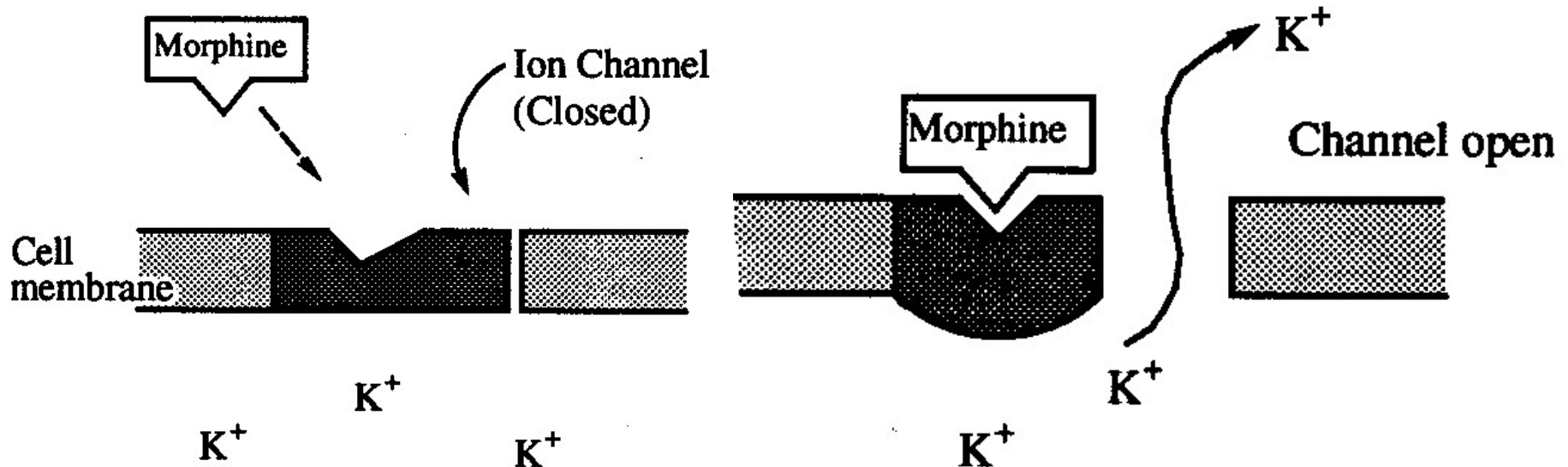


Analgesics – anodyns = opioid = „strong“ = „narcotic“  
analgesics

# Opioid receptors

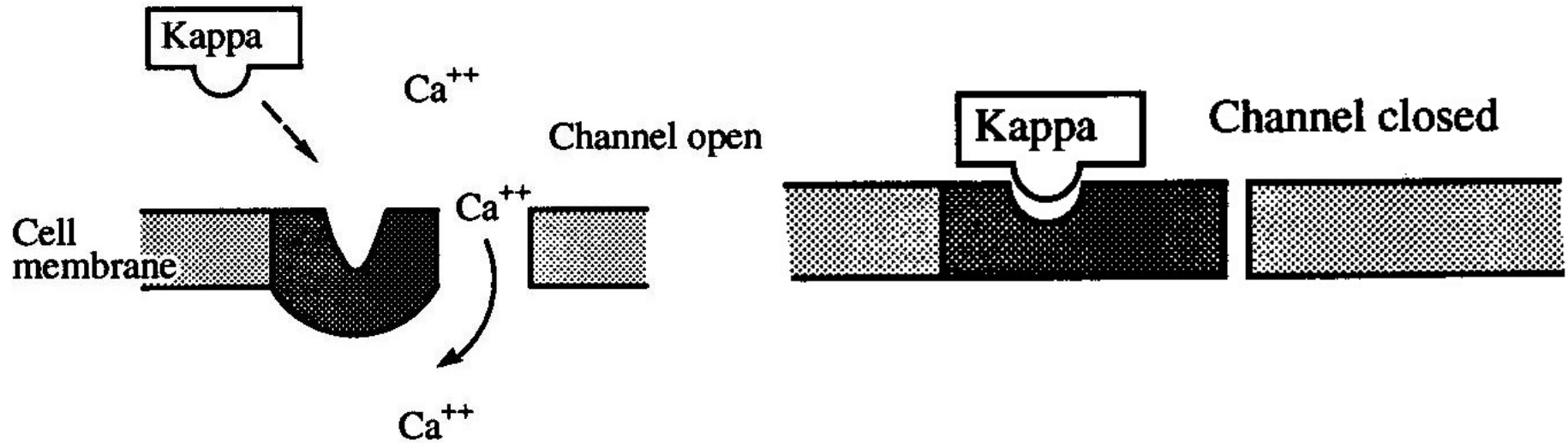
- 4 main types:  $\mu$ ,  $\kappa$ ,  $\delta$  and ORL-1
- ( $\sigma$  receptors currently not recognized as opioid)
- every type has several subtypes
- $\mu$  receptor activation leads to analgesic activity, breathing attenuation etc.
- $\kappa$  receptor activation: also analgesic activity, takes part in diuresis and neuronal activity regulation
- $\delta$  receptor activation: also analgesic activity, attenuation of breathing and peristalsis of GIT

# $\mu$ receptor



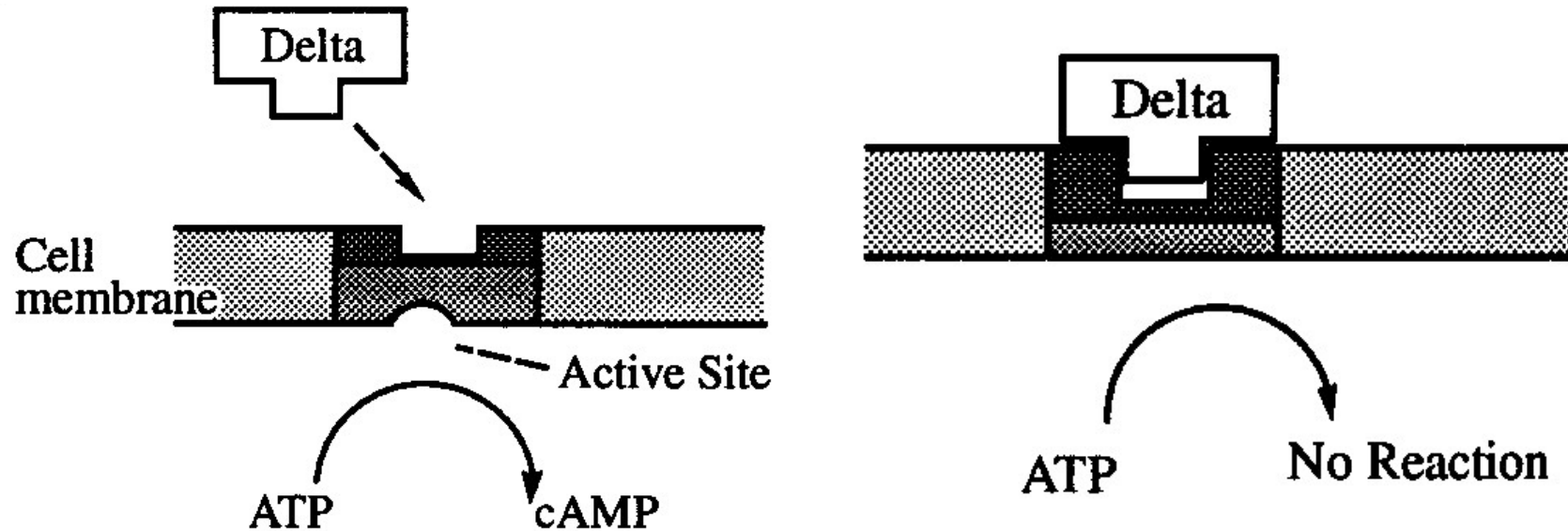
- opens ion channel in cell membrane
- $K^+$  can stream into the cell  $\Rightarrow$  decrease of neurone excitability
- also decreases input of  $Ca^{2+}$  into terminal nerve which decreases neurotransmitter release

# K receptor



- directly linked with Ca<sup>2+</sup> channel
- binding of an agonist to the receptor causes channel closing
- inhibition of all nociceptive signals
- activation leads to myosis, diuresis, analgesia and dysphoria

# $\delta$ Receptor



- not linked with any ion channel
- activation of the receptor probably leads to a change of adenylate cyclase geometry  $\Rightarrow$  active site closure
- activation leads to pain relief, attenuation of breathing and peristalsis of GIT

## ORL-1 receptor

- also „orphan“, discovered quite recently
- natural agonist nociceptine = orfanine (peptide)
- linked with many activities: memory, cardiovascular functions, kidneys
- probably influences dopamine concentrations in CNS and is involved in neurotransmitters release in anxious conditions

## Natural opioid receptors agonists – endogenous analgesics

- morphine receptors exist although it is not endogenous  $\Rightarrow$  body own opioids must exist!
- all endo-opioids are fragments of  $\beta$ -lipotropin, adenohipophyse hormone consisting of 91 amino acid rests which has no opioid effects

**Enkephalins** – binding preferably to  $\delta$ -receptors

Met-enkephalin

**H-Tyr-Gly-Gly-Phe-Met-OH**

Leu-enkephalin

**H-Tyr-Gly-Gly-Phe-Leu-OH**

- pentapeptide, all activities of morphine, occurs in all animals including man**

