ANALGETICI

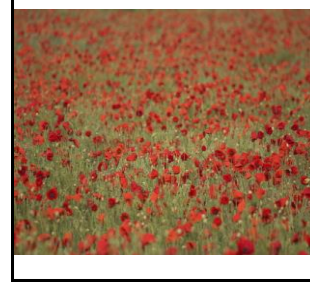
VRSTE BOLA

Nociceptivni

Somatski Visceralni

Neuropatski

- Opioidni analgetici
- Nesteroidni antiinflamatorni lekovi



Opioidi

1. Opijati — opijum; morfin; kodein; tebain

2. Opioidni Derivati — heroin — hidromorfon — oksimorfin — oksikodon — etorfin

3. Sintetski Opioidi — metadon — meperidin — propoksifen — LAAM

4. Endogeni opioidni peptidi

Opioidni analgetici:

- morfin i derivati (polusintetski),
- morfinani,
- dimetilbenzomorfani,
- fenilpiperidini,
- fenilpropilamini (metadoni)
- oripavini i
- opioidi različitih struktura.

} sintetski

Opioidni receptori

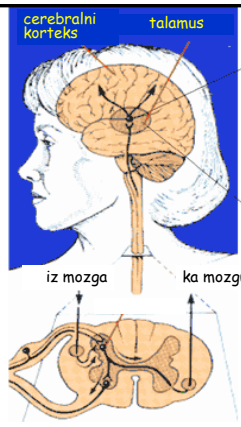
U mozgu, kičmenoj moždini i perifernim tkivima.

Centralna i periferna distribucija receptora je kompleksna.

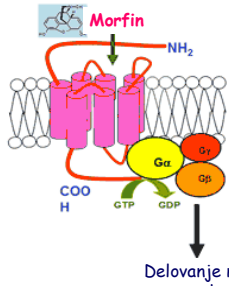
Četiri (pet?) tipova opioidnih receptora:

- μ- (mi),
- κ- (kapa),
- δ- (delta)
- σ- (sigma)

Periferni opioidni receptori dokazani su u ileumu i odgovorni su za antidijaroično dejstvo opioida.



Mi opioidni receptori locirani na membrani nervne ćelije



Delovanje na mozak

inhibiraju aktivnost adenilat ciklaze

Opioidni receptori ~40% identični sa receptorima za somatostatin !

Stimulacija receptora

Mi (OP3)- mesto delovanja endogenih peptida, većine klinički značajnih opioida: morfin, derivati morfinana, benzomorfana, anilidopiperidini i derivati difenilheptana

- -Fizička zavisnost
- -Euforija
- -Analgezija
- -Respiratorna depresija
- -Smanjuju motilitet GIT

Kapa (OP2)-specifični za peptide ekoji na položaju 6 sadrže aminokisleinu arginin, tj specifično vezuju dinorfine ali i salvinorin.

- -Sedacija
- -Analgezija
- -Mioza
- -kapa agonisti ne izazivaju respiratornu depresiju, konstipaciju i fizičku zavisnost

Delta (OP1)

- -Analgezija
- -Mesto delovanja enkefalina i derivata (DA^{2}DLE^5; DSLET)
- -Oslobadja hormon rasta

Orfan opioidni receptori

- Endogeni heptadekapeptid (nociceptin; orfanin FQ)

Sigma

- -Disforija
- -Halucinacije (i vizuelne i auditorne)
- -Resapiratorna i vazomotorna stimulacija
- -Midrijaza

Opioidni analgetici:

- razvijaju toleranciju i zavisnost!
- sedativni efekat - zato ih nazivamo i narkotici!
- poboljšavaju raspoloženje (euforični efekat)
- u većoj meri izazivaju halucinacije
- inhibiraju disanje i kašalj (npr. kodein i folkodin)

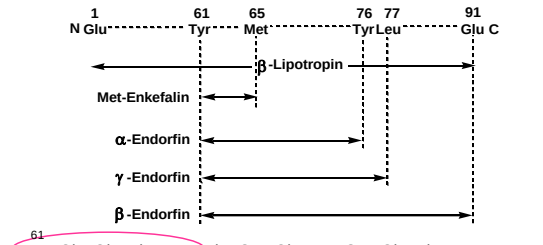
Tolerancija

≠

Psihička zavisnost

Fizička zavisnost

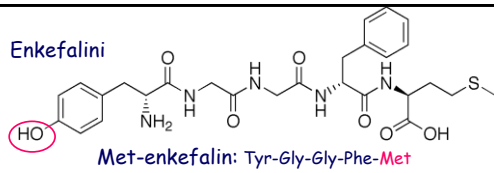
Endogeni opioidi POMC-241 ak



61
–Tyr–Gly–Gly–Phe–Met–Thr–Ser–Glu–Lys–Ser–Gln–Thr–Pro–Leu–Val
Thr
Leu
91
HO–Glu–Gly–Lys–Lys–Tyr–Ala–Asn–Lys–Ile–Ile–Ala–Asn–Lys–Phe

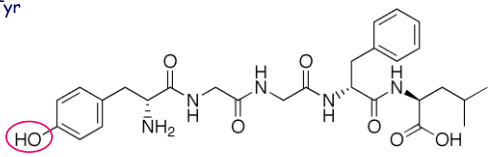
Humani β-endorfin

Enkefalini



Met-enkefalin: Tyr-Gly-Gly-Phe-Met

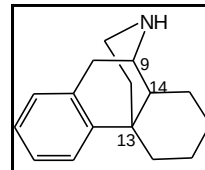
Tyr



Leu-enkefalin: Tyr-Gly-Gly-Phe-Leu

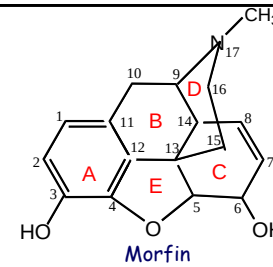
"specifični" endorfini, 1975, pentapeptidi.

