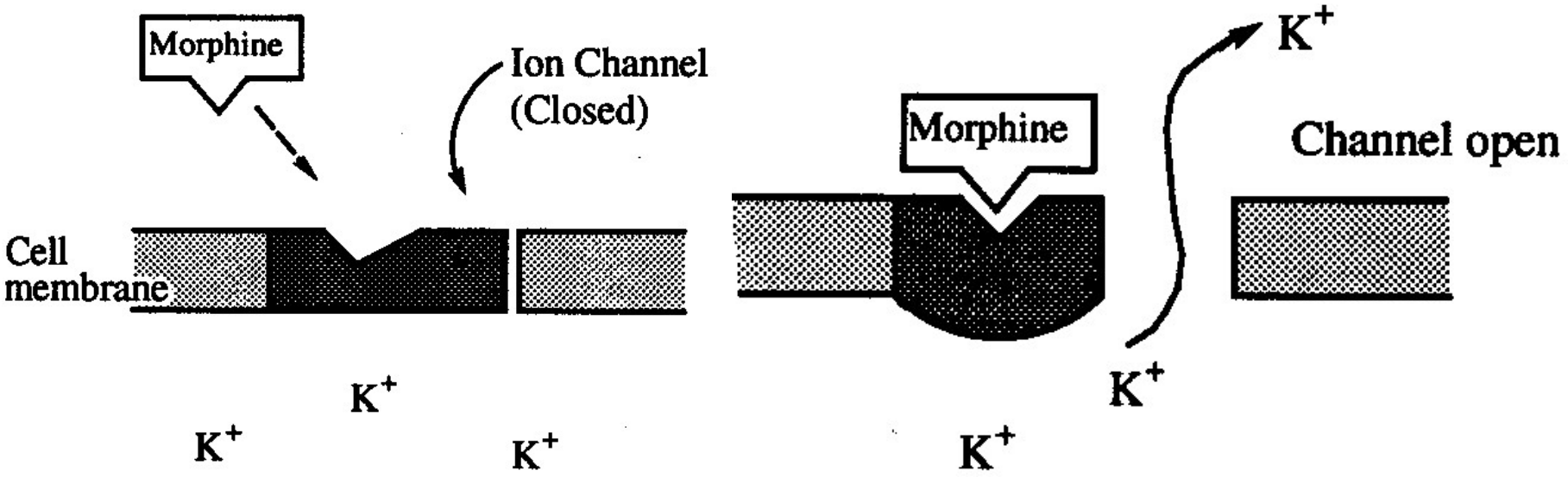
Analgesics – anodyns = opioid = „strong“ = „narcotic“ analgesics

Opioid receptors

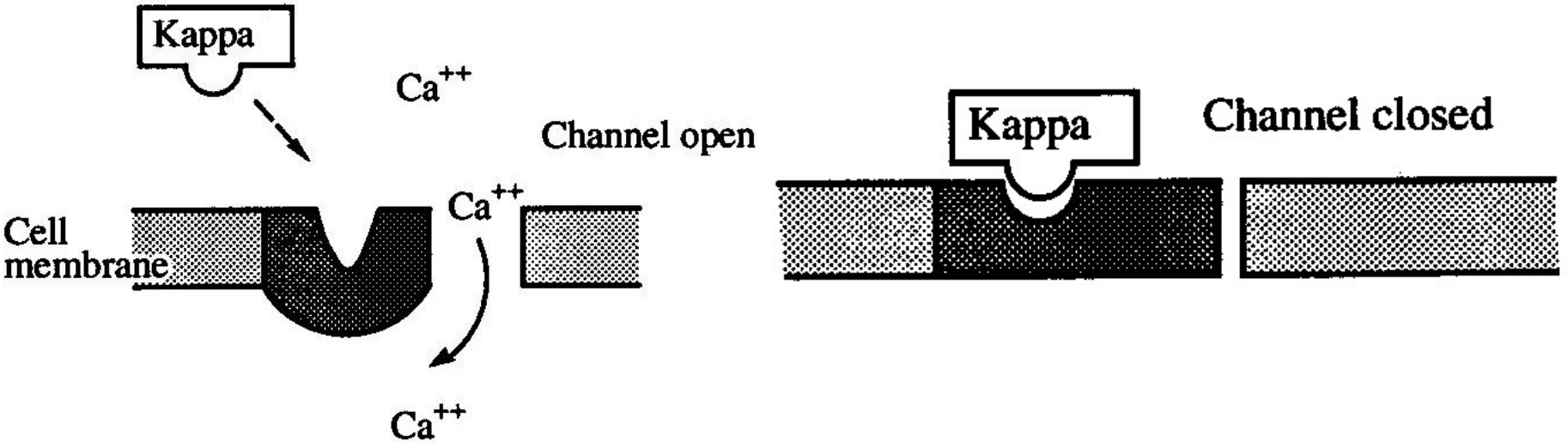
- 4 main types: μ, κ ,δ and ORL-1
- (σ receptors currently not recognized as opioid)
- every type has several subtypes
- μ receptor activation leads to analgesic activity, breathing attenuation etc.
- κ receptor activation: also analgesic activity, takes part in diuresis and neuronal activity regulation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

μ receptor



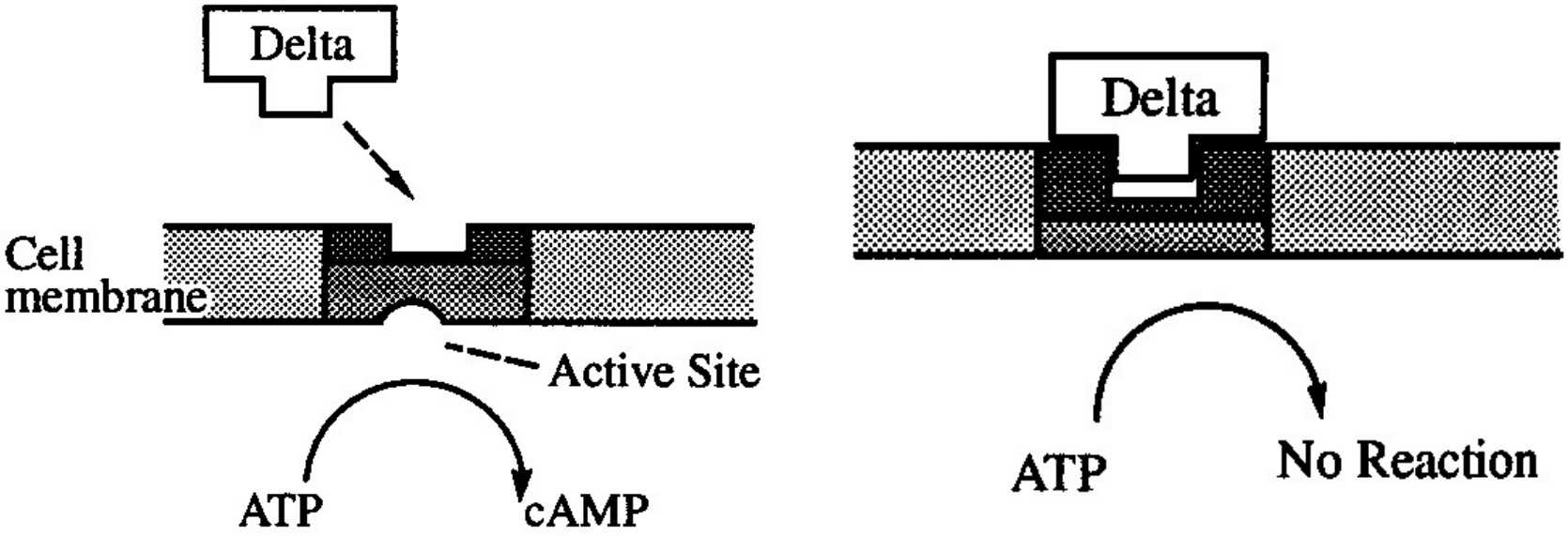
- opens ion channel in cell membrane
- K^+ can stream into the cell $\Rightarrow$ decrease of neurone excitability
- also decreases input of Ca^{2+} into terminal nerve which decreases neurotransmitter release

κ receptor



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

δ Receptor



- not linked with any ion channel
- activation of the receptor probably leads to a change of adenylate cyclase geometry ⇒ 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 ifluences dopamine concentrations in CNS and is involved in neurotransmitters release in anxious conditions

Natural opioid receptors agonists – endogenous analgesics

- morphine receptors exist athough it is not endogenous ⇒ body own opioids must exist!
- all endo-opioids are fragments of β-lipotropin, adenohypophyse hormone consisting of 91 amino acid rests which has no opioid effects

Encephalins – binding preferably to δ-receptors

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

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

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

Endorphins (= „endo-morphines“) - α: 16 AA
β: 31 AA – after *i.v.* application has morphine effects in CNS
χ: 17 AA

- β-lipotropin is not direct precursor of opioid peptides; more precursor peptides exist:

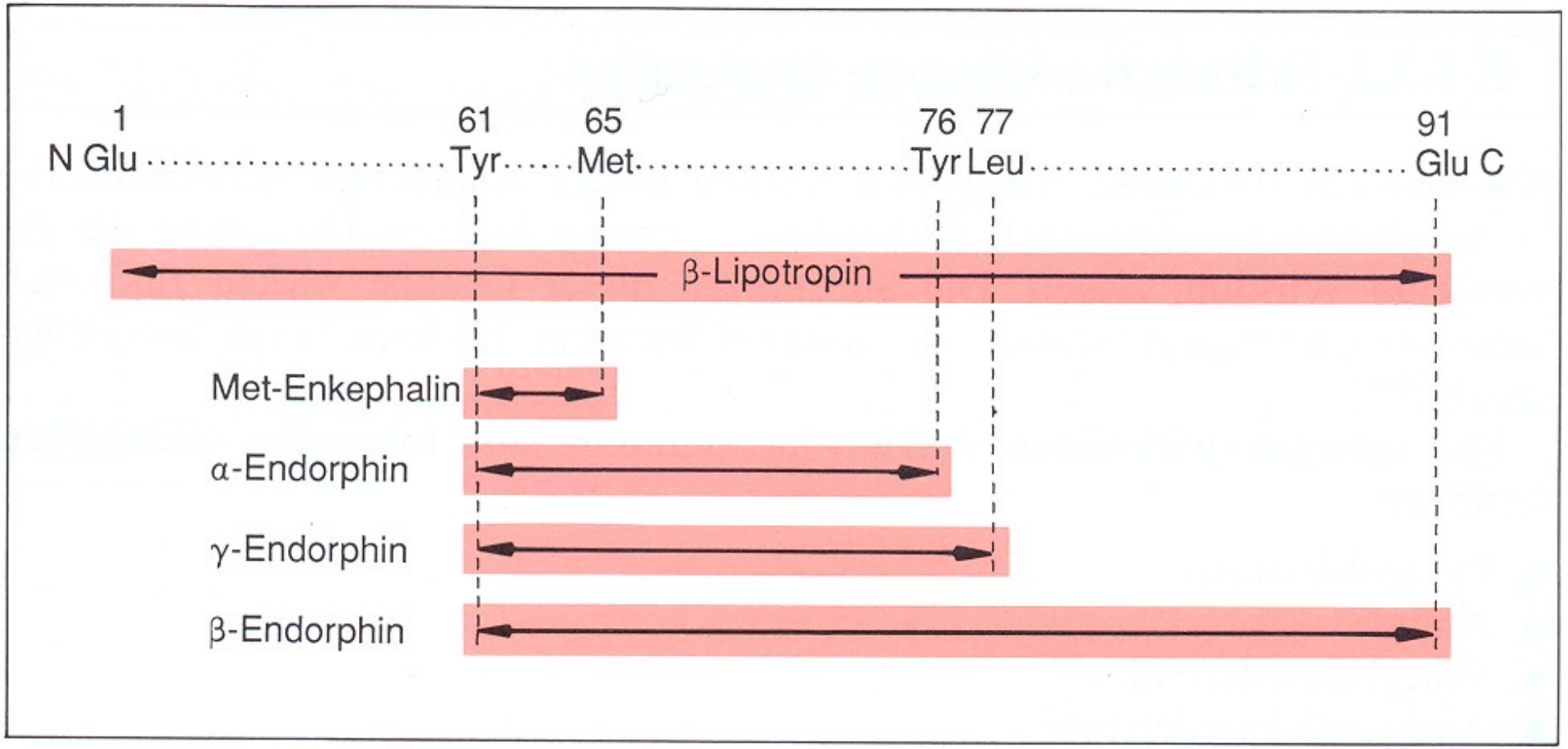
preproencephaline A ⇒ encephalins

preproopiomelanocortine ⇒ endorphines

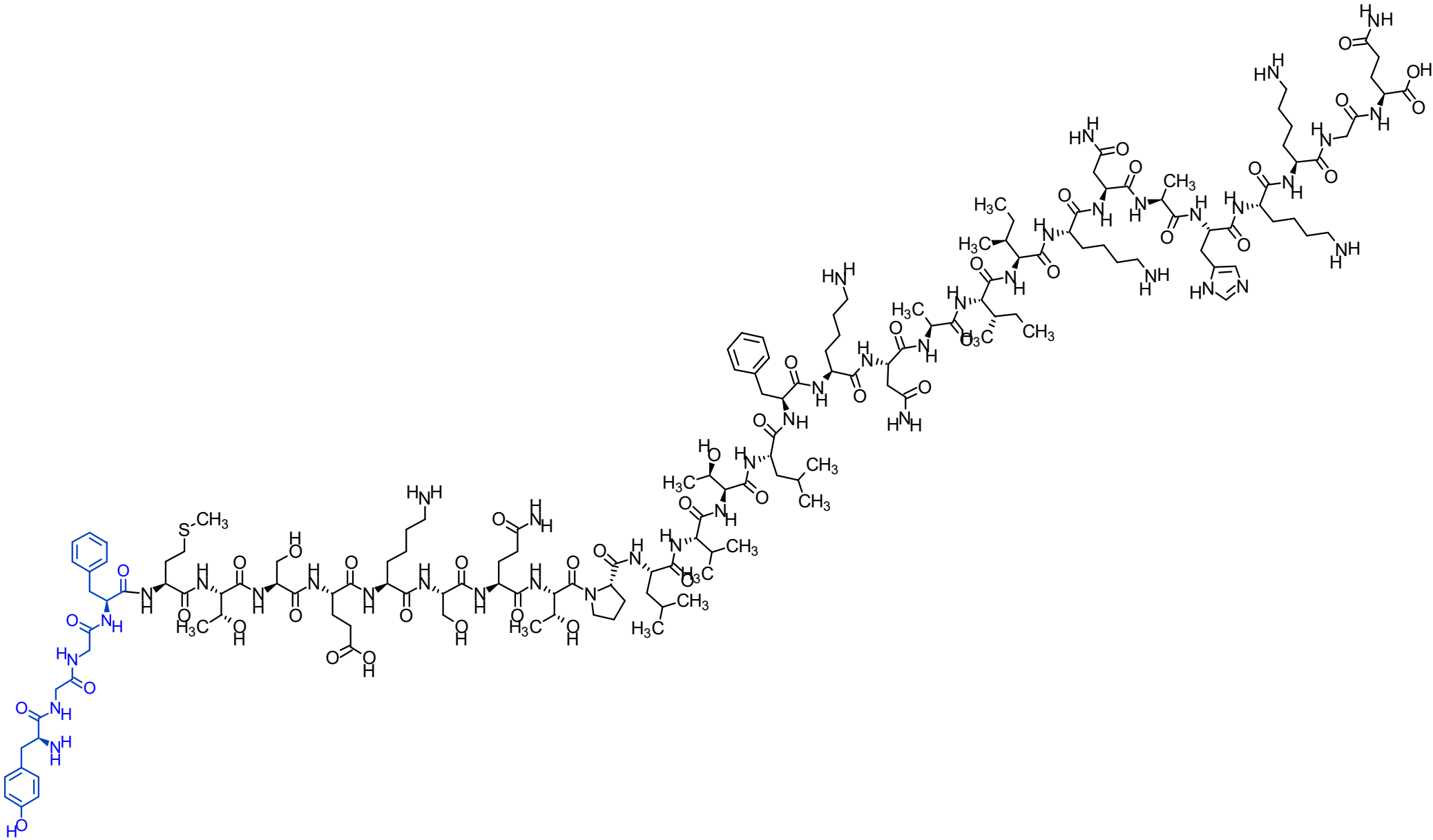
preproencephaline B ⇒ dynorphines

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

Endorphines and encephalins as parts of β-lipotropine sequence



Primary structure of β-endorphine



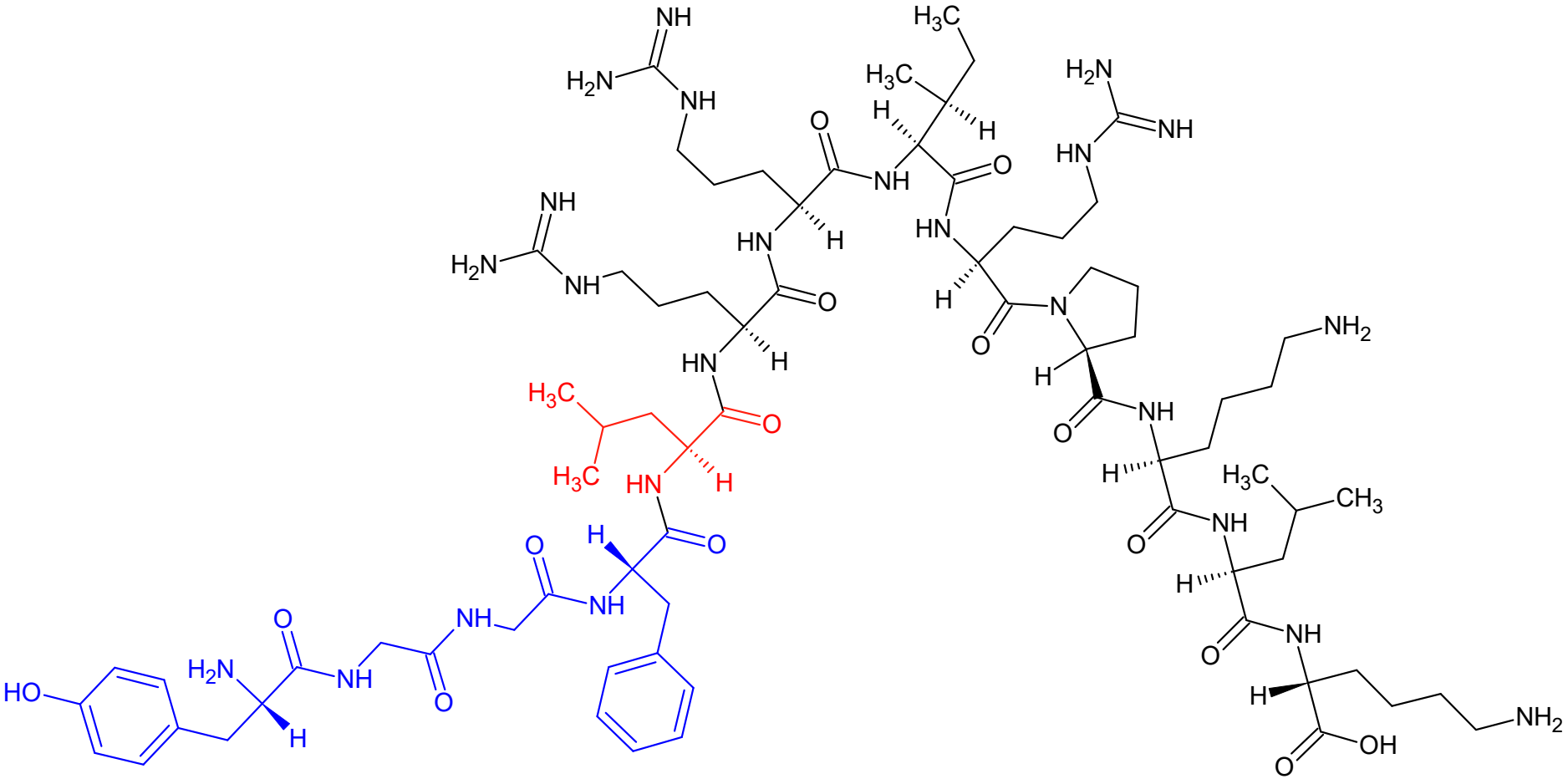
Dynorphine A sequence (1 - 18)

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*)

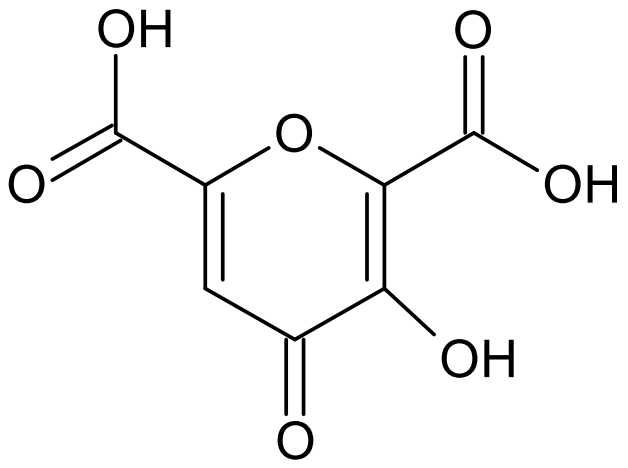
• known from Assyrian manuscripts from 7th century b. C.

•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

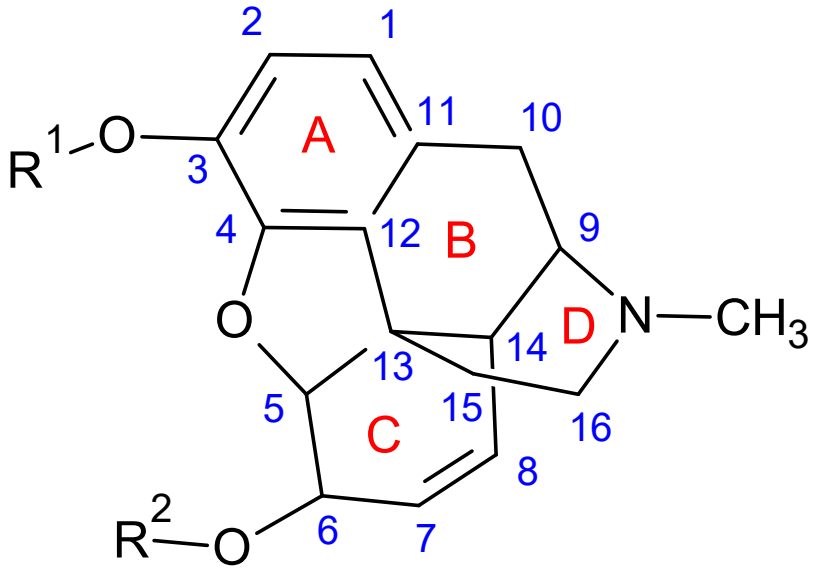
•alkaloids in form of salts with carboxylic acids; meconic acid typical

•beaten-out empty dry poppy heads are alternative resource of opium alkaloids (CZ, SK)



meconic acid

Morphine and its simple derivatives



$R^1 = R^2 = H$ **morphine** MSI®, MST®, Sevredol® ...

•isolated by Friedrich Wilhelm Sertürner, pharmacist in Paderborn, from opium in 1806

