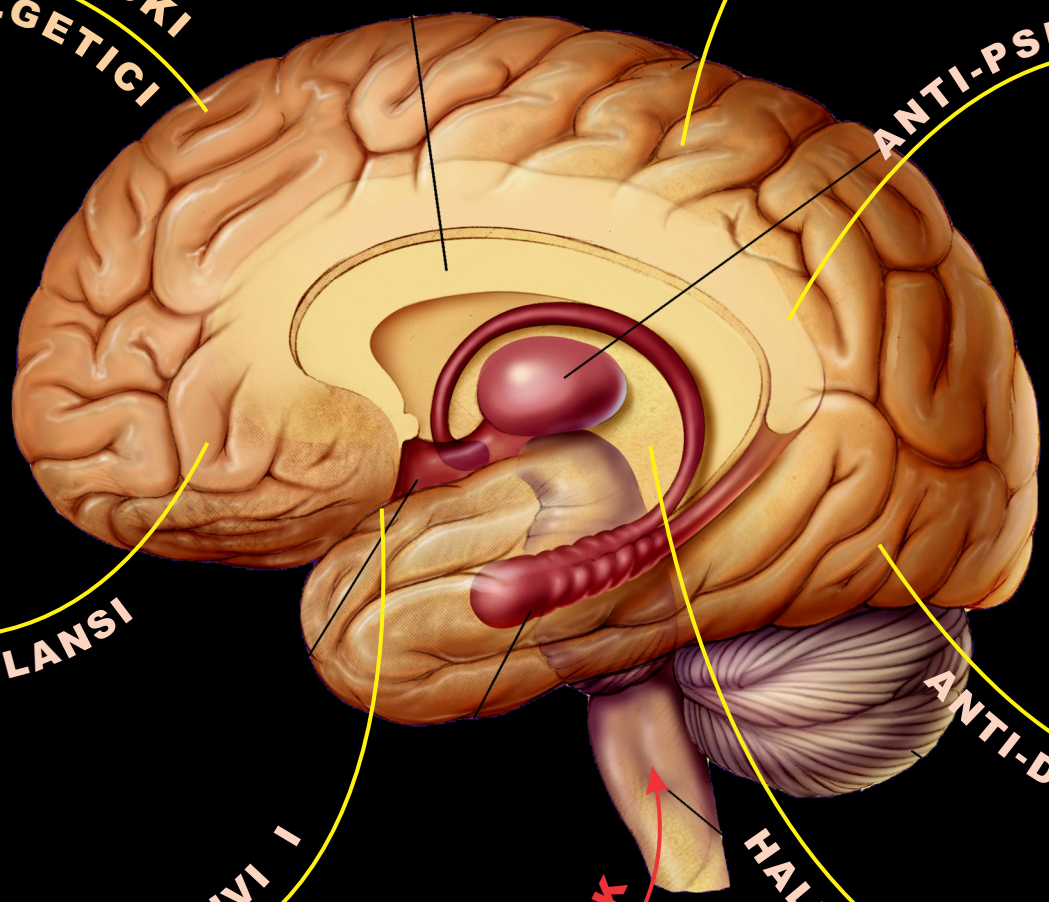
SHEMATSKI PRIKAZ DEJSTVA POJEDNIH KLASA PSIHOAKTIVNIH SUPSTNCI NA MOZAK I PSIHIČKO STANJE



NARKOTIČKI ANALGETICI

DEJSTVO

GUBITAK OSEĆAJA BOLA (CENTRALNA ANALGEZIJA); NE DOLAZI DO USPAVLJIVANJA

CENTRALNI ANESTETICI

DEJSTVO

BESVESNO STANJE SA BITNO SMANJENIM FUNKCIJAMA MOZGA (SAMO KOD HIRURŠKIH INTERVENCIJA)

ANTI-PSIHOTICI

DEJSTVO

U TERAPIJI PACIJENATA KOJI BOLUJU OD ŠIZOFRENIJE I DR.; UBLAŽAVA KLINIČKE SIMPTOME OBOLJENJA

STIMULANSI

DEJSTVO

POVEĆANA KONCEN-TRACIJA I RADNI KAPACITET, BRŽE REFLEKSNO REAGO-VANJE, EUFORIJA, RAZD-RAŽLJIVOST, AGRESIVNOST, NESANICA

ANTI-DEPRESANTI

DEJSTVO

U TERAPIJI PACIJENATA KOJI BOLUJU OD DEPRESIJE; UBLAŽAVA KLINIČKE SIMPTOME OBOLJENJA

SEDATIVI I HIPNOTICI

DEJSTVO

UBLAŽAVANJE RAZDRAŽ-LJIVOSTI I NAPETOSTI, BOLJI SAN, SMANJENA KONCENTRACIJA, USPORENO REFLEKSNO REAGOVANJE. SAMO KOD HIPNOTIKA - DIREKTNO IZAZIVANJE SNA

HALUCINOGENI

DEJSTVO

IZAZIVA POREMEĆAJE U VIZUELNOJ I AUDITORNOJ PERCEPCIJI, “HALUCINACIJE”, KAO I TEŠKE POREMEĆAJE U PONAŠANU I RASUĐIVANJU

KRVOTOK

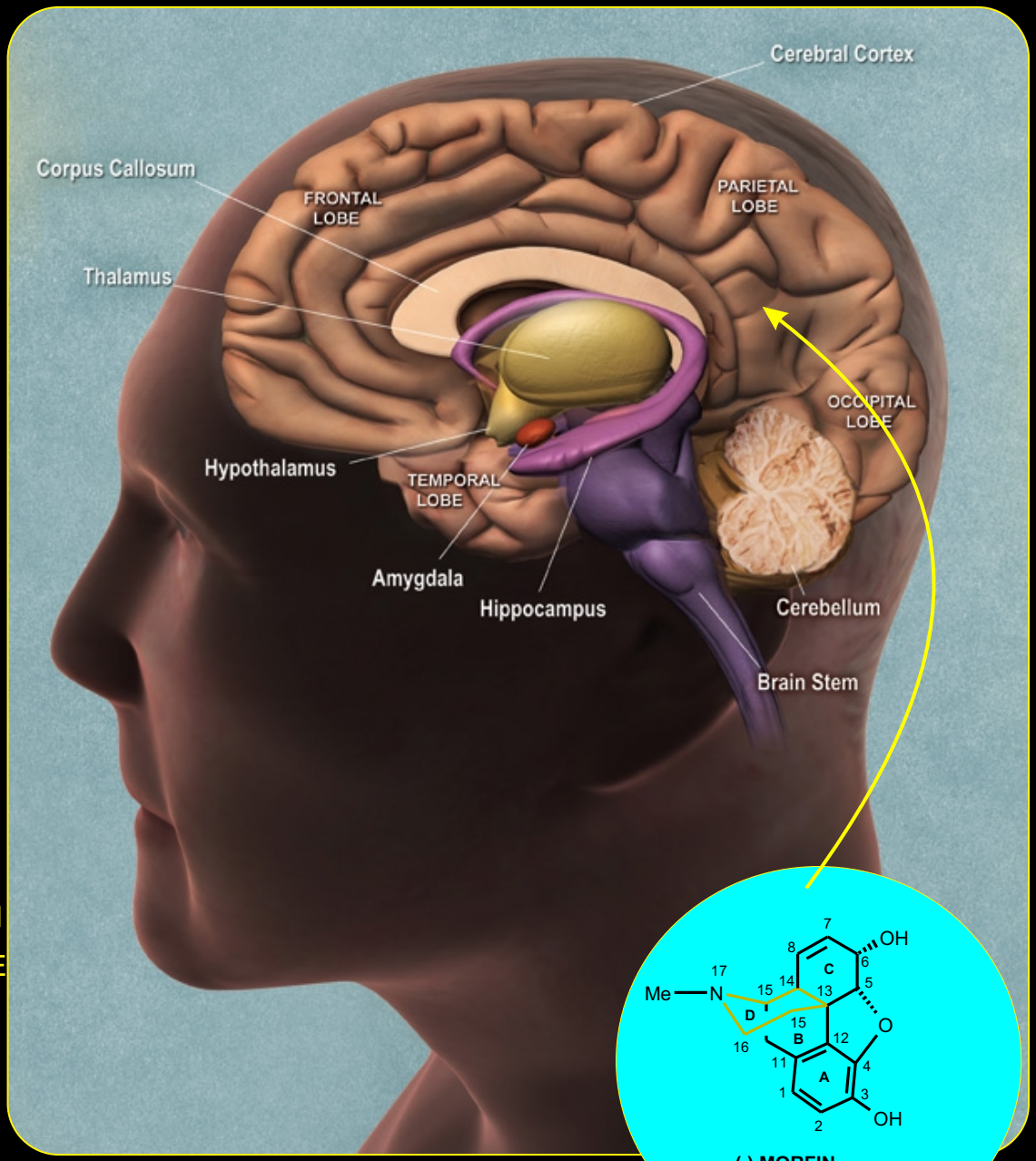
PSIHOAKTIVNA SUPSTANCA

NARKOTIČKI ANALGETICI- UVOD

-SUPSTANCE BILJNOG ILI SINTETIČKOG POREKLA, KOJE, UNESENE U ORGANIZAM ČOVEKA (I DRUGIH SISARA), DOVODE DO POTPUNOG, ALI PRIVREMENOG GUBITKA OSEĆAJA BOLA BILO KOJE VRSTE.

-DELUJU PRE SVEGA NA MOZAK, (CENTRALNI NERVNI SISTEM) TAKO ŠTO SE VEZUJU ZA OPIOIDNE RECEPTORE - SPECIFIČNE PROTEINE LOCIRANE NA MEMBRANAMA MOŽDANIH ĆELIJA. POŠTO JE OSNOVNA BIOLOŠKA ULOGA OPIOIDNIH RECEPTORA DA UPOZORE ORGANIZAM NA PRISUSTVO BOLNOG NADRŽAJA (NPR. POVREDE, TOPLOTE I DR.), TO NJIHOVA BLOKADA DEJSTVOM MOLEKULA NARKOTIČKOG ANALGETIKA DOVODI DO PRIVREMENOG GUBITKA OSEĆAJA BOLA. PO PRESTANKU DEJSTVA ANALGETIKA, (USLED METABOLIČKE RAZGRADNJE I DRUGIH FAKTORA), OSEĆAJ BOLA SE PONOVO JAVLJA.

-ZA RAZLIKU OD NARKOTIČKIH ANALGETIKA, DRUGE VRSTE ANALGETIČKIH LEKOVA, KAO ŠTO SU ASPIRIN, STEROIDNI ANTI-INFLAMATORNI PREPARATI I DR., NE DELUJU NA MOZAK I NE POKAZUJU NIKAKVO PSIHOAKTIVNO DEJSTVO. MEĐITIM TAKVI NE-NARKOTIČKI ANALGETICI DALEKO SU MANJE EFIKASNI OD NARKOTIČKIH, ŠTO IM OGRANIČAVA PRIMENU SAMO NA TRETMAN SLABIJEG DO UMERENOG BOLA.



ALKALOID MORFIN - AKTIVNI KONSTITUENT OPIJUMA

NARKOTIČKI ANALGETICI- nastavak

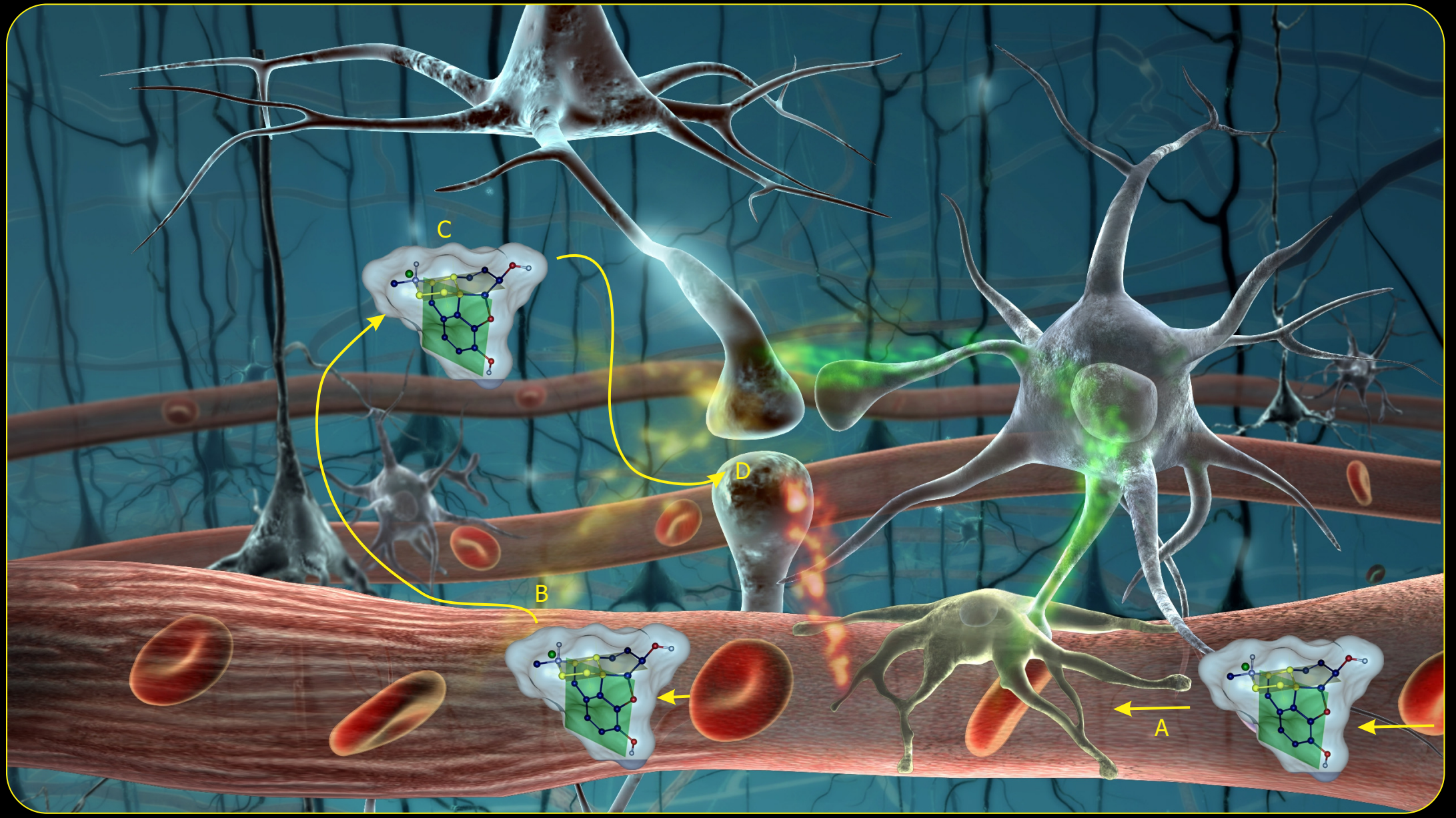
-MEDICINSKI ZNAČAJ NARKOTIČKIH ANALGETIKA JE IZUZETNO VELIKI I NEZAMENLJIV, JER SE SAMO NJIHOVOM PRIMENOM MOŽE UBLAŽITI INTENZIVAN BOL KOJI SE ČESTO JAVLJA KOD TEŽIH POVREDA, ZATIM TOKOM ORTOPEDSKIH I DRUGIH INTERVENCIJA (KOJE SE IZVODE BEZ TOTALNE ANESTEZIJE) A ČESTO I NEPOSREDNO POSLE POJEDINIH HIRURŠKIH INTERVENCIJA. POREDTOGA, UBLAŽAVANJE HRONIČNOG BOLA U SLUČAJEVIMA TERMINALNIH MALIGDNIH OBOLJENJA, PRAKTIČNO JE JEDINO MOGUĆE PRIMENOM NARKOTIČKIH ANALGETIKA.

-OSNOVNI NEDOSTATAK SVIH NARKOTIČKIH ANALGETIKA JE NEIZBEŽNO STVARANJE PSIHIČKE I FIZIČKE ZAVISNOSTI KOD PACIJENTA, UKOLIKO JE POTREBNA REDOVNA PRIMENA U DUŽEM PERIODU (NPR, KOD LEČENJA TEŽIH POVREDA).

-POŠTO SU NARKOTIČKI ANALGETICI PSIHOAKTIVNE SUPSTANCE, NJIHOVO DEJSTVO NIJE OGRANIČENO SAMO NA ANALGEZIJU, VEĆ UTIČU I NA UKUPNO STANJE SVESTI ČOVEKA. TAKO POJEDINCI MOGU ISPOLJAVATI GENERALNO NEGATIVNU REAKCIJU NA OVE SUPSTANCE (DEPRESIJA, MUČNINA, SLABOST, LOŠE I NEPRIJATNO RASPOLOŽENJE) DOK DRUGI, NAPROTIV MOGI IMATI VEOMA PRIJATAN SUBJEKTIVAN OSEĆAJ OPUŠTENOSTI A ČESTO I EUFORIČNA I AGRESIVNA STANJA, POSEBNO POD DEJSTVOM HEROINA.

NARKOTIČKI ANALGETICI- nastavak

KAKO OPIOID PRODIRE U MOZAK I STIŽE DO CILJA - OPIOIDNOG RECEPTORA.



NARKOTIČKI ANALGETICI- nastavak

KAKO SE OPIOID VEZUJE ZA OPIOIDNI RECEPTOR.

А. ДЕО ЋЕЛИЈСКОГ ЗИДА (САСТАВЉЕН ОД ДВОСТРУКОГ СЛОЈА ФОСФО-ЛИПИДНИХ МОЛЕКУЛА) КОЈИ САДРЖИ ТРАНС-МЕМБРАНСКИ РЕЦЕПТОР И ЊЕГОВ ЛИГАНД

СПОЉАШЊИ СЛОЈ (ЗЕЛЕНО)

УНУТРАШЊИ СЛОЈ (ЦРВЕНО)

ХИДРОФОБНИ ДЕО ЗИДА

ХИДРОФИЛНИ ДЕО ЗИДА

УНУТРАШЊОСТ ЋЕЛИЈЕ (ЦИТОСОЛ)

Б. ИСТИ ТРАНС-МЕМБРАНСКИ РЕЦЕПТОР (МОЛЕКУЛ ПРОТЕИНА) ПРИКАЗАН БЕЗ ЋЕЛИЈСКОГ ЗИДА.

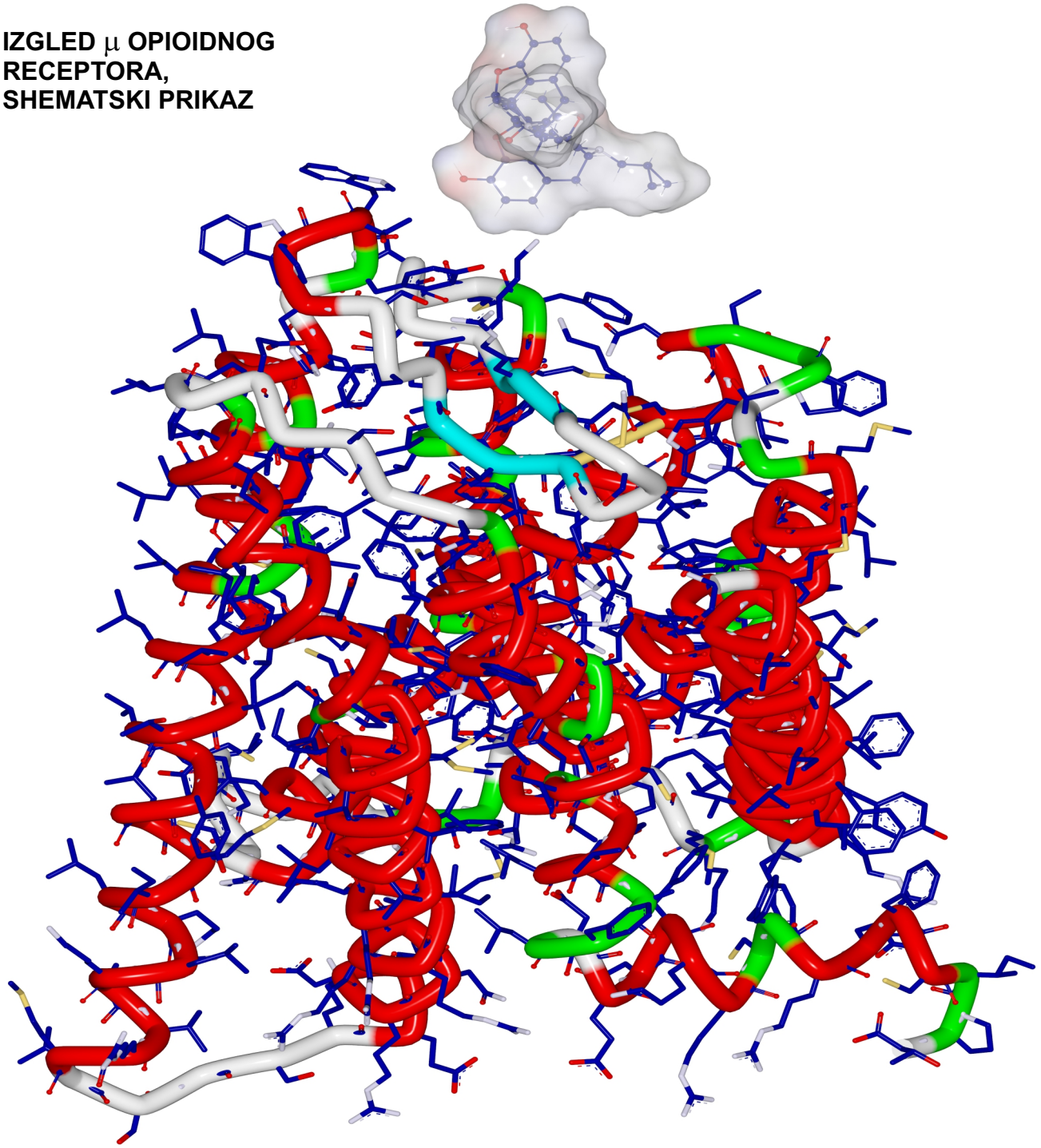
Ц. МАЛИ МОЛЕКУЛ (ЛИГАНД) КОЈИ СЕ РЕВЕРЗИБИЛНО ВЕЗУЈЕ ЗА РЕЦЕПТОР. СВАКИ ТИП РЕЦЕПТОРА ИМА СВОЈЕ СПЕЦИФИЧНЕ ЛИГАНДЕ.

Д. МОЛЕКУЛ ФОСФО-ЛИПИДА КОЈИ ЈЕ ГЛАВНИ КОНСТИТУЕНТ ЋЕЛИЈСКОГ ЗИДА

НАПОМЕНА: СВЕ БОЈЕ СУ ИЗАБРАНЕ ПОРОИЗВОЉНО.

Аутор: М. Д. Ивановић

IZGLED μ OPIOIDNOG RECEPTORA, SHEMATSKI PRIKAZ



NARKOTIČKI ANALGETICI-

nastavak

VRSTE OPIOIDNIH RECEPTORA - POZNATO JE ČETIRI VRSTE OPIOIDNIH RECEPTORA-μ, κ, δ i ORL1

-U SVIM SLUČAJEVIMA , TO SU PROTEINSKI MOLEKULI, RELATIVNO SLIČNE, HOMOLOGNE STRUKTURE, KOJI SU LOCIRANI U MEMBRANAMA ĆELIJSKIH ZIDOVA POJEDINIH VRSTA ĆELIJA, POSEBNO NEURONA

-SVAKI TIP OPIOIDNIH RECEPTORA IMA SVOJE SPECIFIČNE PRIRODNE (ENDOGENE) LIGANDE (PO STRUKTURI PEPTIDE), KOJI SE ZA NJIH VEZUJU REVERZIBILNO I MODULIRAJU NJIHOVU AKTIVNOST, A TIME I FUNKCIONISANJE ORGANIZMA U CELINI

-OPIOIDNI RECEPTORI IMAJU NORMALNU FIZIOLOŠKU ULOGU DA MODULIRANJA OSEĆAJA BOLA, ALI I MNOGE DRUGE, MANJE POZNATE ILI NEPOZNATE FIZIOLOŠKE FUNKCIJE

-SVAKI TIP OPIOIDNIH RECEPTORA TAKOĐE IMA SVOJE SPECIFIČNE “VEŠTAČKE” (EGZOGENE) LIGANDE (PO STRUKTURI MALE, NE-PEPTIDNE MOLEKULE KOJI SADRŽE BAZNI AZOT), A KOJI SE VEZUJU SLIČNO PRIRODNIM LIGANDIMA I IZAZIVAJU SLIČNE ILI IDENTIČNE FIZIOLOŠKE REAKCIJE

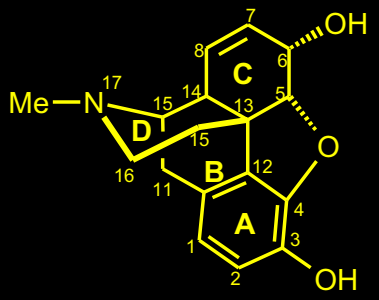
-U TERAPIJSKOM SMISLU, ZA SUZBIJANJE OSEĆAJA BOLA, NAJVAŽNIJI SU AGONISTI - JEDINJENJA KOJA SE VEZUJU ZA RECEPTOR I DOVODE DO NJEGOVE AKTIVACIJE

- LEKOVI KOJI IMAJU AGONISTIČKO (AKTIVIRAJUĆE) DEJSTVO, TERAPIJSKI SU ZNAČAJNI PRE SVEGA ZA μ-RECEPTORE, DALEKO MANJE ZA κ–RECEPTORE I JOŠ MANJE ZA δ–RECEPTORE

-U SLUČAJU ORL1 RECEPTORA, POTENCIJALNI TERAPIJSKI ZNAČAJ IMAJU PREPARATI KOJI ISPOLJAVAJU ANTAGONISTIČKO (DEAKTIVIRAJUĆE) DEJSTVO

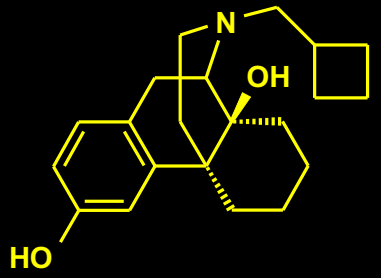
NARKOTIČKI ANALGETICI - UPROŠĆENA PODELA; PREDSTAVNICI POJEDINIH, ZNAČAJNIJIH GRUPA

1.



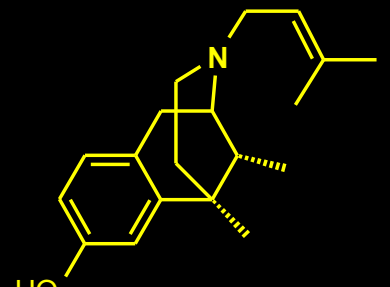
(-) MORFIN
(srednja doza 10 mg)

2.



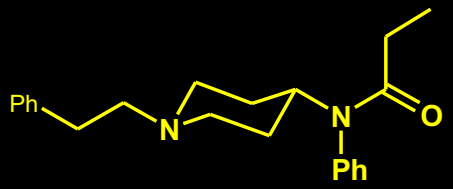
BUTORFANOL

3.