**Endorphins** (= „endo-morphines“) -

$\alpha$ : 16 AA

$\beta$ : 31 AA – after *i.v.* application has morphine effects

in CNS

$\chi$ : 17 AA

- $\beta$ -lipotropin is not direct precursor of opioid peptides; more precursor peptides exist:

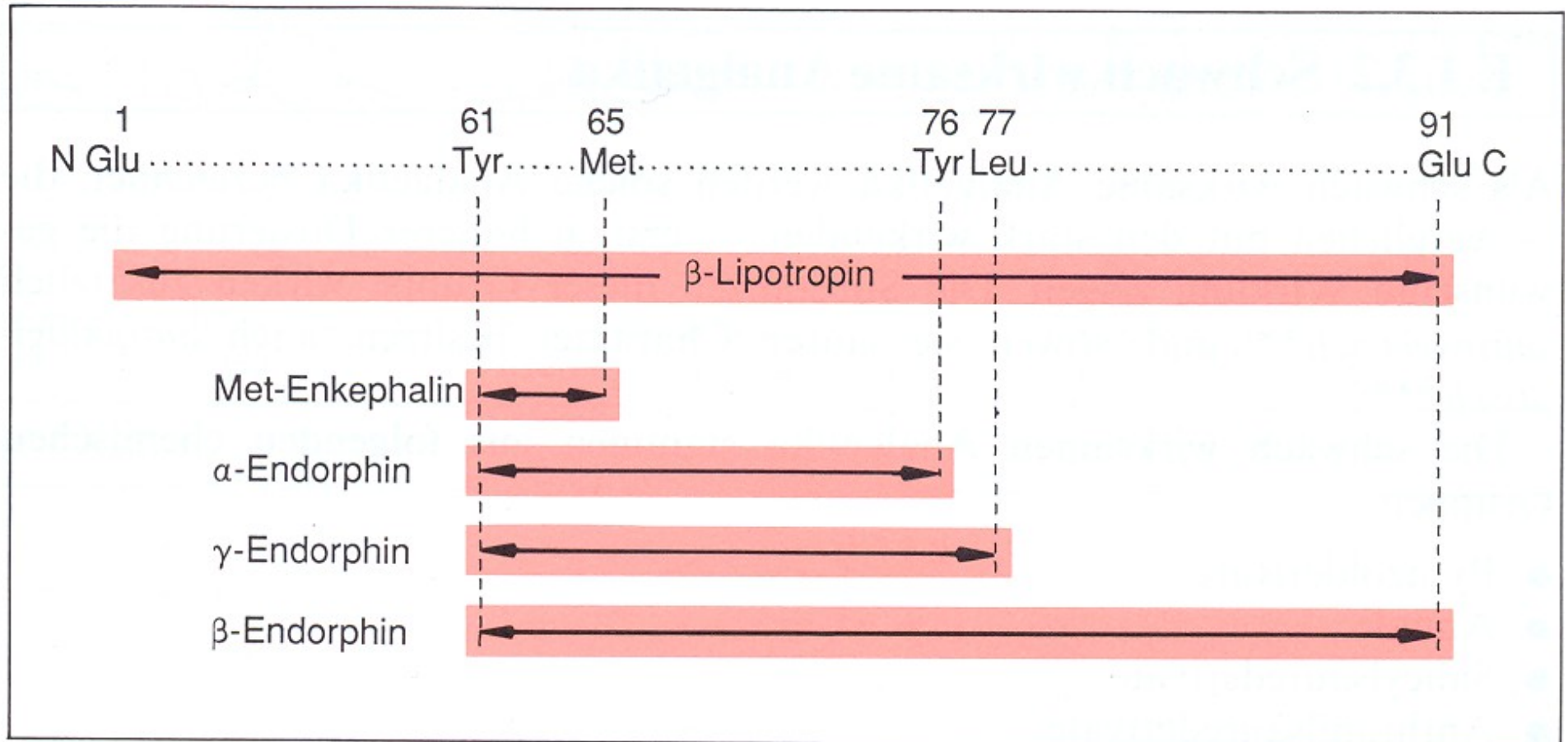
preproenkephalin A  $\Rightarrow$  enkephalins

preproopiomelanocortin  $\Rightarrow$  endorphins

preproenkephalin B  $\Rightarrow$  dynorphins

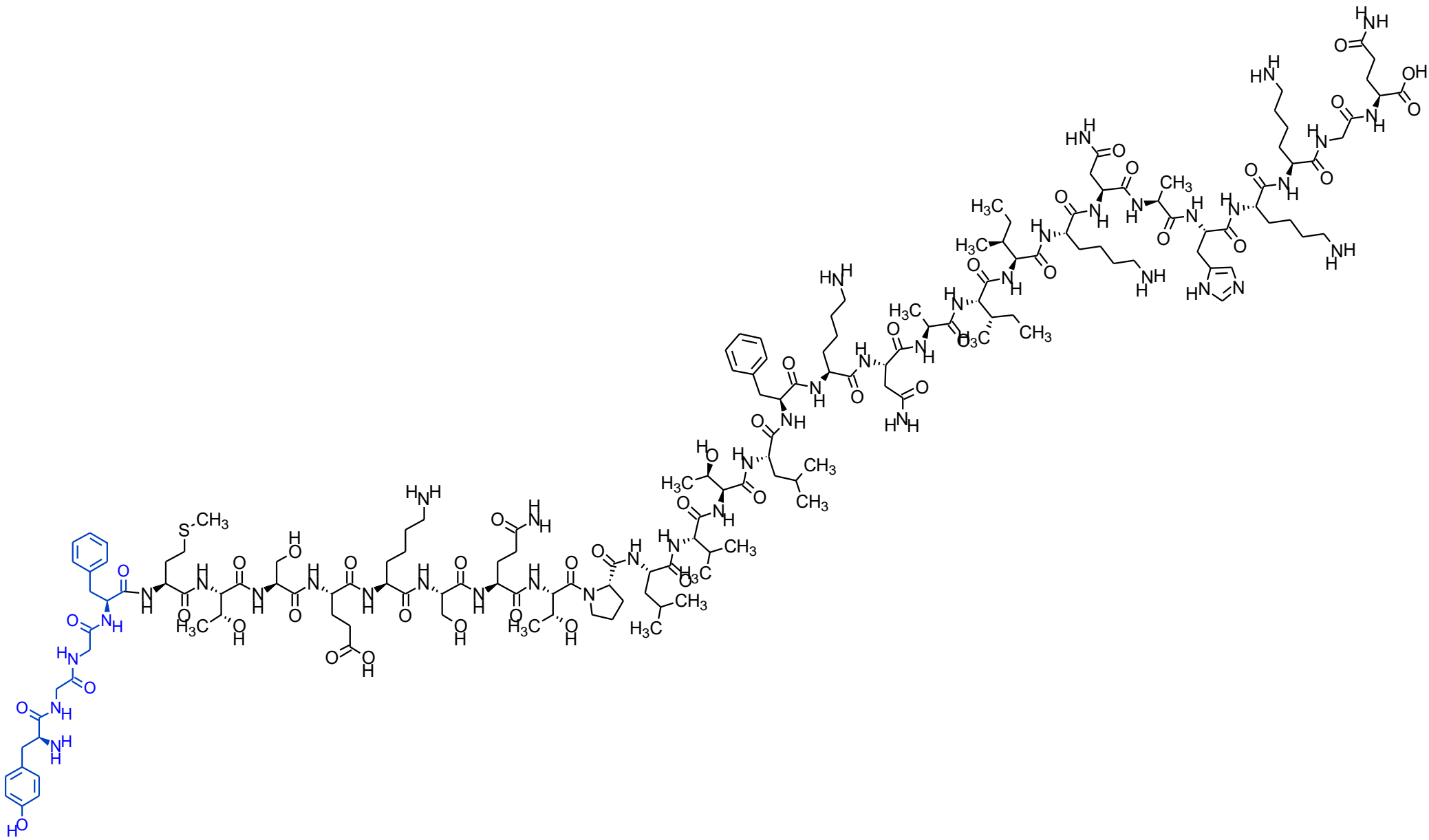
Dynorphins – peptides from 8 -32 AA, analgesic effect, neurotransmitters in CNS, functions not completely clear