•structure elucidation: 1925 Robinson and Gunland proposed stuctural formula, 1952 Gates and Tschudi confirmed structure including stereochemistry by means of total synthesis

•basic anodyn isolated from opium or beaten-out empty dry poppy heads

$R^1 = CH_3$, $R^2 = H$ **codeine**

•basic antitussive

•semi-synthetic; prepared from morpine by selective methylation of phenolic group potentiates effect of weak analgesics

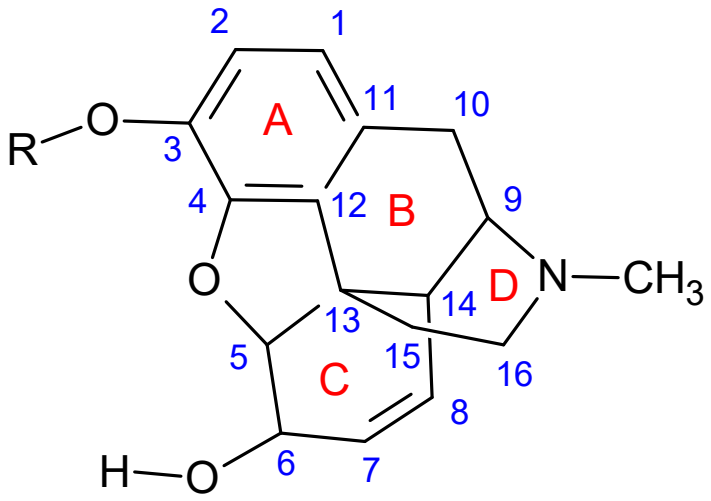
• abot 10 % metabolized to morphine

$R^1 = R^2 = CH_3CO$ **diamorphine** syn. heroine

•2x more effective than morphine, better penetrates into CNS

•misused as an illegal drug of abuse

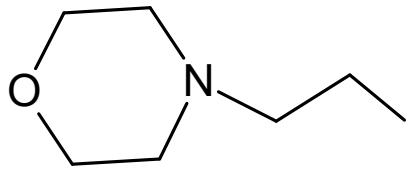
Morphine and its simple derivatives: further ethers used as antitussives



R = H_3C

ethylmorphine
Diolan ®

R =

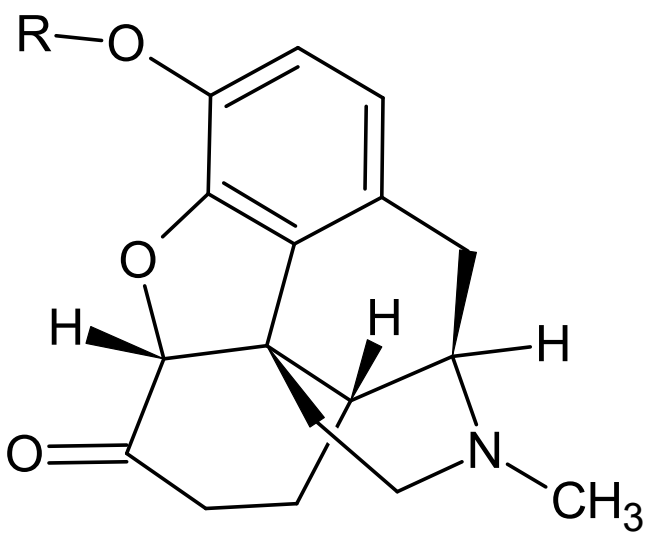


pholcodine
Neocodin ®

Effects of opioid analgesics

- analgesic
- antidiarrhoic (σ -, δ -receptors in gut)
- antitussive – from attenuation of caugh reflection to expiratory centre inhibition
- euphoriant
- physical addiction – very slowely formed during relieving of strong pain