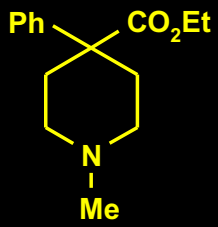
PENTAZOCIN

4.



FENTANIL ~50-100 X MORFIN

5.



PETIDIN[120]
~0.1-0.2 X MORFIN
(kod ljudi)

INTERESANTNO JE DA VELIKA VEĆINA OPIOIDA, KAKO PRIRODNIH (ALKALOIDI), TAKO I SINTETIČKIH SADRŽE PIPERIDINSKI PRSTEN.

NARKOTIČKI ANALGETICI - MEHANIZAM DEJSTVA

-KAO I VEĆINA DRUGIH PSIHOAKTIVNIH SUPSTANCI (A TAKOĐE I FARMAKOLOŠKI AKTIVNIH SUPSTANCI UOPŠTE), NARKOTIČKI ANALGETICI SVOJE DEJSTVO OSTVARUJU INTERAKCIJOM SA VEĆ POMENUTIM, OPIOIDNIM RECEPTORIMA. KOD VIŠIH ORGANIZAMA POSTOJI VRLO VELIKI BROJ RAZNOVRSNIH, SPECIFIČNIH RECEPTORA KOJI SU UVEK, PO SVOJOJ STRUKTURI, RAZLIČITI PROTEINSKI MOLEKULI.

-OPIOIDNI RECEPTORI PRIPADAJU GRUPI TRANSMEMBRANSKIH RECEPTORA, OZNAČENIH KAO μ,κ I δ. NERASKIDIVO SU UGRAĐENI U ĆELIJSKI ZID, PRE SVEGA NEURONSKIH ĆELIJA U MOZGU. REVERZIBILNIM VEZIVANJEM MOLEKULA NARKOTIČKOG ANALGETIKA (”LIGANDA”) I SPECIFIČNOG OPIOIDNOG RECEPTORA, POKREĆE SE SLOŽENI MEHANIZAM DEJSTVA (VEOMA SLABO POZNAT) ČIJA JE OSNOVNA KRAJNJA POSLEDICA UBLAŽAVANJE OSEĆAJA BOLA. KADA LIGAND POSLE NEKOG VREMENA NAPUSTI RECEPTOR, (DISOSUJE) TADA PRESTAJE I NJEGOVO DEJSTVO I VRAĆA SE OSEĆAJ BOLA , POD USLOVOM DA I DALJE POSTOJI OSNOVNI UZROK BOLA (NPR. POVREDA).

-GLAVNA FIZIOLOŠKA FUNKCIJA OPIOIDNIH RECEPTORA JESTE DA PRIVREMENO I PO POTREBI MODULIRAJU PERCEPCIJU NEPRIJATNIH NADRAŽAJA, UKLJUČUJUĆI I RAZNE OBLIKE BOLA. TA MODULACIJA (TJ. UBLAŽAVANJE OSEĆAJA) SE VRŠI REVERZIBILNIM VEZIVANJEM RECEPTORA SA NJIHOVIM PRIRODNIM (ENDOGENIM) LIGANDIMA - OPIOIDNIM PEPTIDIMA ENDORFINIMA.

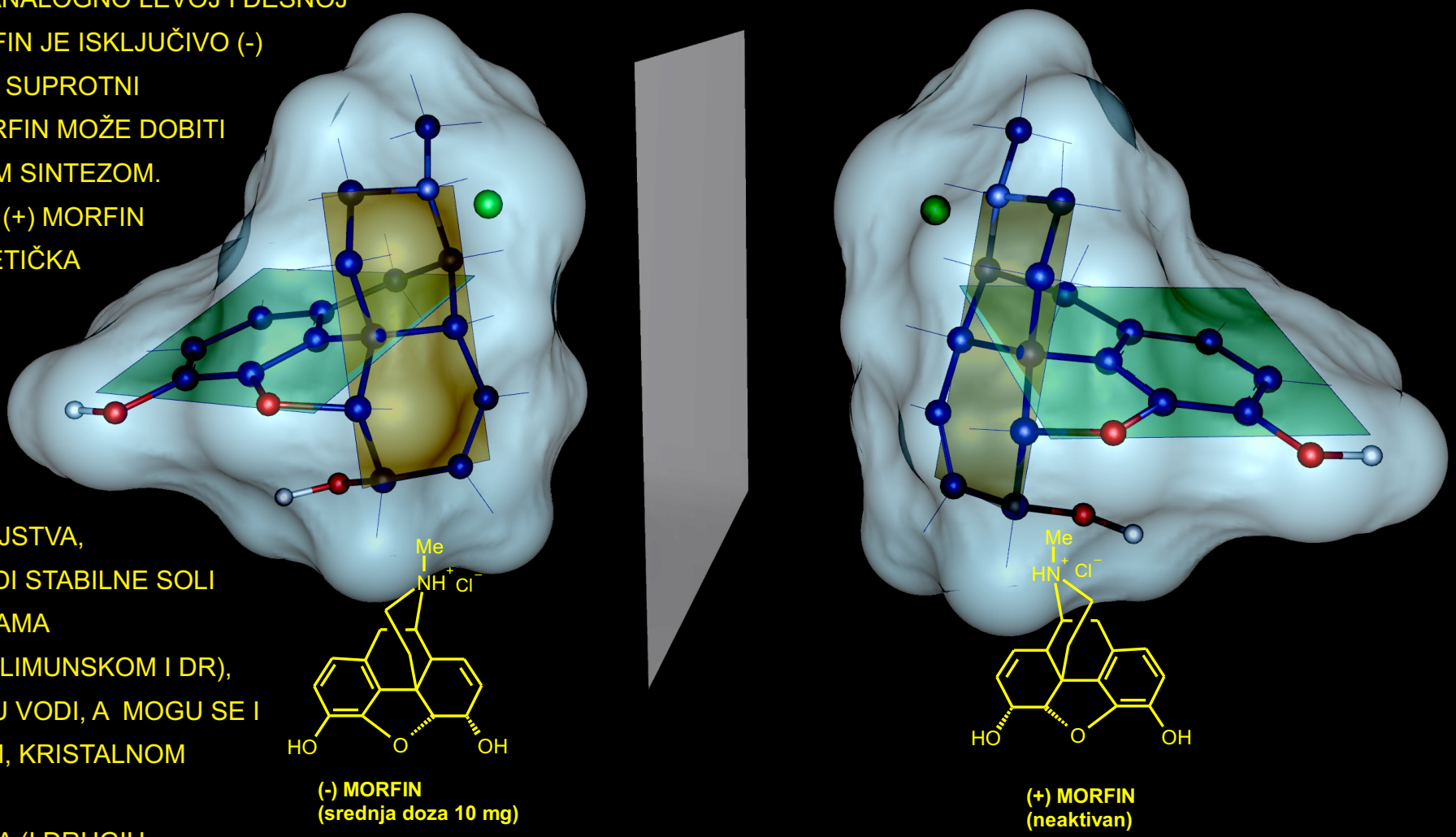
-MEĐUTIM, KAKO JE STRUKTURA RECEPTORA FLEKSIBILNA, UMESTO PRIRODNOG OPIOIDNOG LIGANDA (ENDORFINA), ZA RECEPTOR SE MOŽE VEZATI I EKSTERNI LIGAND - MOLEKUL NARKOTIČKOG ANALGETIKA.OVAKVI MOLEKULI SVOJOM STRUKTUROM U SUŠTINI SIMULIRAJU PRIRODNI LIGAND I PRI TOME DELUJU NA RECEPTOR NA ISTI NAČIN KAO I PRIRODNI LIGAND. DAKLE, MOLEKUL NARKOTIČKOG ANALGETIKA (EKSTERNI LIGAND) SE PONAŠA KAO “UZURPATOR”, VEZUJUĆI SE ZA RECEPTOR KOJI BIOLOŠKI NJEMU NIJE NAMENJEN.

-OVAJ EFEKAT IMA OGROMNU TERAPIJSKU VREDNOST - KORIŠĆENJEM NARKOTIČKIH ANALGETIKA POSTIŽE SE UBLAŽAVANJE BOLA KOJI SAM ORGANIZAM NE MOŽE SPONTANO DA UBLAŽI. MEĐUTIM, ZBOG DRUGIH EFEKATA NA LJUDSKU PSIHU, A PRE SVEGA SUBJEKTIVNOG OSEĆAJA PRIJATNOSTI, ZADOVOLJSTVA I EUFORIJE, UJEDNO PREDSTAVLJA I PODLOGU ZA KRAJNJU ZLOUPOTRBU NARKOTIČKIH ANALGETIKA - NARKOMANIJU.

-REDOVNA PRIMENA NARKOTIČKIH ANALGETIKA, BILO U TERAPIJSKE SVRHE ILI ZBOG ZLOUPOTREBE , BRZO DOVODI DO STVARANJE FIZIČKE ZAVISNOSTI. IAKO JE NA MOLEKULSKOM NIVOU OVAJ PROCES SLABO POZNAT, PREDPOSTAVLJA SE DA DOLAZI DO HEMIJSKIH PROMENA U STRUKTURI RECEPTORA, KOJI POSTEPENO GUBE SPOSOBNOST DA FUNKCIONIŠU NA NORMALAN NAČIN - DAKLE BEZ PRISUSTVA MOLEKULA NARKOTIČKOG ANALGETIKA. .

NARKOTIČKI ANALGETICI: MORFIN I DERIVATI

- DALEKO NAJZNAČAJNIJI NARKOTIČKI ANALGETIK KOJI SE SREĆE U PRIRODI JE MORFIN - JEDINJENJE KOJE PRIPADA OPŠTOJ KLASI ORGANSKIH JEDINJENJA POZNATIH KAO ALKALOIDI. MOLEKUL MORFINA JE HIRALAN - NE MOŽE SE POKLOPITI SA SVOJIM LIKOM U OGLEDALU (ANALOGNO LEVOJ I DESNOJ ŠACI). PRIRODNI MORFIN JE ISKLJUČIVO (-) ENANTIOMER, DOK SE SUPROTNI ENANTIOMER, (+) MORFIN MOŽE DOBITI ISKLJUČIVO TOTALNOM SINTEZOM. INTERESANTNO JE DA (+) MORFIN NE POKAZUJE ANALGETIČKA SVOJSTVA.



(-) MORFIN
(srednja doza 10 mg)

(+) MORFIN
(neaktivan)

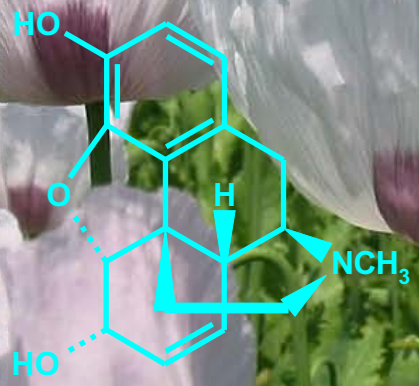
POŠTO IMA BAZNA SVOJSTVA, MORFIN MOŽE DA GRADI STABILNE SOLI SA RAZLIČITIM KISELINAMA (HLOROVODONIČNOM, LIMUNSKOM I DR), KOJE SU RASTVORNE U VODI, A MOGU SE I IZOLOVATI U ČVRSTOM, KRISTALNOM OBLIKU.

OSOBINA MORFINA (I DRUGIH ALKALOIDA) DA FORMIRA SOLI OD VELIKOG JE PRAKTIČNOG ZNAČAJA KAKO U PROCESU IZOLOVANJA ČISTOG MORFINA IZ BILJNOG MATERJALA TAKO I U NJEGOVOJ PRIPREMI ZA MEDICINSKU PRIMENU. NAIME, SOLI ALKALOIDA SE DALEKO LAKŠE RASTVARAJU U VODI OD ODGOVARAJUĆIH ALKALOIDA-SLOBODNIH BAZA, A TAKO POSTALI RASTVORI NAJČEŠĆE SE KORISTE PUTEM INJEKCIJA.

FUNKCIONALIZOVANI PIPERIDINI - KAO PRIRODNI PROIZVODI

MORFIN (SNAŽNI ANALGETIK)

PAPAVER SOMNIFERUM CONVAR OPIIFERUM



Monograph Number: 6300
Title: Morphine
CAS Registry Number: 57-27-2
Therap-Cat: Analgesic (narcotic)

POLJA BELOG MAKA.

UOKVIRENO - CVET MAKA I ČAURA SA SEMENOM, KOJA ZAOSTAJE POŠTO CVET PRECVETA.

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA

A

UPOTREBA MAKA U PREHRAMBENOJ INDUSTRIJI - POŠTO CVET, *A*, PRECVETA I ČAURA SAZRI, *B*, DOBIJA SE SEME, *C*, KOJE NE SADRŽI ALKALOIDE I POGODNO JE ZA ISHRANU. U OVU SVRHU, OBIČNO SE KORISTI SOJ BILJKE KOJA IMA CRVENI CVET.

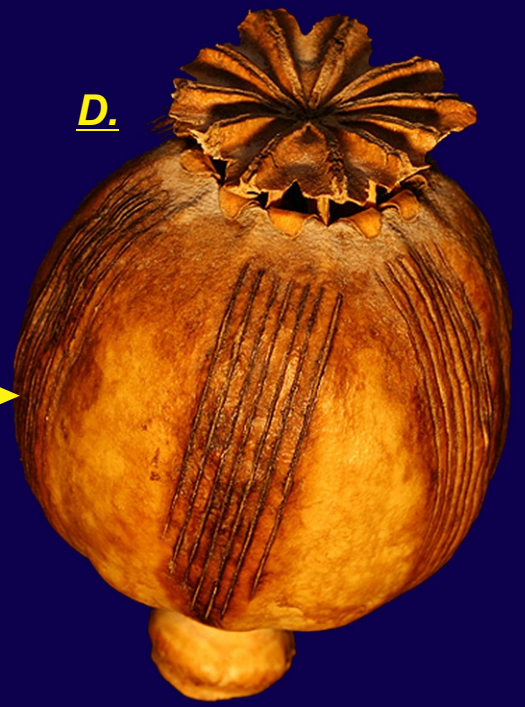
MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA

KONTROLISANO GAJENJA MAKA RADI
LEGITIMNE, MEDICINSKE PROIZVODNJE
MORFINA, TASMANIJA.

OPIJUM JE SMOLA KOJA KAPLJE IZ NEZRELIH, ZAREZANIH, ČAURA MAKA, *A* i *B*. NA VAZDUHU TAMNI I OČVRSNE, A ZATIM SE RUČNO SAKUPLJA, *C*.

A.

B.



D.

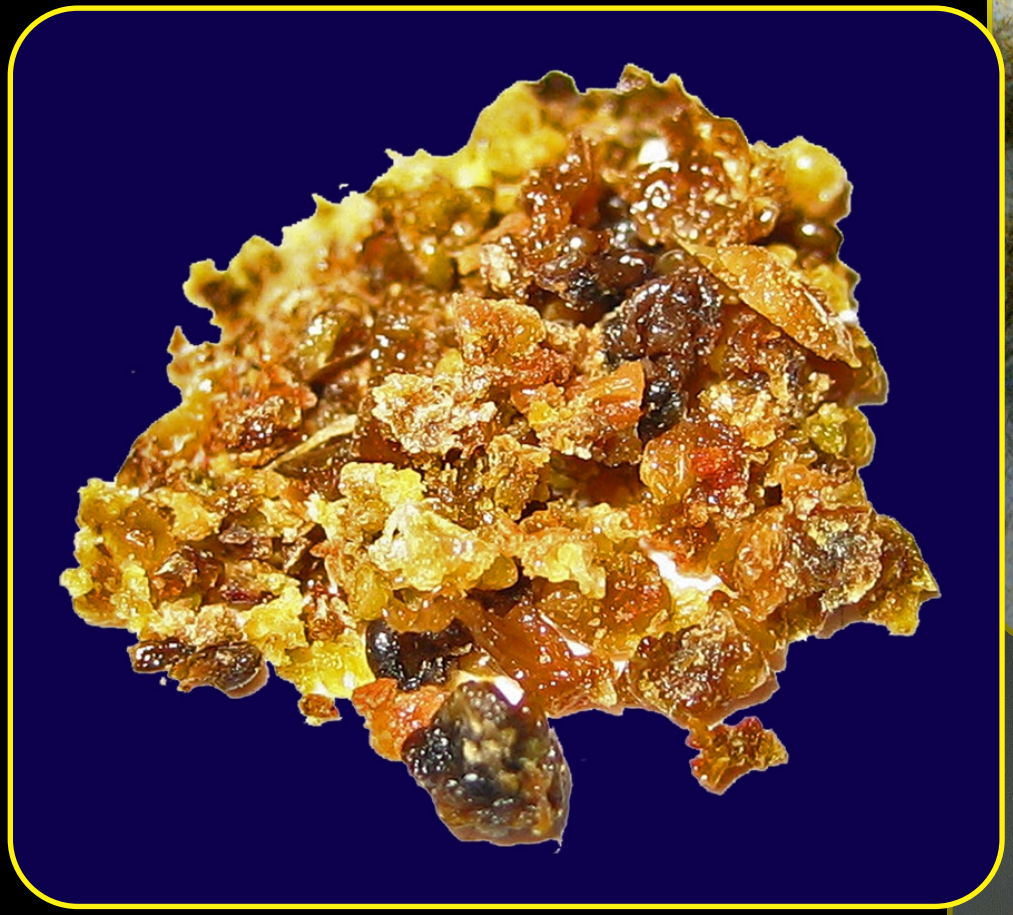
OSUŠENA ČAURA MAKA, ZAOSTALA POSLE UKLANJANJA

C.

C. SAKUPLJEN, SVEŽ, SIROVI OPIJUM

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA

A.



B.

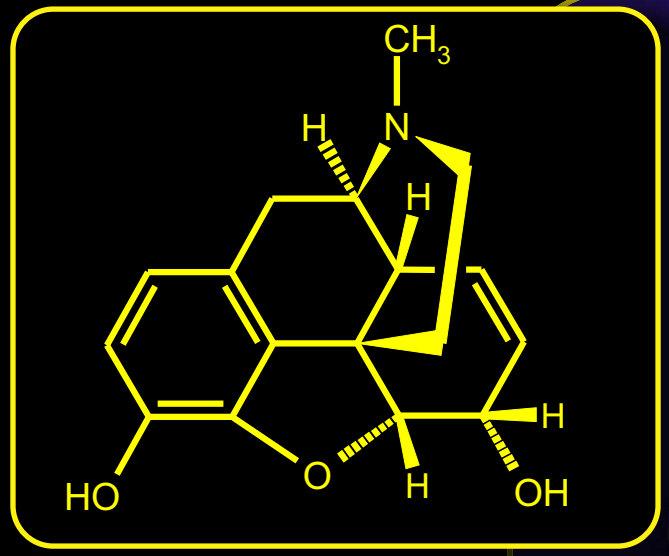
IZGLED OPIJUMSKE SMOLE

A. SVEŽ, SIROVI OPIJUM

B. SUŠENI OPIJUM

C. DODATNO PRERAĐENI OPIJUM U OBLIKU CRNE SMOLE

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA



MORFIN -

2D STRUKTURA

I

3D SIMULACIJA

(SLIKA JE

“FOTOGRAFIJA”

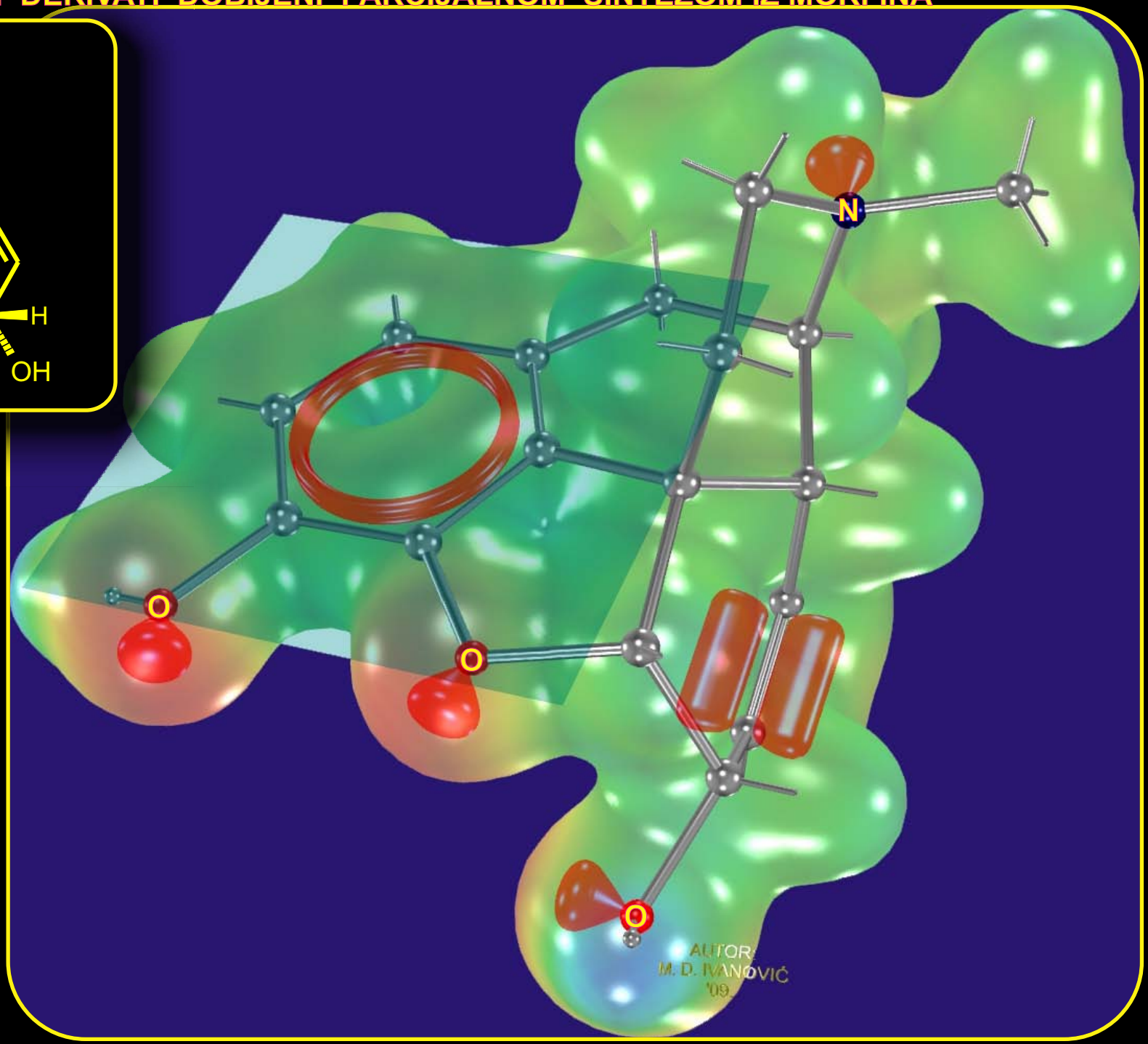
AKTIVNOG 3D MODELA

I PREDSTAVLJA

SLOBODNU

REPREZENTACIJU

MOLEKULA



THE MERCK INDEX Monograph Number: 6923

Title: Opium

Additional Names: Gum opium; crude opium
Literature References: Air-dried, milky exudation from incised, unripe capsules of Papaver somniferum L., or P. album Mill., Papaveraceae. Habit. of the plant: Asia Minor, Persia, China, Africa, India; cultivated in the Balkan States, Hungary, Southern Russia. In Japan the strain cultivated from the production of opium is called "Ikkanshu." Appearance and sources: Chem. & Eng. News 32, 2701 (1954). Constit. About 20 alkaloids, constituting about 25% of the opium; meconic acid, some lactic and sulfuric acids, sugar, resinous and waxy-like substances; 12-25% water. Morphine is the most important alkaloid and occurs to the extent of 10-16%, noscapine 4-8%, codeine 0.8-2.5%, papaverine 0.5-2.5%, thebaine 0.5-2%.

Derivative Type: Deodorized opium
Additional Names: "Denarcotized" opium
Properties: Powdered opium freed from its odor and nauseating substances by treatment with petr ether. Contains 10-10.5% anhydr morphine.

Derivative Type: Granulated opium
Properties: Opium dried at not above 70°, reduced to a 16-50 mesh powder and adjusted with lactose or other inert diluent to contain 10-10.5% anhydr morphine.

Derivative Type: Powdered opium
Properties: Opium dried at a temp not above 70°, finely powdered and adjusted with lactose or other inert diluent to contain 10-10.5% anhydr morphine.

CAUTION: May be habit forming: 21 CFR, 329.1 and is a controlled substance: 21 CFR, 1308.12.
Use: Largely for the manuf of morphine, codeine and other opium alkaloids.
Therap-Cat: Analgesic (narcotic). Hypnotic.
Therap-Cat-Vet: Analgesic (narcotic); antidiarrheal; antitussive.