Dinorfini-iz prodinorfina (32 ak); A i B

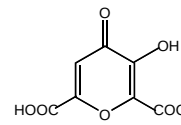


Morfinan

1,2,3,9,10,10a-Heksahidro-10,4a (4*H*)-iminoetano fenantren



Morfin

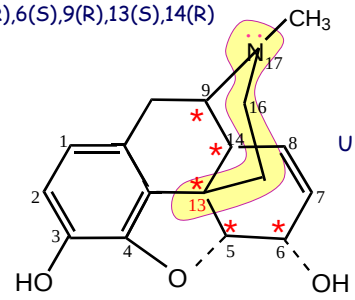


Mekonska kiselina

3-hidroksi-γ-piron-2,6-dikarbonska kiselina

analgezija, euforija i sedacija, depresija disanja i supresija kašlja, mučnina i povraćanje, sužavanje zenica, smanjen motilitet u gastrointestinalnom traktu, što dovodi do opstipacije

5(R),6(S),9(R),13(S),14(R)

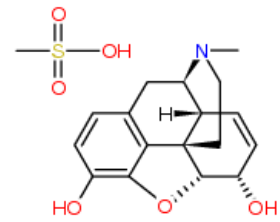


SAR

U palijativnoj terapiji

Morfin: (5a,6a)-7,8-didehidro-4,5-epoksi-17-metil-morfinan-3,6-diol

16 optičkih izomera



Hloridi, sulfati, fosfati. Morfin baza-nerastvorna u vodi.

SAR

Uklanjanje OH smanjuje aktivnost

Uklanjanje povećava aktivnost

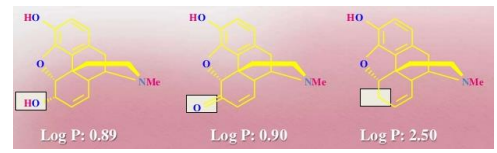
N-$CH_2CH{=}CH_2$ antagonosti

Oksidacija zajedno sa redukcijom 7,8 C=C ↑, Acetilovanje ↑

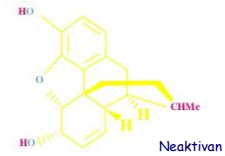
Redukcija ↑

Uvodjenje OH ↑

SAR



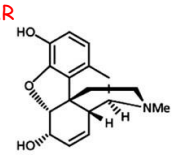
Smanjenjem polarnosti povećava se ativnost.



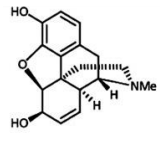
Neaktivan

Azot je neophodan za dejstvo.

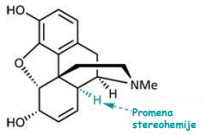
SAR



„Prirodni" morfin

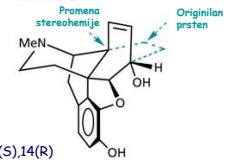


„Neprirodni" morfin
(lik u ogledalu)



10 % aktivnosti morfina

=

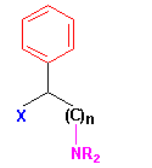


5(R),6(S),9(R),13(S),14(R)

Promena stereohemije smanjuje ativnost.

Stereohemija morfina

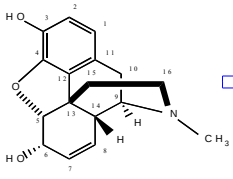
(-) morfinan (B/C = *cis*; C/D = *trans*)

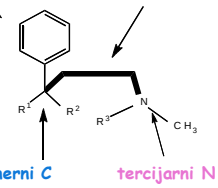


Farmakofora odgovorna za analgetsko delovanje

aromatični prsten

spacer

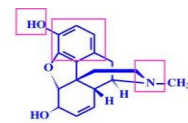


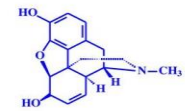


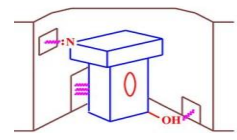
kvaternerni C

tercijarni N

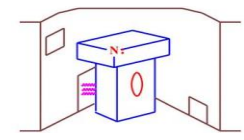
„Prirodni" morfin je levoaktivan (-), dok se (+) morfin dobija sintezom i nema analgetičko dejstvo.