Semi-synthetic morphine and codeine derivatives



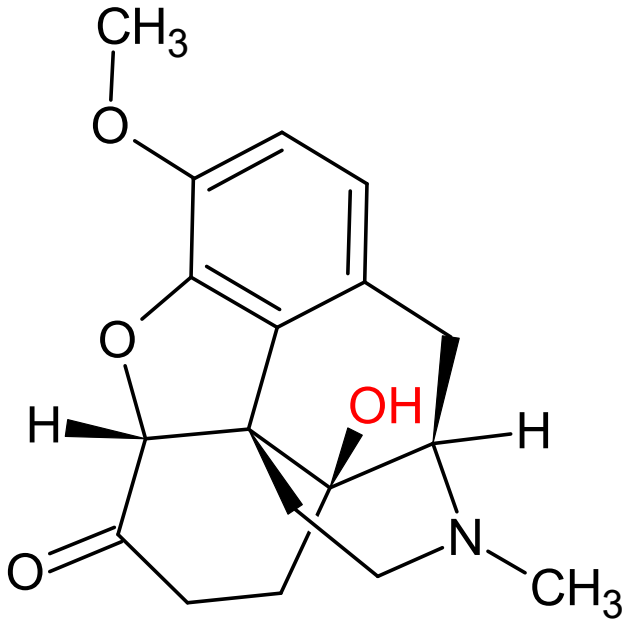
R = H **hydromorphone**

•10x more active than morphine

Jurnista®, Palladone® cps. ...

R = CH_3 **hydrocodone**

•more effective antitussive than codeine



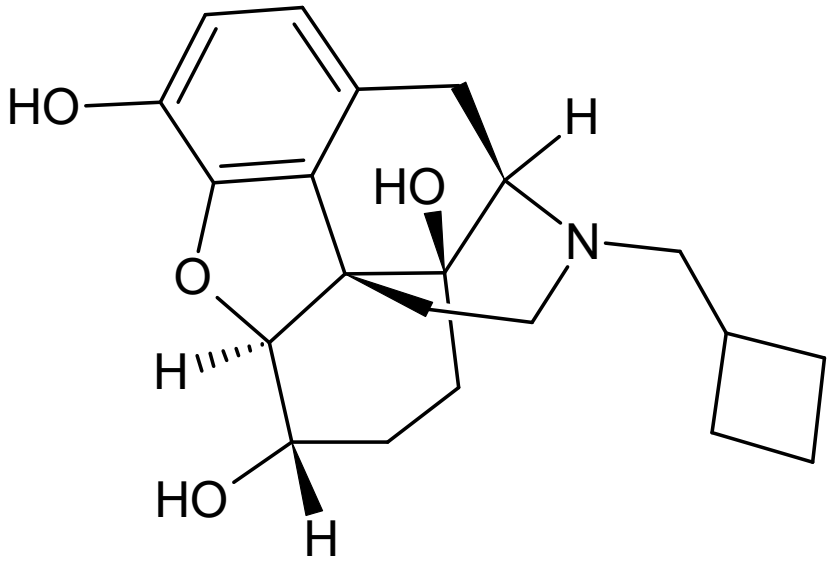
oxycodone

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

•antitussive

Oxycodon (*firm*)® tbl.

Semi-synthetic morphine and codeine derivatives

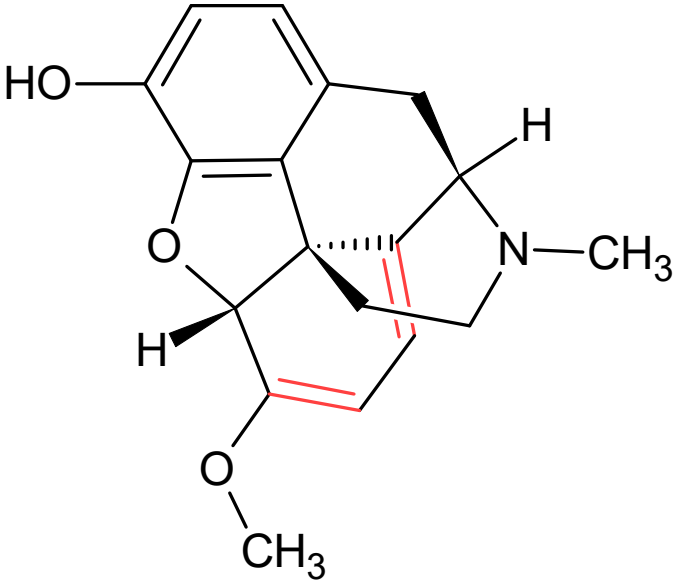


nalbuphine

Nalbuphin® OrPha inj.

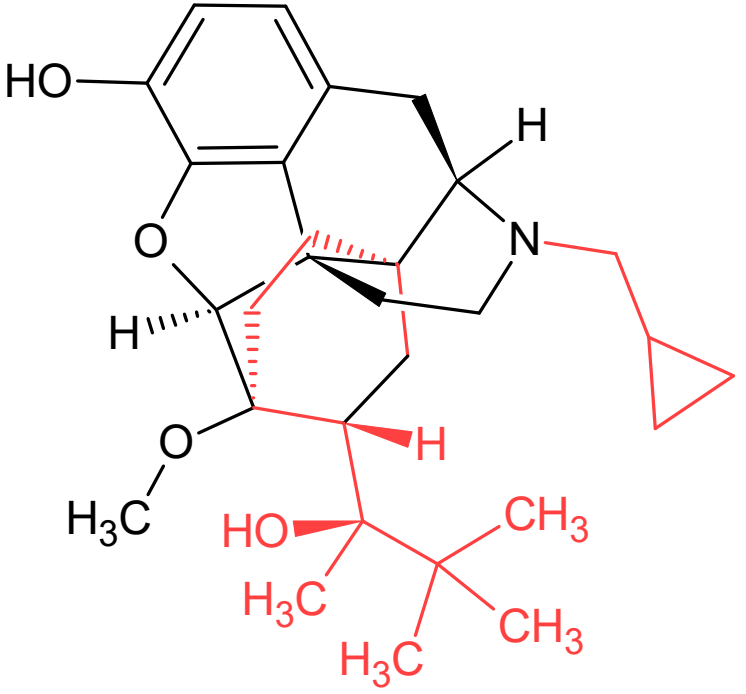
•short period treatment of medium to strong pains, before- and post-operating analgesia

Oripavine derivatives



oripavine

•alkaloide from *Papaver orientale*



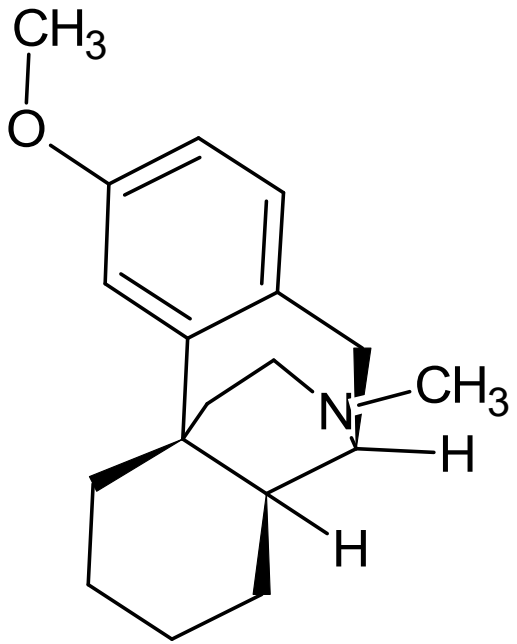
buprenorphine

•relief of non-malignant pain of medium intensity

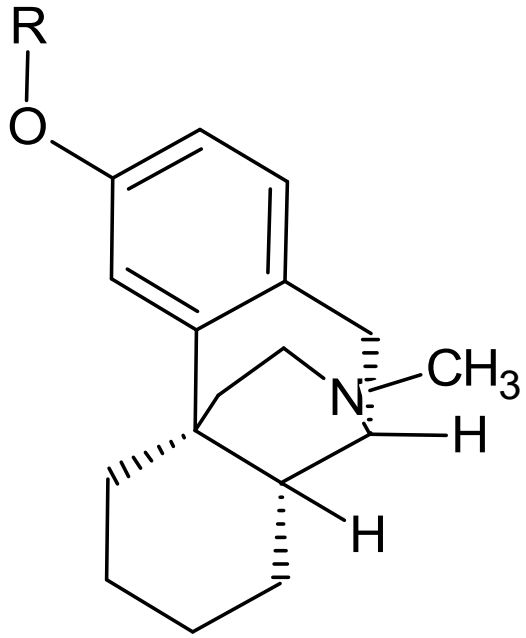
•opioid withdrawal therapeutic programs

Norspan® emp. tdr., Transtec® emp. tdr.