British Pharmacopoeia 2005

File Edit Search Help

British Pharmacopoeia 2005

Incorporating the requirements of the 5th Edition of the European Pharmacopoeia 2004 as amended by Supplements 5.1 and 5.2

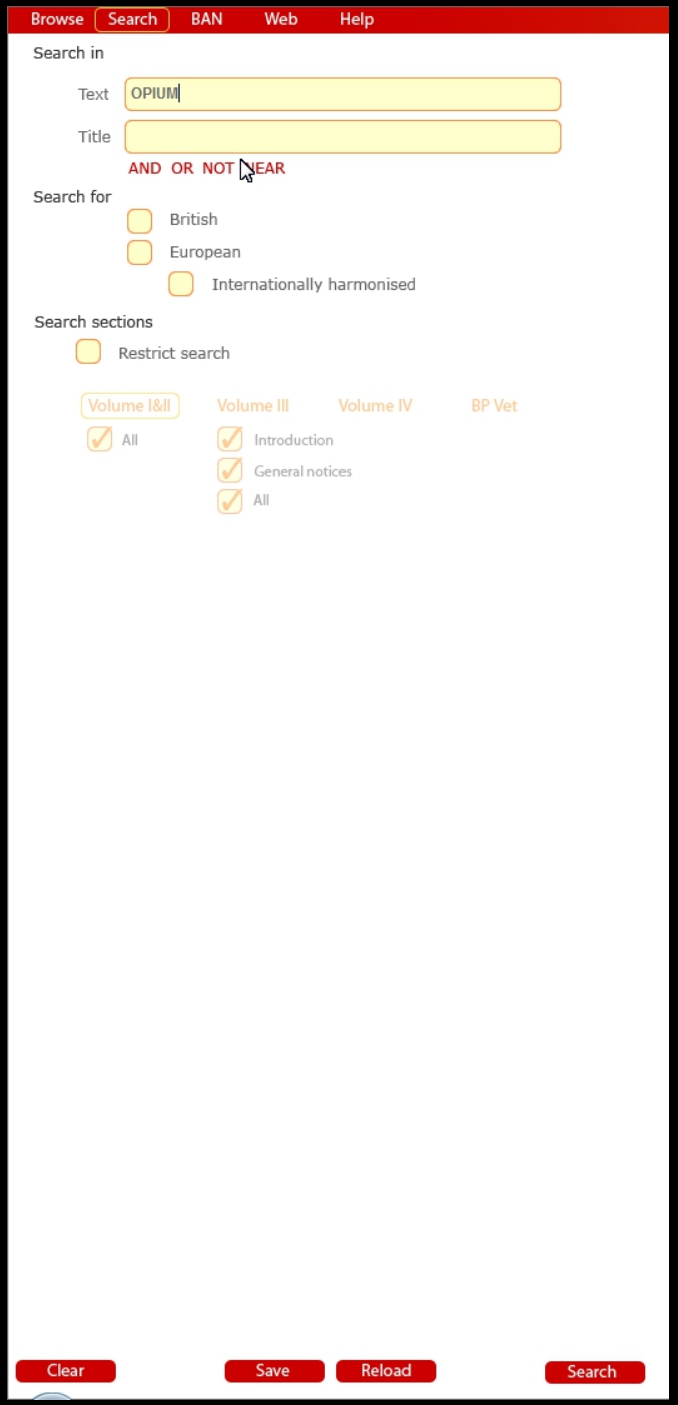
Version 10.0

Data © Crown Copyright 2005
Index+ © System Simulation Ltd

TSO

Enter

BRITISH PHARMACOPEIA 2005 MONOGRAPH OPIUM



Monographs: Medicinal and Pharmaceutical substances
Racemic Camphor

Monographs: Medicinal and Pharmaceutical substances
Opium

Monographs: Medicinal and Pharmaceutical substances
Prepared Opium

Formulated Preparations: General Monographs
Tinctures of the British Pharmacopoeia

Formulated Preparations: Specific Monographs
Opium Tincture

Formulated Preparations: Specific Monographs
Camphorated Opium Tincture

Formulated Preparations: Specific Monographs
Concentrated Camphorated Opium Tincture

Formulated Preparations: Specific Monographs
Opiate Squill Linctus

Formulated Preparations: Specific Monographs
Paediatric Opiate Squill Linctus

Appendix I A. General Reagents
Thebaine

Opium

General Notices

(Raw Opium, Ph Eur monograph 0777)
Action and use

Narcotic analgesic.

Preparation

Opium Tincture

Ph Eur

DEFINITION

Raw opium is intended only as starting material for the manufacture of galenical preparations. It is not dispensed as such.

Raw opium is the air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* L. It contains not less than 10.0 per cent of morphine ($C_{17}H_{19}NO_3$; M_r 285.3) and not less than 2.0 per cent of codeine ($C_{18}H_{21}NO_3$; M_r 299.4), both calculated with reference to the drug

©Crown Copyright 2005

dried at 100 °C to 105 °C.

CHARACTERS

Raw opium has a characteristic odour and a blackish-brown colour. It has the microscopic characters described in identification test A. It consists of masses of various sizes, which tend to be soft and shiny and, after drying, become hard and brittle.

IDENTIFICATION

Strip off any covering, cut the substance to be examined into thin slices, if necessary, dry at about 60 °C for 48 h and reduce to a powder (500)

A. Examined under a microscope, a suspension of raw opium in a 20 g/l solution of *potassium hydroxide R* is seen to consist of granules of latex agglomerated in irregular masses, and of light-brown elongated filaments. Some fragments of vessels and rather elongated, refringent crystals are also visible, as well as a smaller number of round pollen grains and fragments of elongated fibres. Hairs of various lengths with sharp points and a few grains of starch introduced during the handling of the latex may be present. Fragments of epicarp consisting of polygonal cells with thick walls defining a stellate lumen may also be present.

B. Examine by thin-layer chromatography *(2.2.27)*, using *silica gel G R* as the coating substance.

Test solution Triturate 0.10 g of the powdered drug with 5 ml of *alcohol (70 per cent V/V) R*, add 3 ml of *alcohol (70 per cent V/V) R*, transfer to a 25 ml conical flask and heat in a water-bath at 50 °C to 60 °C with stirring for 30 min. Cool, filter, wash the filter with *alcohol (70 per cent V/V) R* and

©Crown Copyright 2005

dilute the filtrate to 10 ml with the same solvent.

Reference solution Dissolve 2.0 mg of *papaverine hydrochloride R*, 12.0 mg of *codeine phosphate R*, 12.0 mg of *noscapine hydrochloride R* and 25.0 mg of *morphine hydrochloride R* in *alcohol (70 per cent V/V) R* and dilute to 25.0 ml with the same solvent.

Apply separately to the plate as bands 20 mm by 3 mm 20 µl of each solution. Develop over a path of 15 cm using a freshly prepared mixture of 2 volumes of *concentrated ammonia R*, 6 volumes of *alcohol R*, 40 volumes of *acetone R* and 40 volumes of *toluene R*. Dry the plate at 100 °C to 105 °C for 15 min, allow to cool and spray with *potassium iodobismuthate solution R2* and then with a 4 g/l solution of *sulphuric acid R*. The chromatogram obtained with the reference solution shows in the lower part an orange-red or red zone (morphine), above it a similarly coloured zone (codeine) and in the upper part an orange-red or red zone (papaverine) and above it a similarly coloured zone (noscapine). The chromatogram obtained with the test solution shows orange-red or red zones corresponding to those in the chromatogram obtained with the reference solution. The chromatogram obtained with the test solution may also show a dark red zone (thebaine) situated between those due to codeine and to papaverine.

C. To 1.0 g of the powdered drug add 5 ml of *water R*, shake for 5 min and filter. To the filtrate add 0.25 ml of *ferric chloride solution R2*. A red colour develops which does not disappear on the addition of 0.5 ml of *dilute hydrochloric acid R* .

TESTS

Thebaine

Not more than 3.0 per cent, determined by liquid chromatography *(2.2.29)* and calculated with

©Crown Copyright 2005

reference to the dried drug.

Test solution Prepare the test solution as described in the assay.

Reference solution Dissolve 25.0 mg of *thebaine R* in the mobile phase and dilute to 25.0 ml with the mobile phase. Dilute 10.0 ml of the solution to 100.0 ml with the mobile phase.

The chromatographic procedure is carried out as described in the assay. The test is not valid unless the mass distribution ratio for thebaine is at least 3.0 and the number of theoretical plates is at least 3000. Calculate the percentage content of thebaine from the expression given in the assay.

Loss on drying ***(2.2.32)***

Not more than 15.0 per cent, determined on 1.000 g of raw opium cut into thin slices, by drying in an oven at 100 °C to 105 °C for 4 h.

Total ash ***(2.4.16)***

Not more than 6.0 per cent.

ASSAY

Examine by liquid chromatography *(2.2.29)*.

Test solution Suspend 1.00 g of raw opium, cut into thin slices, in 50 ml of *alcohol (50 per cent V/V) R*, mix with the aid of ultrasound for 1 h, allow to cool and dilute to 100.0 ml with the same solvent. Allow to stand. To 10.0 ml of the supernatant liquid add 5 ml of *ammonium chloride buffer solution pH 9.5 R*, dilute to 25.0 ml with *water R* and mix. Transfer 20.0 ml of the solution to a

©Crown Copyright 2005

chromatography column about 0.15 m long and about 30 mm in internal diameter containing 15 g of *kieselguhr for chromatography R*. Allow to stand for 15 min. Elute with two quantities, each of 40 ml, of a mixture of 15 volumes of *2-propanol R* and 85 volumes of *methylene chloride R*. Evaporate the eluate to dryness *in vacuo* at 40 °C. Transfer the residue to a volumetric flask with the aid of the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution Dissolve 0.100 g of *morphine hydrochloride R* and 25.0 mg of *codeine R* in the mobile phase and dilute to 25.0 ml with the mobile phase. Dilute 10.0 ml of the solution to 100.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

—a column 0.25 m long and 4.6 mm in internal diameter packed with *octylsilyl silica gel for chromatography R* (5 µm), equipped with a guard column 40 mm long and 4.6 mm in internal diameter packed with *octylsilyl silica gel for chromatography R* (5 µm),

—as mobile phase at a flow rate of 1.5 ml/min a solution prepared as follows: dissolve 1.0 g of *sodium heptanesulphonate monohydrate R* in 420 ml of *water R*, adjust to pH 3.2 by addition of phosphoric acid (4.9 g/l H_3PO_4) (about 5 ml) and add 180 ml of *acetonitrile R*,

—as detector a spectrophotometer set at 280 nm,

—an loop injector.

Inject suitable volumes of each solution.

The assay is not valid unless the resolution between the peaks corresponding to morphine and codeine is at least 2.5. If necessary, adjust the volume of acetonitrile in the mobile phase. Inject the reference solution six times. The assay is not valid unless the relative standard deviation of the peak area for morphine is at most 1.0 per cent. Inject alternately the test solution and the reference solution.

©Crown Copyright 2005

Calculate the percentage content of each alkaloid from the expression:

$$\frac{m_1 \times A_2 \times 625}{m_2 \times A_1 \times 5} \times \frac{100}{100 - h}$$

m_1	=	mass in grams of the alkaloid used to prepare the reference solution,
m_2	=	mass in grams of the substance to be examined used to prepare the test solution,
A_1	=	area of the peak corresponding to the alkaloid in the chromatogram obtained with the reference solution,
A_2	=	area of the peak corresponding to the alkaloid in the chromatogram obtained with the test solution,
h	=	percentage loss on drying.

For the calculation, 1 mg of *morphine hydrochloride R* is taken to be equivalent to 0.759 mg of morphine and 1 mg of *codeine R* is taken to be equivalent to 0.943 mg of codeine.

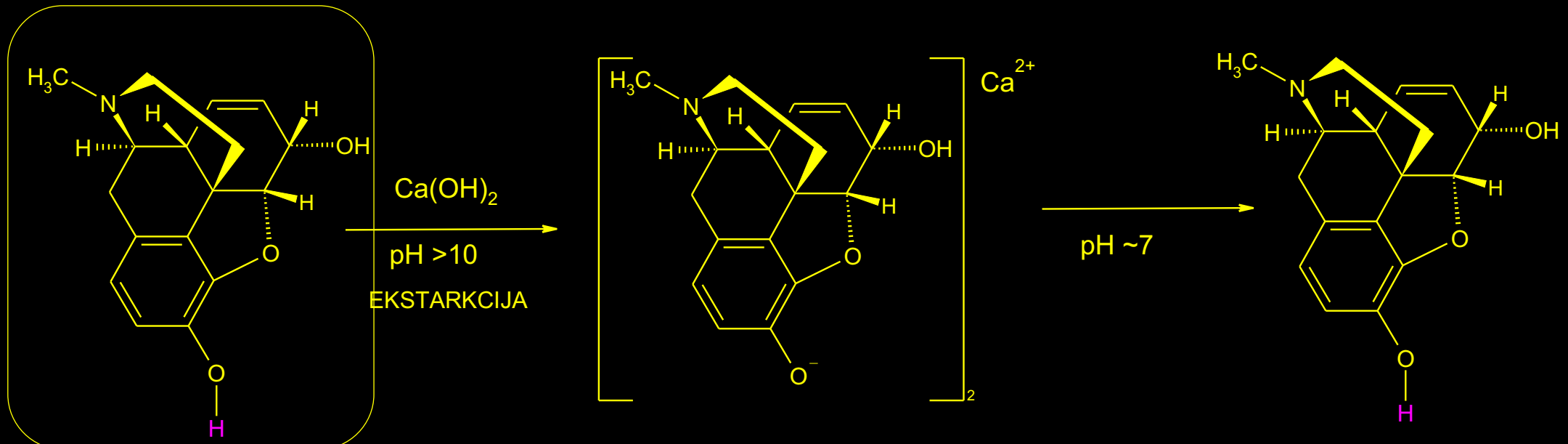
STORAGE

Store protected from light.

©Crown Copyright 2005


OSUŠENA MAKOVA TRSKA

EKSTRAKCIJA MORFINA IZ KONCENTRATA MAKOVE TRSKE. PROCES PREMA JÁNOS KABAY-u



KONCENTRAT MAKOVE TRSKE;
SADRŽI SMESE ALKALOIDA

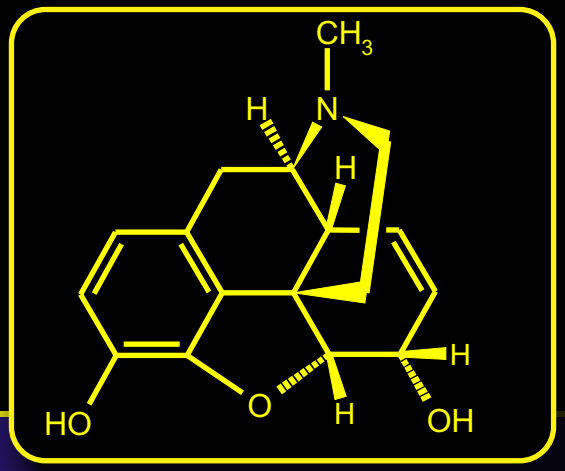
FENOKSID

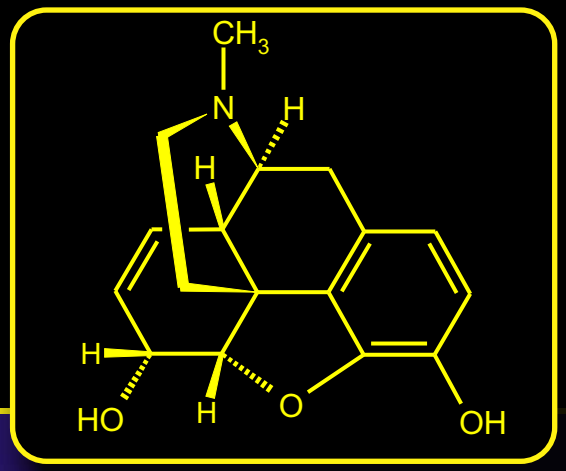
SLOBODNA BAZA

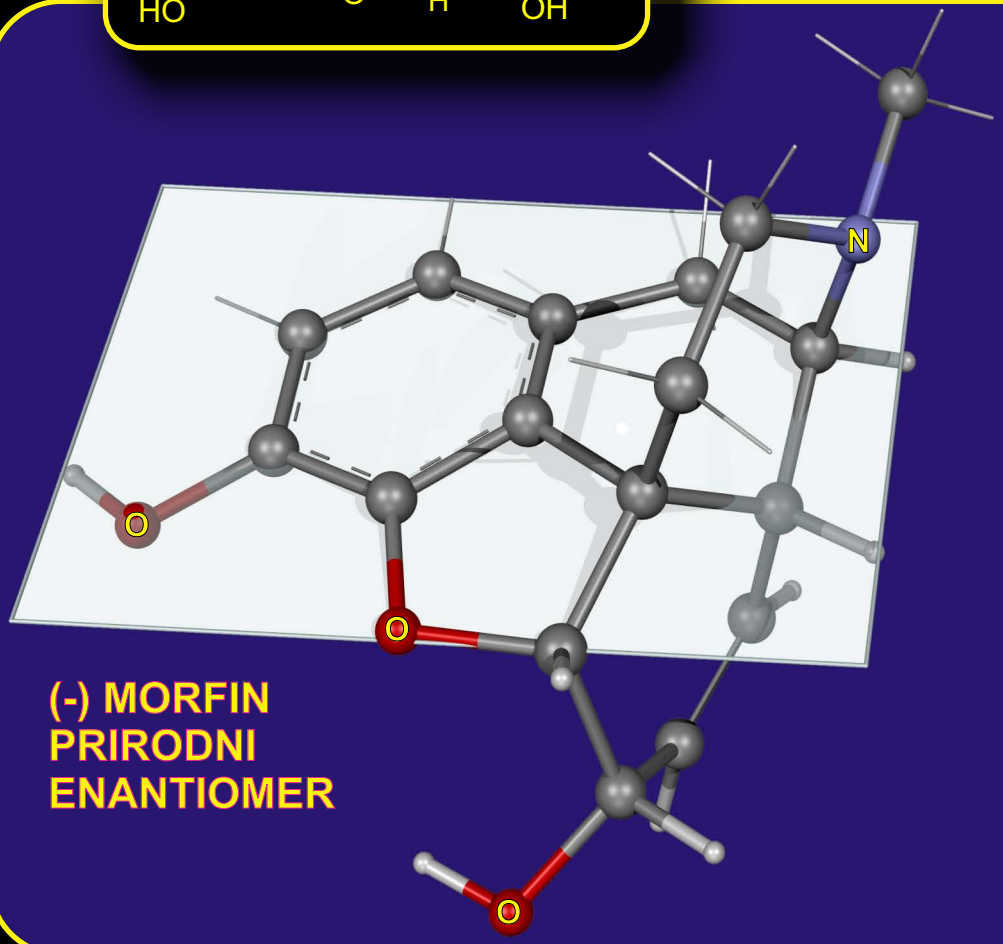
OPŠTI PROCES IZOLOVANJA MORFINA IZ KONCENTRATA MAKOVE TRSKE. PROCES JE PRVI RAZVIO MAĐARSKI HEMIČAR JÁNOS KABAY, TRIDESETIH GODINA XX VEKA.

PROCES SE U MODIFIKOVANIM OBLICIMA PRIMENJUJE I DANAS. OKO 90% LEGALNOG, MEDICINSKOG MORFINA DOBIJA SE NA OVAJ NAČIN.

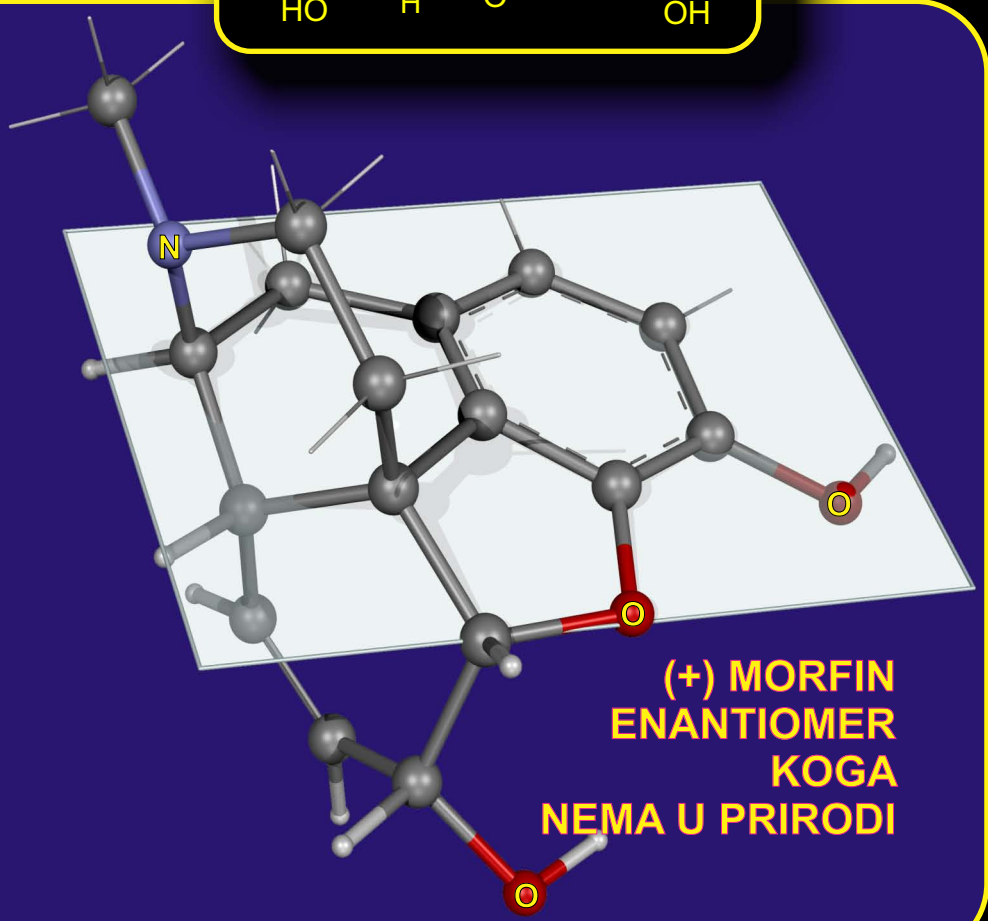
MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA







(-) MORFIN
PRIRODNI
ENANTIOMER



(+) MORFIN
ENANTIOMER
KOGA
NEMA U PRIRODI

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

THE MERCK INDEX Monograph Number: 6300

Title: Morphine

CAS Registry Number: 57-27-2
CAS Name: (5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol
Additional Names: morphium; morphia
Trademarks: Dolcontin (Kabi); Duromorph (L.A.B.); Morphina; Nepenthe (Evans)
Molecular Formula: C17H19NO3
Molecular Weight: 285.34.
Percent Composition: C 71.56%, H 6.71%, N 4.91%, O 16.82%
Literature References: Principal alkaloid of opium which contains 9-14% anhydr morphine. Occurs naturally as the (-)-form. Also found in normal brain, blood and liver. Extraction procedures: Achor, Geiling, Anal. Chem. 26, 1061 (1954); Leete, J. Am. Chem. Soc. 81, 3950 (1959). Structure: Knorr, Ber. 22, 1113 (1889); Knorr, Hörlein, Ber. 40, 2032, 3341, 4889 (1907); Gulland, Robinson, J. Chem. Soc. 123, 980 (1925). Total synthesis: Gates, Tschudi, J. Am. Chem. Soc. 74, 1109 (1952); 78, 1380 (1956); Ginsburg et al., J. Chem. Soc. 1951, 936; 1953, 1524, 2664; 1954, 3052. Synthesis of (+)-form: I. Iijima et al., J. Org. Chem. 43, 1462 (1978); of (-)-form: E. J. Bijsterveld, H. J. Sinnige, Rec. Trav. Chim. 95, 24 (1976); H. C. Beyerman et al., ibid. 97, 127 (1978). Biogenesis: Leete, J. Am. Chem. Soc. 81, 3948 (1959). Configuration: G. Stork in The Alkaloids, vol. II, Manske, Holmes, Eds. (Academic Press, New York, 1952) pp 171-189; Bick, Nature 169, 755 (1952); Rapoport, Lavigne, J. Am. Chem. Soc. 75, 5329 (1953); Bose, Chem. & Ind. (London) 1954, 130; Mackay, Hodgkin, J. Chem. Soc. 1955, 3261; Kalvoda et al., Helv. Chim. Acta 38, 1847 (1955). Infrared and polarographic data: Seagers et al., J. Am. Pharm. Assoc., Sci. Ed. 41, 640 (1952). Toxicity data: M. E. Buchwald, G. S. Eadie, J. Pharm. Exp. Ther. 71, 197 (1941). GC-MS determn in biological fluids: R. Wasels, F. Belleville, J. Chromatog A 674, 225 (1994). Review: K. W. Bentley, The Chemistry of the Morphine Alkaloids (Oxford, 1954) 433 pp. Comprehensive description: F. J. Muhtadi, Anal. Profiles Drug Subs. 17, 259-366 (1988). Review of pharmacology of endogenous morphine: S. Benyhe, Life Sci. 55, 969-979 (1994).
Properties: Short, orthorhombic, columnar prisms from anisole, dec 254°, also a metastable phase, mp 197°. High melting form sublimes at 190-200° (0.2 mm pressure at 2 mm distance).
Melting point: mp 197°

Derivative Type: Monohydrate
Molecular Formula: C17H19NO3.H2O
Molecular Weight: 303.35.
Percent Composition: C 67.31%, H 6.98%, N 4.62%, O 21.10%
Properties: Orthorhombic, sphenoidal prisms, needles from methanol. Dec 254-256° with rapid heating. Darkens on exposure to light. Loses water at 130°. d420 1.32. [α]D25 -132° (methanol). pKb at 20° = 6.13; pKa 9.85. pH of satd soln, 8.5. uv max in acid: 285 nm; in alkali: 298 nm. One gram dissolves in about 5000 ml water, 1100 ml boiling water, 210 ml alcohol, 98 ml boiling alc, 1220 ml chloroform, 6250 ml ether, 114 ml amyl alc, 10 ml boiling methanol, 525 ml ethyl acetate. Freely sol in solns of fixed alkali and alkaline earth hydroxides, in phenol, cresols; moderately sol in mixtures of chloroform with alcohols; slightly sol in ammonia, benzene.
pKa: pKb at 20° = 6.13; pKa 9.85
Optical Rotation: [α]D25 -132° (methanol)
Absorption maximum: uv max in acid: 285 nm; in alkali: 298 nm
Density: d420 1.32

Derivative Type: Acetate trihydrate
Molecular Formula: C19H23NO5.3H2O
Molecular Weight: 399.43.
Percent Composition: C 57.13%, H 7.32%, N 3.51%, O 32.04%
Properties: Yellowish-white powder; slight acetic odor. [α]D15 -77° (water). One gram dissolves in 2.25 ml water, 2 ml boiling water, 22 ml alc, 2 ml alc at 60°, 4.5 ml glycerol, 4.75 ml chloroform. Practically insol in ether. Keep well closed and protected from light.
Optical Rotation: [α]D15 -77° (water)

Derivative Type: Mucate
CAS Registry Number: 596-19-0
CAS Name: Galactaric acid compd with (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol (1:1)
Additional Names: morphine hyperduric
Molecular Formula: C23H29NO11
Molecular Weight: 495.48.
Percent Composition: C 55.75%, H 5.90%, N 2.83%, O 35.52%

Derivative Type: Tartrate trihydrate
Molecular Formula: (C17H19NO3)2.C4H6O6.3H2O
Molecular Weight: 774.81.
Percent Composition: C 58.91%, H 6.50%, N 3.62%, O 30.97%
Properties: Crystalline powder. Sol in 11 parts water; slightly sol in alcohol. Practically insol in chloroform, ether, carbon disulfide.

Derivative Type: 6-Methyl ether
Additional Names: Heterocodeine
Molecular Formula: C18H21NO3
Molecular Weight: 299.36.
Percent Composition: C 72.22%, H 7.07%, N 4.68%, O 16.03%

CAUTION: May be habit forming: 21 CFR, 329.1 and is a controlled substance (opiate): 21 CFR, 1308.12.
Therap-Cat: Analgesic (narcotic).
Therap-Cat-Vet: Analgesic (narcotic), preanesthetic, antitussive, antiperistaltic.

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

BRITISH PHARMACOPEIA 2005 MONOGRAPH Morphine Sulphate (Ph Eur monograph 1244)

C34H40N2O10S,5H2O 759 6211-15-0

Action and use

Opioid analgesic.

Preparations

Morphine Sulphate Injection

Morphine and Atropine Injection

Morphine Suppositories

Morphine Tablets

Prolonged-release Morphine Tablets

Ph Eur

DEFINITION

Di(7,8-didehydro-4,5a-epoxy-17-methylmorphinan-3,6a-diol) sulphate pentahydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in toluene.

IDENTIFICATION

First identification A, E.

Second identification B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 20 mg in 1 ml of water R, add 0.05 ml of 1 M sodium hydroxide and shake. A precipitate is formed. Filter, wash twice with 0.5 ml of water R and dry the precipitate at 145 °C for 1 h. Prepare discs using the dried precipitate.