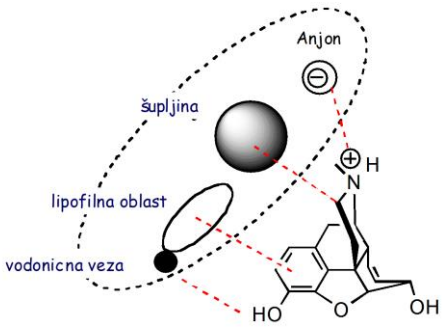




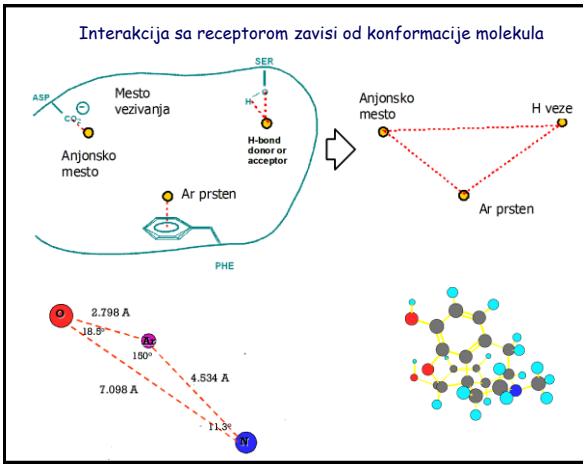
3 interakcije sa receptorom

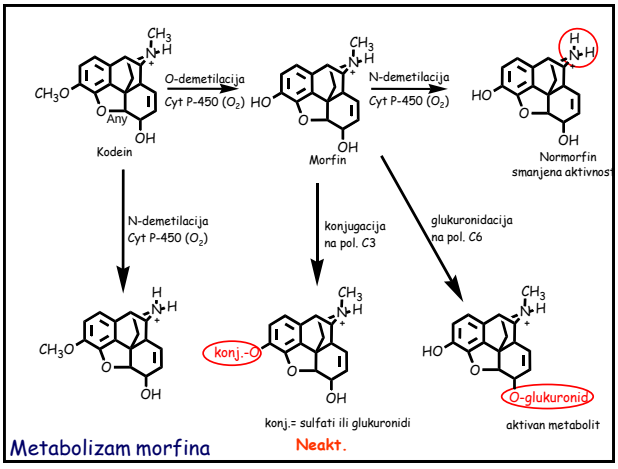


1 interakcija sa receptorom



Vezivanje morfina za receptor

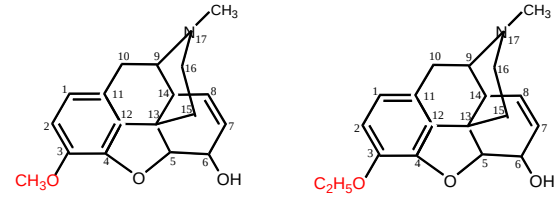




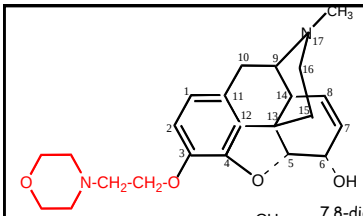
Metabolizam morfina

POLUSINTETSKI OPIOIDNI ANALGETICI

Eterifikacija

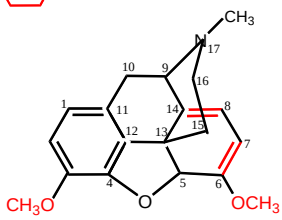


Kodein Dionin



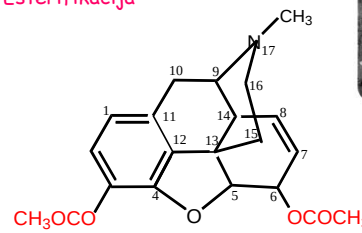
Folkodin

7,8-didehidro- 4,5a-epoksi- 17-metil -3-[2-(morfolin-4-il) etoksi] morfinan-6a-ol



Tebain (prirodni)

Esterifikacija



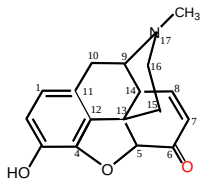
Heroin 1895 (Bayer)

morfin
heroin
6-acetilmorfin

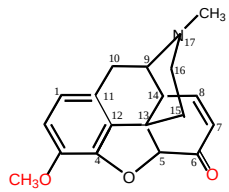
Čisti heroin je bele boje, gorkog ukusa.

Jaka psihička i fizička zavisnost!

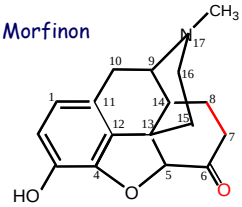
Oksidacija i redukcija



Morfinon



Kodeinon

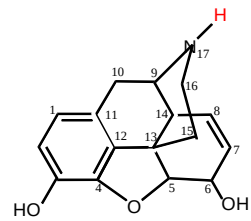


Dihidromorfinon

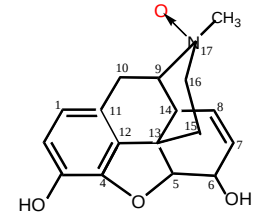
Veća fleksibilnost molekule

8 do10 puta efikasniji analgetik od morfina

Promene na N

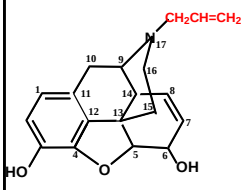


Normorfin

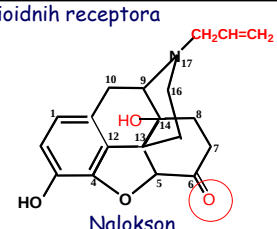


Genmorfin

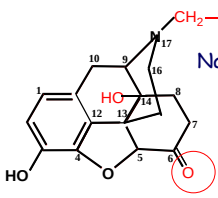
Antagonisti opioidnih receptora



Nalorfin (parcijalni)



Nalokson



Naltrekson

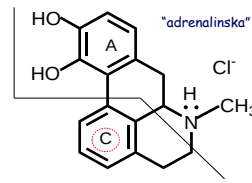
Puni antagonista

4 oblik naltreksona-ne prolazi HEB, za lečenje opstipacije

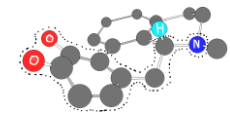
Dominantno redukcija-aktivni metabolit

Autoklaviranje

Morfin —(3 % HCl, 140° C, p, katalizator)→ Apomorfin



"adrenalinska" struktura

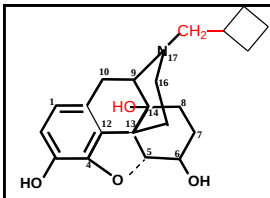


Isprekidanim linijama označen dopaminski fragment molekula.

