



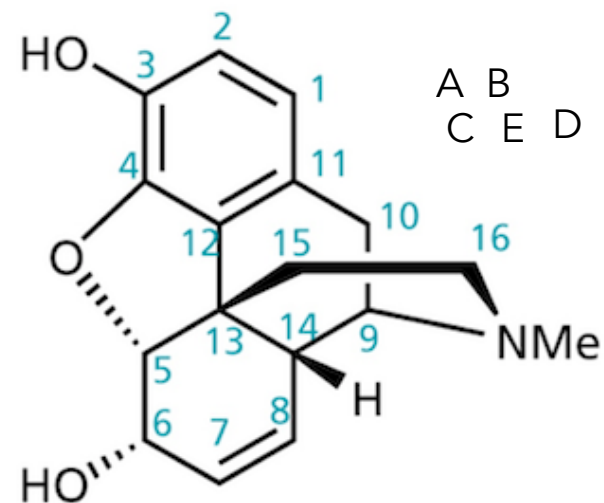
a. Foye's Principles of Medicinal Chemistry

Narcotic Analgesics

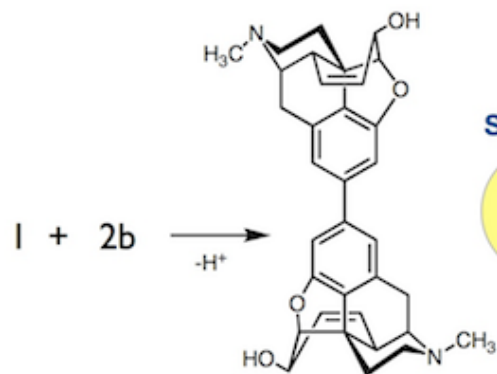
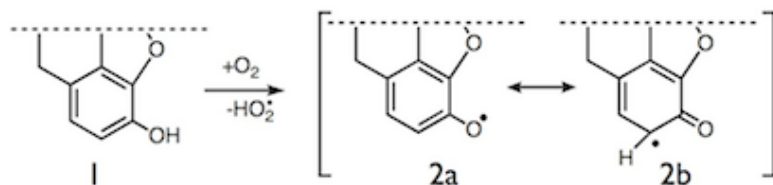
Dr. Alsyah Saad
FAR344/4
Mar 2013

b. Graham Patrick
An Introduction to Medicinal Chemistry

c. Toth, Eger & Troschütz;
Pharmaceutical Chemistry,
Vol. 2 : Drug Analysis, Ellis
Horwood, 1991

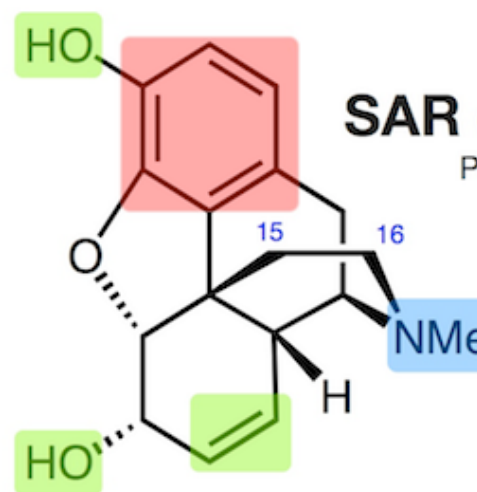


4,5-epoxy-17-methyl-7-morphinene-3,6a-diol



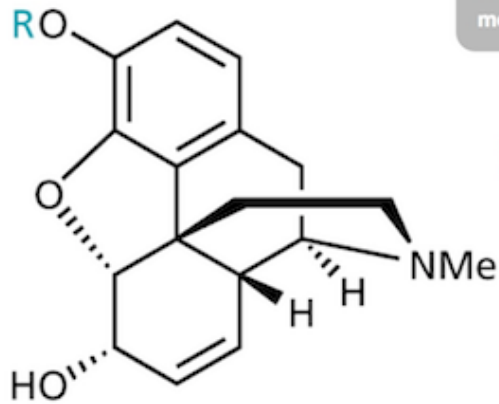
STABILITY OF MORPHINE

Oxidative decomposition of Morphine
must keep morphine solution or salt in closed containers!