Comparison Repeat the operations with morphine sulphate CRS.

B. Dissolve 25.0 mg in water R and dilute to 25.0 ml with the same solvent (solution A). Dilute 10.0 ml of solution A to 100.0 ml with water R. Examined between 250 nm and 350 nm (2.2.25), the solution shows a single absorption maximum, at 285 nm. The specific absorbance at the absorption maximum, is 37 to 43. Dilute 10.0 ml of solution A to 100.0 ml with 0.1 M sodium hydroxide . Examined between 250 nm and 350 nm (2.2.25), the solution shows a single absorption maximum, at 298 nm. The specific absorbance at this absorption maximum is 64 to 72.

C. To about 1 mg of powdered substance in a porcelain dish add 0.5 ml of sulphuric acid- formaldehyde reagent R. A purple colour develops and becomes violet.

D. It gives the reaction of alkaloids (2.3.1).

E. It gives the reactions of sulphates (2.3.1).

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

BRITISH PHARMACOPEIA 2005 MONOGRAPH Morphine Sulphate (Ph Eur monograph 1244) - nastavak

TESTS

Solution S

Dissolve 0.500 g in carbon dioxide-free water R and dilute to 25.0 ml with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y6 or BY6 (2.2.2, Method II).

Acidity or alkalinity

To 10 ml of solution S add 0.05 ml of methyl red solution R. Not more than 0.2 ml of 0.02 M sodium hydroxide or 0.02 M hydrochloric acid is required to change the colour of the indicator.

Specific optical rotation (2.2.7)

- 107 to - 110 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.330 g of the substance to be examined and 0.100 g of sodium octanesulphonate R in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (a) Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (b) Dissolve 25 mg of codeine R in 1.0 ml of the test solution and dilute to 50.0 ml with the mobile phase.

Column:

—size: l = 0.25 m, Ø= 4.6 mm,

—stationary phase: octylsilyl silica gel for chromatography R (5 µm).

Mobile phase To 1.08 g of sodium octanesulphonate R, add 250 ml of acetonitrile R and 20 ml of glacial acetic acid R and dilute to 1000 ml with water R.

Flow rate 2.0 ml/min.

Detection Spectrophotometer at 283 nm.

Injection 10 µl.

Run time 4 times the retention time of morphine.

Relative retention With reference to morphine (retention time = about 4 min): impurity D = about 0.8; impurity A = about 1.6; impurity C = about 2.0; impurity B = about 2.4.

System suitability Reference solution (b):

— resolution : minimum 9 between the peaks due to morphine and impurity A.

Limits:

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

BRITISH PHARMACOPEIA 2005 MONOGRAPH Morphine Sulphate (Ph Eur monograph 1244) - nastavak

—correction factor: for the calculation of content, multiply the peak area of impurity C by 0.25,

—impurity B: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent),

—impurities A, C, D: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

—any other impurity: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

—total: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),

—disregard limit: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Iron (2.4.9)

Maximum 5 ppm.

Dissolve the residue from the test for sulphated ash in water R and dilute to 10.0 ml with the same solvent.

Water (2.5.12)

10.4 per cent to 13.4 per cent, determined on 0.100 g.

Sulphated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 120 ml of anhydrous acetic acid R. Titrate with 0.1 M perchloric acid , determining the end-point potentiometrically (2.2.20).

1 ml of 0.1 M perchloric acid is equivalent to 66.88 mg of $C_{34}H_{40}N_2O_{10}S$.

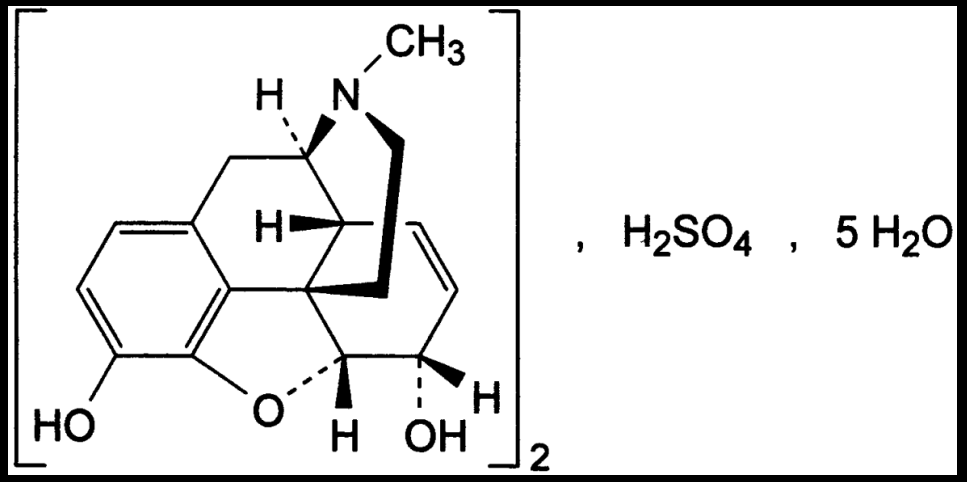
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B, C, D.

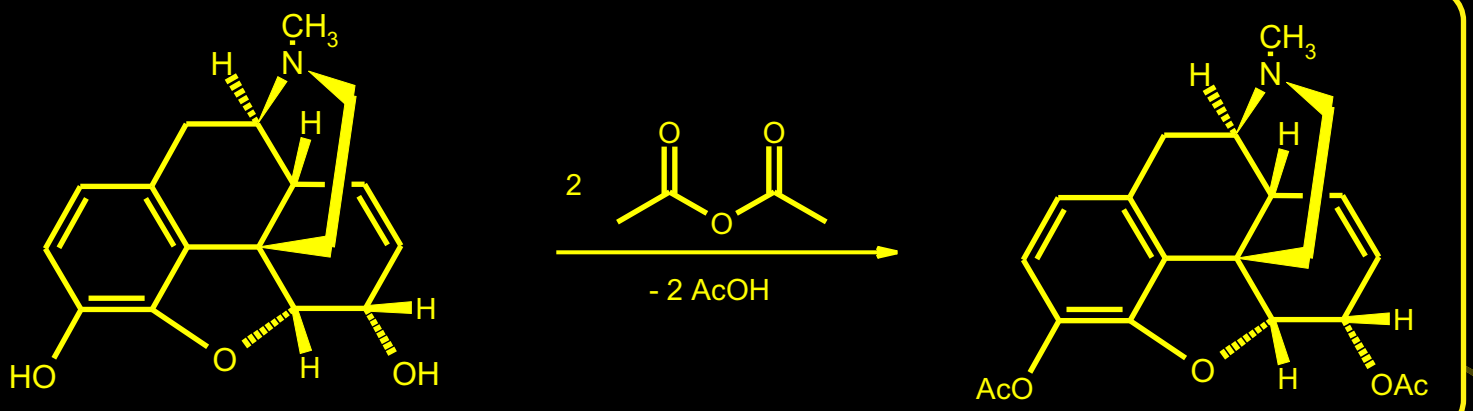
Other detectable impurities E.



, H_2SO_4 , $5\ H_2O$

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

HEROIN (DIAMORPINE)



MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

HEROIN (DIAMORPINE)

HEROIN (ZAPLENJENI UZORCI): A. BRAON HEROIN; B. BELI HEROIN (”CHINA WHITE”)

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

HEROIN (DIAMORPINE)

HEROIN (ZAPLENJENI UZORAK): CRNA SMOLA

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

HEROIN (DIAMORPINE)

THE MERCK INDEX Monograph Number: 2987
TITLE: DIACETYLMORPHINE
CAS Registry Number: 561-27-3
CAS Name: (5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol diacetate (ester)
Additional Names: heroin; diamorphine; acetomorphine
Molecular Formula: C21H23NO5
Molecular Weight: 369.41.
Percent Composition: C 68.28%, H 6.28%, N 3.79%, O 21.66%
Literature References: Narcotic analgesic prepared from morphine and acetic anhydride: O. Hesse, Ann. 220, 203 (1883); from morphine and acetyl chloride: Small, Lutz, Chemistry of the Opium Alkaloids, Supplement No. 103, Public Health Reports, Washington (1932); K. W. Bentley, The Chemistry of the Morphine Alkaloids (Oxford, 1954). Comparison with acetylmorphine: N. B. Eddy, H. A. Howes, J. Pharmacol. Exp. Ther. 53, 430 (1935).
Pharmacodynamics: J. G. Umans, C. E. Inturrisi, ibid. 218, 409 (1981). Toxicity: eidem, Eur. J. Pharmacol. 85, 317 (1982). Vapor pressure studies: A. H. Lawrence et al., Can. J. Chem. 42, 1886 (1984). Comprehensive description: D. K. Wyatt, L. T. Grady, Anal. Profiles Drug Subs. 10, 357-403 (1981).
Properties: Orthorhombic plates, tablets from ethyl acetate. mp 173°. bp12 272-274°. [α]D25 -166° (c = 1.49 in methanol). One gram dissolves in 1.5 ml chloroform, 31 ml alcohol, 100 ml ether, 1700 ml water. Slightly sol in ammonia or sodium carbonate soln, sol in alkalies, dec by boiling with water. Turns pink and emits acetic odor on prolonged exposure to air. LD50 i.v. in mice: 59 μmol/kg (Umans, Inturrisi).
Melting point: mp 173°
Boiling point: bp12 272-274°
Optical Rotation: [α]D25 -166° (c = 1.49 in methanol)
Toxicity data: LD50 i.v. in mice: 59 μmol/kg (Umans, Inturrisi)

Derivative Type: Hydrochloride monohydrate
Molecular Formula: C21H23NO5.HCl.H2O
Molecular Weight: 423.89.
Percent Composition: C 59.50%, H 6.18%, N 3.30%, O 22.65%, Cl 8.36%
Properties: Fine crystals, mp 243-244°. [α]D24 -156° (c = 1.044). Sol in 2 parts water, 11 parts alcohol. Insol in ether.
Melting point: mp 243-244°
Optical Rotation: [α]D24 -156° (c = 1.044)

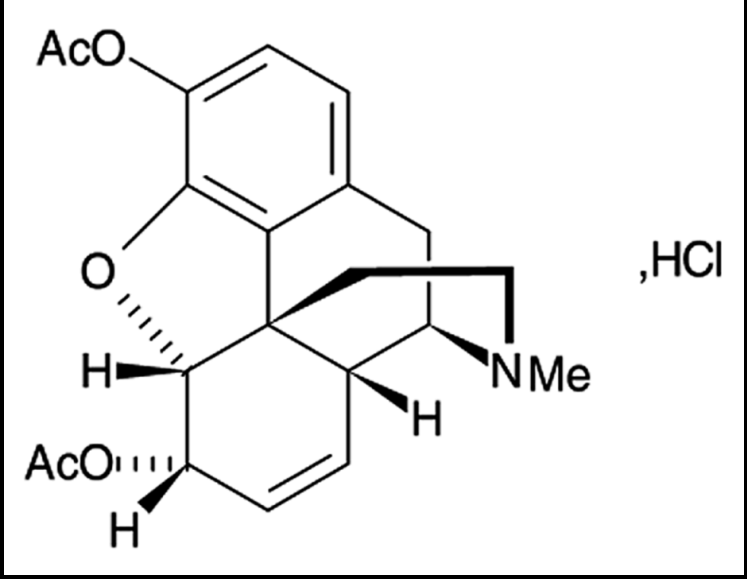
Derivative Type: Methyl iodide
Molecular Formula: C21H23NO5.CH3I
Molecular Weight: 511.35.
Percent Composition: C 51.67%, H 5.12%, N 2.74%, O 15.64%, I 24.82%
Properties: Needles, mp 252°, [α]D15 -107° (c = 0.896).
Melting point: mp 252°
Optical Rotation: [α]D15 -107° (c = 0.896)

NOTE: "China White" has been used as a term for very pure Southeast Asian heroin. This term has also been erroneously used to refer to 3-methylfentanyl and α-methylfentanyl, q.v., which are potent derivs of fentanyl, q.v. See: S. Stinson, Chem. & Eng. News, 59, 71 (Jan. 19, 1981).
CAUTION: May be habit forming: 21 CFR, 329.1 and is a controlled substance (opium derivative): 21 CFR, 1308.11.

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

HEROIN (DIAMORPINE)

BRITISH PHARMACOPEIA 2005 MONOGRAPH DIAMORPHINE HYDROCHLORIDE



Diamorphine Hydrochloride

C21H23NO5,HCl,H2O 423.9 1502-95-0

Action and use

Narcotic analgesic.

Preparation

Diamorphine Injection

DEFINITION

Diamorphine Hydrochloride is 4,5-epoxy-17-methylmorphinan-3,6-diyl diacetate hydrochloride monohydrate. It contains not less than 98.0% and not more than 102.0% of C21H23NO5,HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Freely soluble in water and in chloroform; soluble in ethanol (96%); practically insoluble in ether .

IDENTIFICATION

A. Dissolve a sufficient quantity in the minimum volume of dichloromethane and evaporate to dryness. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of diamorphine hydrochloride (RS 093).

B. Yields reaction A characteristic of chlorides, Appendix VI.

TESTS

Acidity

Dissolve 0.2 g in 10 ml of carbon dioxide-free water and titrate with 0.02M sodium hydroxide VS using methyl red solution as indicator. Not more than 0.2 ml of 0.02M sodium hydroxide VS is required.

Related substances

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

HEROIN (DIAMORPINE)

BRITISH PHARMACOPEIA 2005 MONOGRAPH DIAMORPHINE HYDROCHLORIDE - nastavak

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. Solution (1) contains 0.5% w/v of the substance being examined in water. For solution (2) dilute 1 volume of solution (1) to 50 volumes with water. For solution (3) use a freshly prepared solution containing 1% w/v of the substance being examined in 0.01M sodium hydroxide. For solution (1) allow the chromatography to proceed for twice the retention time of the principal peak.

The chromatographic procedure may be carried out using (a) a stainless steel column (12.5 cm × 4.6 mm) packed with stationary phase B (5 µm) (Lichrosphere RP-select B 5µ is suitable), (b) as the mobile phase with a flow rate of 1 ml per minute a solution containing 0.11 % w/v of sodium octanesulphonate in 10 volumes of glacial acetic acid, 10 volumes of methanol , 115 volumes of acetonitrile and 365 volumes of water and (c) a detection wavelength of 283 nm.

The chromatogram obtained with solution (3) exhibits two secondary peaks with retention times relative to the principal peak of about 0.23 (morphine) and 0.43 (6-O-acetyl-morphine). The test is not valid unless the resolution factor between the peaks due to morphine and 6-O-acetyl-morphine is at least 2.

In the chromatogram obtained with solution (1) the area of any peak corresponding to 6-O- acetylmorphine is not greater than the area of the peak in the chromatogram obtained with solution (2) (2%) and the sum of the areas of any other secondary peaks is not greater than 0.25 times the area of the peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.05 times the area of the peak in the chromatogram obtained with solution (2) (0.1%).

Loss on drying

When dried to constant weight at 105°, loses 3.0 to 4.5% of its weight. Use 1 g.

Sulphated ash

Not more than 0.1%, Appendix IX A.

ASSAY

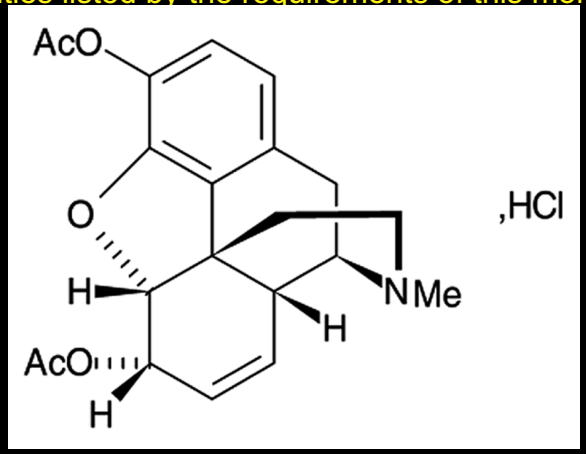
Dissolve 0.40 g in 50 ml of ethanol (96%) and add 5.0 ml of 0.01M hydrochloric acid VS. Titrate with 0.1M sodium hydroxide VS , determining the end point potentiometrically. Measure the volume of titrant required between the two points of inflection. Each ml of 0.1M sodium hydroxide VS is equivalent to 40.59 mg of C21H23NO5,HCl.

STORAGE

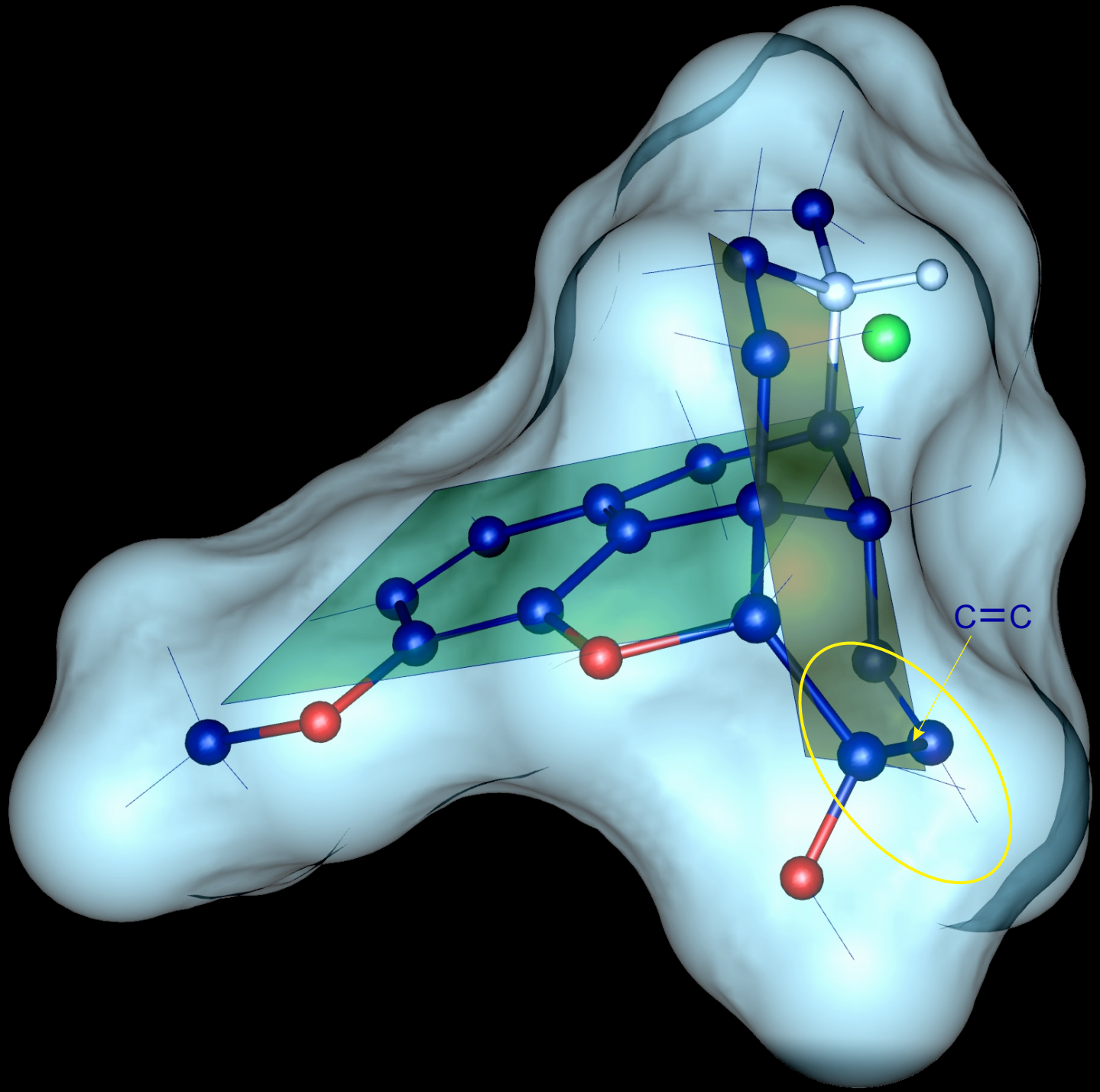
Diamorphine Hydrochloride should be protected from light.

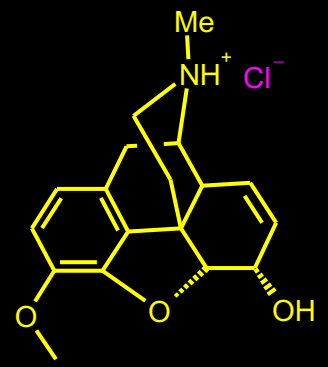
IMPURITIES

The impurities listed by the requirements of this monograph include:



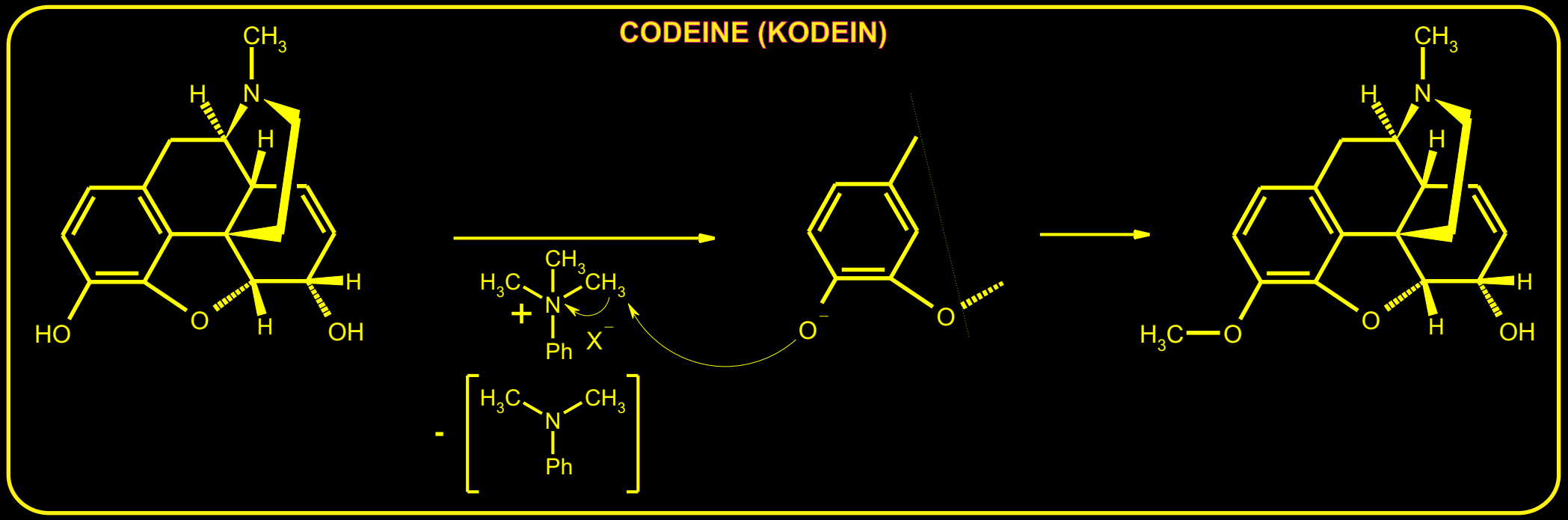
MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak



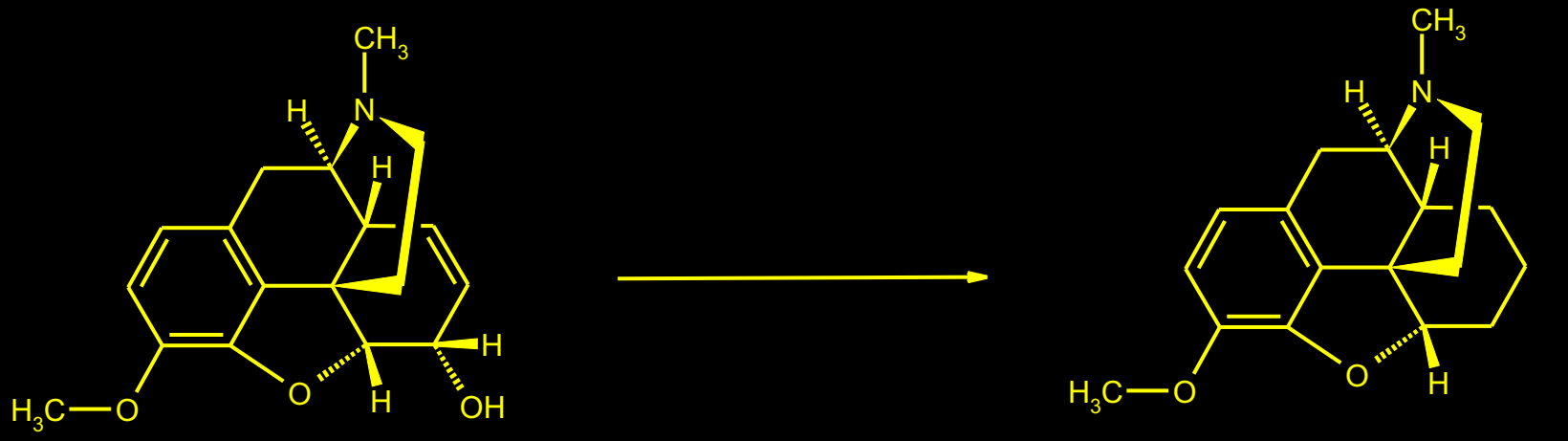


CODEINE HCl

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak



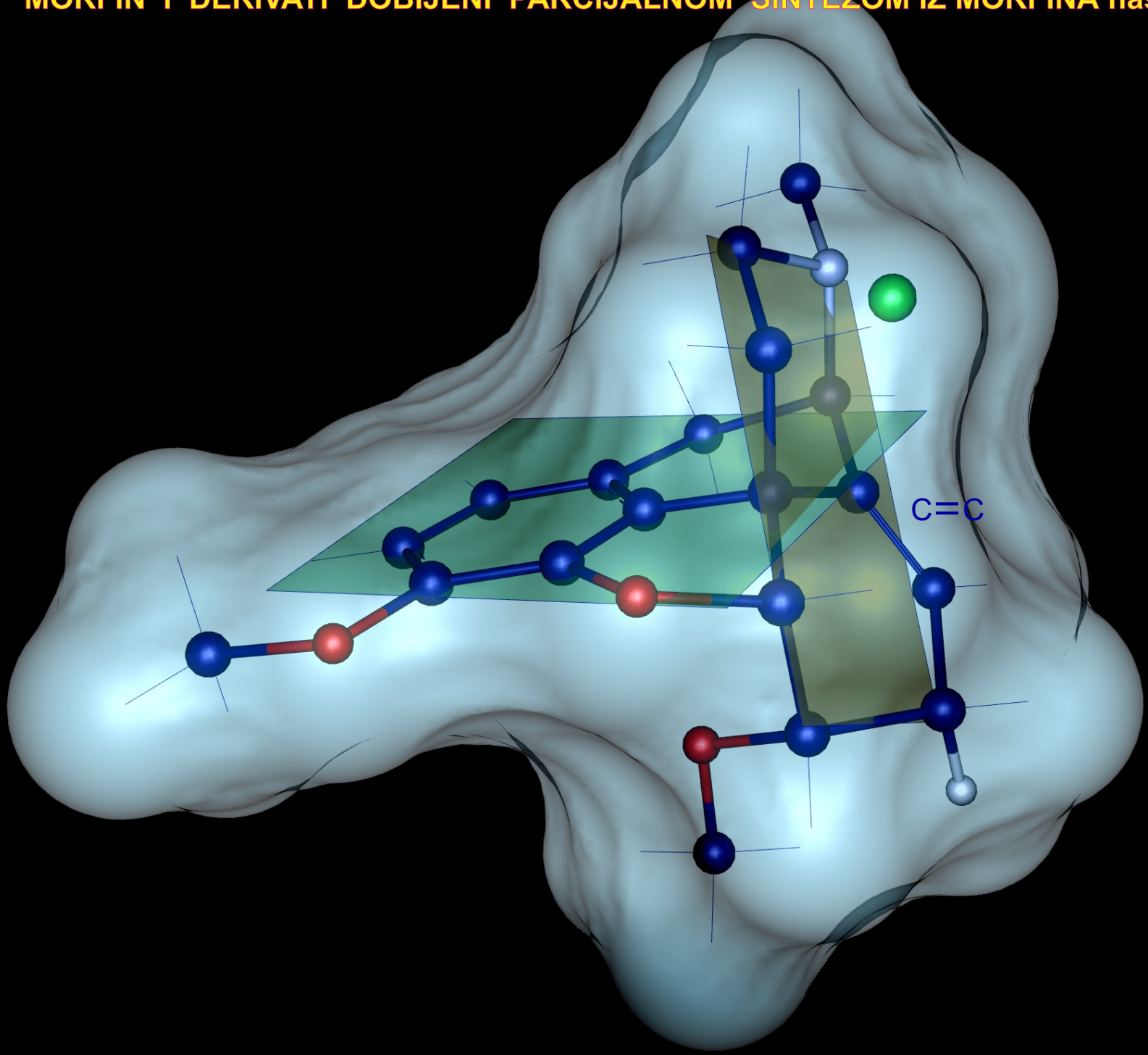
MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

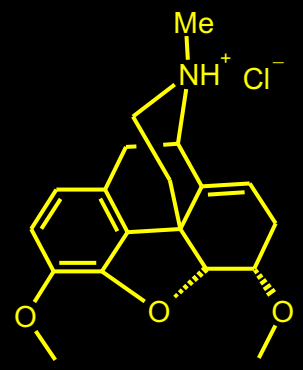


Monograph Number: 2944
Title: Desomorphine

KADA SE DESOMORPHINE DOBIJA ILEGALNO IZ CODEINE-a, POSTAJU IZUZETNO TOKSIČNE SMESE POROIZVODA KOJE SADRŽE I NEORGANSKE KONTAMINANTE. OVAKVA ULIČNA DROGA POZNATA JE POD NAZIVOM “KROKODIL” I UZROKOVALA JE VELIKI BROJ SMRTNIH SLUČAJEVA I TEŠKIH TROVANJA.