# Endorphines and encephalins as parts of $\beta$ -lipotropine sequence

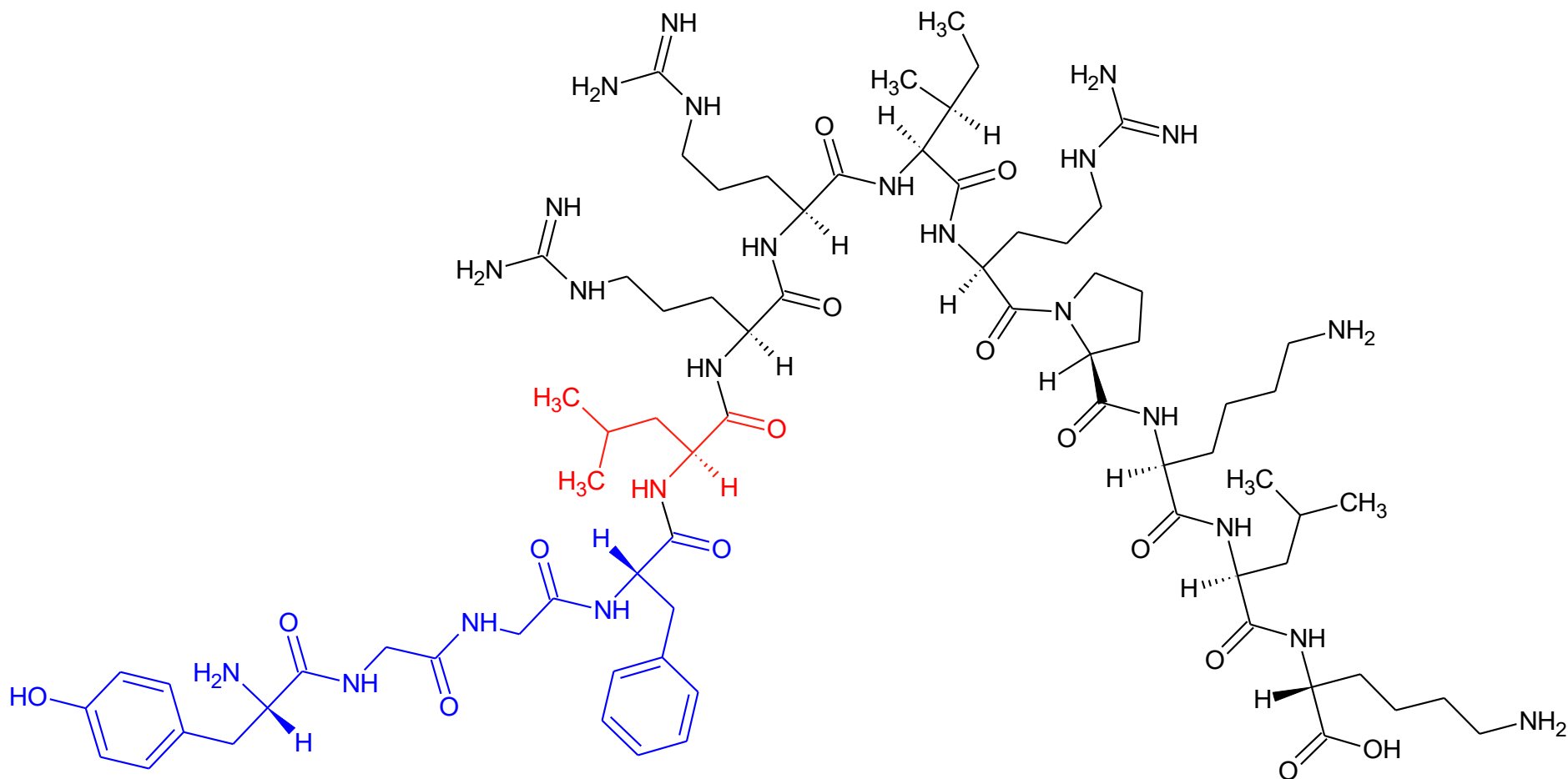




# Primary structure of $\beta$ -endorphine



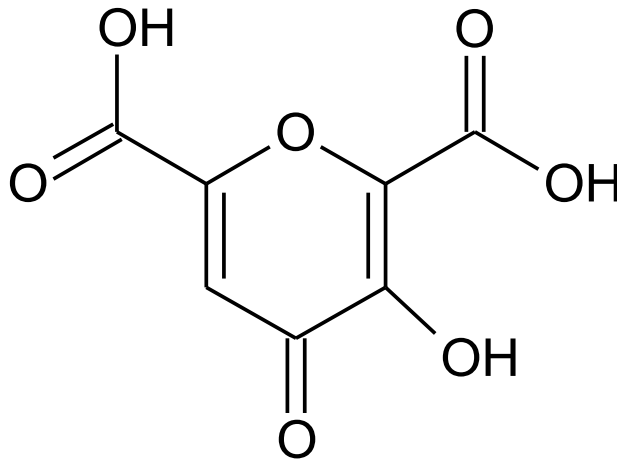
Dynorphine A sequence (1 - 18)  
**H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-**  
**5**  
**Arg-Pro- Lys-Leu-Lys-Trp-Asp-Asn-Gln-OH**  
**10 15**



Primary structure of dynorphine A (1 – 13) - swine

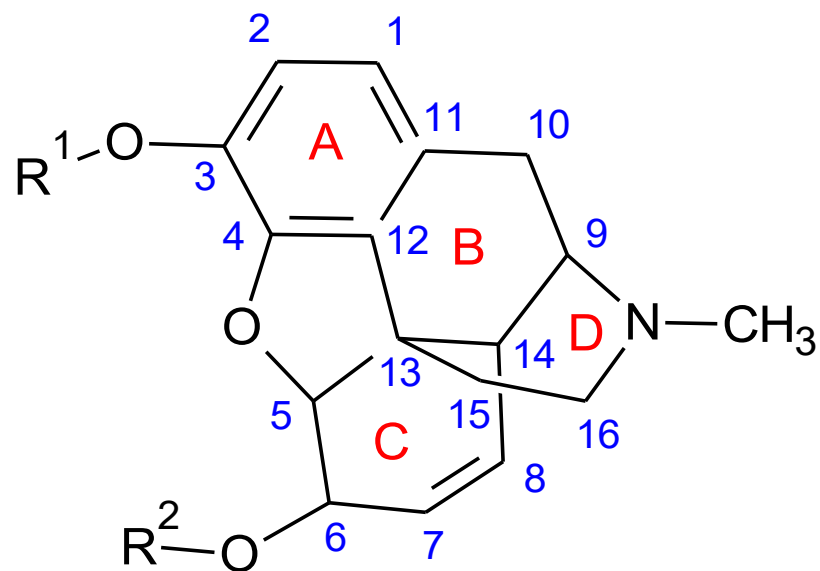
## Opium

- dry milky juice (latex) from immature poppy heads (*Papaver somniferum*)
- known from Assyrian manuscripts from 7<sup>th</sup> century b. C.
- contains 20 – 25 % alkaloids: morphine 3 – 23 %, narcotine 2 – 12 %, codeine 0.3 – 3 %, papaverine 0.8 – 1.2 %; in sum up about 40 various alkaloids
- morphine the most important
- alkaloids in form of salts with carboxylic acids; meconic acid typical
- beaten-out empty dry poppy heads are alternative resource of opium alkaloids (CZ, SK)



meconic acid

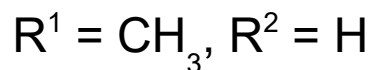
## Morphine and its simple derivatives



**morphine**

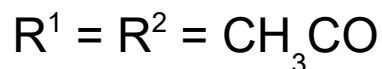
MSI<sup>®</sup>, MST<sup>®</sup>, Sevredol<sup>®</sup> ...

- isolated by Friedrich Wilhelm Sertürner, pharmacist in Paderborn, from opium in 1806
- structure elucidation: 1925 Robinson and Gunland proposed structural formula, 1952 Gates and Tschudi confirmed structure including stereochemistry by means of total synthesis
- basic anodyne isolated from opium or beaten-out empty dry poppy heads



**codein**

- basic antitussive
- semi-synthetic; prepared from morphine by selective methylation of phenolic group
- potencuje účinek slabých analgetik potentiates effect of weak analgesics
- abot 10 % methabolized to morphine

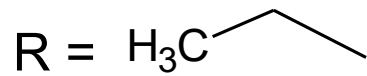
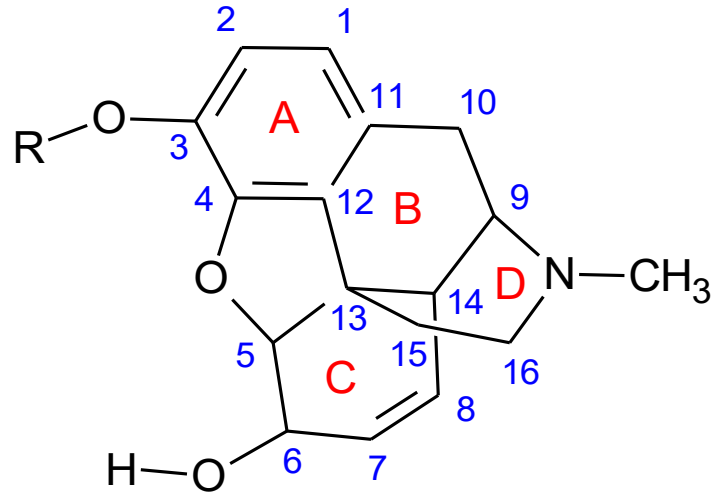


**diamorphine**

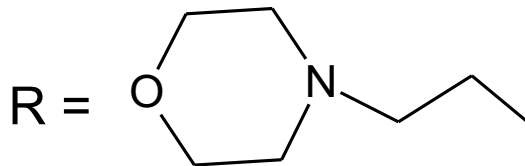
syn. heroine

- 2x more effective than morphine, better penetrates into CNS
- misused as an illegal drug of abuse

