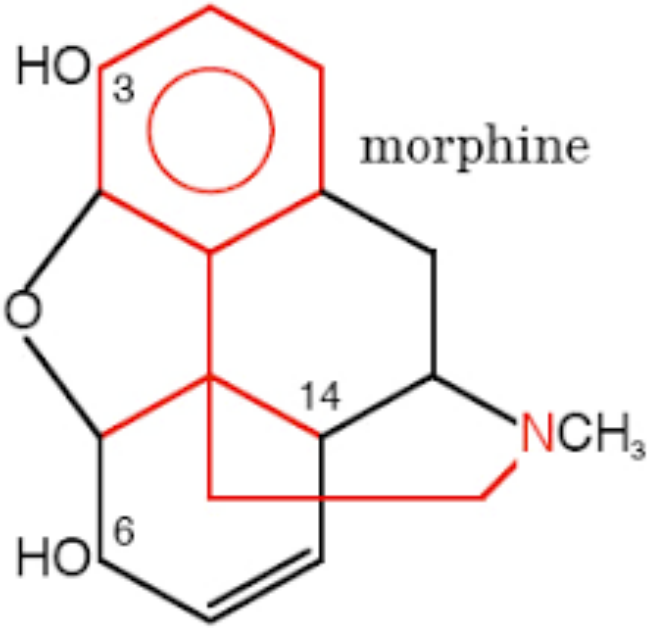
Can add rings

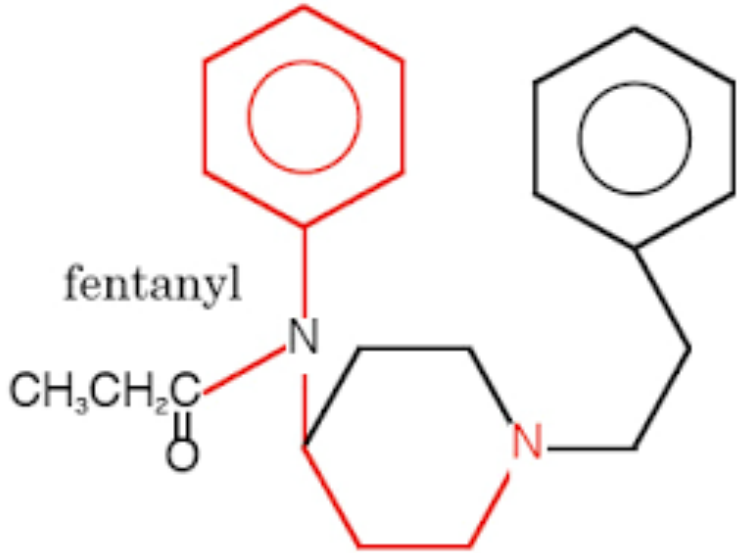


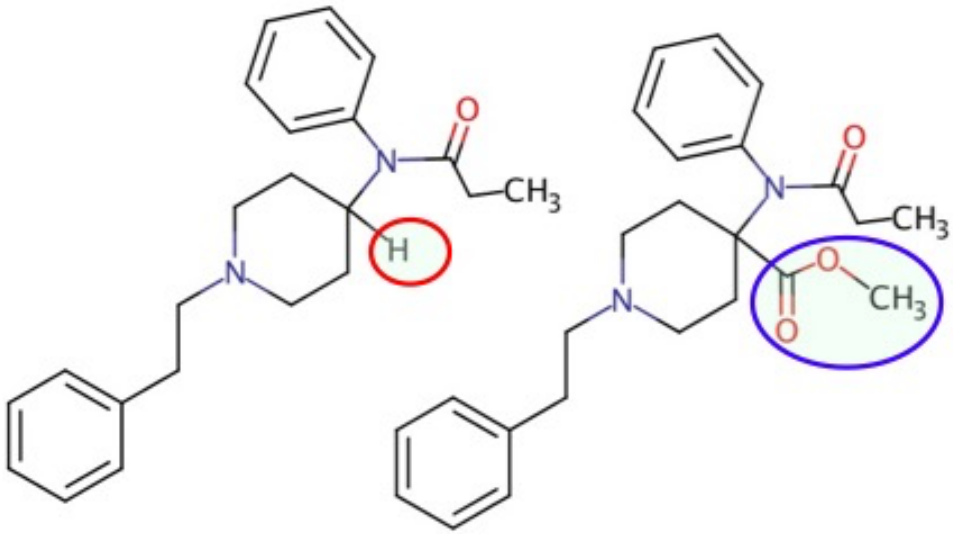
Immobilon
(for large animals)

Etorphine
- crosses BBB
300x faster than morphine
- 20x the affinity for receptor