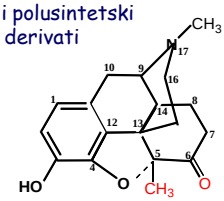
Nije analgetik !

Dopaminergik, emetik, ekspektorans. Isključivo parenteralno.

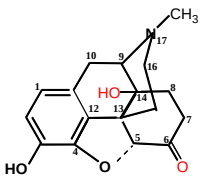
Ostali polusintetski derivati



Nalbufin/agon, antagon

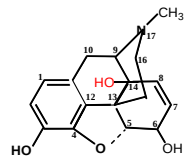


Metopon (1948)



Numorfan (oksimorfon)

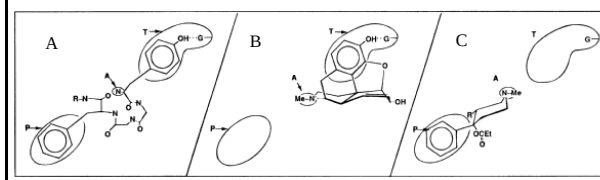
hidroksihidromorfinon



Oksimorfin

SINTETSKI OPIOIDNI ANALGETICI

Zbog različitih konformacionih oblika koje mogu da zauzimaju, opioidi se ne vezuju samo za jedan opioidni receptor već ostvaruju interakciju sa različitim receptorima i sa različitim delovima istog receptora čime se i objašnjavaju sporedni efekti.



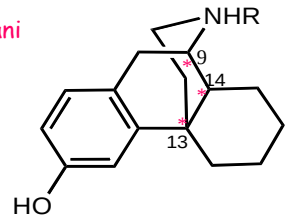
Vezivanje enkefalina, morfina i meperidina za μ-opioidne receptore

-Sintetska jedinjenja sa fenolnom grupom-kao tirozin enkefalina (T)

-Sintetska jedinjenja bez fenolne grupe-kao fenilalanin enkefalina (P)

-Zajedničko za obe serije opioida-slobodna amino grupa tirozina reaguje sa anjonskim delom receptora.

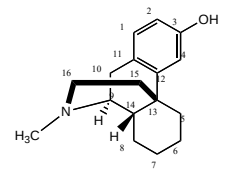
Morfinani



R= $-CH_3$ Levorfanol (5x od morfina)

R= $-CH_2-CH=CH_2$ Levalorfan (5x od nalorfina)

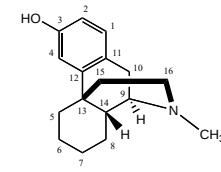
R= $-CH_2$  Butorfanol/



Dekstrorfan

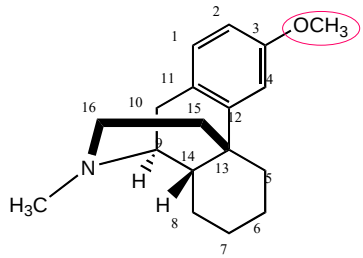
Antitusik

ogledalo



Levorfanol

Analgetik+Antitusik

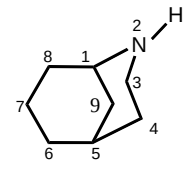


Dekstrometorfan

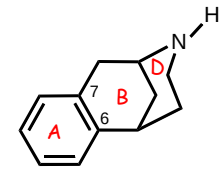
Antitusik (sintetski, bez analgetskog delovanja)

(6,7)-benzomorfani

manja sklonost ka navikavanju, toleranciji, jednostavniji su za sintezu.

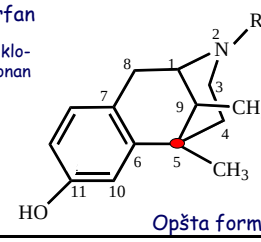


Morfan



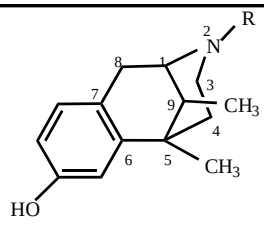
6,7-benzomorfan

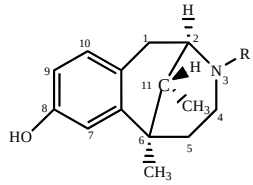
2-azabiciklo-[3,3,1]-nonan



cis

Opšta formula





R= -CH_3 Metazocin

R= -CH_2-CH_2-C_6H_5 Fenazocin 20 x jači od metazocina

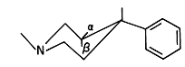
R= -$CH_2CH{=}C(CH_3)_2$ Pentazocin

Pentazocin: agonist κ-receptora i slab antagonist μ-receptora.

Manje toksičan i manje izaziva zavisnost.

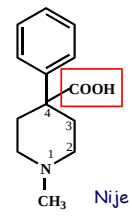
Derivati 4-fenilpiperidina (fleksibilna struktura)

- derivati 4-fenilpiperidinkarboksilne kiseline
- derivati 4-fenilpiperidinola

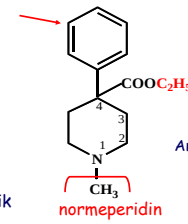


Identične hemijske modifikacije ne dovode do istih bioloških efekata!

derivati 4-fenilpiperidinkarboksilne kiseline



Nije analgetik



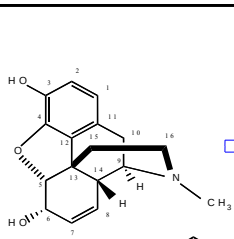
Meperidin (Petidin)

Antimuskarinsko dejstvo

normeperidin

CNS ekscitacija

Ravan simetrije !