# Morphine and its simple derivatives: further ethers used as antitussives



**ethylmorphine**  
Diolan®

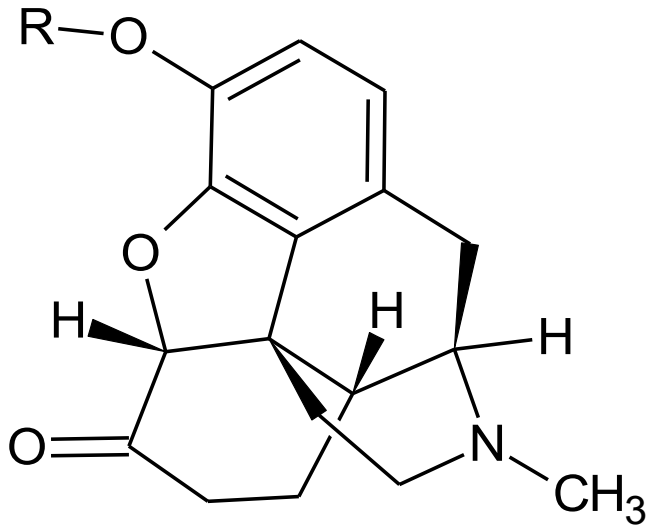


**pholcodine**  
Neocodin®

## Effects of opioid analgesics

- analgesic
- antidiarrhoic ( $\sigma$  -,  $\delta$  -receptors in gut)
- antitussive – from attenuation of cough reflexion to expiratory centre inhibition
- euphoriant
- physical addiction – very slowly formed during relieving of strong pain

## Semi-synthetic morphine and codeine derivatives



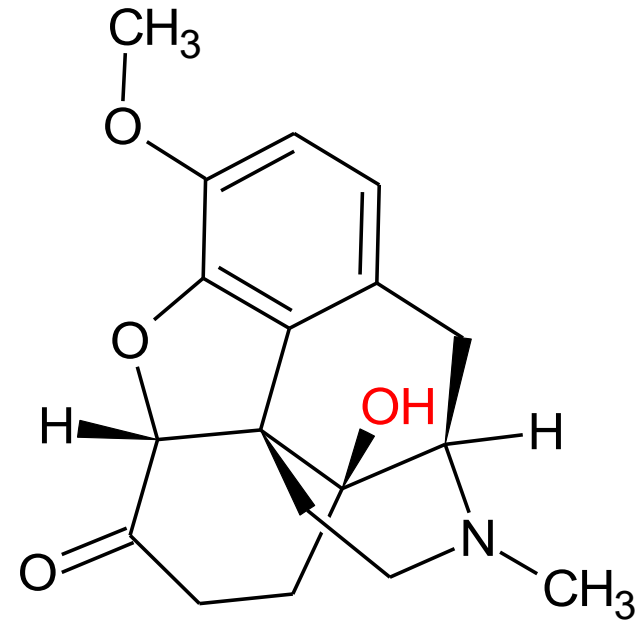
R = H      **hydromorphone**

•10x more active than morphine

Jurnista<sup>®</sup>, Palladone<sup>®</sup> cps. ...

R = CH<sub>3</sub>      **hydrocodone**

•more effective antitussive than codeine



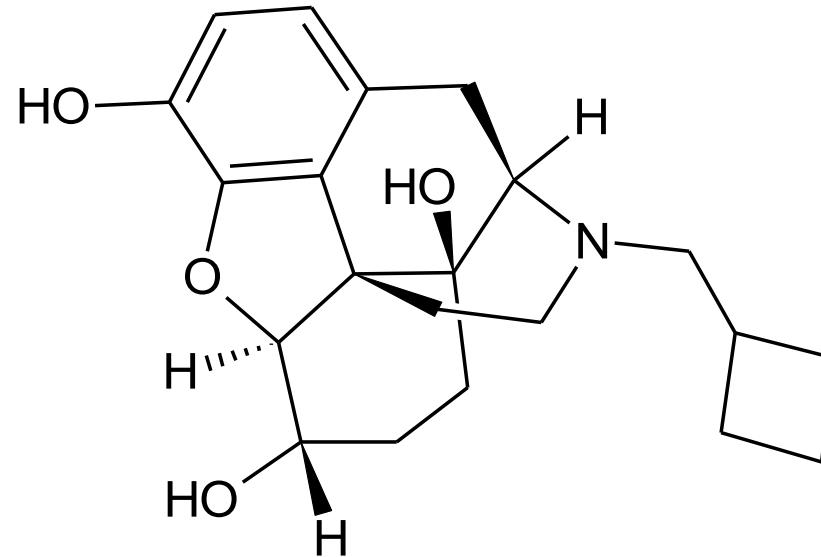
**oxycodone**

•2x less active analgesic than morphine; faster onset of action

•antitussive

Oxycodon (*firm*)<sup>®</sup> tbl.:

## Semi-synthetic morphine and codeine derivatives



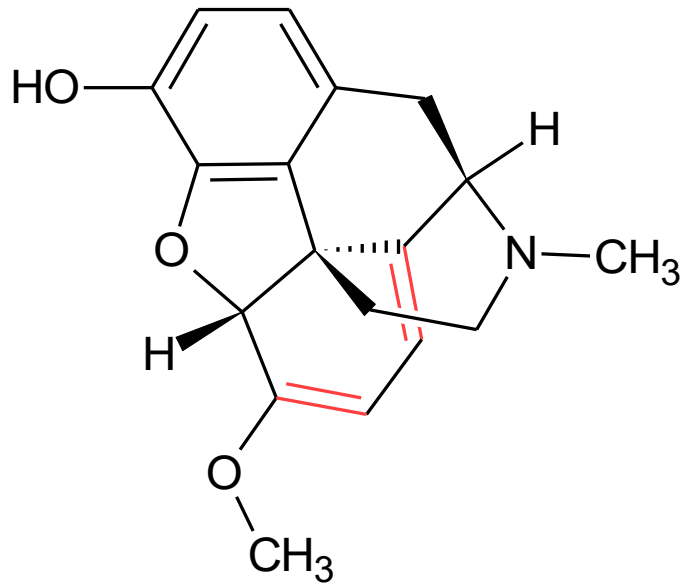
**nalbuphine**

Nalbuphin<sup>®</sup> OrPha inj.

- short period treatment of medium to strong pains, before- and post-operating analgesia

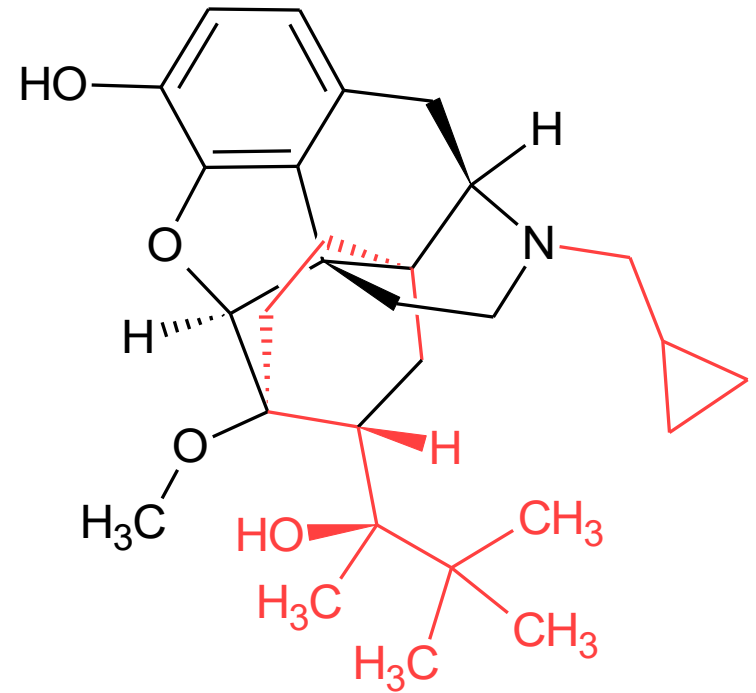


## Oripavine derivatives



oripavine

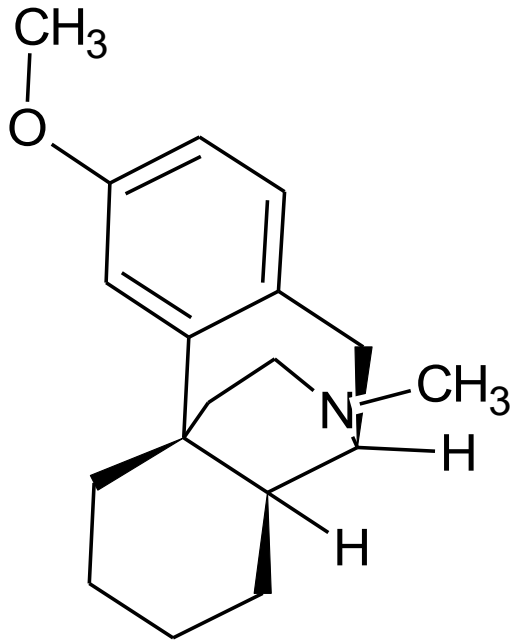
- alkaloide from *Papaver orientale*



**buprenorphine**

- relief of non-malignant pain of medium intensity
- opioid withdrawal therapeutic programs  
Norspan<sup>®</sup> emp. tdr., Transtec<sup>®</sup> emp. tdr.