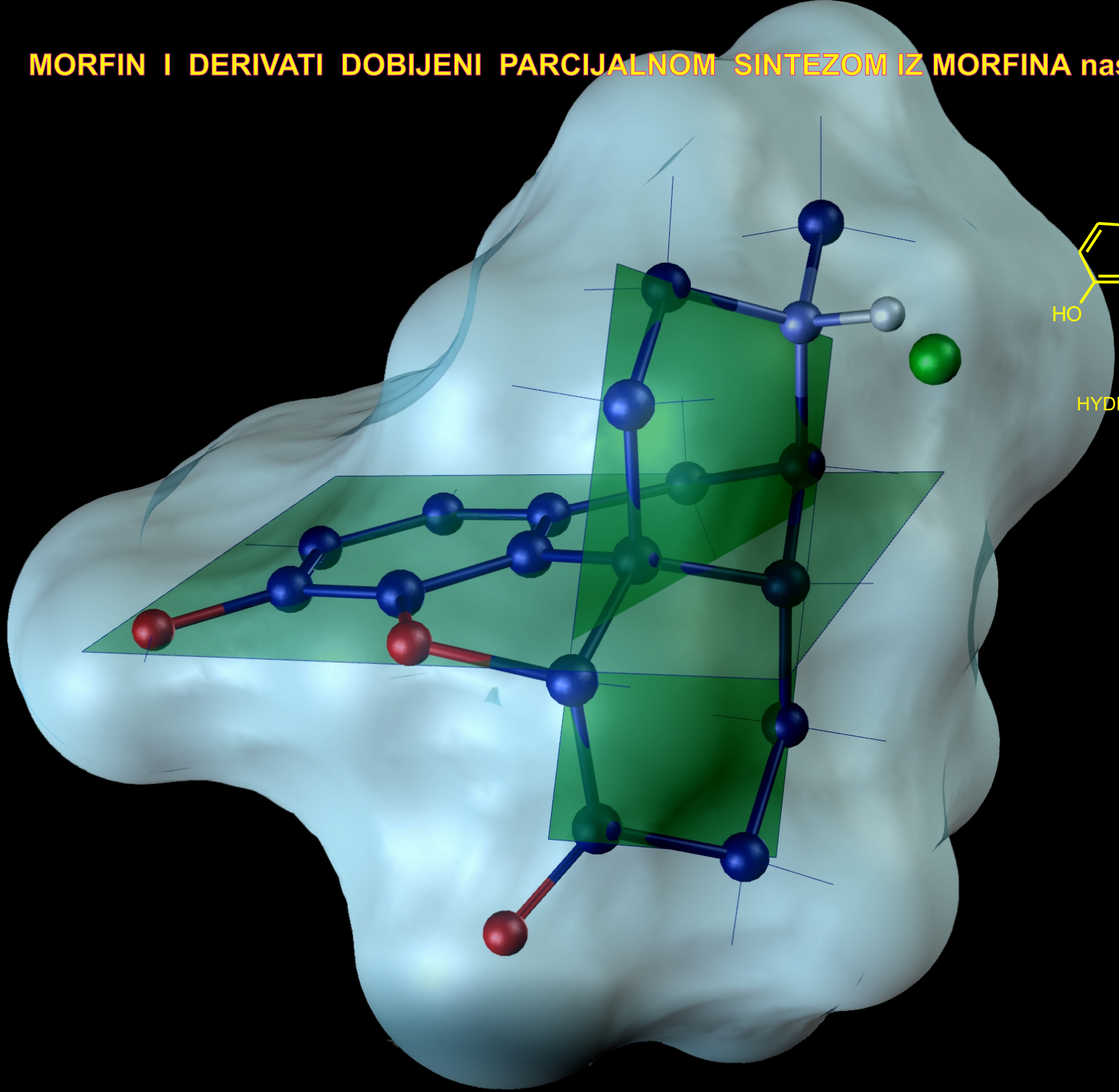
MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

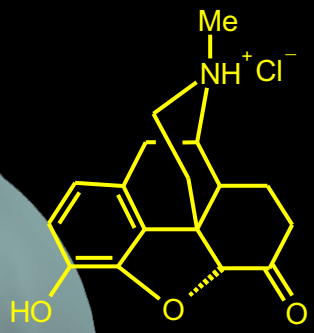




THEBAINE HCl

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak



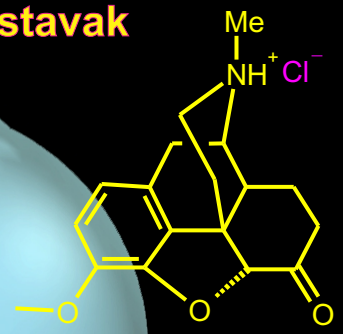


HYDROMORPHONE HCl

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

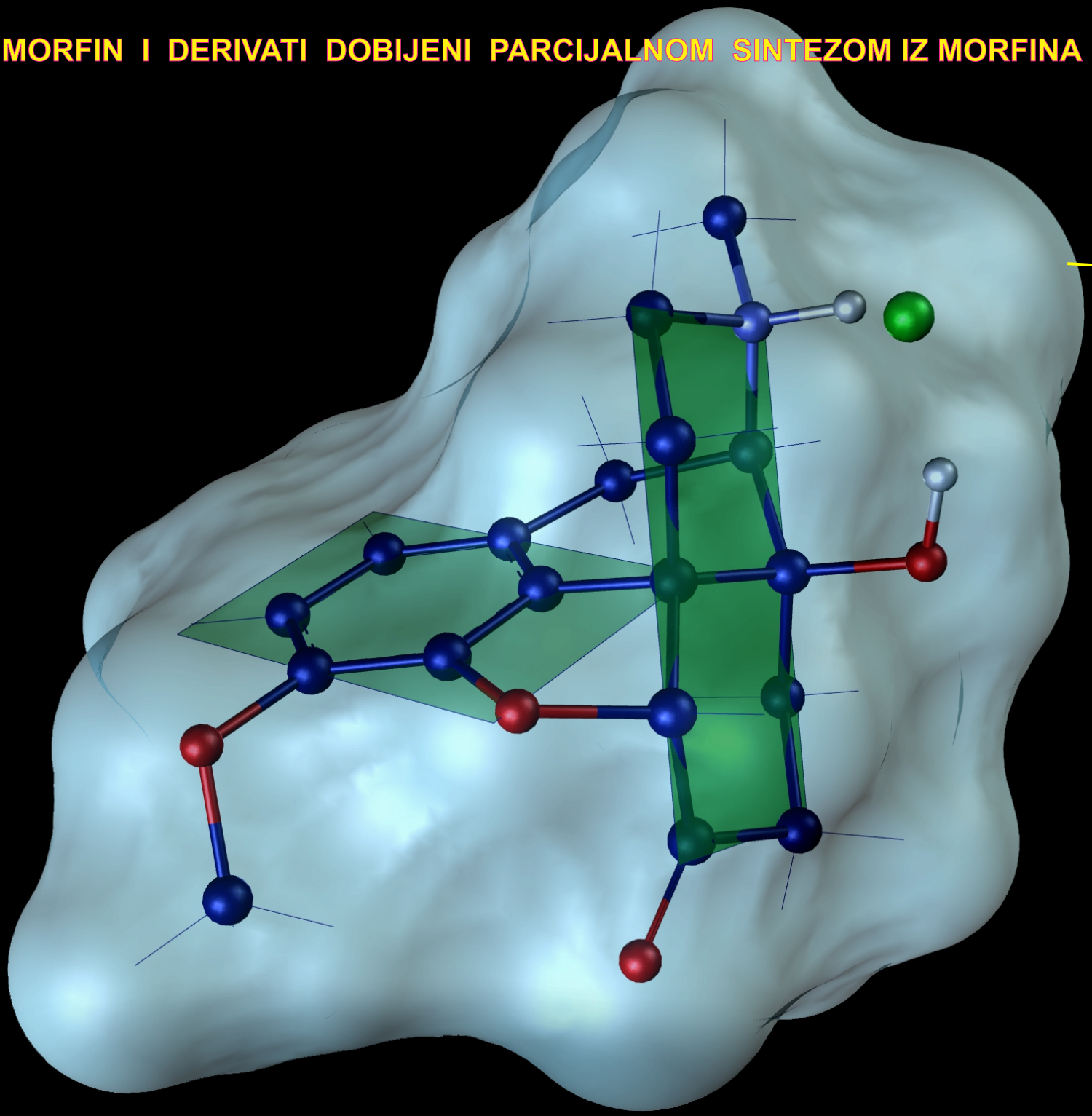
HYDROMORPHONE

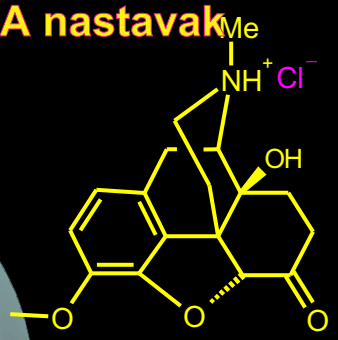
MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak



HYDROCODONE HCl

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

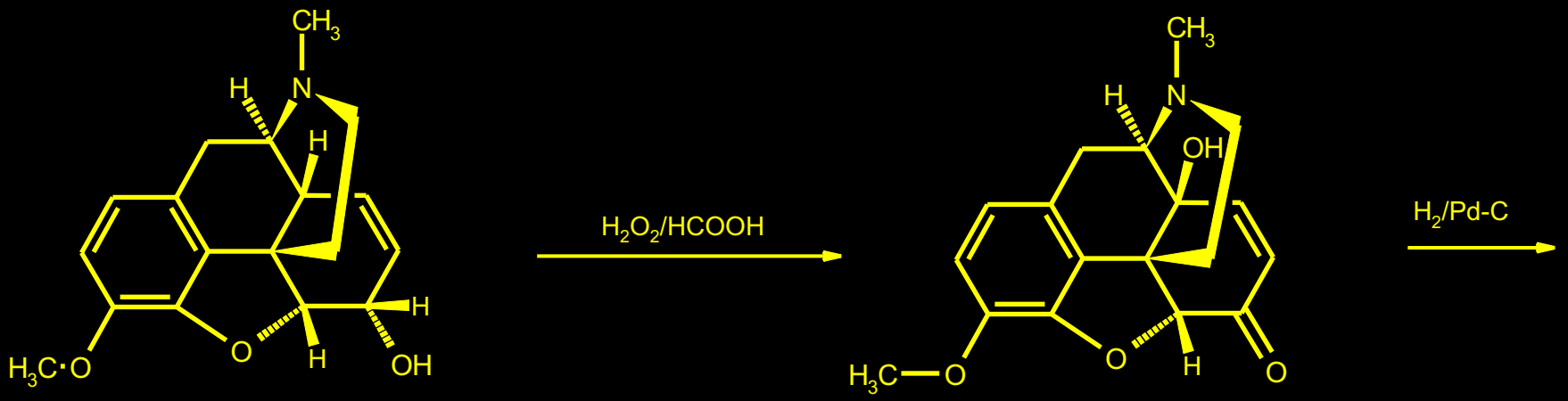




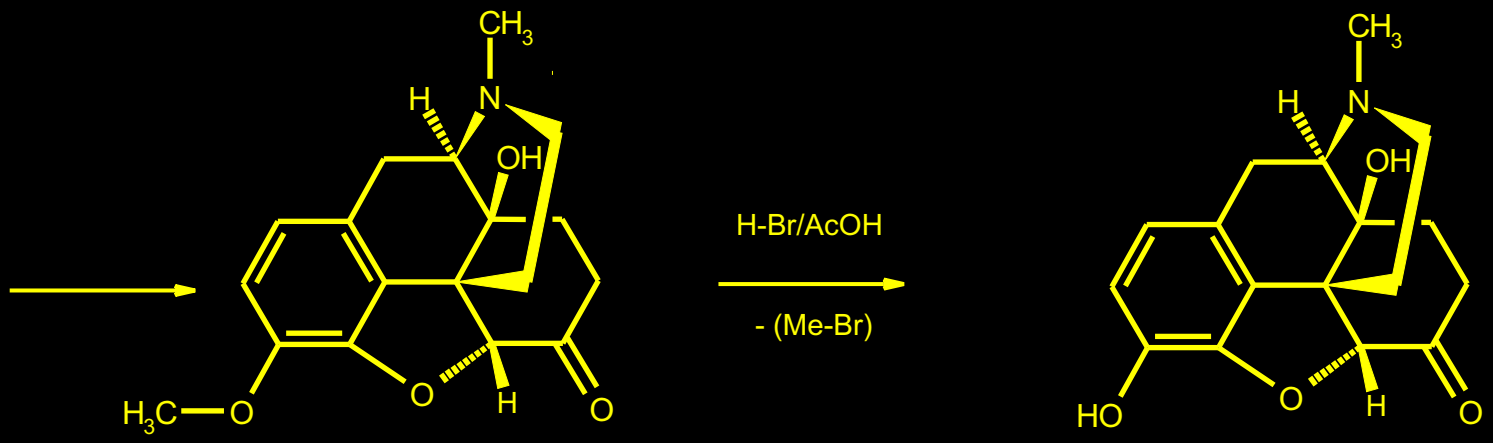
OXYCODONE HCl

MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak

OXYCODONE I OXYMORPHONE



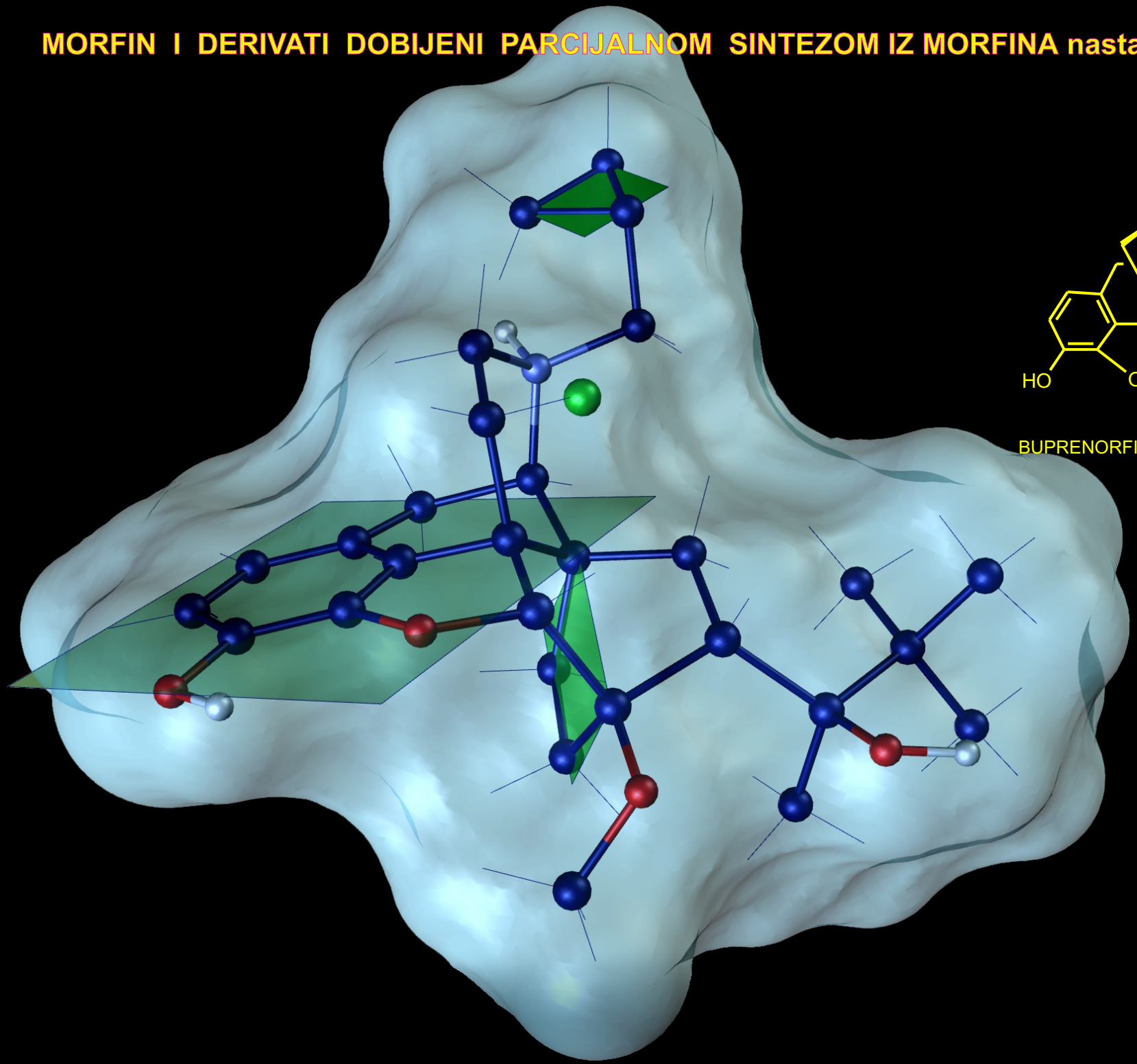
CODEINE (KODEIN)

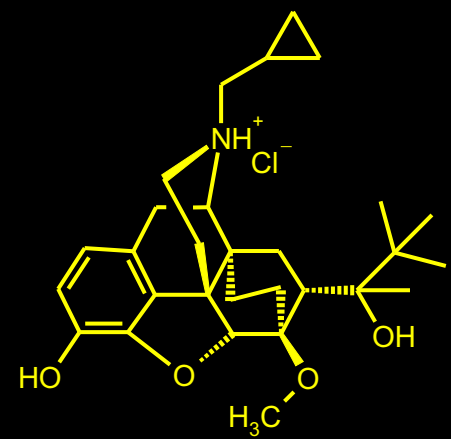


OXYCODONE

OXYMORPHONE

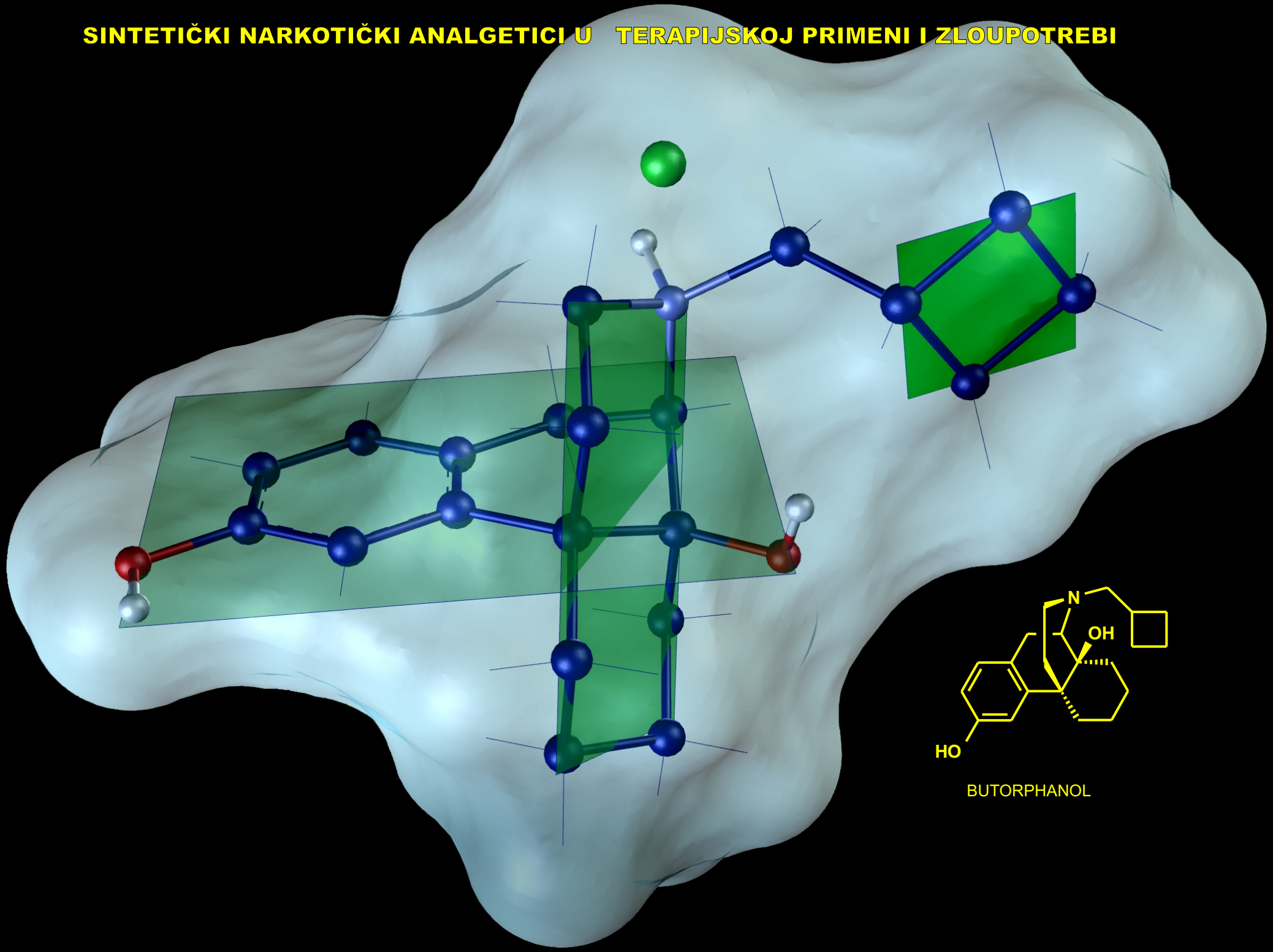
MORFIN I DERIVATI DOBIJENI PARCIJALNOM SINTEZOM IZ MORFINA nastavak





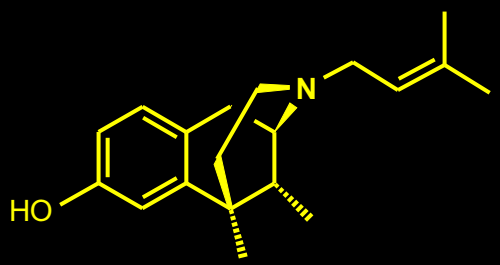
BUPRENORFIN (BUPRENORPHINE)