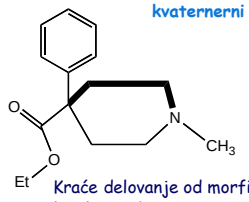


aromatični prsten

spacer

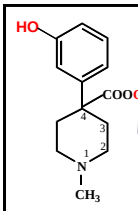
kvaternerni C

tercijarni N



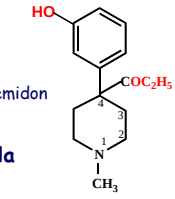
Meperidin

Kraće delovanje od morfina, bezbedniji, manje izaziva zavisnost, spazmolitični efekat?



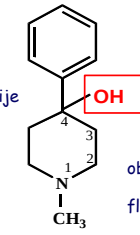
Bemidon

Ketobemidon



Derivati 4-fenilpiperidinola

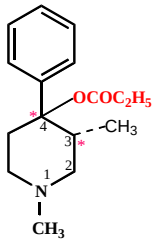
Identične hemijske modifikacije ne dovode do istih bioloških efekata!



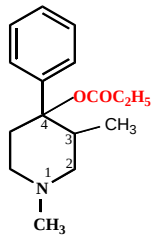
obrnuti (reverzni) estri

fleksibilna struktura

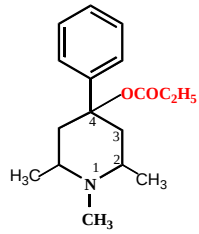
Homolozi reverznih estara petidina:



α-prodin



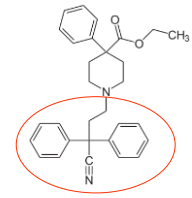
β-prodin



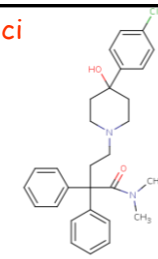
Promedol
dimetilmeperidin

Nemaju kvaternerni C-atom !

Opioidni antidijaroici



Difenoksilat



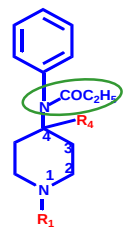
Loperamid

Derivat petidina, u malim dozama ne prolazi HEB, ne dovodi do opioidnog efekta

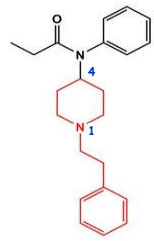
derivat 4-fenilpiperidinola

Da bi se sprečilo uzimanje većih doza i zloupotreba leka, često se koriste sa atropinom, antiholinergikom koji proizvodi slabost i mučninu u prevelikim dozama.

Derivati 4-anilidopiperidina (analozi fentanila)



Amid propionske kiseline



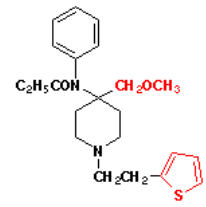
Fentanil (1960)

N-fenil-*N*-[1-(feniletil)-piperidin-4-il] propanamid

Jedan od najjačih opioidnih analgetika (80x (μ), 30 min).

Manje neželjenih efekata,transdermalno (72 sata), anestezija i analgezija.

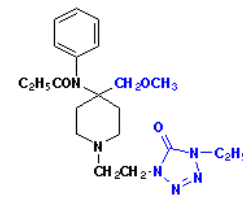
0,3-0,4 mg iv (sa npr droperidolom)- **neuroleptanalgezija**



Sulfentanil

Jako lipofilan, brzo i kratko delovanje.

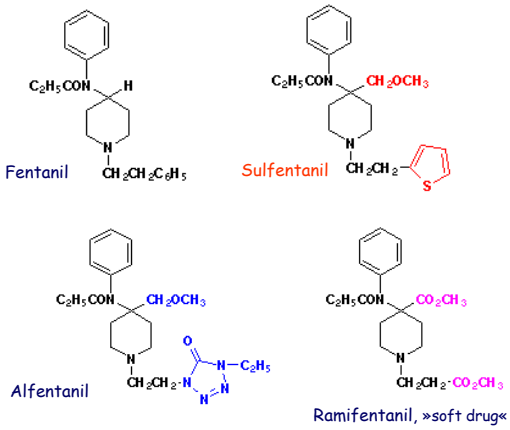
Manje izražena respiratorna depresija.



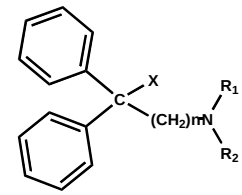
Alfentanil

25 puta slabiji od morfina

Niža pKa, manje jonizovan, lakše prolazi kroz HEB.



Metadon i analozi metadona

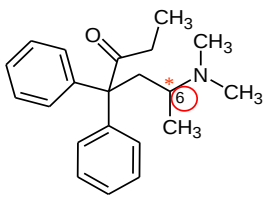


Nemaju piperidinski prsten !

Slobodna pokretljivost baznog niza je ograničena.

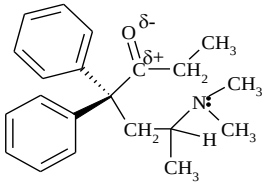
Opšta formula metadonske grupe analgetika

X: -CO-R; -CHOH-R; -COO-R; -$CONH_2$
"**n**" je najčešće 2
R_1,R_2: CH3



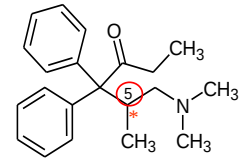
Metadon
6-dimetilamino-4,4-difenil-3-heptanon

Kod zavisnika samo oralni oblici.
iv-euforija !

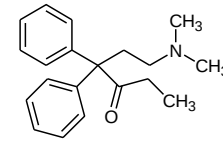


U rastvoru-delimično cikličan oblik.