SAR of Morphine

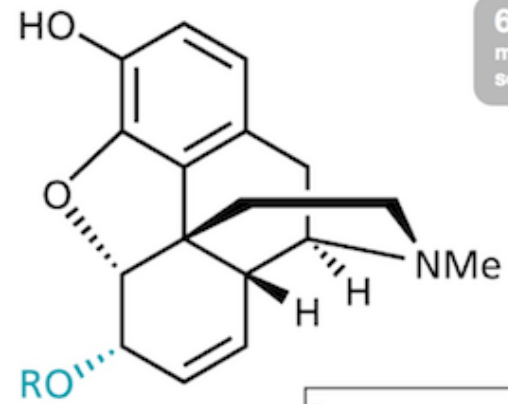
Peripheral modifications



Phenolic OH
modifications not tolerated

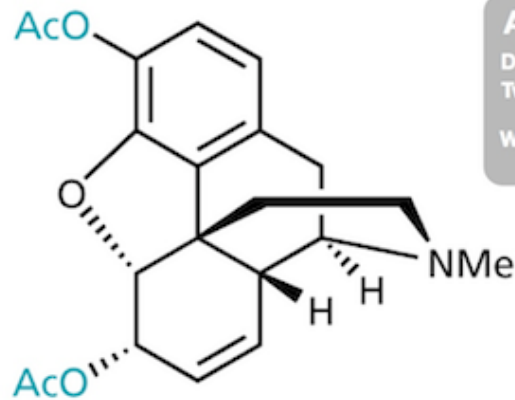
Codeine
used for treating moderate pain, cough and diarrhoea
prodrug of morphine
O-demethylation

R = Me Codeine
R = Et 3-Ethylmorphine
R = Acetyl 3-Acetylmorphine } Analgesic activity ↓



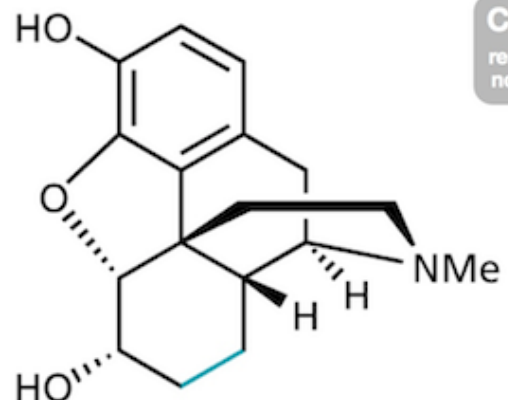
6-OH
modifications is not required
some enhance analgesia

R		Analgesia with respect to morphine
Me	Heterocodeine	5×
Et	6-Ethylmorphine	greater
Acetyl	6-Acetylmorphine	4×



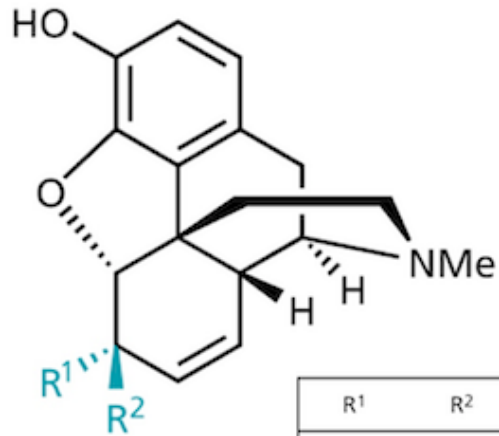
Acetylation at 3, 6-OH

Diamorphine = Heroin
Twice as potent as analgesia
Better at crossing BBB
Worse side effects, tolerance & dependence

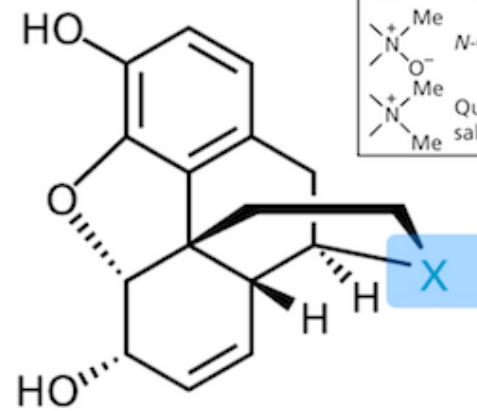


C=C at 7,8
removal is tolerated
not needed for analgesia

Dihydromorphine

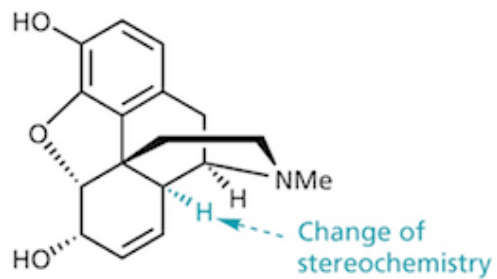


R^1	R^2	Analgesia with respect to morphine
H	OH (flipped)	Increased
H	H	or similar
	Ketone	