## Morphinane derivatives



dextromethorphan

*Dextrometorphani hydrobromidum*

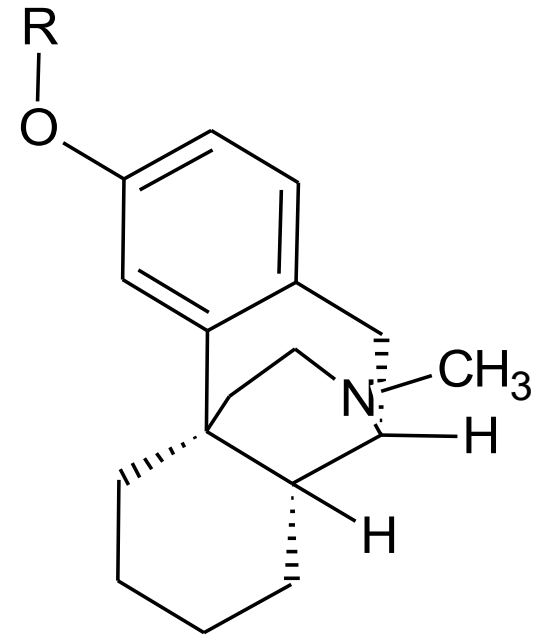
*monodydricum* PhEur

•antitussive

•euphoriant in higher doses

Humex ® , Robitussin ® , Stopex ® ,

Tussidril ® - OTC

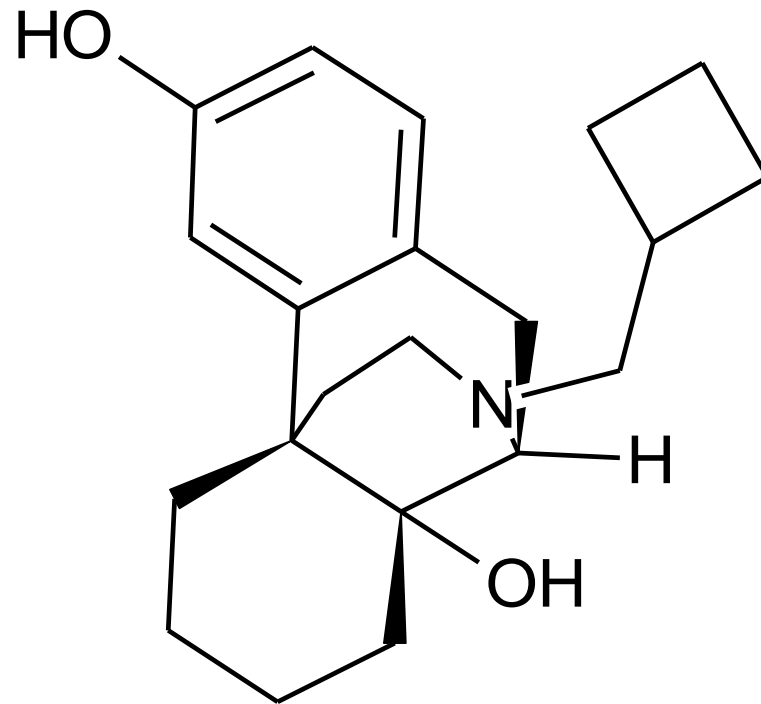


R = H **levorphanol**

•better analgesic than morphine

R = CH<sub>3</sub> levomethorphan

## Morphinane derivatives (continued)

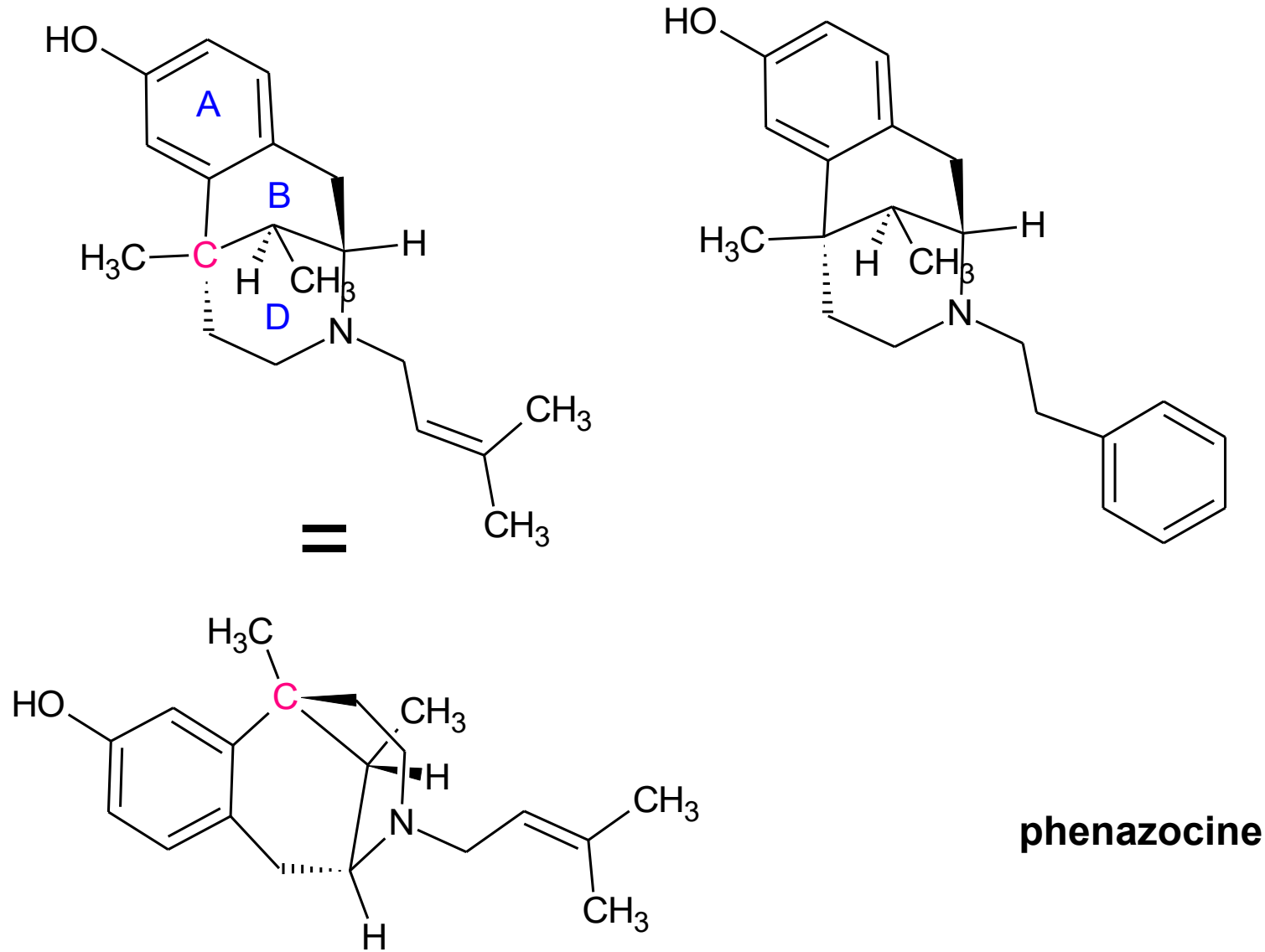


### **butorphanol**

- treatment of moderate to severe pain
- a potent  $\kappa$ -receptor agonist and an antagonist at  $\mu$ -receptor
- intensive hepatic first-pass metabolism  $\Rightarrow$  parenteral administration (nasal sprays)

## Benzomorphone derivatives

- removal of the C-ring  $\Rightarrow$  greater affinity for  $\kappa$ -receptor; weak for  $\mu$ -receptor
- central C-atom remained quaternary  $\Rightarrow$  truncated open analogues of the C-ring



### pentazocine

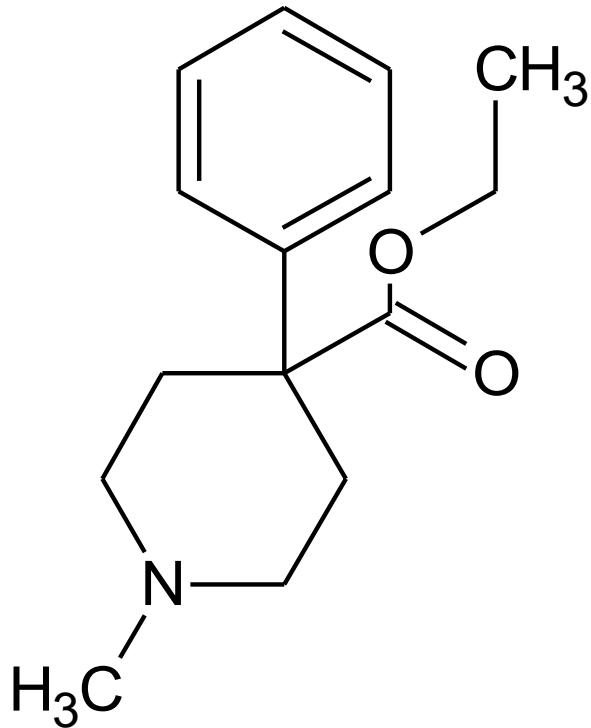
- treatment of moderate pain

Fortral<sup>®</sup> tbl., inj. sol.