Morphinane derivatives

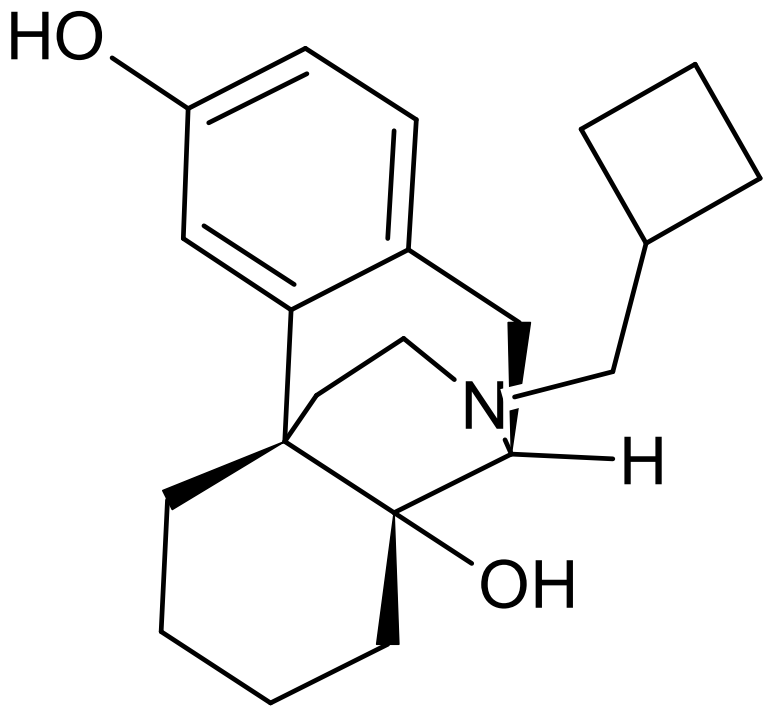


dextromethorphan
Dextrometorphani hydrobromidum monodydricum PhEur
•antitussive
•euphoriant in higher doses
Humex ® , Robitussin ® , Stopex ® , Tussidril ® - OTC



R = H **levorphanol**
•better analgesic than morphine
R = CH_3 levomethorphan

Morphinane derivatives (continued)

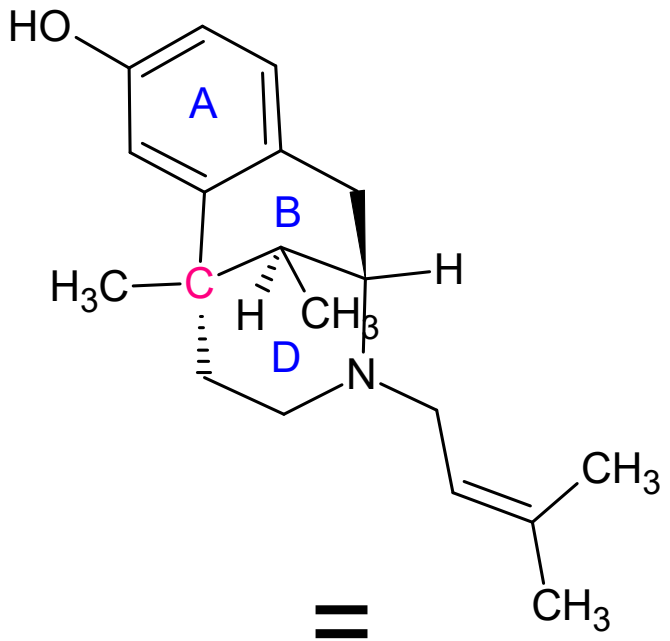


butorphanol

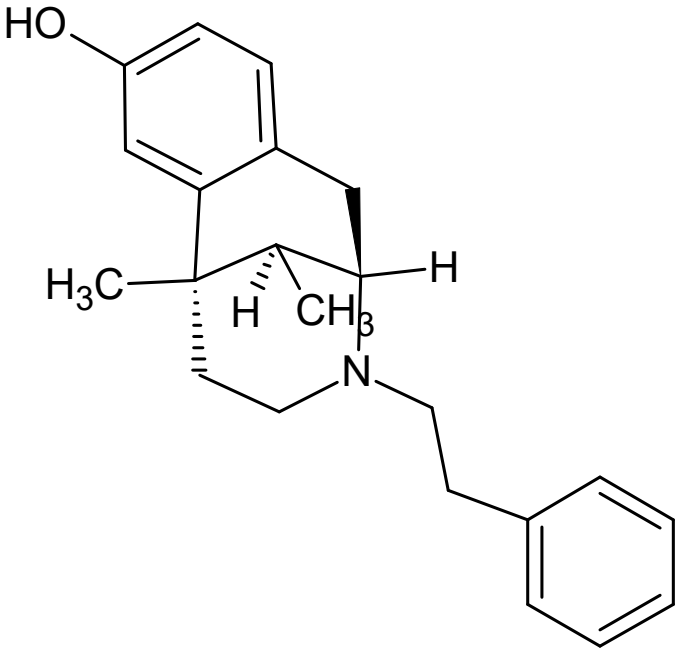
- treatment of moderate to severe pain
- a potent κ-receptor agonist and an antagonist at μ-receptor
- intensive hepatic first-pass metabolism $\Rightarrow$ par-enteral administration (nasal sprays)

Benzomorphane derivatives

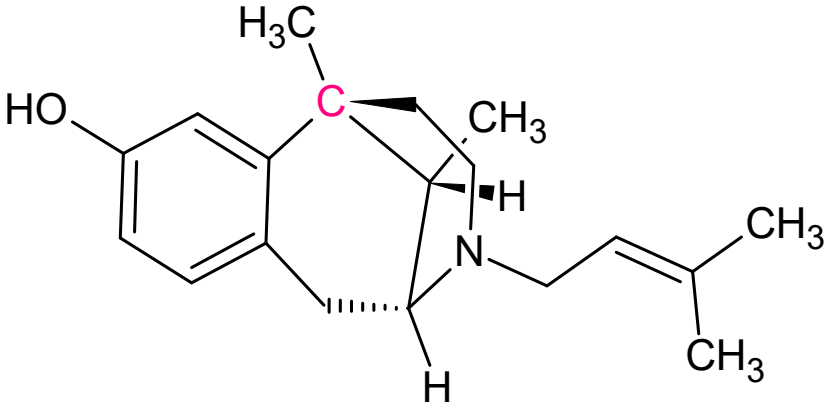
- removal of the C-ring ⇒ greater afinity for κ-receptor; weak for μ-receptor
- central C-atom remained quarternary ⇒ truncated open analogues of the C-ring