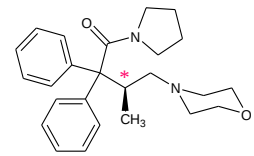
Konformacija metadona stabilizovana dipolarnim interakcijama.



Izometadon
6-dimetilamino-5-metil-3-heksanon



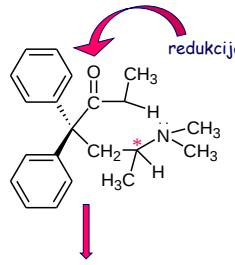
Normetadon
Optički neaktivan



Dekstromoramid
1-[(3S)-3-metil-4-(4-morfolinil)-1-okso-2,2-difenilbutil] pirolidin

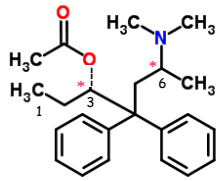
Derivat izometadona

Redukcijom metadona-metadoli



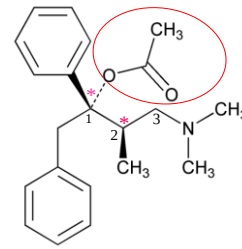
Alkoholi

Slabo analgetičko dejstvo



Metadolacetat
(estar)

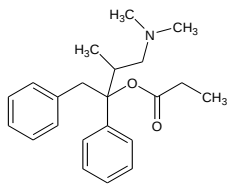
L-a-acetilmetadol (LAAM)

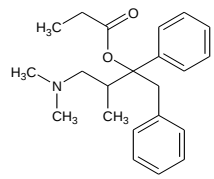


Slab opiodni analgetik, antitusik.

Propoksifen

(1*S*,2*R*)-1-benzil-3-(dimetilamino)-2-metil-1-fenilpropil propionat





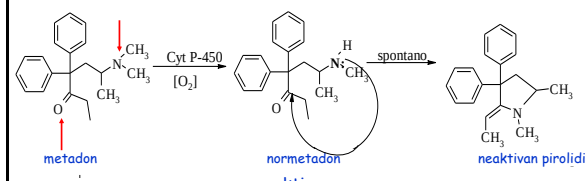
Stereozomeri propoksifena

Dekstropropoksifen
Analgetik

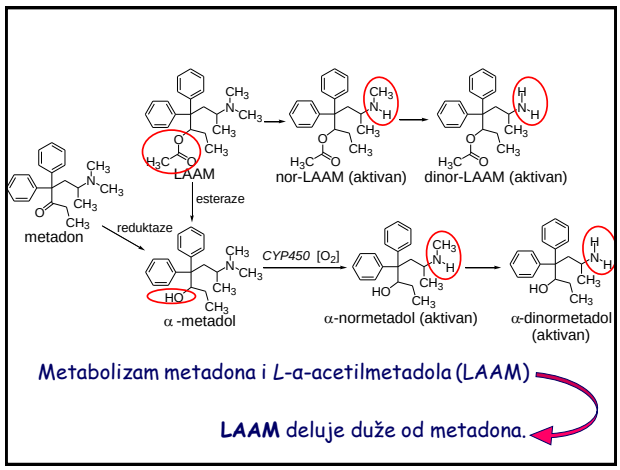
Levopropoksifen
Antitusik

[*S*-(*R**,*S**)]-α-[2-(Dimetilamino)-1-metiletil]-α-fenilbenzenetanol propanoat (estar)

Soli: hidrohloridi, napsilati (2-naftalensulfonati)



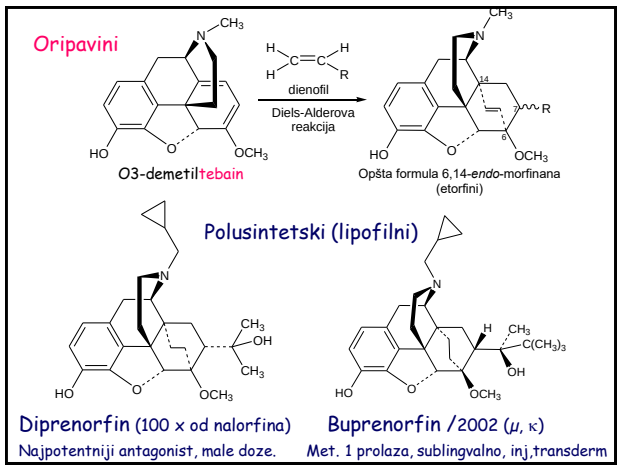
Metabolizam metadona



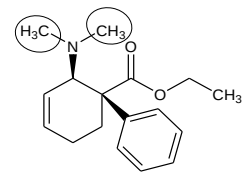
Metabolizam metadona i *L*-α-acetilmetadola (LAAM)

LAAM deluje duže od metadona.

Naziv	R_1	R_2	opioidna aktivnost
Metadon	$-C(=O)-C_2H_5$	$-CH_2CH(CH_3)N(CH_3)_2$	1,0
Levanon	$-C(=O)-C_2H_5$	$-CH_2CH(CH_3)N(CH_3)_2$	1,9
Izometadon	$-C(=O)-C_2H_5$	$-CH(CH_3)CH_2N(CH_3)_2$	0,65
Normetadon	$-C(=O)-C_2H_5$	$-CH_2CH_2N(CH_3)_2$	0,44
Dipanon	$-C(=O)-C_2H_5$	$-CH_2CH(CH_3)$-N	0,80
Heksalgon	$-C(=O)-C_2H_5$	$-CH_2CH_2$-N	0,5
Fenadokson	$-C(=O)-C_2H_5$	$-CH_2CH(CH_3)$-N	1,4
alfacetilmetadol	$-CH(OCOCH_3)-C_2H_5$	$-CH_2CH(CH_3)N(CH_3)_2$	1,3
betacetilmetadol	$-CH(OCOCH_3)-C_2H_5$	$-CH_2CH(CH_3)N(CH_3)_2$	2,3
dioksafenilbutirat	$-COOC_2H_5$	$-CH_2CH_2$-N	0,25
racemoramid	$-C(=O)$-N	$-CH(CH_3)CH_2$-N	0,36
dekstromoramid	$-C(=O)$-N	$-CH(CH_3)CH_2$-N	13