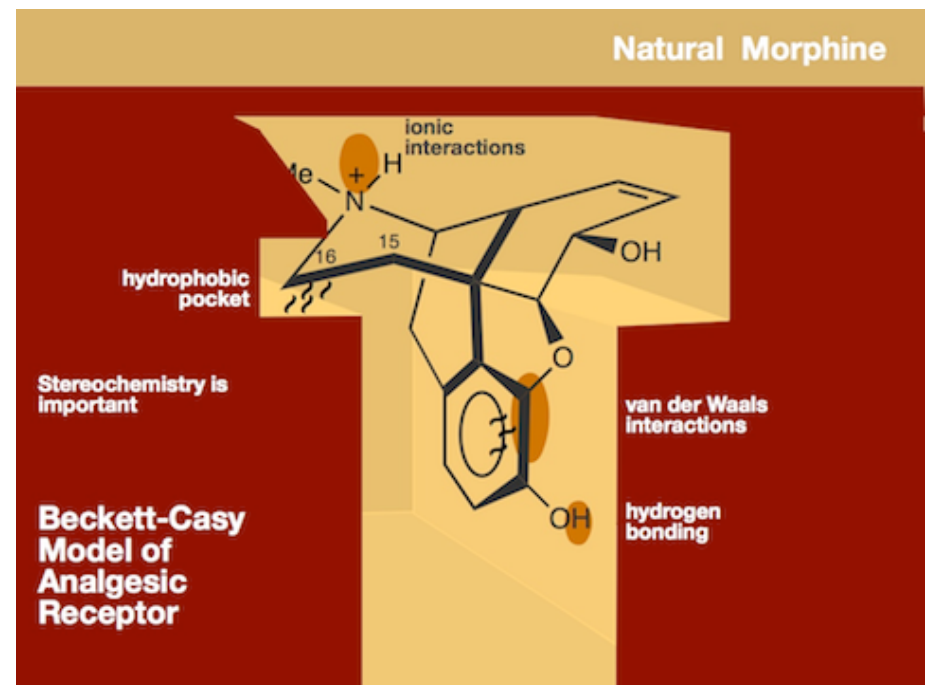
X	Analgesic activity with respect to morphine
NH	Normorphine 25%
$\begin{matrix} \text{Me} \\ \\ \text{N}^+ \\ \\ \text{O}^- \end{matrix}$	<i>N</i> -Oxide 0%
$\begin{matrix} \text{Me} \\ \\ \text{N}^+ \\ \\ \text{Me} \end{matrix}$	Quaternary salt 0%