SINTETIČKI NARKOTIČKI ANALGETICI U TERAPIJSKOJ PRIMENI I ZLOUPOTREBI



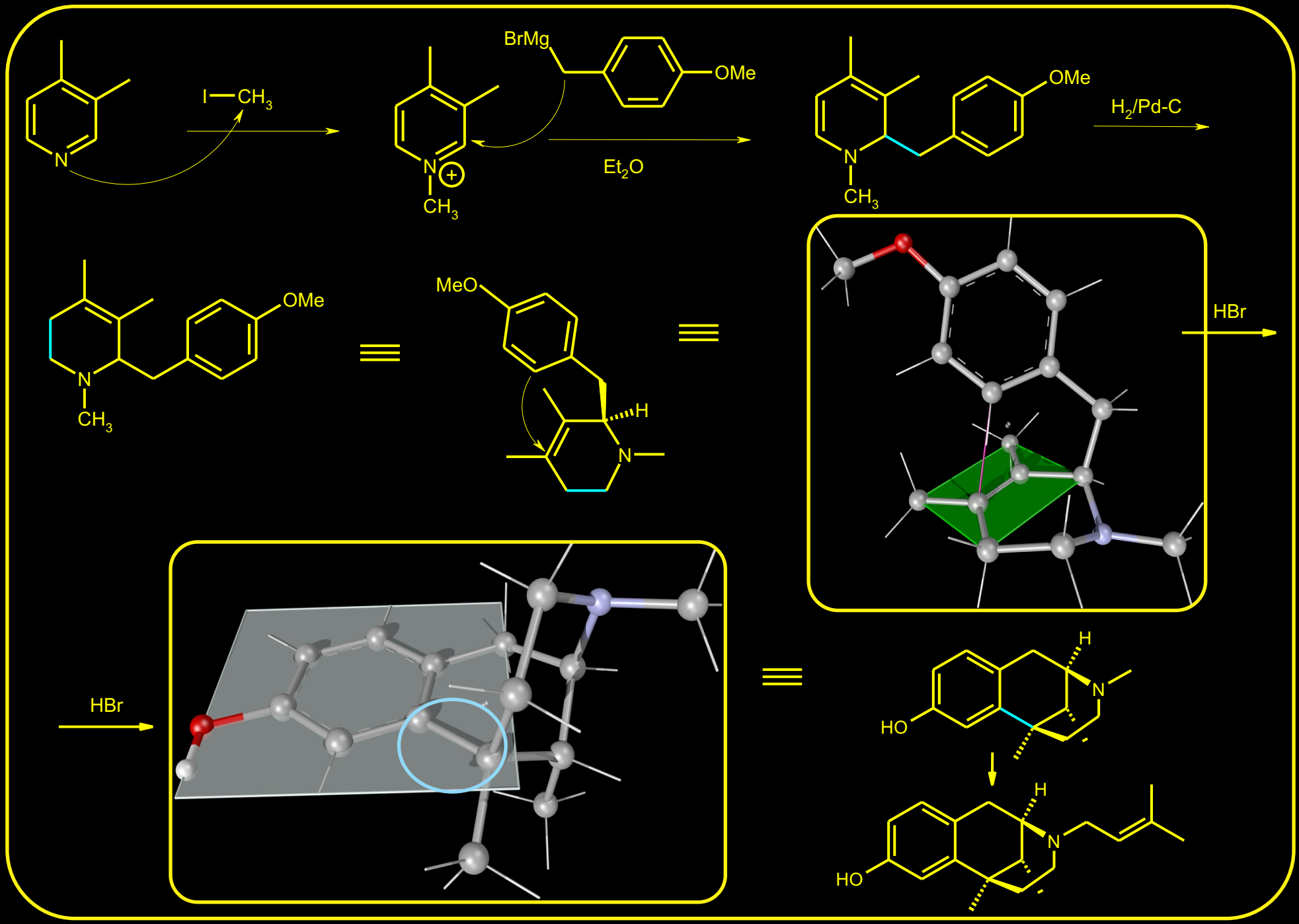
BUTORPHANOL

SINTETIČKI NARKOTIČKI ANALGETICI U TERAPIJSKOJ PRIMENI I ZLOUPOTREBI

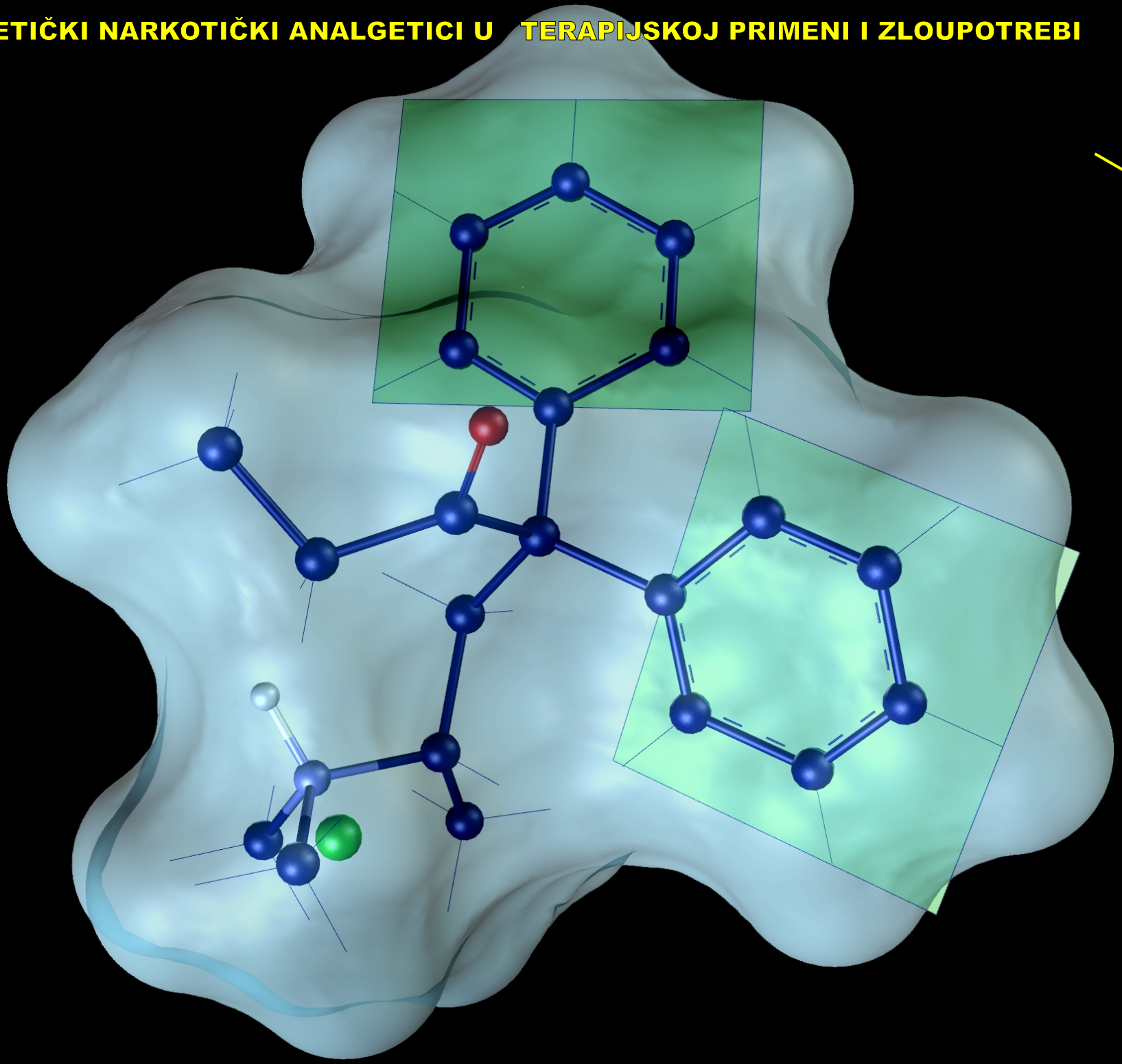


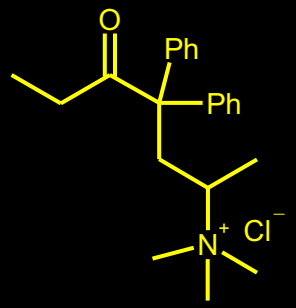
PENTAZOCINE

ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - PENTAZOCINE



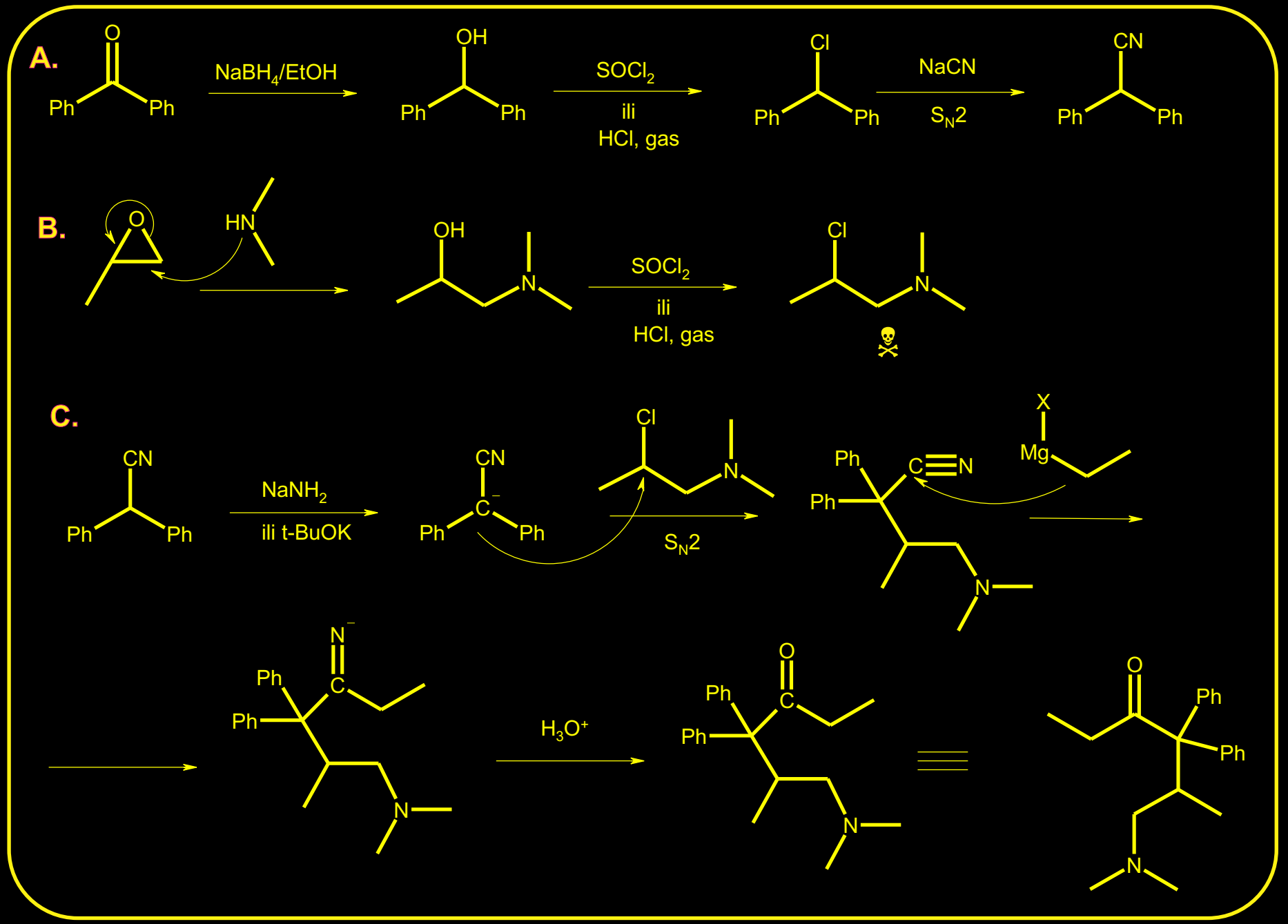
SINTETIČKI NARKOTIČKI ANALGETICI U TERAPIJSKOJ PRIMENI I ZLOUPOTREBI



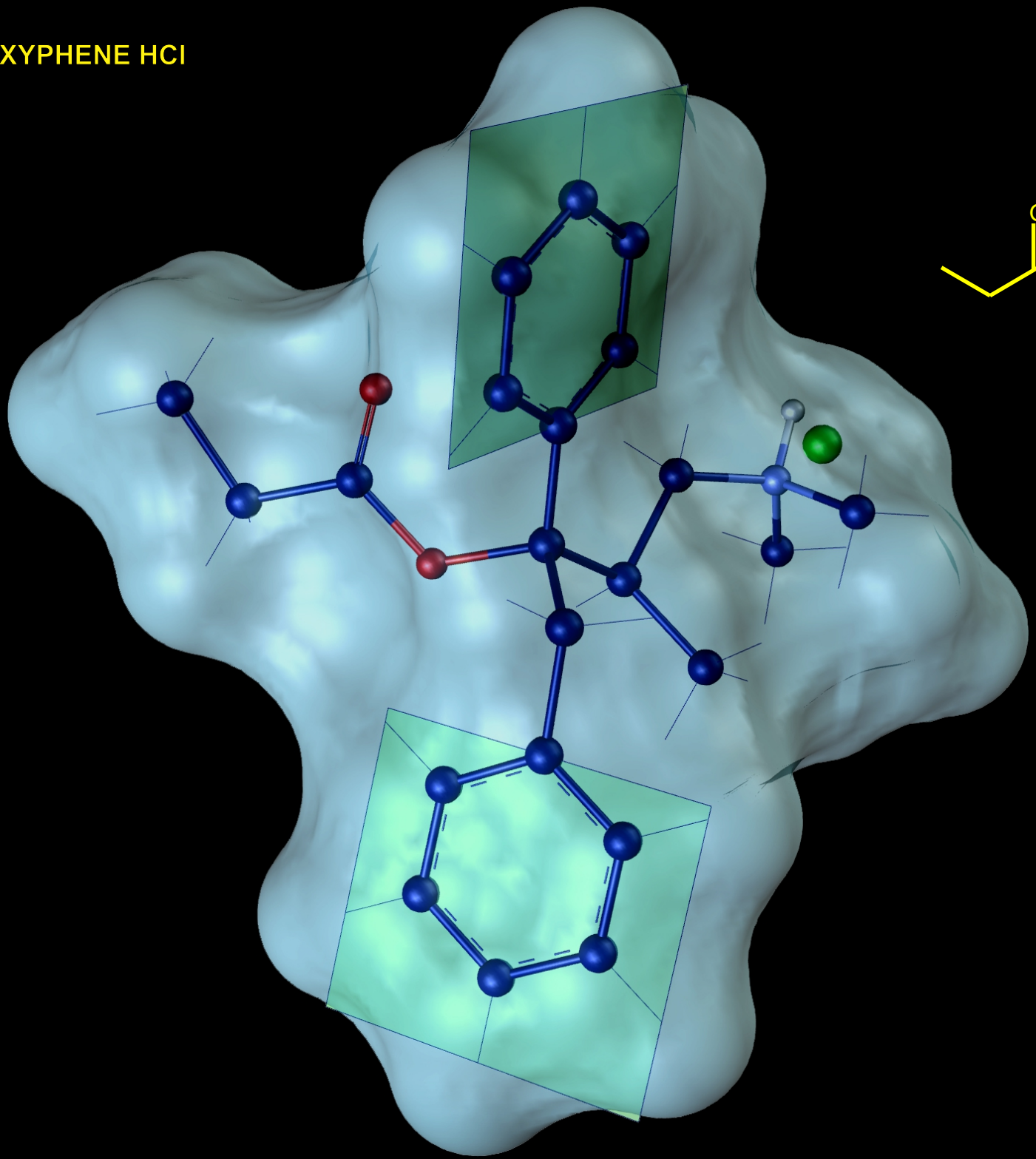


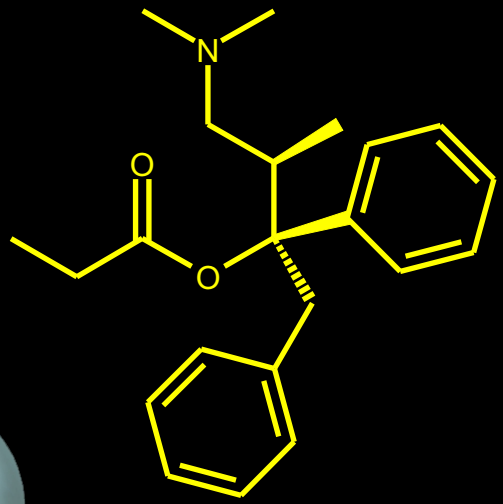
METHADONE HCl

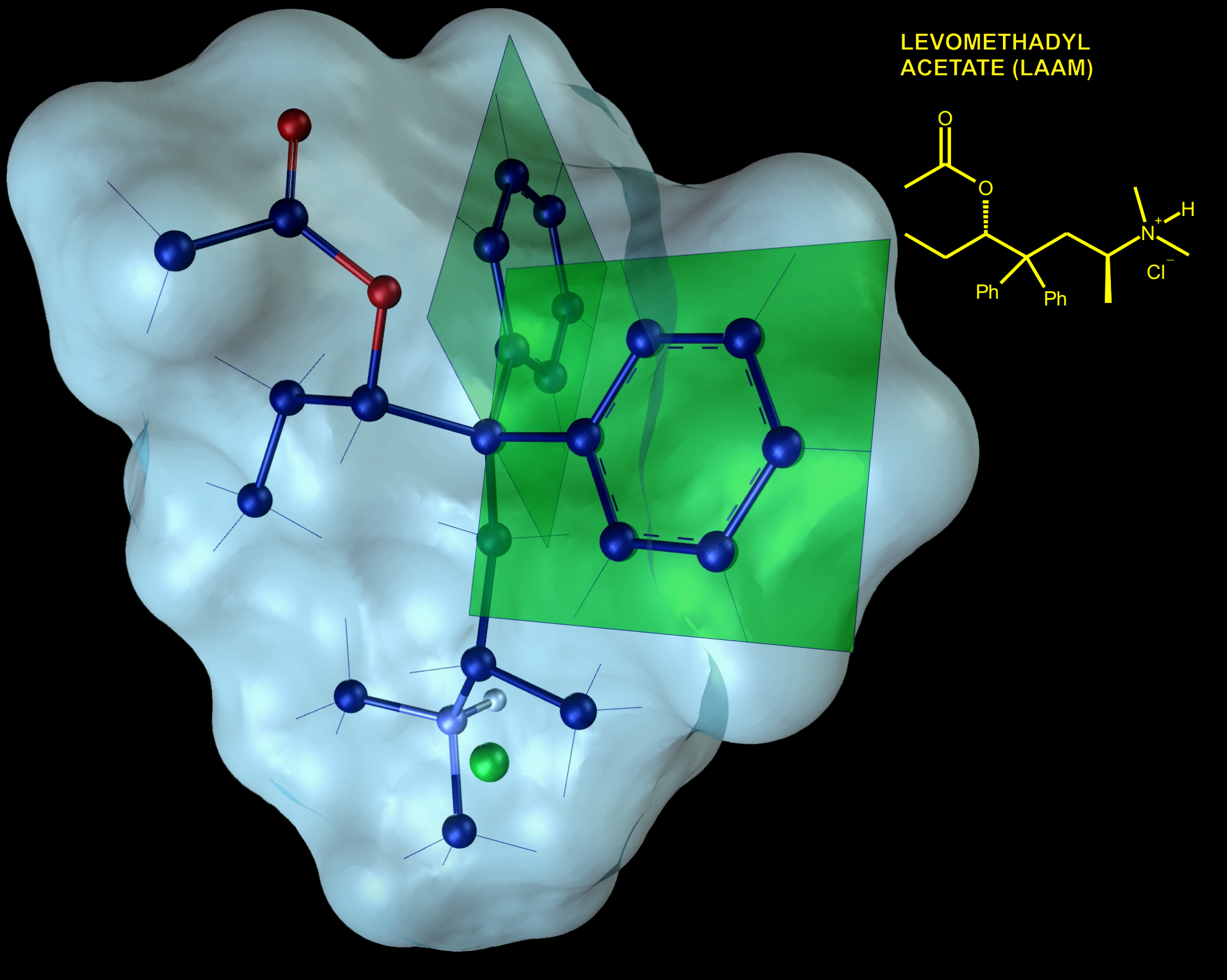
ANALOZI MORFINA POSTALI TOTALNOM SINTEZOM - METHADONE:

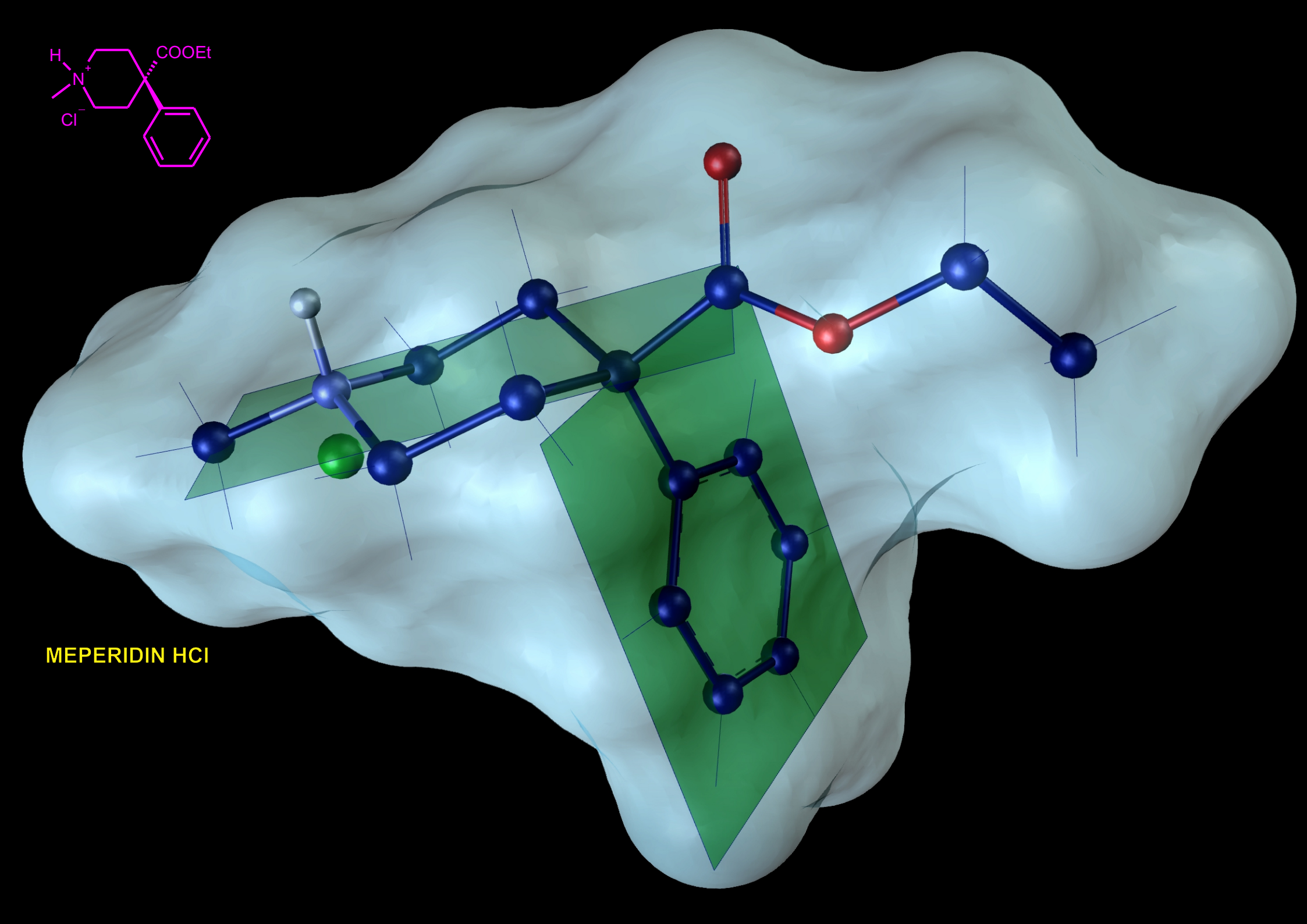


DEXTROPROPOXYPHENE HCl

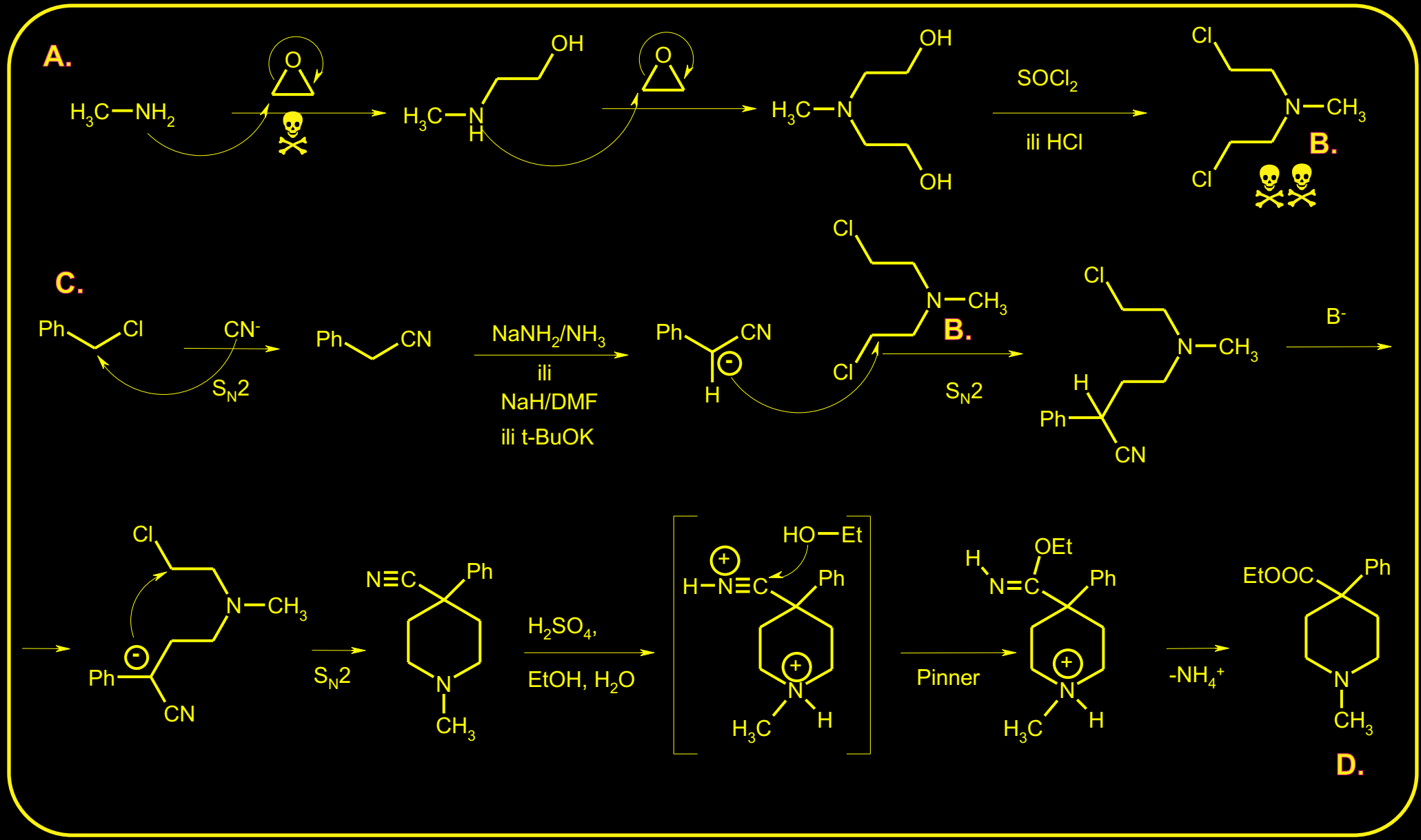




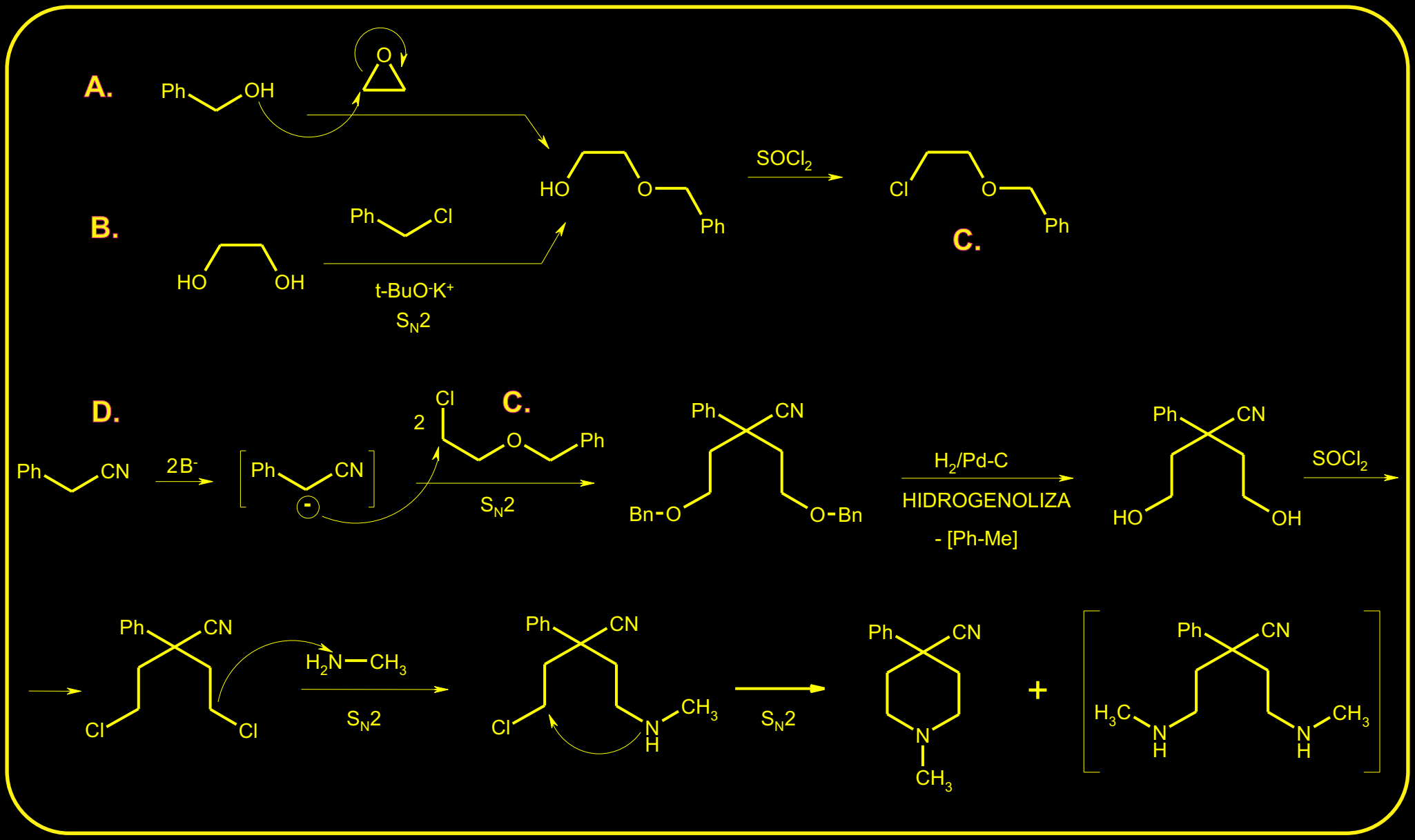

LEVOMETHADYL
ACETATE (LAAM)
O
O
N+
H
Cl−
Ph
Ph


H
N+
COOEt
Cl−
MEPERIDIN HCl

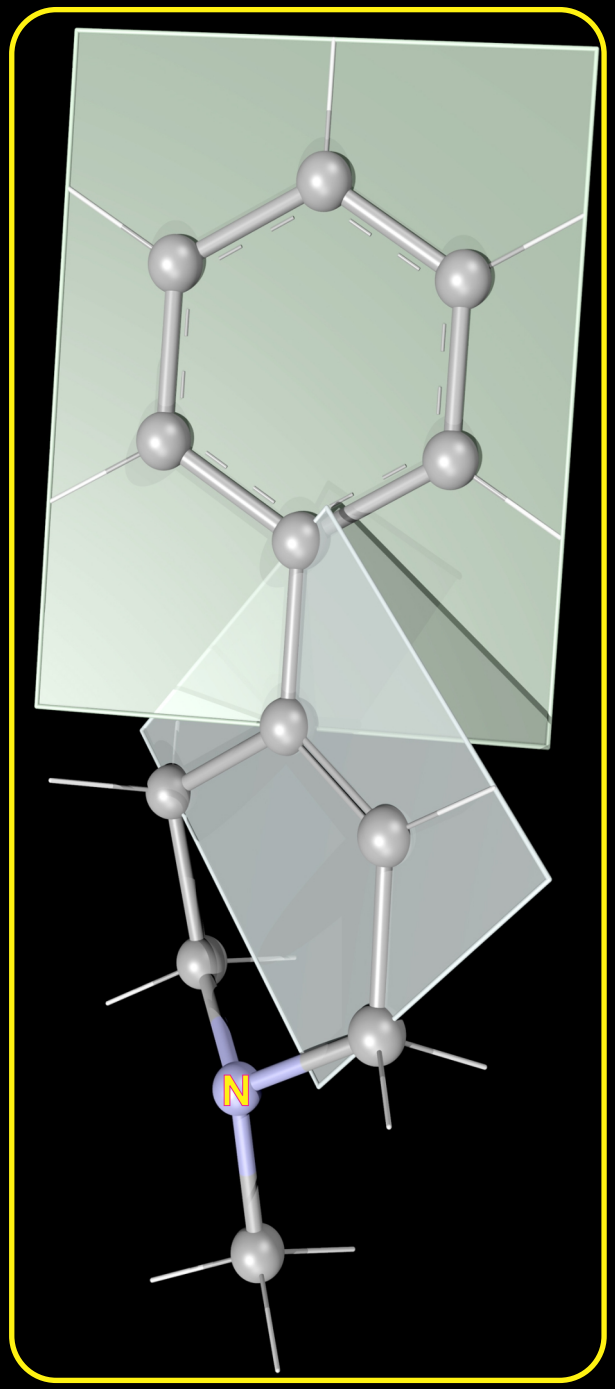
ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - MEPERIDIN (MEPERIDINE):



ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - MEPERIDIN - ALTERNATIVNA SINTEZA



ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - "REVERZNI" ESTRI MEPERIDINA



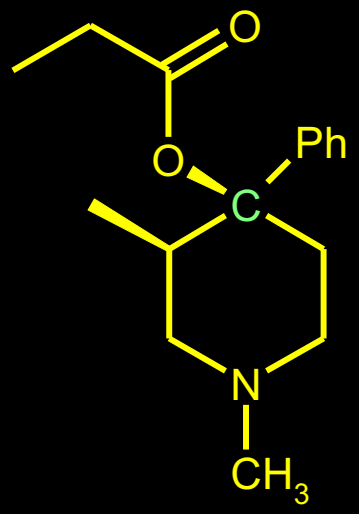
THE MERCK INDEX Monograph Number: 6319
Title: MPTP
CAS Registry Number: 28289-54-5
CAS Name: 1,2,3,6-Tetrahydro-1-methyl-4-phenylpyridine
Additional Names: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Molecular Formula: C12H15N
Molecular Weight: 173.25.
Percent Composition: C 83.19%, H 8.73%, N 8.08%

Literature References: Piperidine derivative which causes irreversible symptoms of parkinsonism in humans, monkeys.
Prepn as hydrochloride by Grignard reaction: A. Ziering et al., J. Org. Chem. 12, 894 (1947). Alternative prepn: C. J. Schmidle, R. C. Mansfield, J. Am. Chem. Soc. 78, 425 (1956).

Selective destruction of dopaminergic neurons in primates: R. S. Burns et al., Proc. Nat. Acad. Sci. USA 80, 4546 (1983).

In vitro metabolism by rat brain monoamine oxidase to 1-methyl-4-phenylpyridinium ion (MPP+): K. Chiba et al., Biochem. Biophys. Res. Commun. 120, 574 (1984). Studies on mechanism of neurotoxicity: J. W. Langston et al., Science 225, 1480 (1984); S. P. Markey et al., Nature 311, 464 (1984). Binding studies in rat brain: C. M. Wieczorek et al., Eur. J. Pharmacol. 98, 453 (1984); B. Parsons, T. C. Rainbow, ibid. 102, 375 (1984); in rat, human brain: J. A. Javitch et al., Proc. Nat. Acad. Sci. USA 81, 4591 (1984). Comparison of idiopathic and MPTP-induced parkinsonism in humans: R. S. Burns et al., N. Engl. J. Med. 312, 1418 (1985). Review: T. P. Singer et al., Trends Biochem. Sci. 12, 266-270 (1987); L. M. Sayre, Toxicol. Lett. 48, 121-149 (1989).
Properties: Crystals from heptane, mp 40-42°. bp0.8 85-90°.
Melting point: mp 40-42°
Boiling point: bp0.8 85-90°

ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - "REVERZNI" ESTRI MEPERIDINA



(+/-)

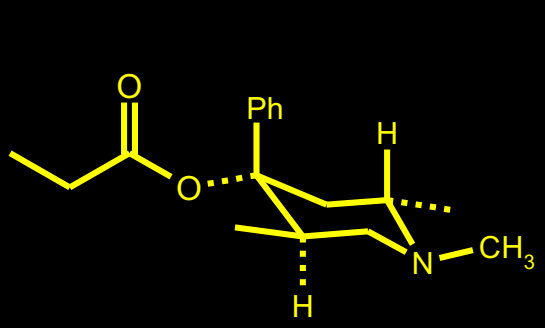
THE MERCK INDEX Monograph Number: 307
Title: Alphaprodine
CAS Registry Number: 77-20-3
CAS Name: (cis)-1,3-Dimethyl-4-phenyl-4-piperidinol propanoate
Additional Names: (±)- -1,3-dimethyl-4-phenyl-4-piperidinyl propionate; dl- -1,3-dimethyl-4-phenyl-4-propionoxypiperidine; (±)- -prodine
Molecular Formula: C16H23NO2
Molecular Weight: 261.36.
Percent Composition: C 73.53%, H 8.87%, N 5.36%, O 12.24%
Literature References: Mixture of the two cis isomers of prodine; betaprodine is the mixture of trans isomers. Prepn: J. Lee, A. Ziering, US 2498433 (1950 to Hoffmann-La Roche); A. H. Beckett et al., J. Pharm. Pharmacol. 9, 939 (1957); A. Ziering et al., J. Org. Chem. 22, 1521 (1957). Configurational studies: F. R. Ahmed et al., Chem. & Ind. (London) 1959, 485; eidem, ibid. 1962, 97. Stereostructure-activity studies: M. M. Abdel-Monem et al., J. Med. Chem. 15, 494 (1972). Pharmacology and toxicology: G. M. Gruber et al., J. Pharmacol. Exp. Ther. 99, 312 (1950). Review of clinical experience: R. C. Lunt, H. E. Howard, Pediatr. Dent. 10, 121-126 (1988).

Derivative Type: Hydrochloride
CAS Registry Number: 561-78-4
Manufacturers' Codes: Nu-1196
Trademarks: Nisentil (Roche)
Molecular Formula: C16H23NO2.HCl
Molecular Weight: 297.83.
Percent Composition: C 64.53%, H 8.12%, N 4.70%, O 10.74%, Cl 11.90%
Properties: Crystals from acetone, mp 220-221°. Slightly saline taste. Freely sol in water, alc, chloroform. Practically insol in ether. pH of 1% aq soln 4.5-5.2. LD50 in mice: 54 mg/kg i.v., 73 mg/kg i.p.; in rats: 22 mg/kg i.p. (Gruber).
Melting point: mp 220-221°
Toxicity data: LD50 in mice: 54 mg/kg i.v., 73 mg/kg i.p.; in rats: 22 mg/kg i.p. (Gruber)

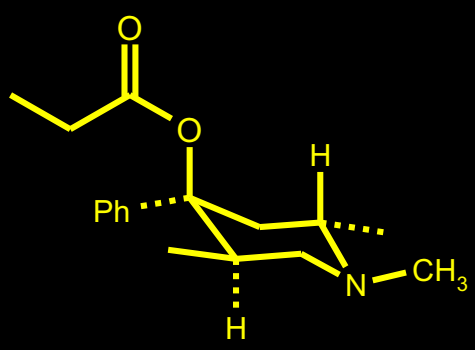
Derivative Type: Betaprodine hydrochloride
CAS Registry Number: 49638-23-5
Additional Names: (±)- -Prodine hydrochloride
Manufacturers' Codes: Nu-1779
Properties: Crystals from methyl ethyl ketone, mp 195-196° (Beckett); from acetone + methanol, mp 199-200° (Ziering).
Melting point: mp 195-196° (Beckett); mp 199-200° (Ziering)

NOTE: These are controlled substances (opiates): 21 CFR, 1308.11 (betaprodine) and 1308.12 (alphaprodine).
Therap-Cat: Analgesic (narcotic).

ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - "REVERZNI" ESTRI MEPERIDINA - PROMEDOL



α-isomer



γ-isomer

THE MERCK INDEX Monograph Number: 7876
Title: Promedol
CAS Registry Number: 64-39-1
CAS Name: 1,2,5-Trimethyl-4-phenyl-4-piperidinol propanoate (ester)
Additional Names: 1,2,5-trimethyl-4-phenyl-4-propionyloxypiperidine; 1,2,5-trimethyl-4-phenyl-4-piperidyl propionate; dimethylmeperidine
Molecular Formula: C17H25NO2
Molecular Weight: 275.38.
Percent Composition: C 74.15%, H 9.15%, N 5.09%, O 11.62%
Literature References: Prepn: Nazarov et al., J. Gen. Chem. USSR 26, 3117 (1956); Nazarov, Shvestov, ibid. 3533. Conformation studies: Prostakov, Mikheeva, ibid. 31, 108 (1961); 33, 2931 (1963); eidem, Russ. Chem. Rev. 31, 556 (1962). Of the four possible isomers and are shown.

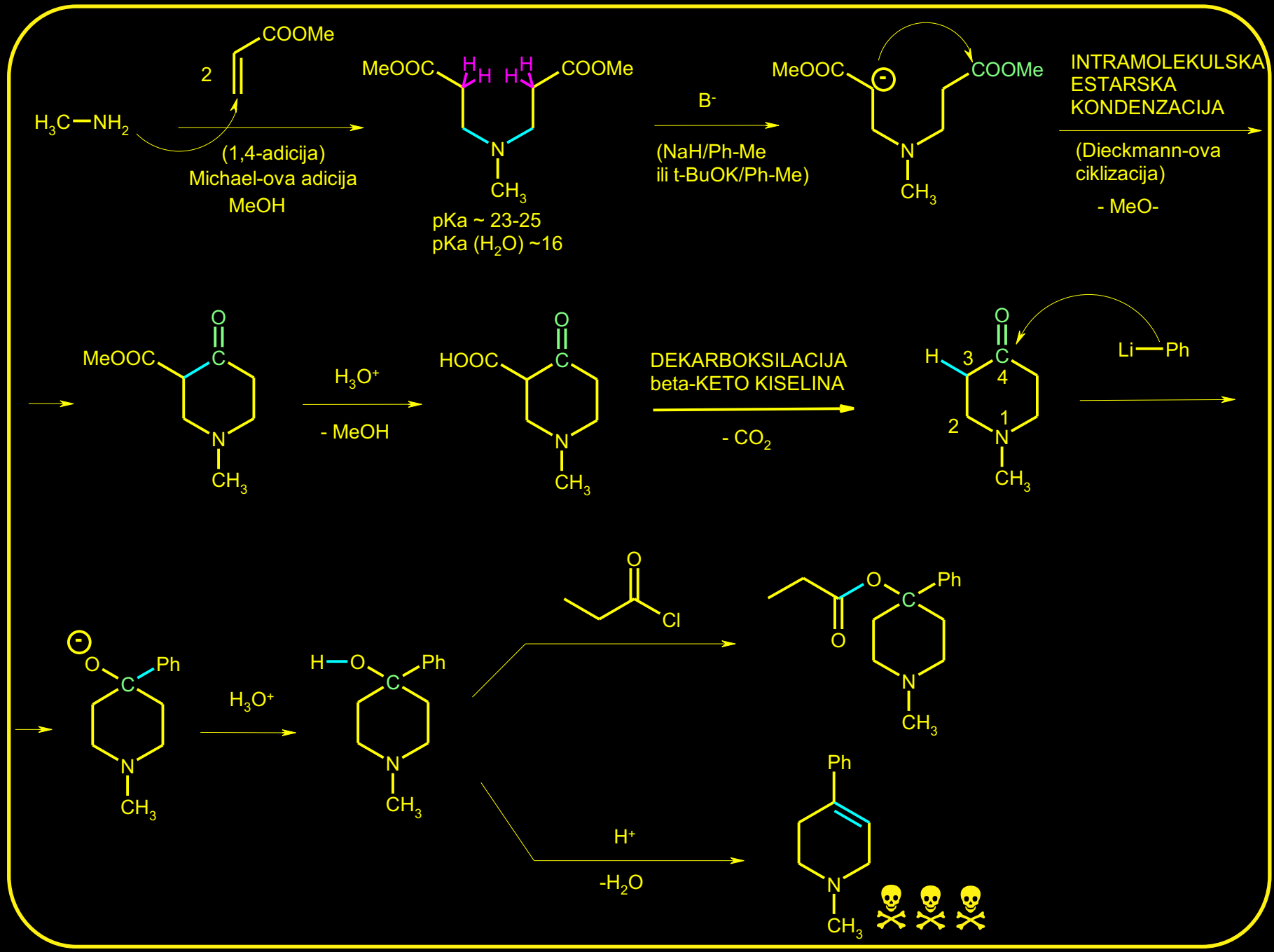
Derivative Type: -Isomer hydrochloride
Additional Names: -Promedol
Molecular Formula: C17H25NO2.HCl
Molecular Weight: 311.85.
Percent Composition: C 65.48%, H 8.40%, N 4.49%, O 10.26%, Cl 11.37%
Properties: Crystals from benzene, mp 153-154°. Has been also reported as mp 106-107° or 126-131° (Prostakov, Mikheeva, 1961).
Melting point: mp 153-154°; mp 106-107° or 126-131° (Prostakov, Mikheeva, 1961)

Derivative Type: -Isomer hydrochloride
Additional Names: Isopromedol
Properties: Crystals, mp 183-184°, Nazarov, Shvestov, Bull. Acad. Sci. USSR Phys. Ser. 1959, 2059.
Melting point: mp 183-184°

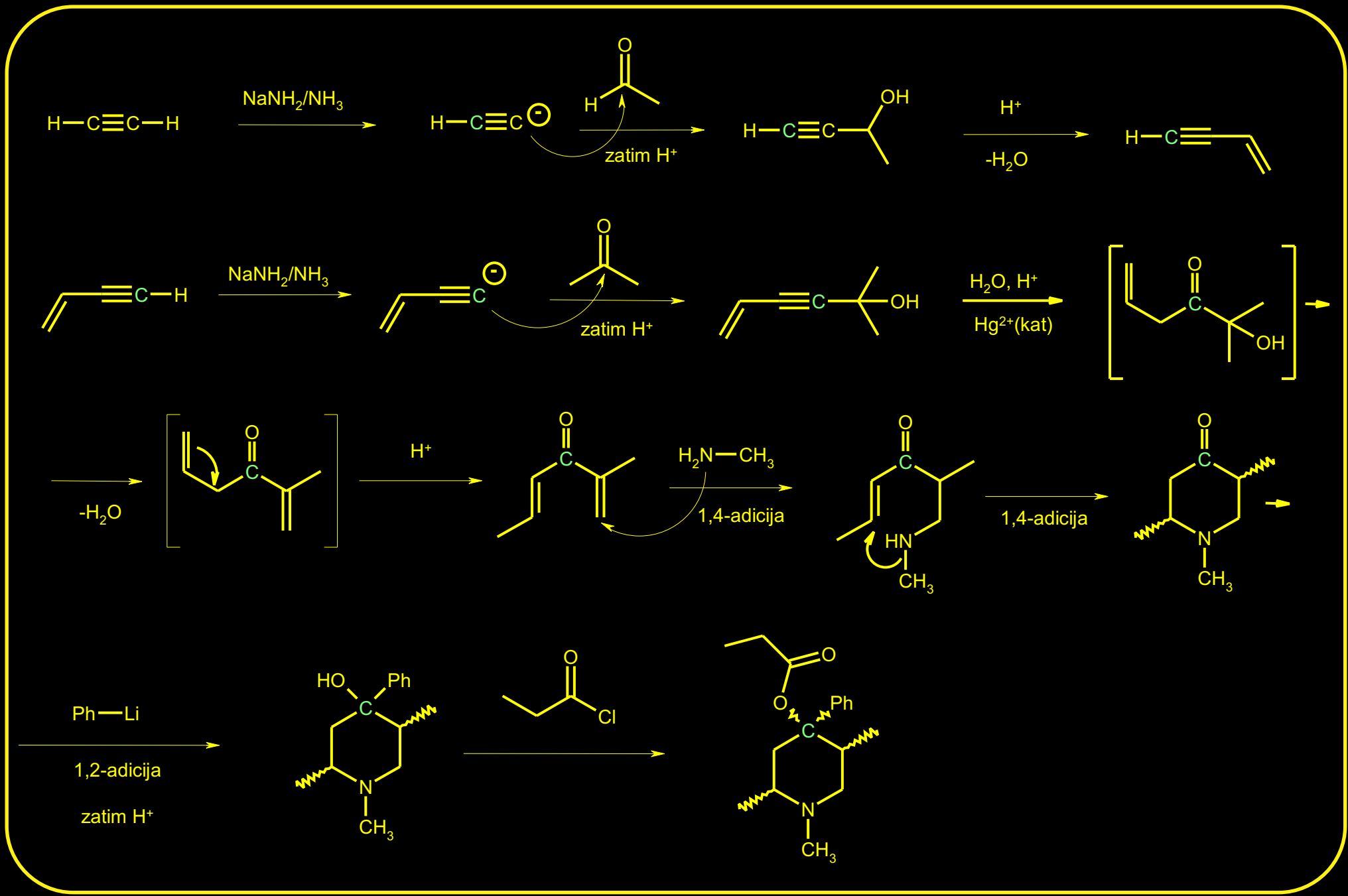
Derivative Type: -Isomer hydrochloride
Additional Names: Trimeperidine; -promedol
Properties: Crystals from acetone, mp 222-223°.
Melting point: mp 222-223°

NOTE: This is a controlled substance (opiate): 21 CFR, 1308.11.
Therap-Cat: Analgesic (narcotic).

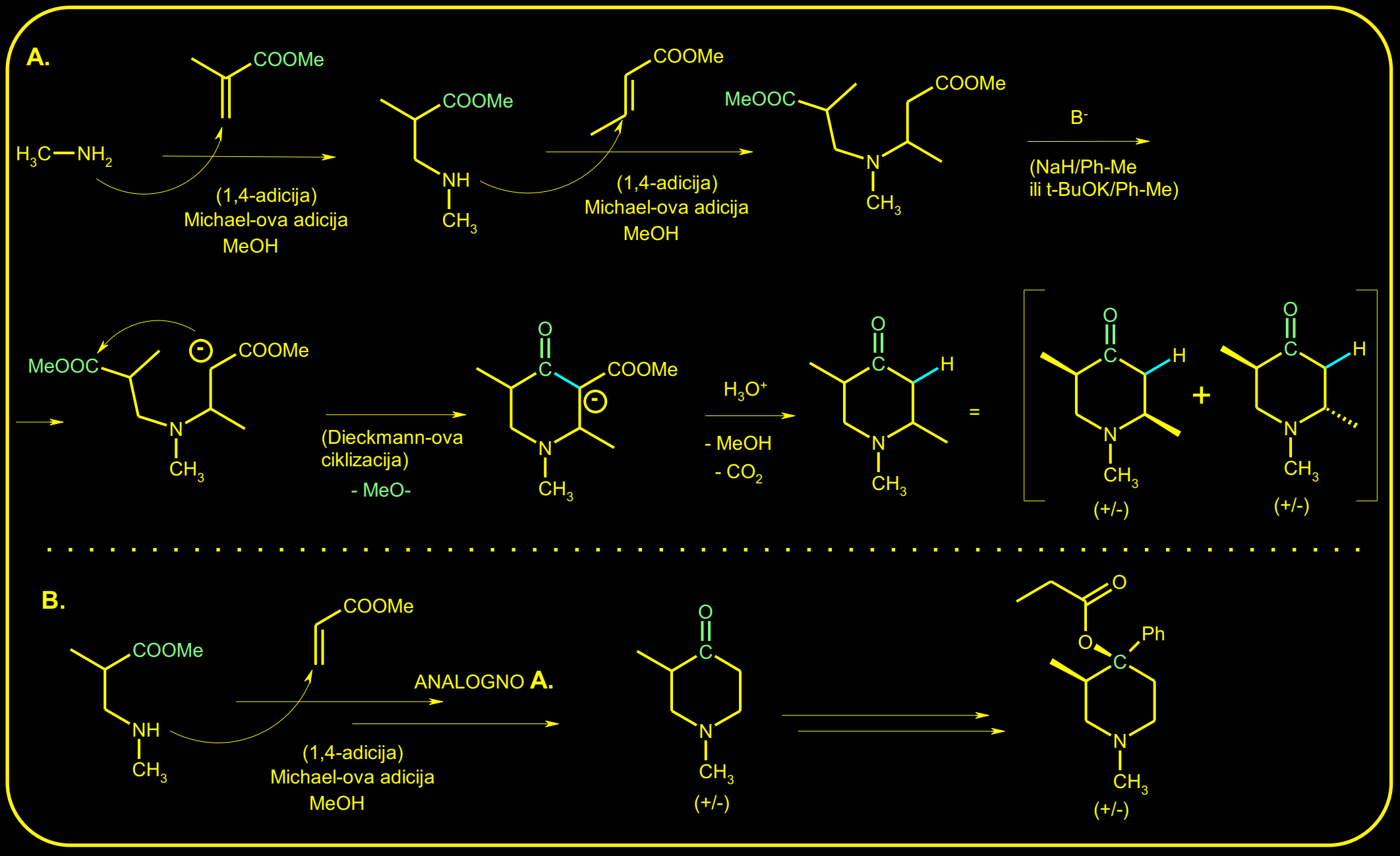
ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - "REVERZNI" ESTRI MEPERIDINA