### phenazocine

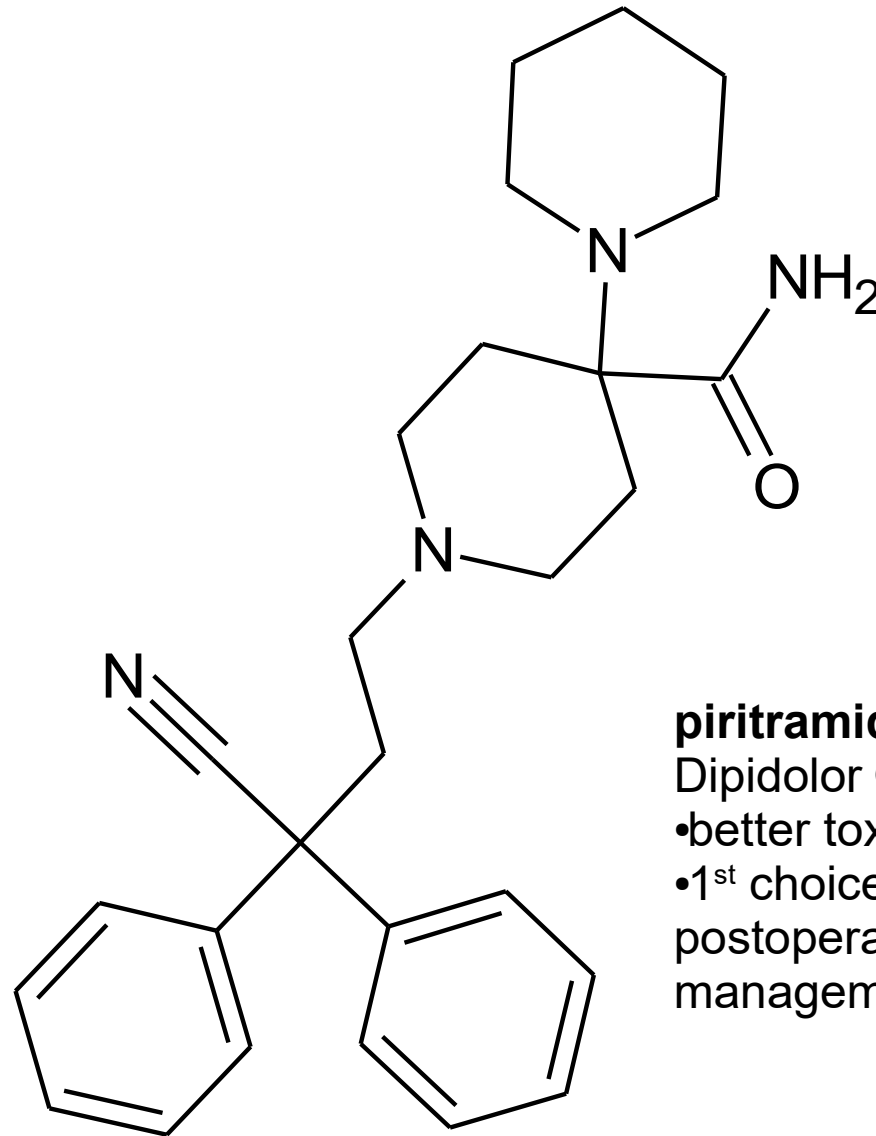
## Phenylpiperidine derivatives and compounds derived from them

- originated by removal of the B,C and E rings which are not necessary for the activity
- faster onset and shorter lasting of action
- remaining AE: addiction, expiratory centre attenuation



### **pethidine**

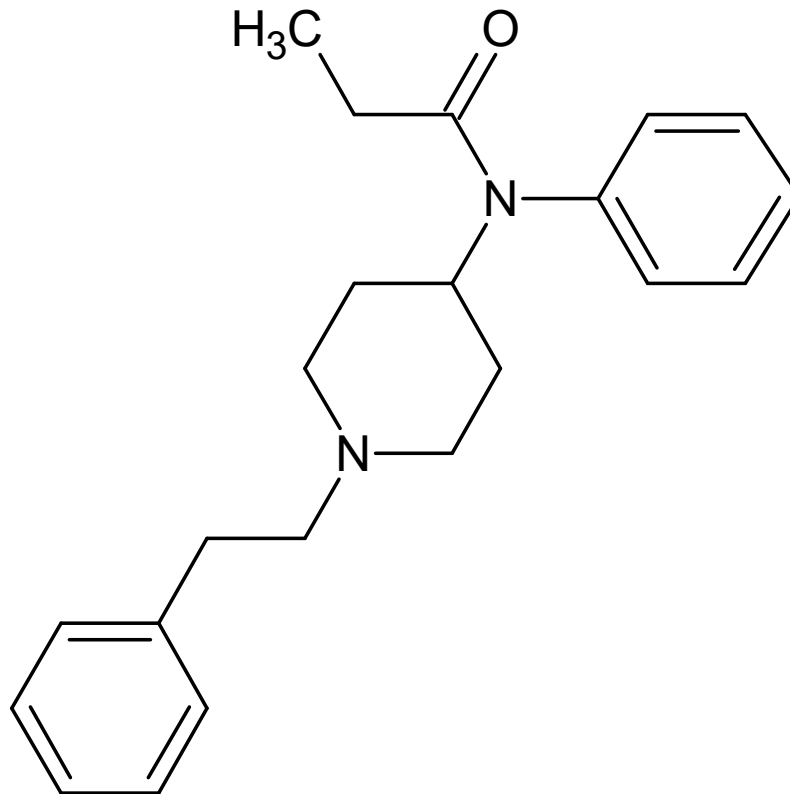
syn. meperidine [USAN]  
Dolsin ® inj. sol.



### **piritramide**

Dipidorol ® inj.  
•better toxicity profile  
•1<sup>st</sup> choice in  
postoperative pain  
management in EU

Phenylpiperidine derivatives and compounds derived from them  
4-anilidopiperidines: fentanyl



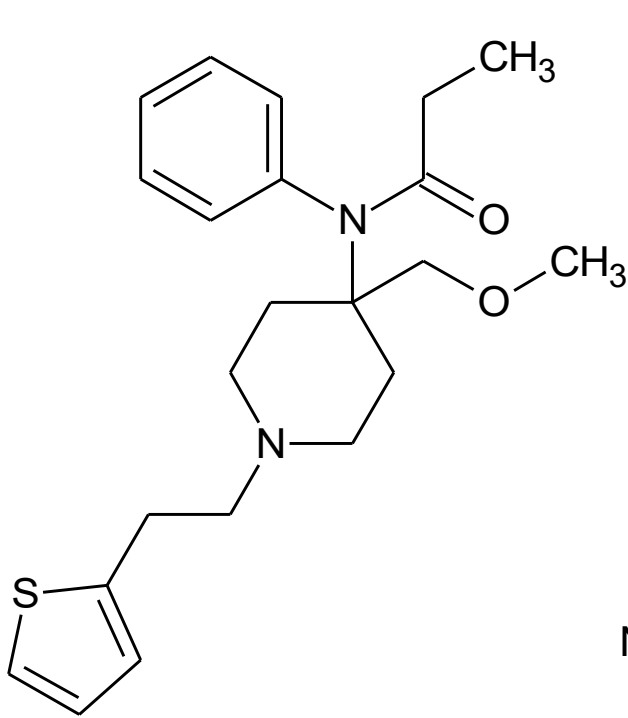
**fentanyl**

*Fentanylum* PhEur (free base) – transdermally

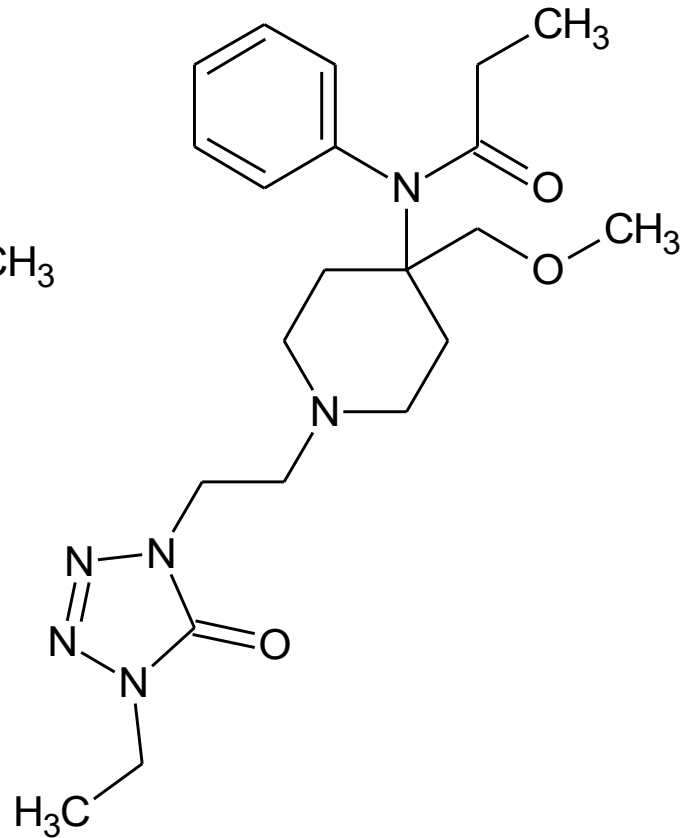
*Fentanyl citras* PhEur – i.m., i.v.

Durogesic ® derm. emp. tdr.