Stereochemistry is important



Activity with respect to morphine = 10%

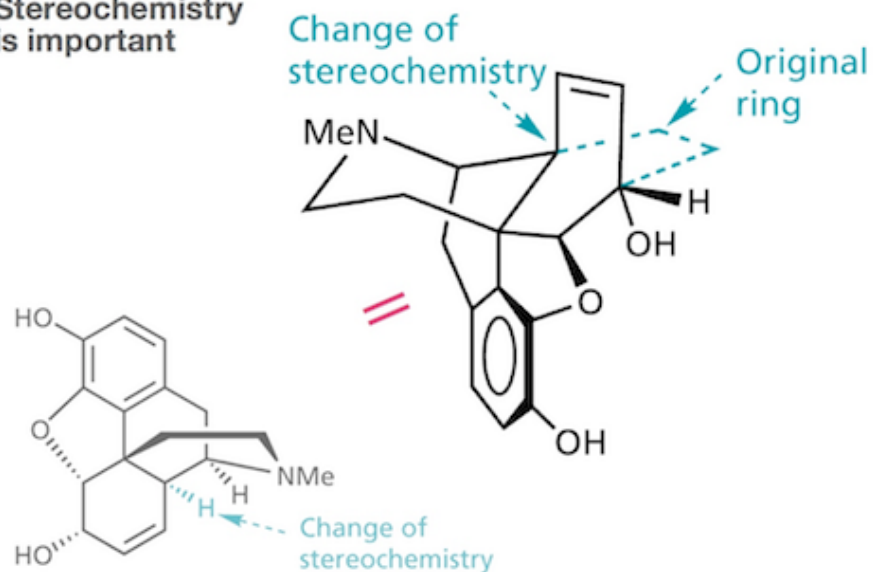
Natural Morphine



Stereochemistry is important

Beckett-Casy Model of Analgesic Receptor

Stereochemistry is important

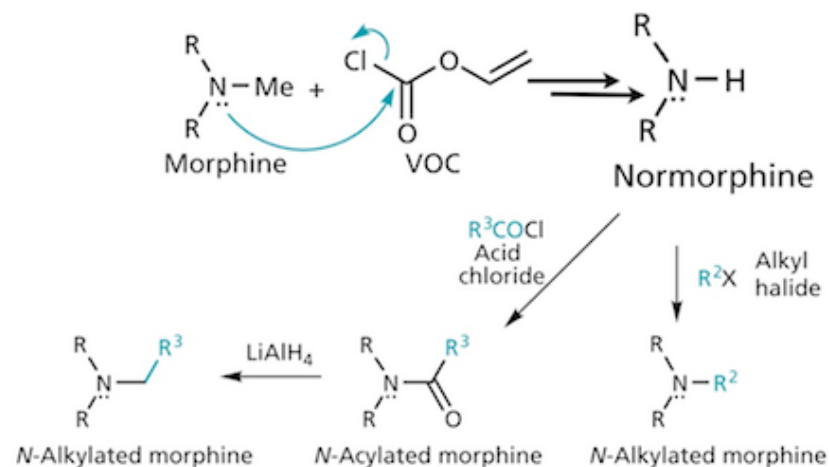


Analogues of Morphine

why bother?

Retains analgesic effects
Reduce/Eliminate Side effects

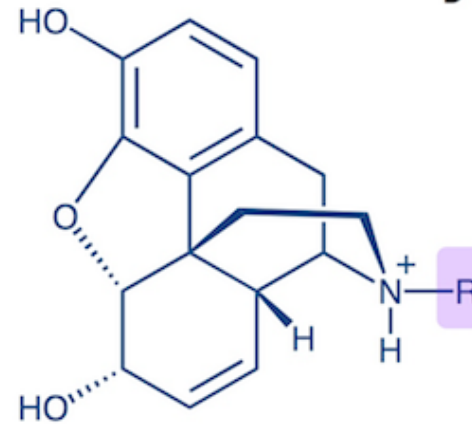
Analogues of Morphine



not much activity

except for
two key modifications...

Alkyl group (R)