=



phenazocine



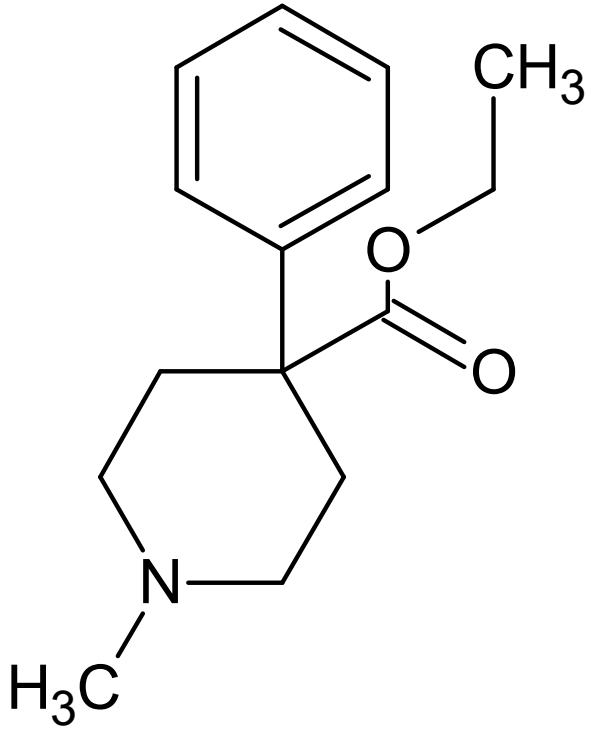
pentazocine

- treatment of moderate pain

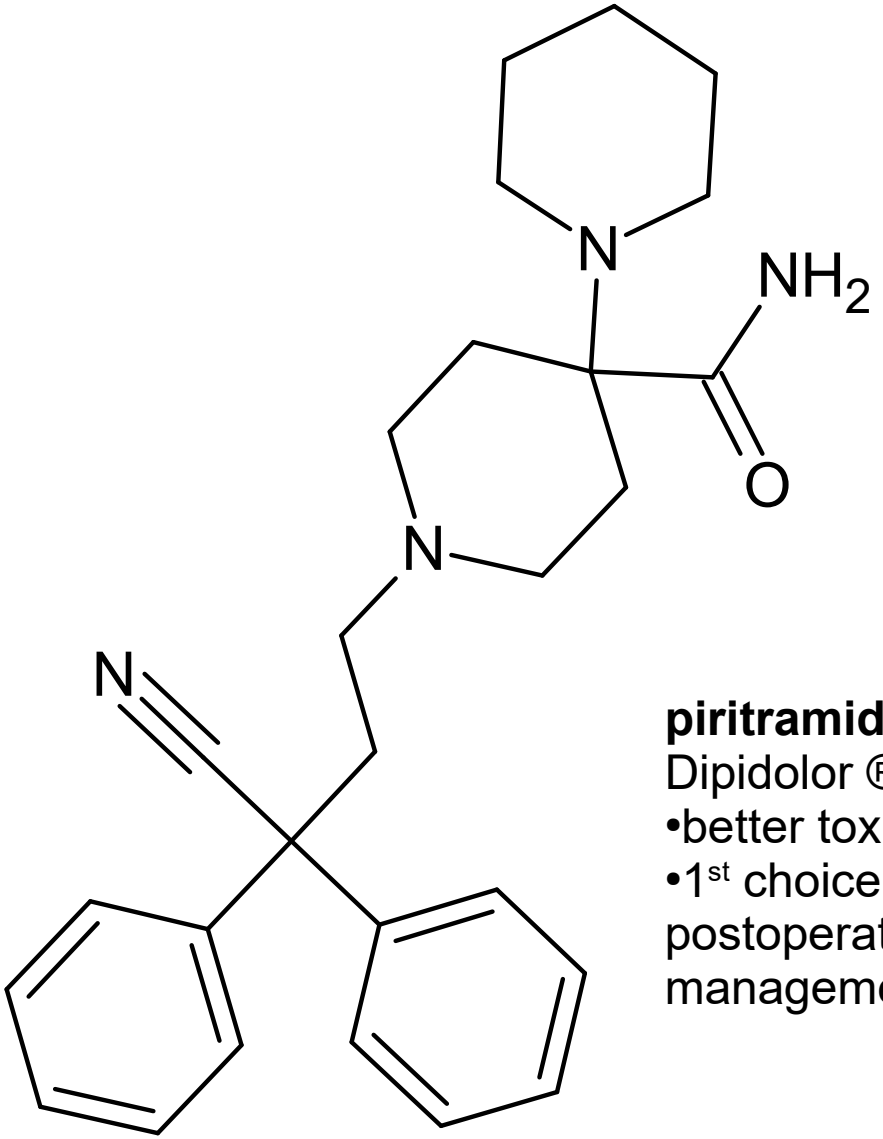
Fortral® tbl., inj. sol.

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, respiratory center attenuation



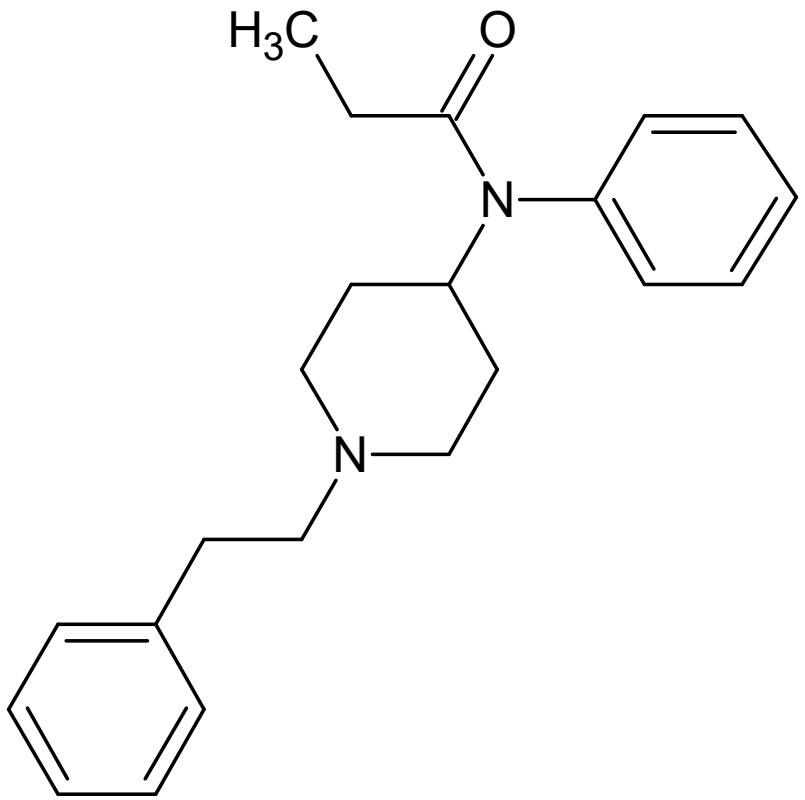
pethidine
syn. meperidine [USAN]
Dolsin ® inj. sol.



piritramide
Dipidolor ® inj.

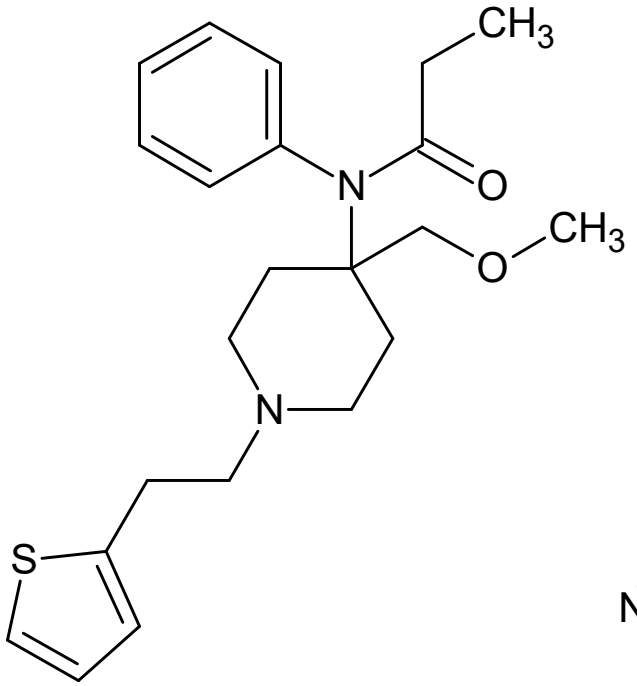
- better toxicity profile
- 1st choice in postoperative pain management in EU

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

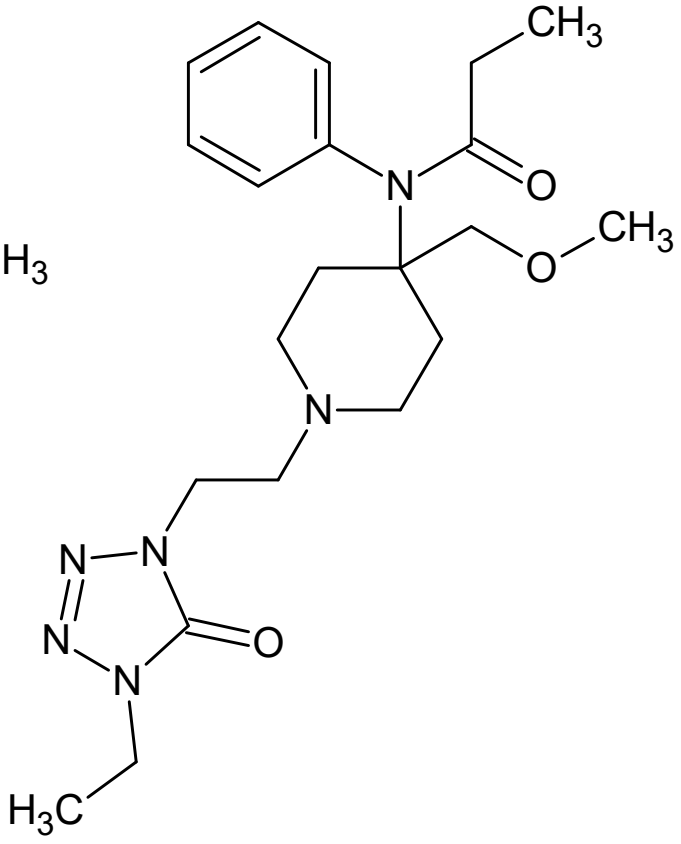


fentanyl
Fentanylum PhEur (free base) – transdermaly
Fentanyli citras PhEur – i.m., i.v.
Durogesic ® derm. emp. tdr.