Opioidni analgetici različitih struktura



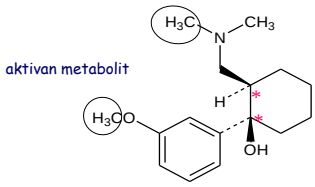
Tilidin (E)

(1R,2S)-2-(dimetilamino)-1-fenil-3-cikloheksen-1-karboksilne kiseline ili (±)-trans-2-(dimetilamino)-1-fenil-3-cikloheksen-1-karboksietilestar

Slab opioid (per os 100 mg =20 mg morfina); per os, supp, inj

Ne izaziva euforiju ni naviku.

Nortilidin, bisnortilidin-aktivni metaboliti.



aktivan metabolit

Tramadol (Trodon)

(1*R*,2*R*)-2-[(dimetilamino)metil]-1-(3-metoksifenil) cikloheksanol ili

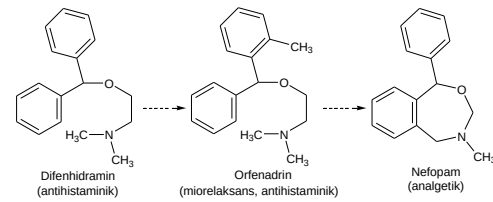
(±)-*trans*-2[(dimetilamino)metil]-1-(3-metoksifenil)cikloheksanol

U obliku racemata: (+) izomer-opioidno (*μ*); (-) izomer-inhibitor preuzimanja NOR, Ser

Kombinuje se sa paracetamolom.

Metabolizam: CYP 3A4 i CYP2D6. Interakcija sa TCA, SSRI;

Nefopam: centralno delujući neopioidni analgetik



Difenhidramin (antihistaminik)

Orfenadrin (miorelaksans, antihistaminik)

Nefopam (analgetik)

Ciklizacije antihistaminika i prevođenje u rigidniju strukturu nefopama

Nefopam: (3,4,5,6-tetrahidro-5-metil-1-fenil-1*H*-2,5-benzoksazocin)

Umereno jak analgetik **bez afiniteta za opioidne receptore**, povećava hepatotoksičnost paracetamola.

ANTITUSICI

Mehanizam delovanja:

Centralno, povišenjem praga nadražaja neurona koji se nalaze u centru za kašalj u CNS.

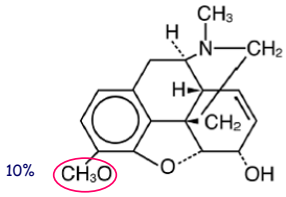
Periferno, smanjenjem nadražaja ili čak i blokadom receptora za kašalj koji se nalaze u plućima.

Centralni antitusici

Opioidni antitusici (morfin, kodein, etilmorfin, dihidrokodein, hidrokodon, dekstrometorfan, folkodin, noskapin)

Neopioidni antitusici (butamirat, pentoksiverin, pipazetat)

Centralni antitusici sa opioidnim delovanjem

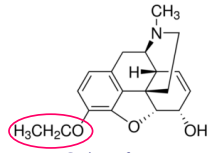


10%

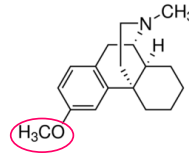
Kodein (fosfat); 15-20 mg

tablete, kapsule, sirup

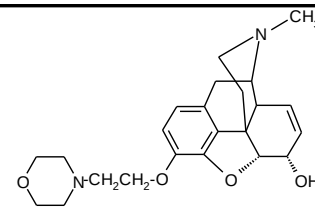
Plivadon, Caffetin



Etilmorfin



Dekstrometorfan



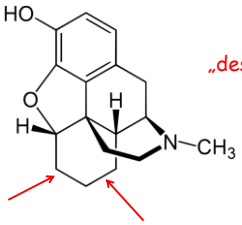
Folkodin

(+)-3-metoksi-17-metil-9α,13α,14α-morfinan

Nije analgetik, ne povećava spazam u GIT, ne deprimira disanje, ne stvara se tolerancija;

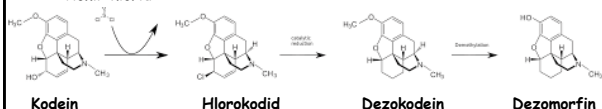
Odnos antitusičkog i sedativno-opioidnog delovanja zavisi od doze.

Metabolizam: oksidacija i konjugacija, najvažniji metabolit-konjugovani morfin (+ rezultati na opioide u urinu!)!



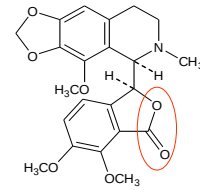
"krokodil," "crocodile", „desomorphine","desoxymorphine"

Tionil-hlorid

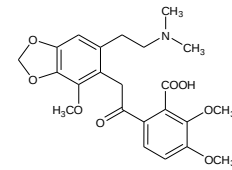


Kodein — Hlorokodid — Dezokodein — Dezomorfin

Dihidrodezokodein



Noskapin



Narcein

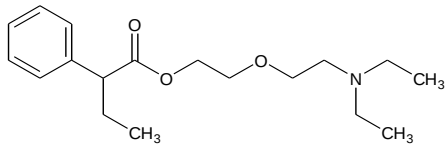
Polusintetski antitusik

Prirodni proizvod, izolovan iz opijuma (11%).