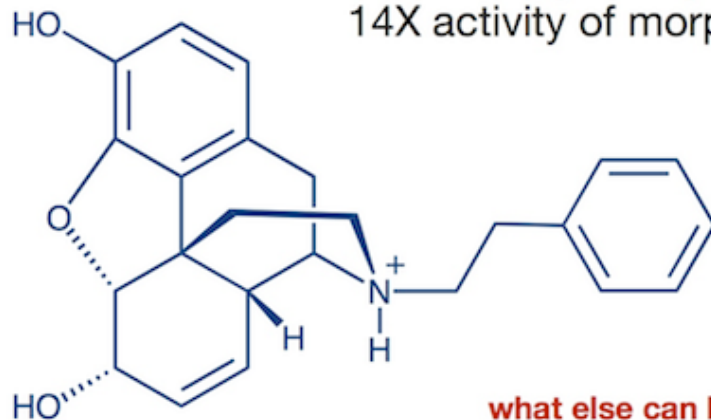


R	Activity
Me	Agonism
Et	
Pr	
Bu	Null
Pentyl	Agonism
Hexyl	
CH ₂ CH ₂ Ph	14X

ExtensionofStructure

N-Phenethylmorphine

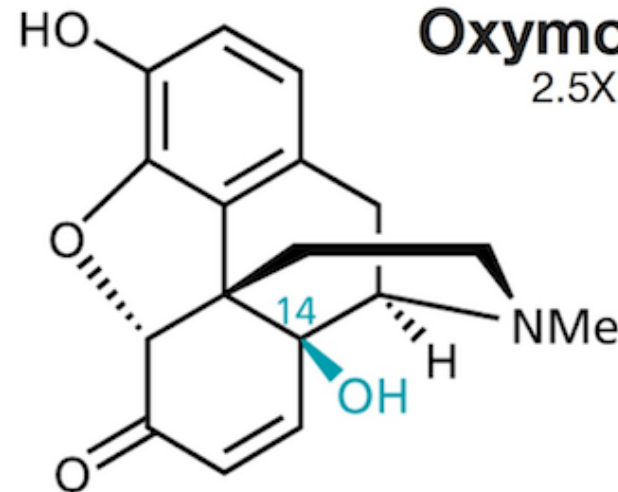
14X activity of morphine



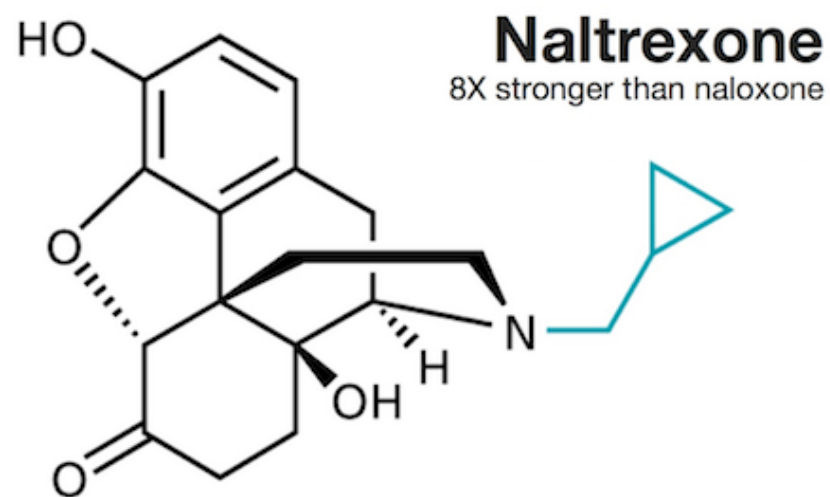
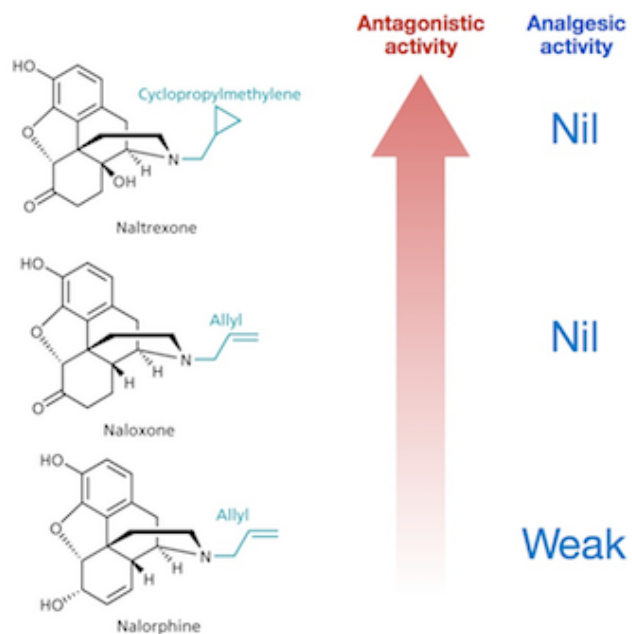
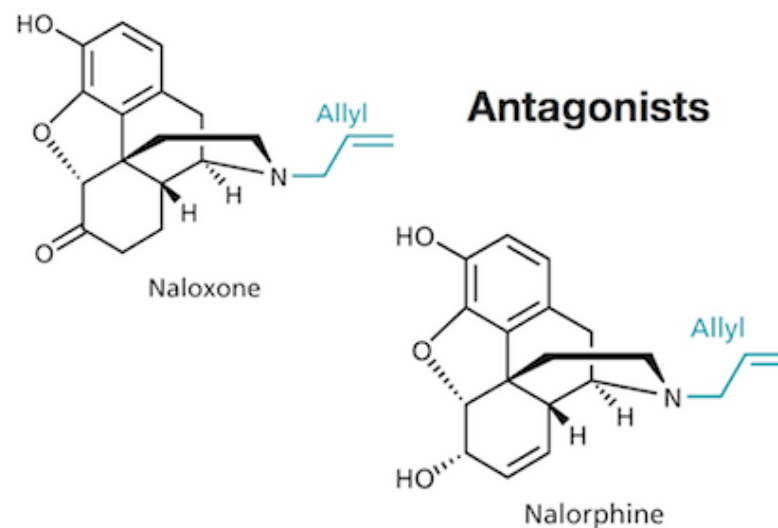
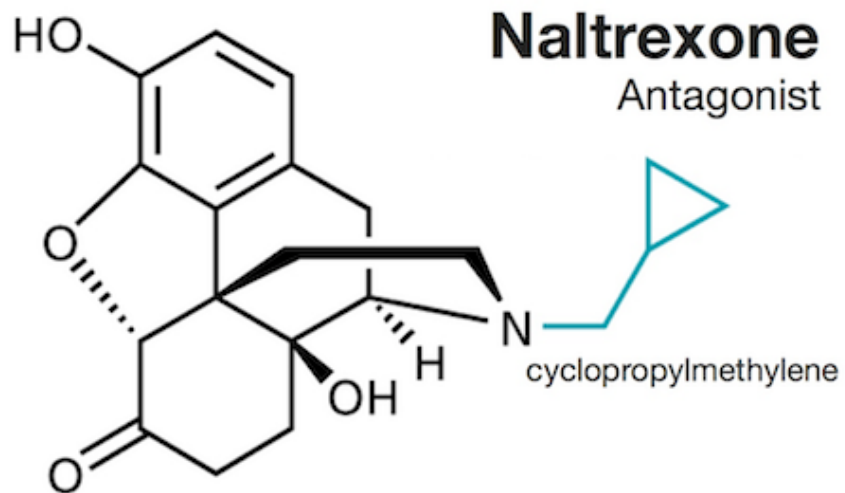
what else can happen
when R is extended?