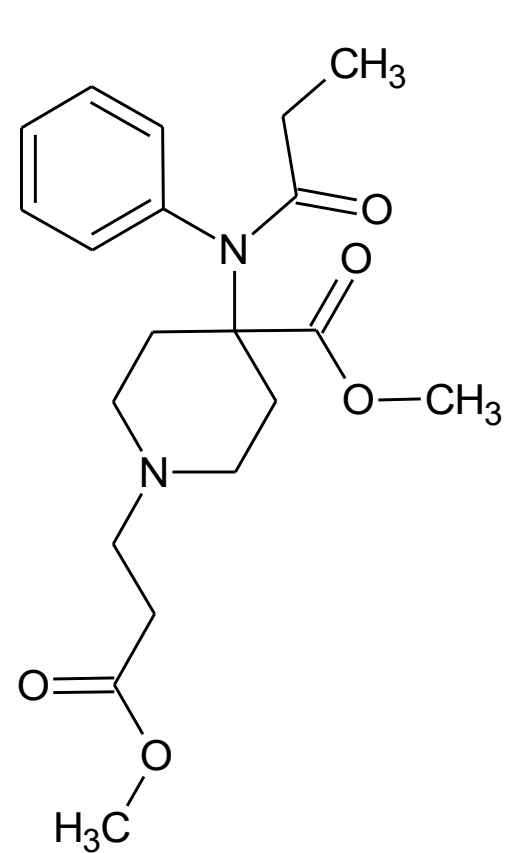
Phenylpiperidine derivatives and compounds derived from them  
Fentanyl analogues - 4-anilidopiperidines



**sufentanil**  
•also in anaesthesia  
Sufenta<sup>®</sup> inj.

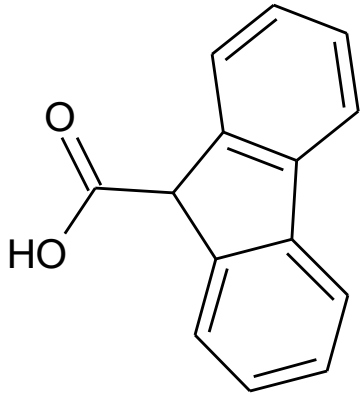


**alfentanil**  
Rapifen<sup>®</sup> inj.



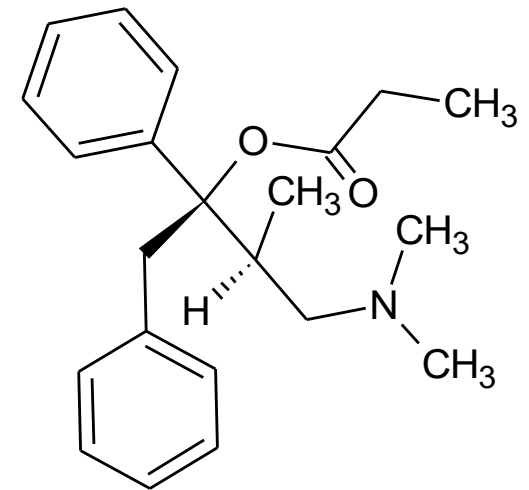
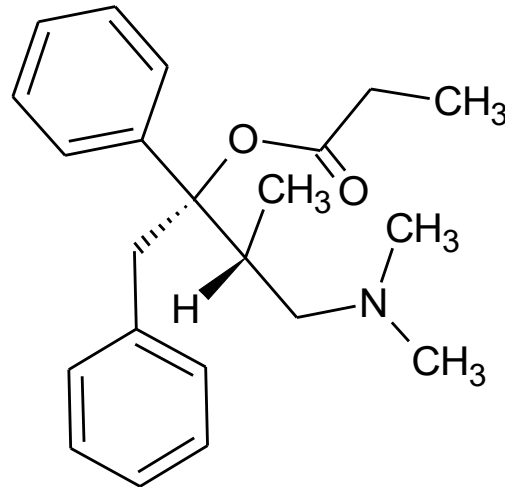
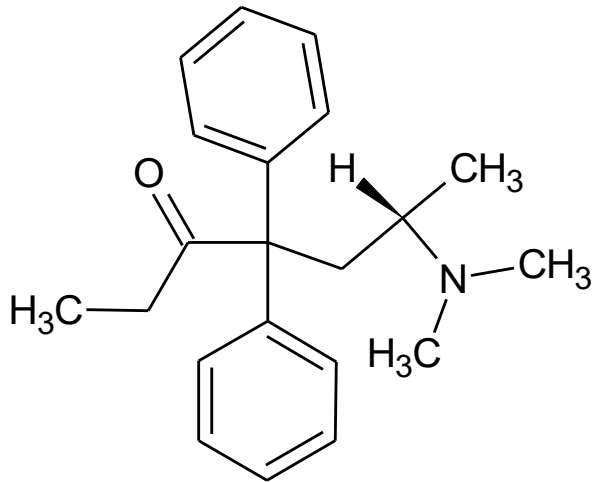
**remifentanyl**  
Ultiva<sup>®</sup> inj.

•so called opioid anaesthetics (combined with propofol, ketamine)



## Phenylpropylamine derivatives

- can be derived from 4-phenylpiperidines by formal deleting of one methylene group of piperidine ring
- structurally related to fluorene-9-carboxylic acid
- the most simplified structures still to have opioid receptor activity
- activity comparable to morphine
- efficient p.o.
- less AE than morphine



### methadone

- withdrawal symptoms less severe and more gradual as compared to morphine  $\Rightarrow$  opioid-withdrawal programmes
- withdrawal programmes

Methadon Zentiva  $\text{\textcircled{R}}$  oral solution

### dextropropoxyphene

- substitution of one phenyl with benzyl  $\Rightarrow$  2<sup>nd</sup> chiral centre
- (+)-(2*S*, 3*R*)-analgesic; 1/10 of methadone activity

Darvon  $\text{\textcircled{R}}$  (USA)

### levopropoxyphene

- (-)-(2*R*, 3*S*)-antitussive

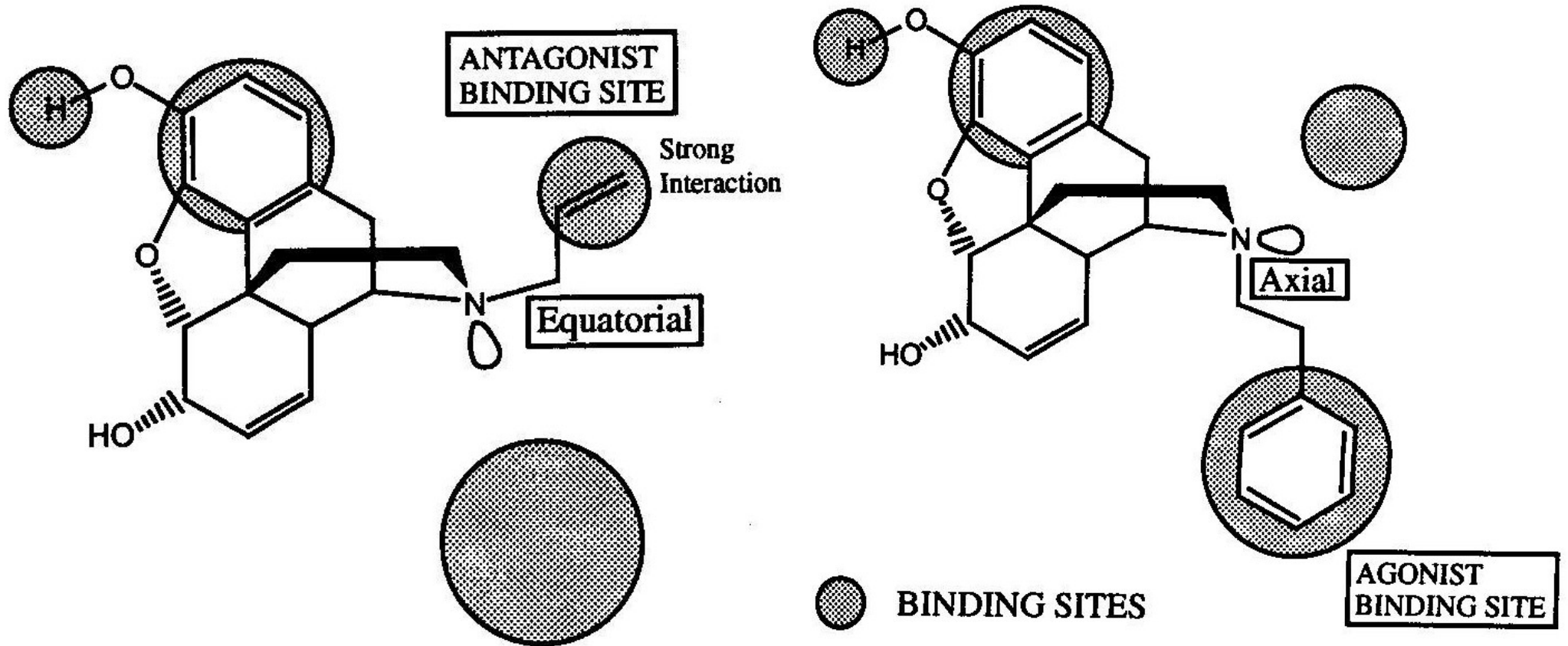
Novrad  $\text{\textcircled{R}}$  (USA)