[*S*-(*R**,*S**)]-6,7-dimetoksi-3-(5,6,7,8-tetrahidro-4-metoksi-6-metil-1,3-dioksolo[*4,5-g*]izohinolin-5-il)-1(3*H*)-izobenzofuranon

Za razliku od kodeina ne stvara naviku, ne deluje depresivno na CNS, disanje i peristaltiku creva.

Sintetski antitusici (bazni estri i etri)



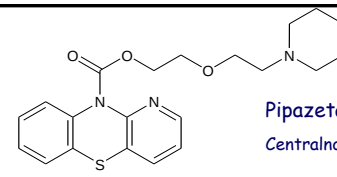
Butamirat
(Sinecod)

2-[(2-dietil amino)etoksi] etilestar-α-etilfenil-sirćetne kiseline
(fenilbuterne kiseline)

Sintetski **neopioidni antitusik**, blokira centar za kašalj u produženoj moždini, najprepisivaniji lek.

Kod jakog akutnog i hroničnog suvog kašlja, za pre- i postoperativno smirivanje kašlja kod hirurških zahvata i bronhoskopija.

Bezbedniji od kodeina, ne izaziva zavisnost.

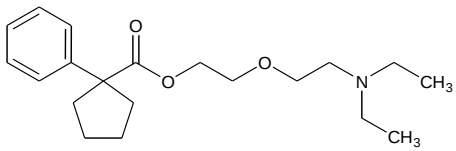


Pipazetat (azafenotiazin)

Centralno i periferno

Prednost neopioidnih centralnih antitusika:

- selektivno deluju na centar za kašalj-ne deluju depresivno na CNS i centar za disanje;
- ne deluju na opioidne receptore i ne dovode do stvaranja zavisnosti,;
- ne deluju na tonus glatkih mišića GIT i ne dovode do opstipacije,
- imaju veliku terapijsku širinu;
- dobro se resorbuju iz GIT-a;
- ne stupaju u interakciju sa drugim lekovima.



Karbetapentan (pentoksiverin)

Periferni antitusik.

Mehanizam nije dovoljno objašnjen;

Antagonista M1, agonista σ;

Citrat, hidrohlorid

Kao antitusici koriste se i neke druge grupe lekova:

- Antihistaminici
- Simpatomimetici
- Parasimpatolitici
- Ekspektoransi

EKSPEKTORANSI

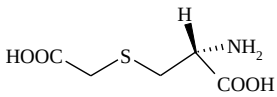
➢Sekretolitici (pojačavaju bronhijalnu sekreciju vode, stimulišu aferentna parasimpatikusna vlakna ili direktno deluju na ćelije koje stvaraju mukus)-NH_4Cl, KJ...

➢Sekretomotorici (povećavaju pokretljivost sekreta i njihovo izbacivanje putem kašlja).

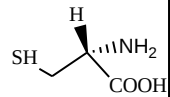
➢Mukolitici (smanjuju viskozitet mukusa)

kidaju disulfidne veze (karbocistein, acetilcistein),

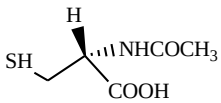
enzimski (proteolitički enzimi-tripsin i himotripsin)



Karbocistein: S-(karboksimetil)-L-cystein

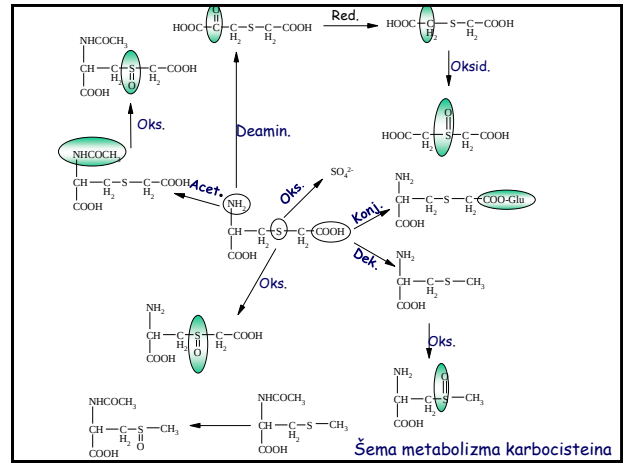


L-Cystein

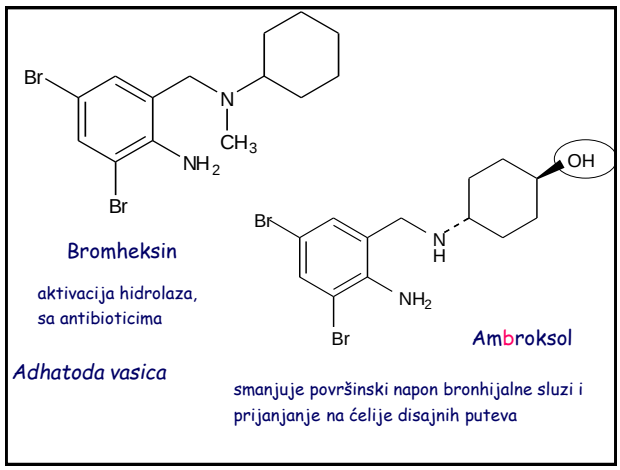


Acetilcistein: N-acetil-L-cystein

Može se primeniti i parenteralno, za razliku od karbocisteina.



Šema metabolizma karbocisteina



Bromheksin

aktivacija hidrolaza,
sa antibioticima

Adhatoda vasica

Ambroksol

smanjuje površinski napon bronhijalne sluzi i prijanjanje na ćelije disajnih puteva