Oxymorphone

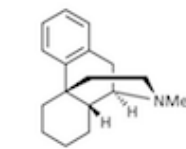
2.5X activity of
morphine



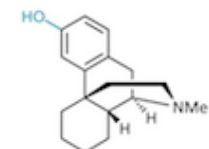
ExtensionofStructure



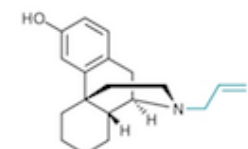
Analogues of Morphine



N-Methylmorphinan
($\frac{1}{6}$ activity of Morphine)



Levorphanol
(5x stronger than Morphine)

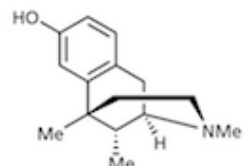


Levallorphan
Antagonist
(15x activity than Nalorphine)

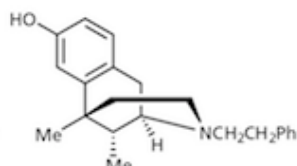
Easier to synthesise of Morphine

More potent and longer acting than Morphine
More toxic and higher dependence

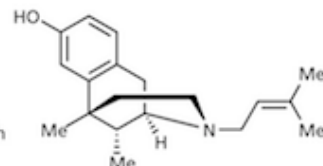
the morphinans



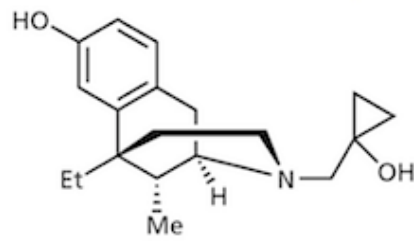
Metazocine
(= activity as Morphine)



Phenazocine
(4x stronger without dependence)



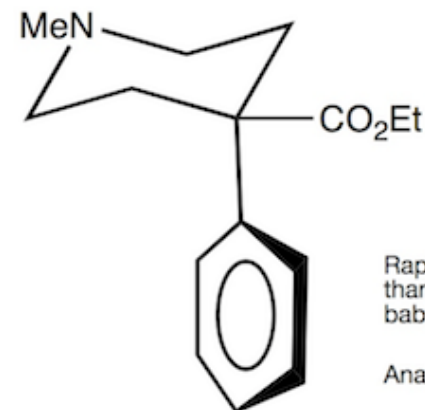
Pentazocine
($\frac{1}{3}$ activity of morphine;
short acting; low risk of addiction)