3200 - 10,000 x more potent than morphine





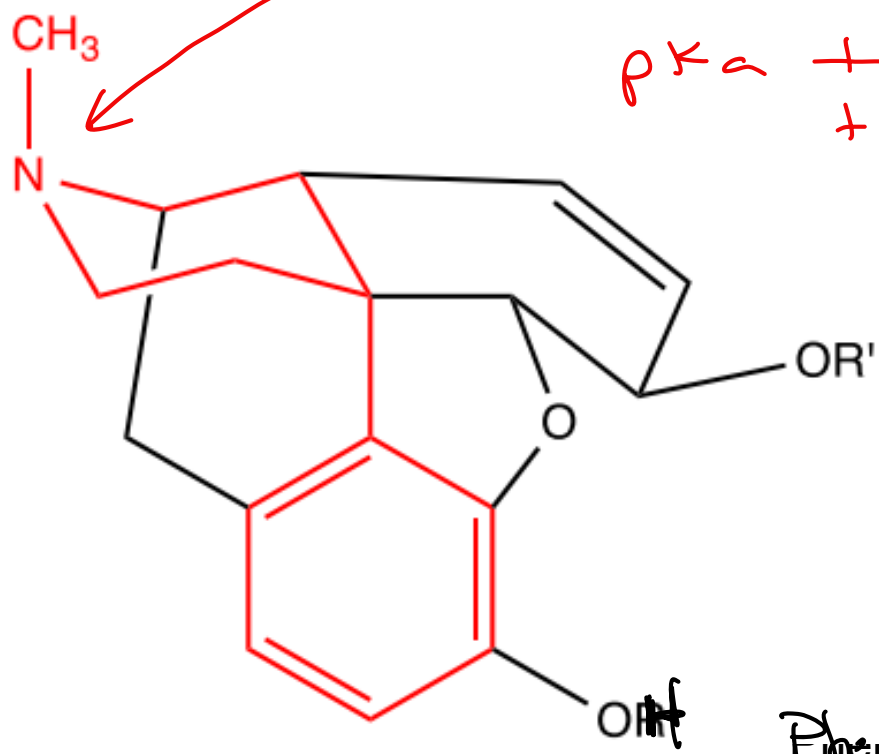


Fentanyl (50 X) **Carfentanyl (1,000 X)**

Summary

N-methyl group

3° amine N-H with a pKa to both assorb + then be charged



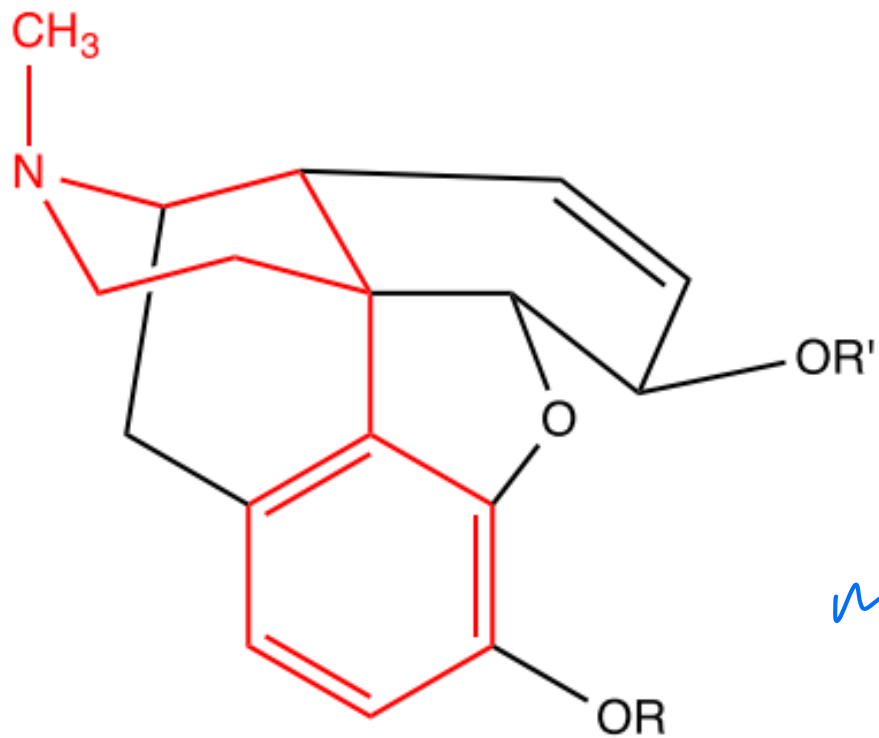
Phenolic -OH

Aromatic Ring

can't replace Lond. Disp. interactions

H-bonding activity ↓ if covered up

3 Point Pharmacophore — 3 interactions between drug + target



more interactions
→ better specificity
→ longer t½
→ usually more difficult to absorb

Neuroactive Drugs 2-4 pts

Non-neuroactive Drugs 3-6