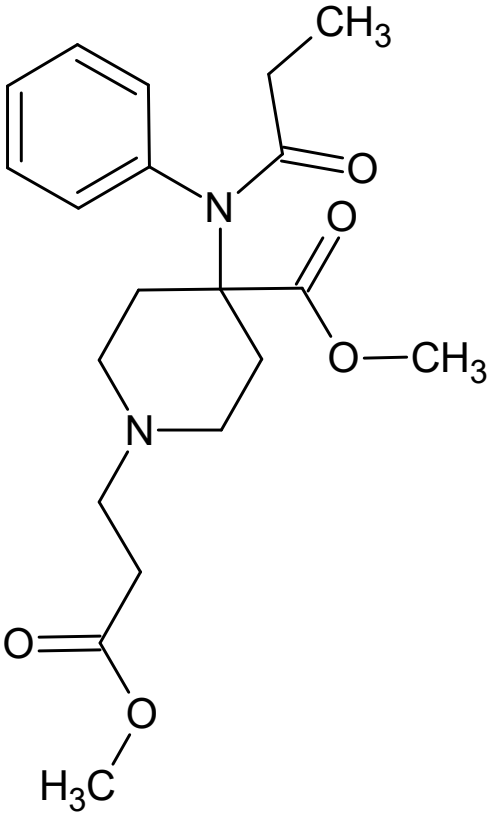
Phenylpiperidine derivatives and compouds derived from them
Fentanyl analogues - 4-anilidopiperidines



sufentanyl
•also in anesthesia
Sufenta®inj.

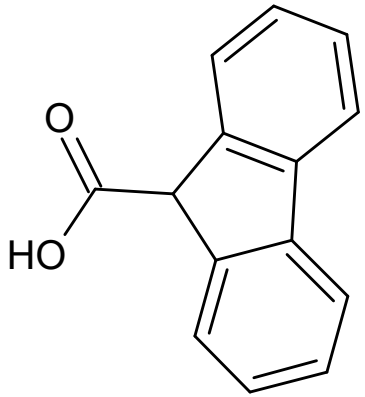


alfentanyl
Rapifen® inj.



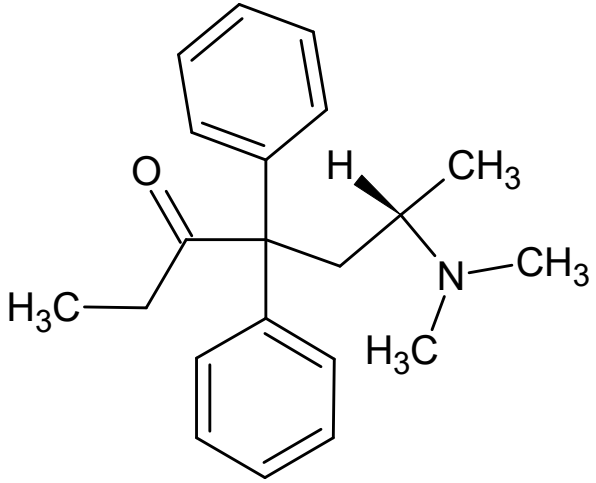
remifentanyl
Ultiva® inj.

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



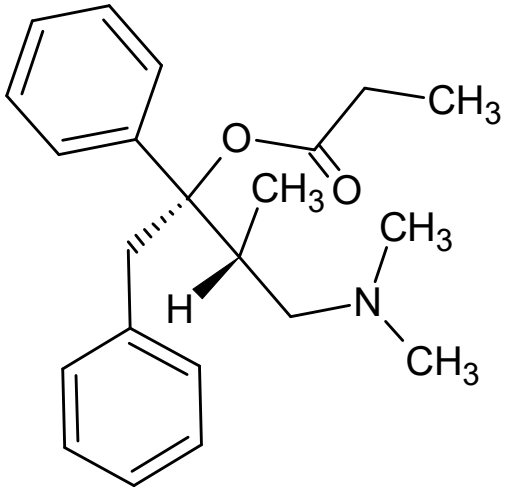
Phenylpropylamine derivatives

•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



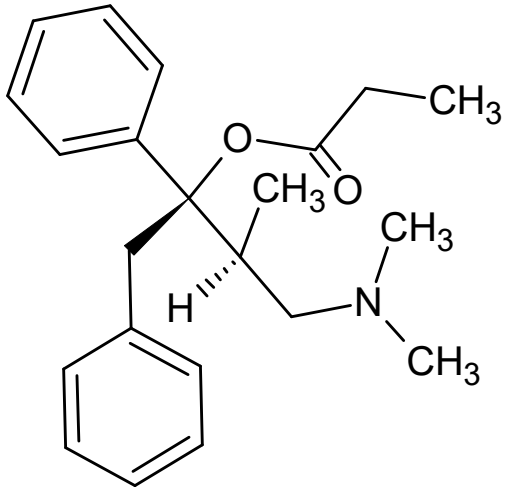
methadone

•withdrawal symptoms less severe and more gradual as compared to morphine ⇒ opioid-withdrawal therapeutical programs
Methadon Zentiva ® oral solution



dextropropoxyphene

•substitution of one phenyl with benzyl ⇒ 2nd chiral centre
(+)-(2*S*, 3*R*)-analgesic; 1/10 of methadone activity
Darvon ® (USA)



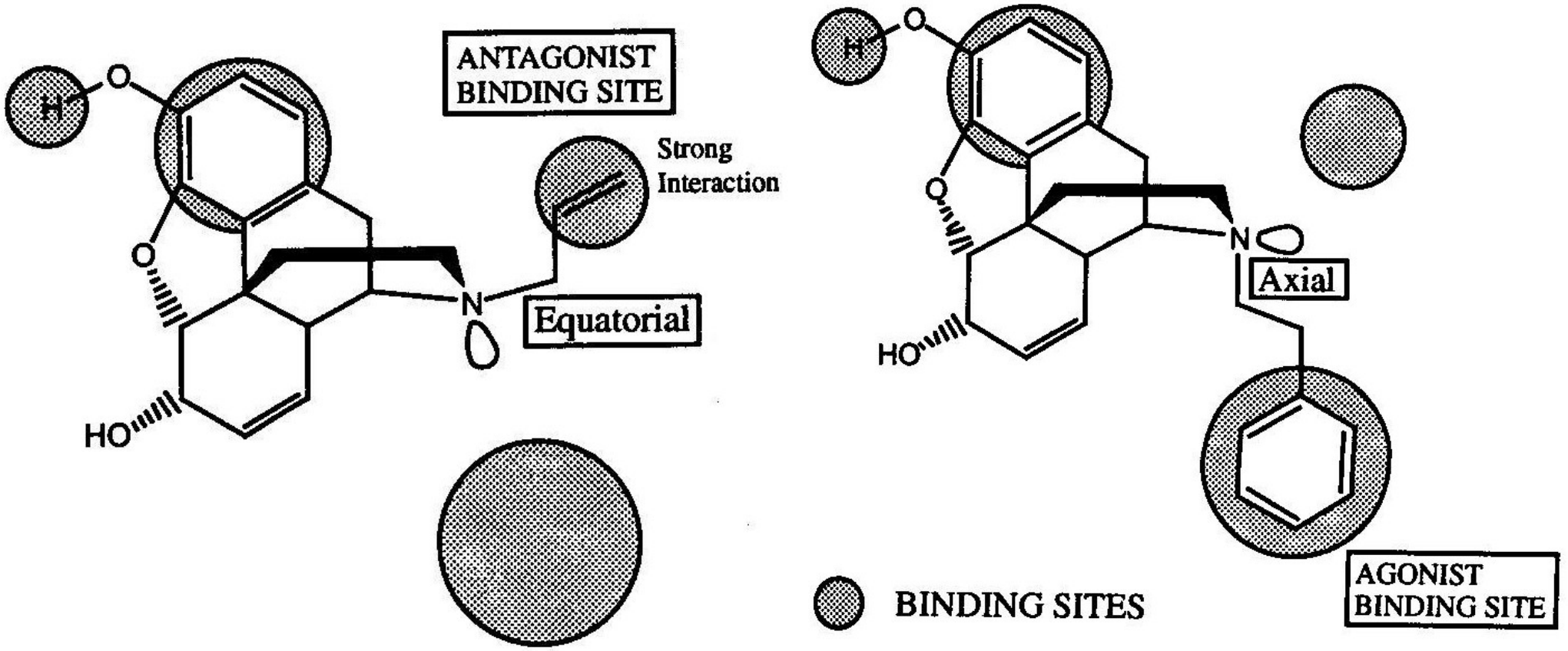
levopropoxyphene

(-)-(2*R*, 3*S*)-antitussive
Novrad ® (USA)

Structure-activity relationships (SAR)