Bremazocine
(200x stronger; non-addictive;
doesn't cause respiratory depression)

Easier to synthesise of Morphine
Stronger analgesia than morphine
also display hallucinogenic properties

the benzomorphans



Pethidine

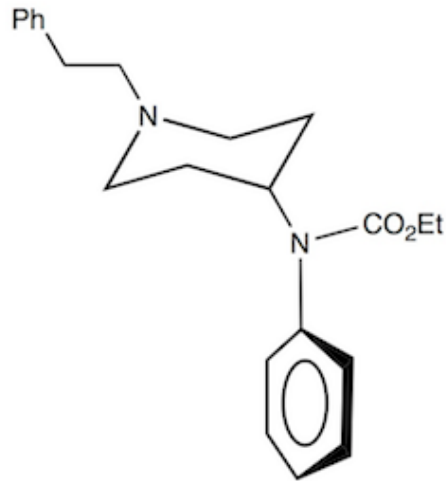
(Meperidine)

Weaker than Morphine
(only 20% activity retained)

Display same unwanted side effects of Morphine

Rapid onset and shorter acting than morphine - little effects on babies

Analgesia of choice for childbirth

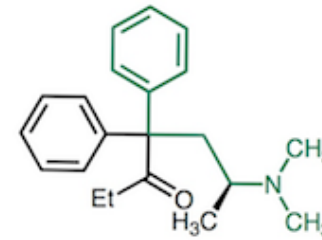


Fentanyl

100X stronger as sedative and analgesia

Lipophilic, able to cross BBB

Fatal overdose: Respiratory depression



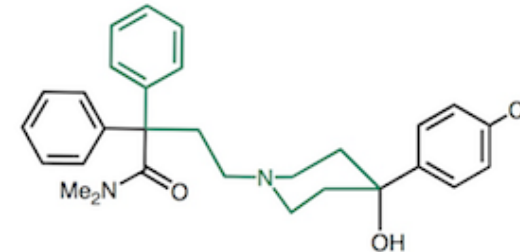
Methadone

(R)-isomer: 2x stronger than Morphine

(S)-isomer: Inactive

administered to addicts to wean their addiction

still addictive but withdrawal symptoms are much less severe



Loperamide

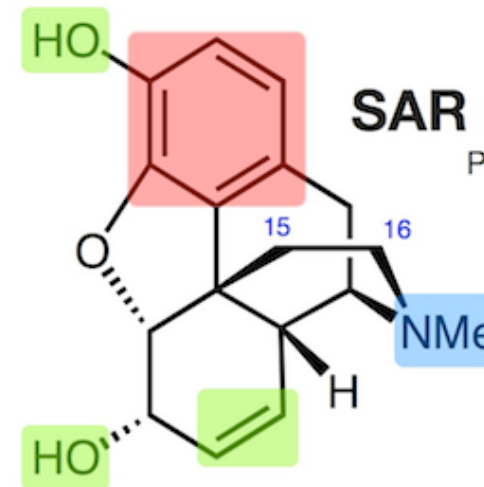
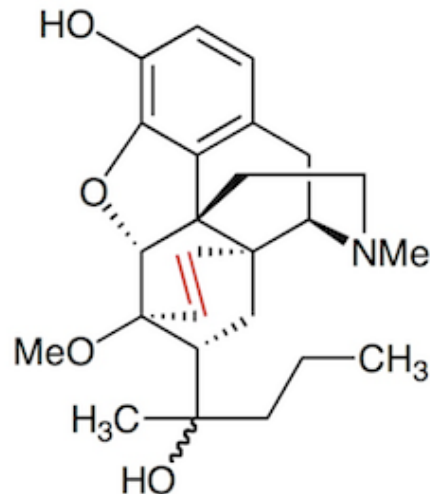
Imodium®

Etorphine

10,000 more potent than morphine

very lipophilic, crosses BBB much easier

requires little to sedate a big animals



SAR of Morphine

Peripheral modifications