## Structure-activity relationships (SAR)

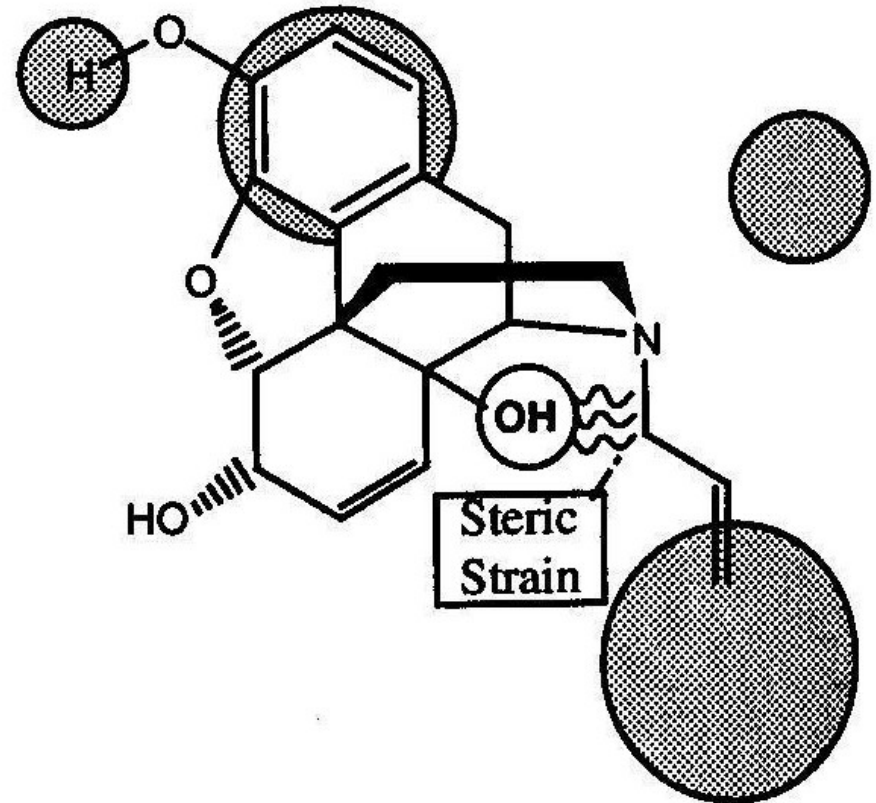
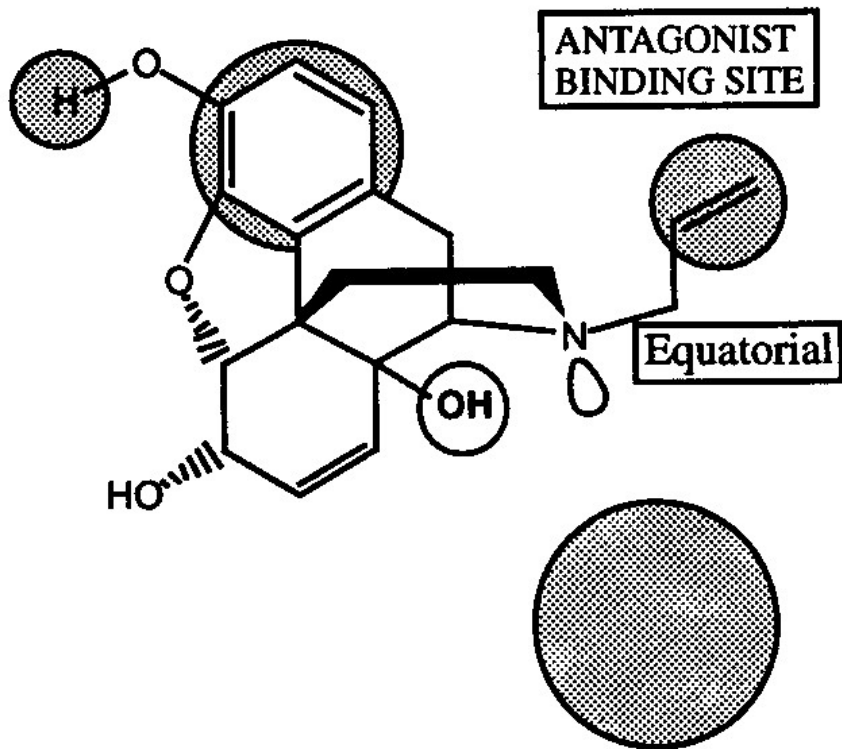
- an aromatic ring and a basic nitrogen atom are necessary for action, a phenolic group is not( $\Leftrightarrow$  the rings B, C, D and E of the morphine skeleton are not necessary for analgesic action)
- quarternary (tetrasubstituted) C(4) of piperidine derivatives is necessary in the frame of this group, with exception of fentanyl
- substitution of methyl at nitrogen in D ring of morphine: to **allyl** leads to antagonists (equatorial position), to **phenethyl** leads to agonists; explanation by presence of 2 different hydrophobic binding sites
- OH group at C(14) supports the placement of a substituent into equatorial position; this moiety as a steric hindrance orients into equatorial position also other substituents than allyl (e.g. cyclopropylmethyl)

N-substituted morphine derivatives acting as agonists and antagonists – a model of interaction with a receptor

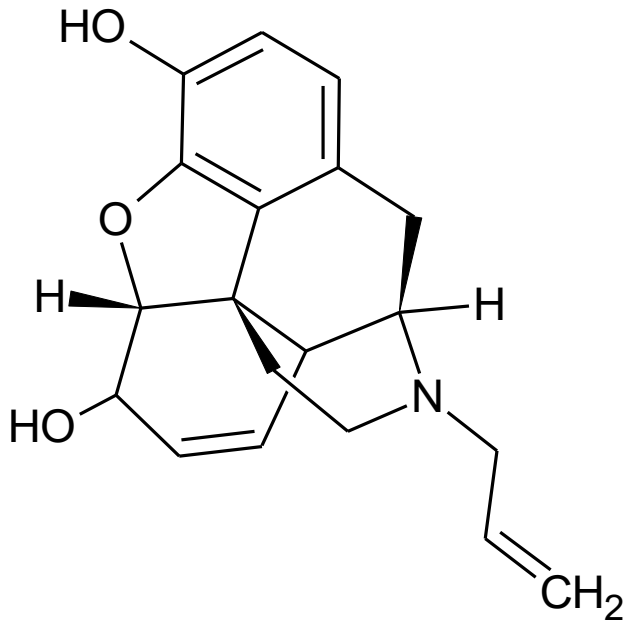


## Morphine receptor antagonists with -OH group at C(14)

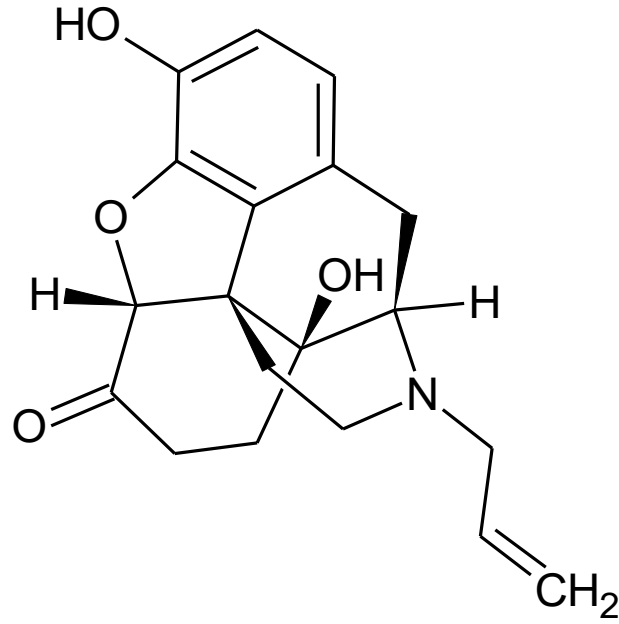
- OH group is a steric hindrance which supports to dominance of the equatorial position of allyl



## Morphine receptor antagonists



**nalorphine**



**naloxone**

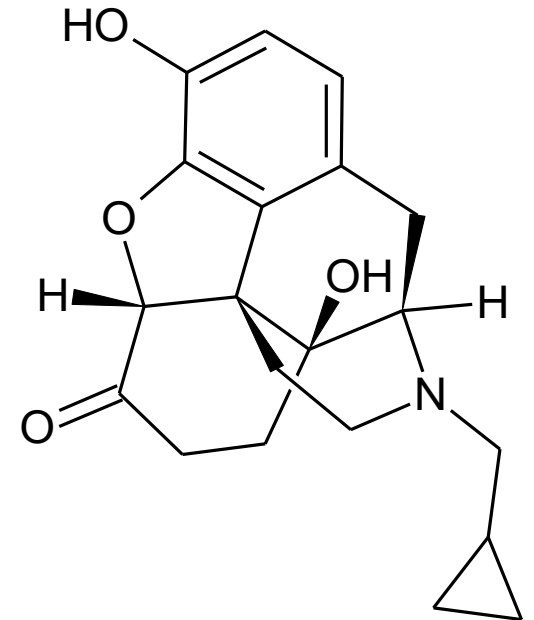
*Naloxoni hydrochloridum  
dihydricum* PhEur

- *i.v.* administration only;  
extensively

metabolised in liver

Naloxone WZF ® Polfa

- antidotes in opiates overdose



**naltrexone**

*Naltrexoni hydrochloridum*  
PhEur

- *p.o.*

- useful also in treatment of  
alcoholism (blocks binding  
of endo opioids)

Revia ® por tbl flm