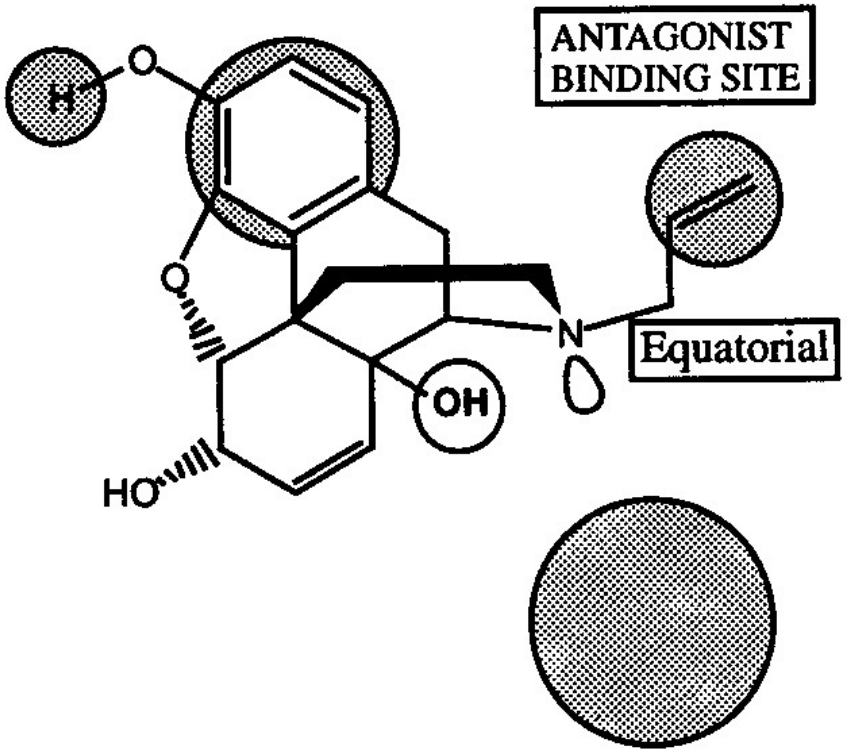
- an aromatic ring and a basic nitrogen atom are necessary for action, a phenolic group is not(⇔ the rings B, C, D and E of the morphine skeleton are not necessary for analgesic action)
- quarternary (tetrasubstituted) C(4) of piperidine derivatives is necessary in the frame of this group, with exception 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 equtorial position; this moiety as a steric hindrance orients into equatorial position also other substituents than allyl (e.g. cyclopropylmethyl)

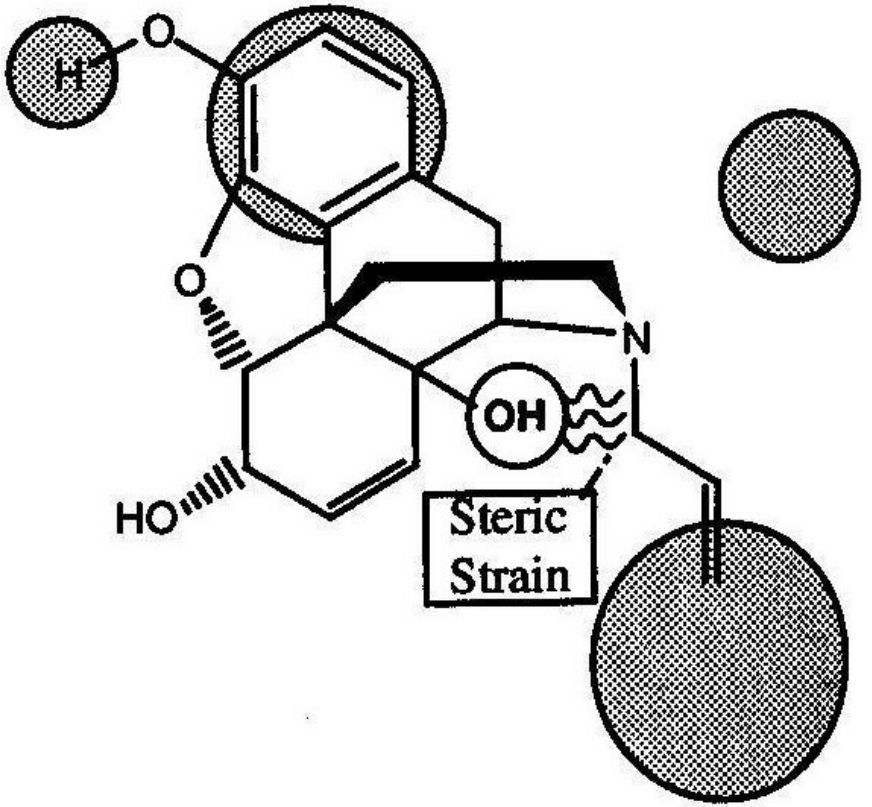
N-substituted morphine derivatives acting as agonists and antagonists – a model of interaction with a receptor



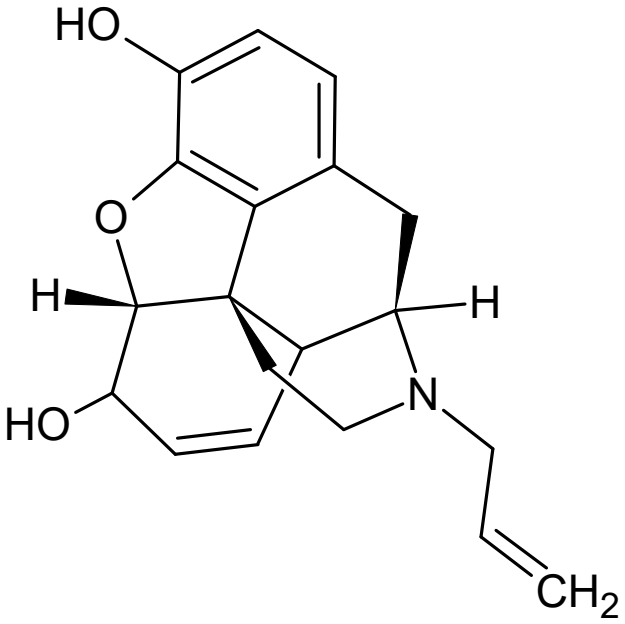
Morphine receptor antagonists with -OH group at C(14)

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

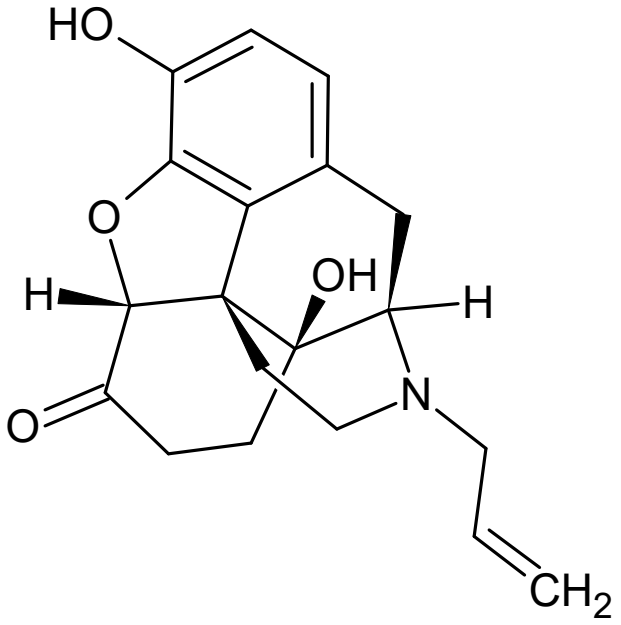




Morphine receptor antagonists

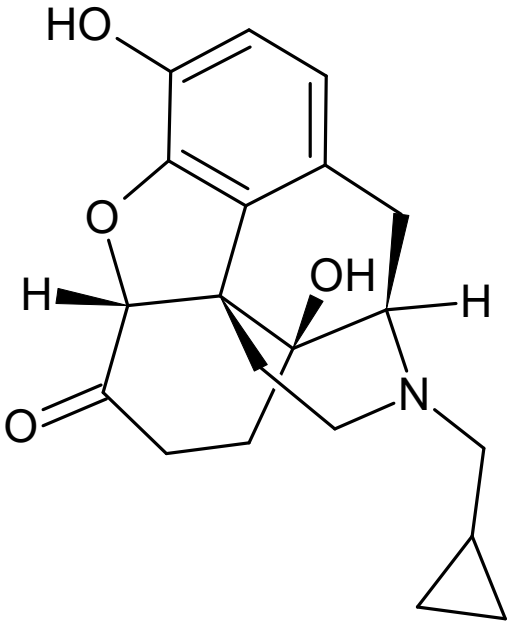


nalorphine



naloxone
Naloxoni hydrochloridum dihydricum PhEur
•*i.v.* administration only; extensively methabolised in liver
Naloxone WZF ® Polfa

•antidots in opiates overdosage



naltrexone
Naltrexoni hydrochloridum PhEur
•*p.o.*
•useful also in treatment of alcoholism (blocks binding of endoopioids)
Revia ® por tbl flm