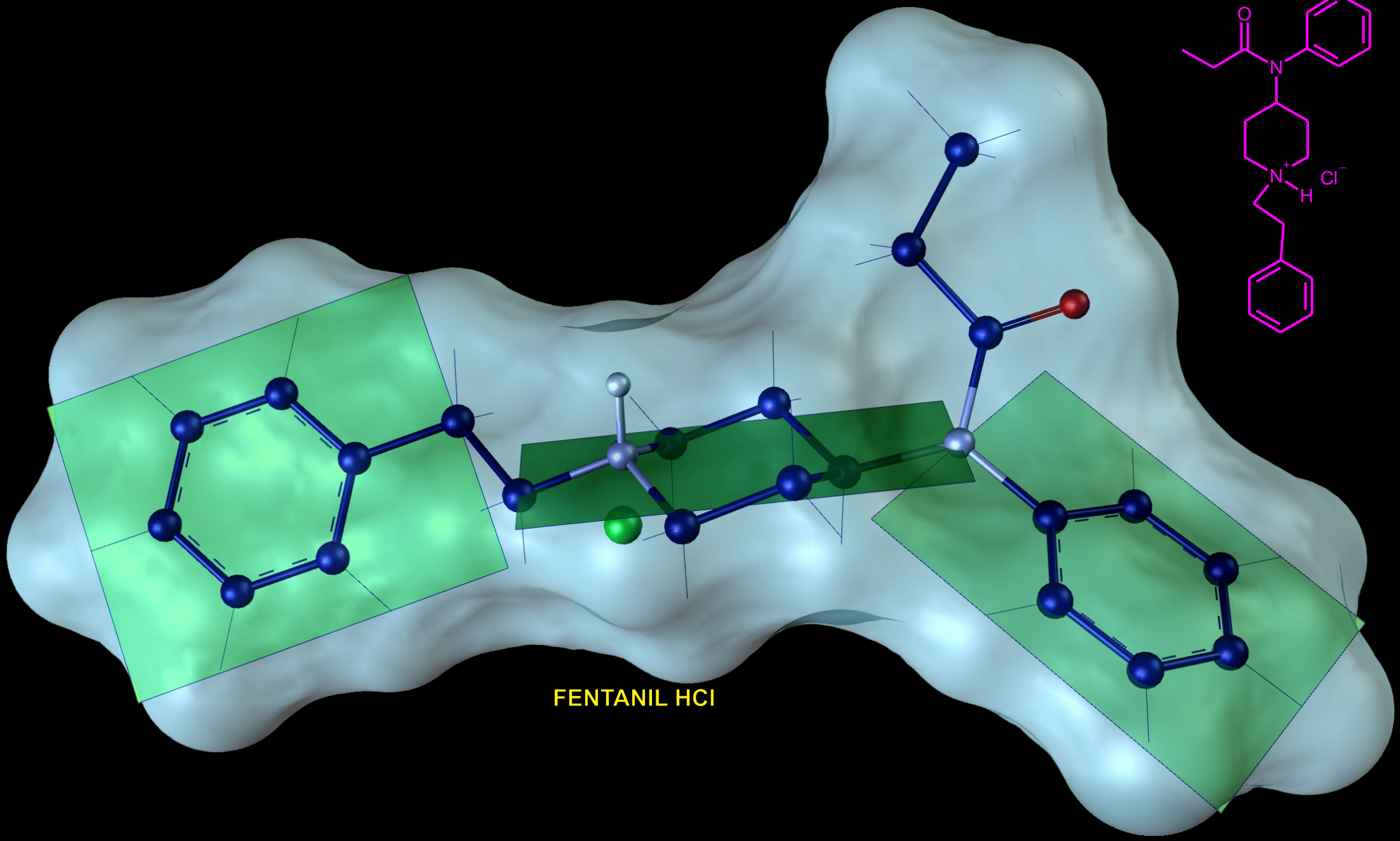
ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - "REVERZNI" ESTRI MEPERIDINA - PROMEDOL



SINTEZE POJEDINIH 4-PIPERIDONA PRIMENOM SUKCESIVNIH 1,4-ADICIJA PRIMARNIH AMINA NA AKRILATE

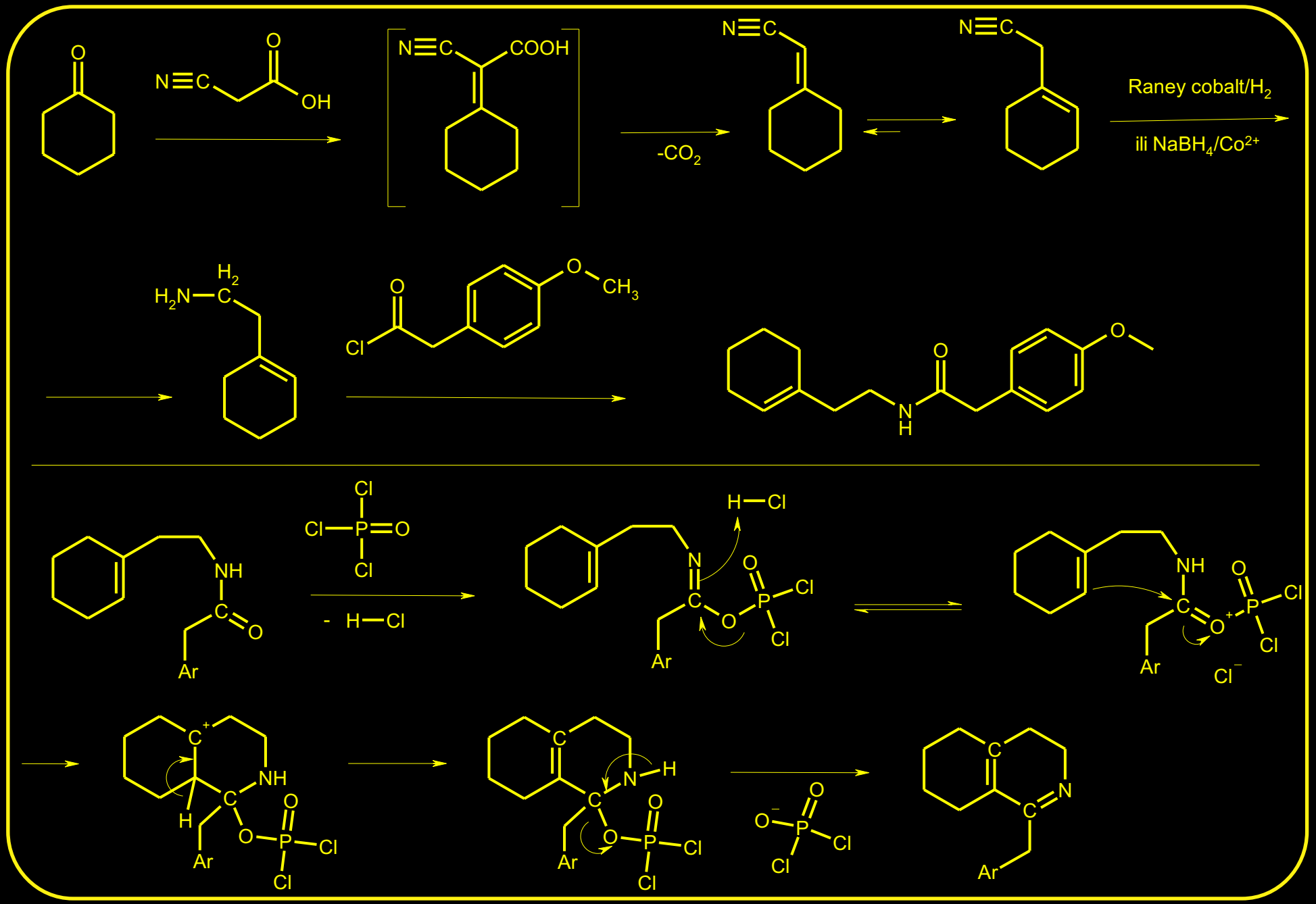


ALPHAPRODINE

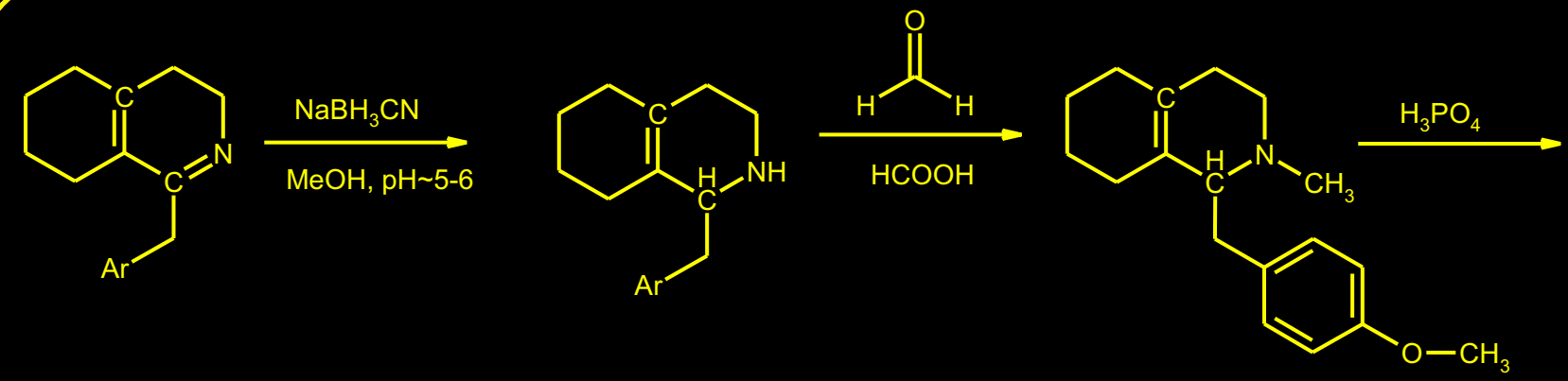


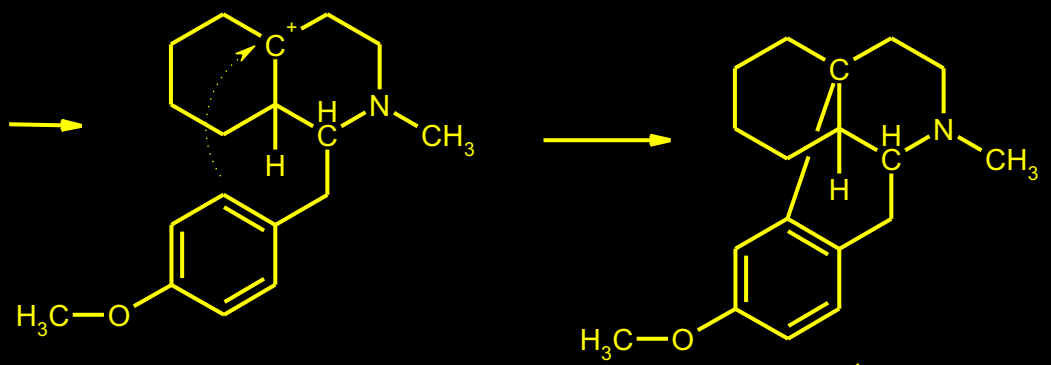
FENTANIL HCl

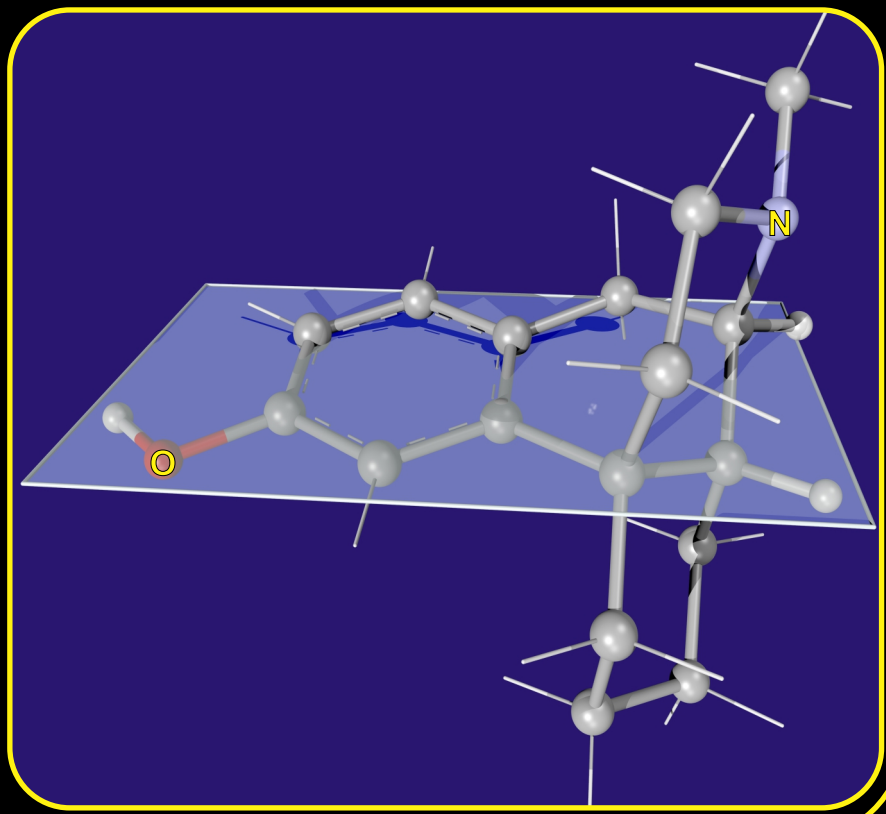
ANALOZI MORFINA DOBIJENI TOTALNOM SINTEZOM - LEVORPHANOL

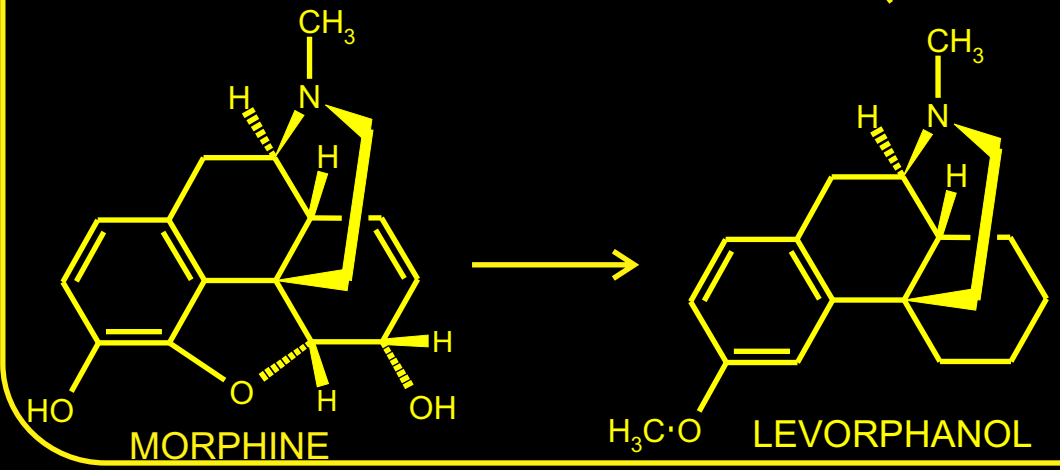


ANALOZI MORFINA POSTALI TOTALNOM SINTEZOM - LEVORPHANOL nastavak

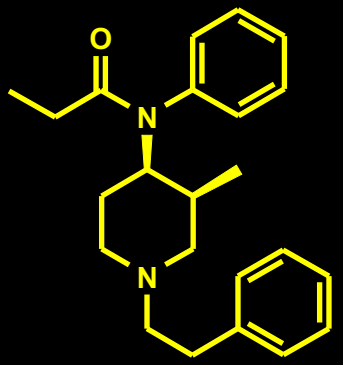






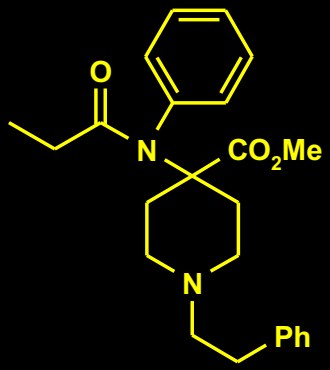


NEKI ODRANIJE POZNATI DERIVATI FENTANILA SA IZRAŽENOM OPIOIDNOM AKTIVNOŠĆU

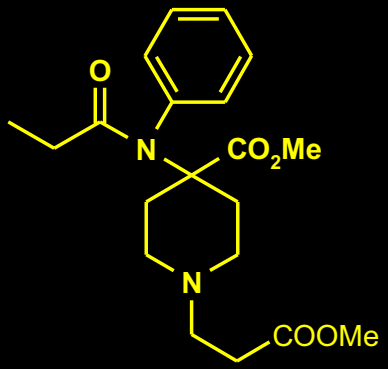


CIS-3-METIL
FENTANIL
~8 X FENTANIL

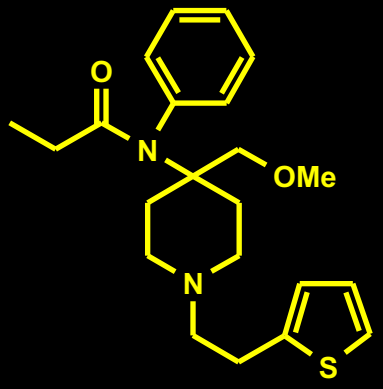
FENTANIL
~50-100 X
MORFIN



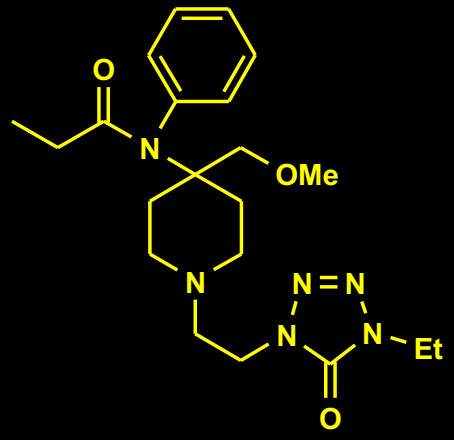
KARFENTANIL
~30 X FENTANIL



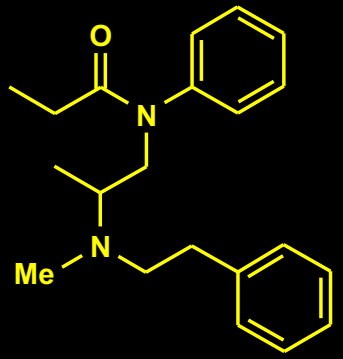
REMIFENTANIL



SUFENTANIL
~30 X FENTANIL



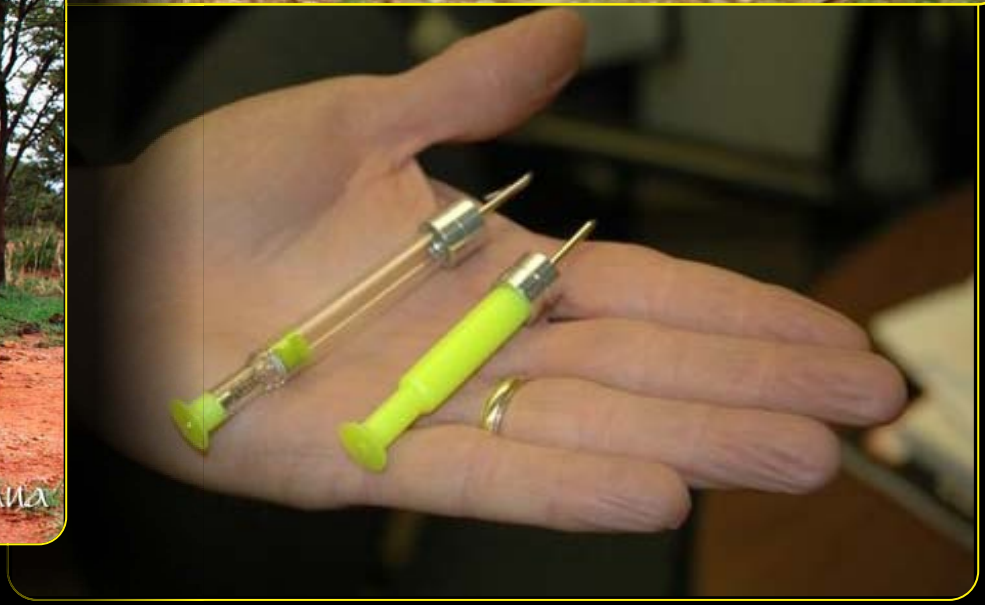
ALFENTANIL
~ 1-2 X FENTANL



DIAMPROMID
(seko analog)
~< MORFIN
(pacovi, miševi)

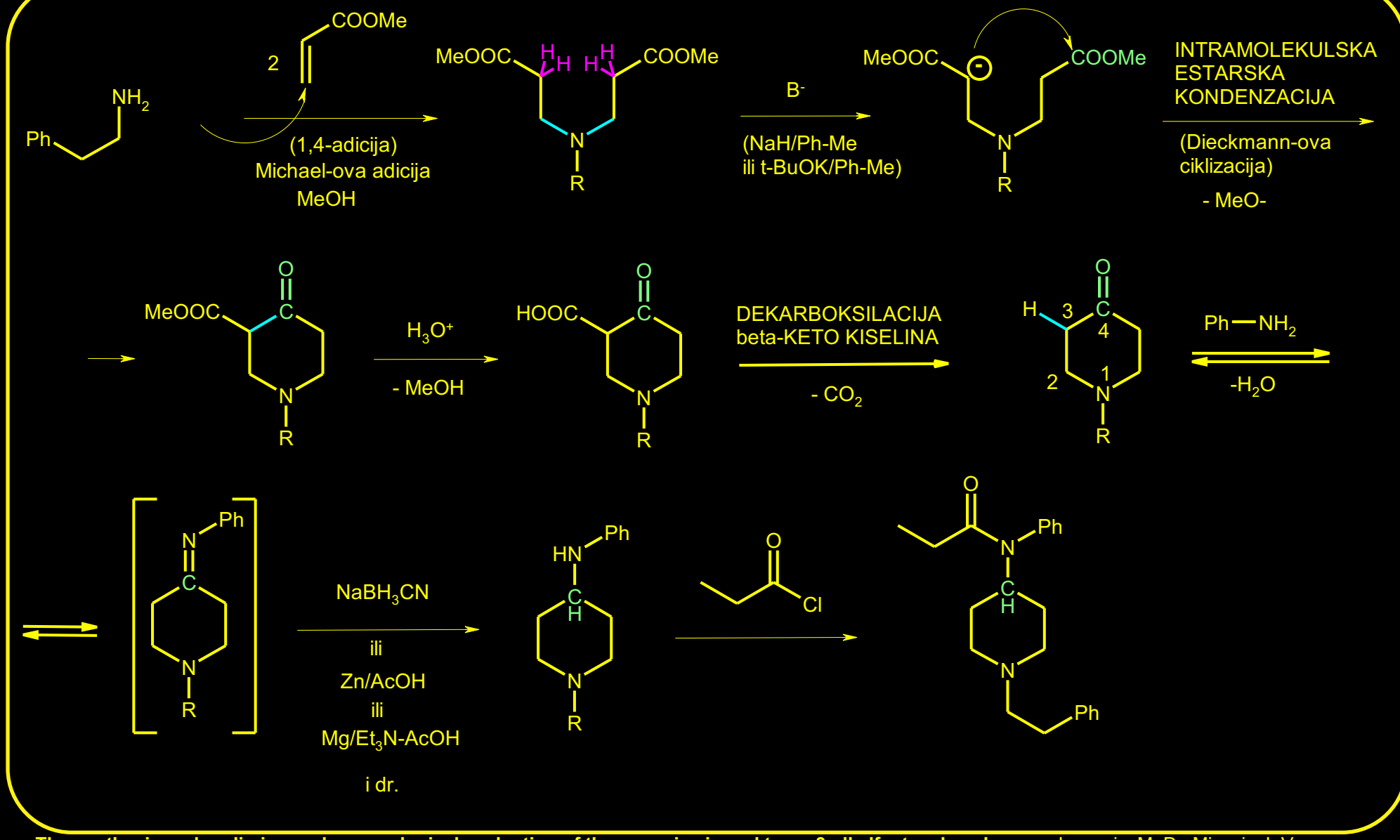
PRIMENA ANALOGA FENTANYL-a (CARFENTANIL) ZA USPAVLJIVANJE DIVLJIH ŽIVOTINJA

KARFENTANIL
~30 X FENTANIL



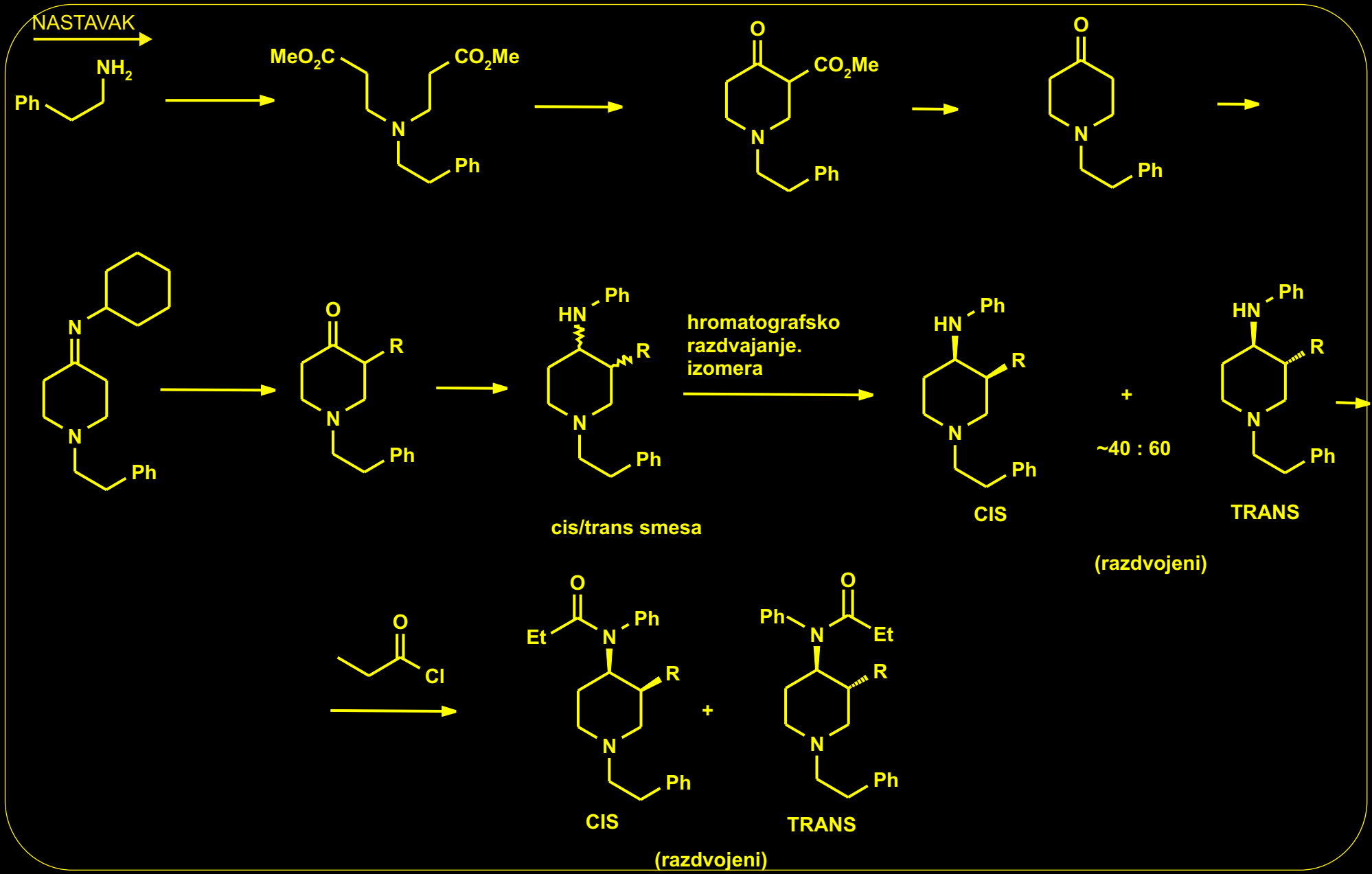
PRIMENA ANALOGA FENTANYL-a (CARFENTANIL) ZA USPAVLJIVANJE DIVLJIH ŽIVOTINJA

SINTEZE 4-ANILIDO-PIPERIDINA - FENTANIL

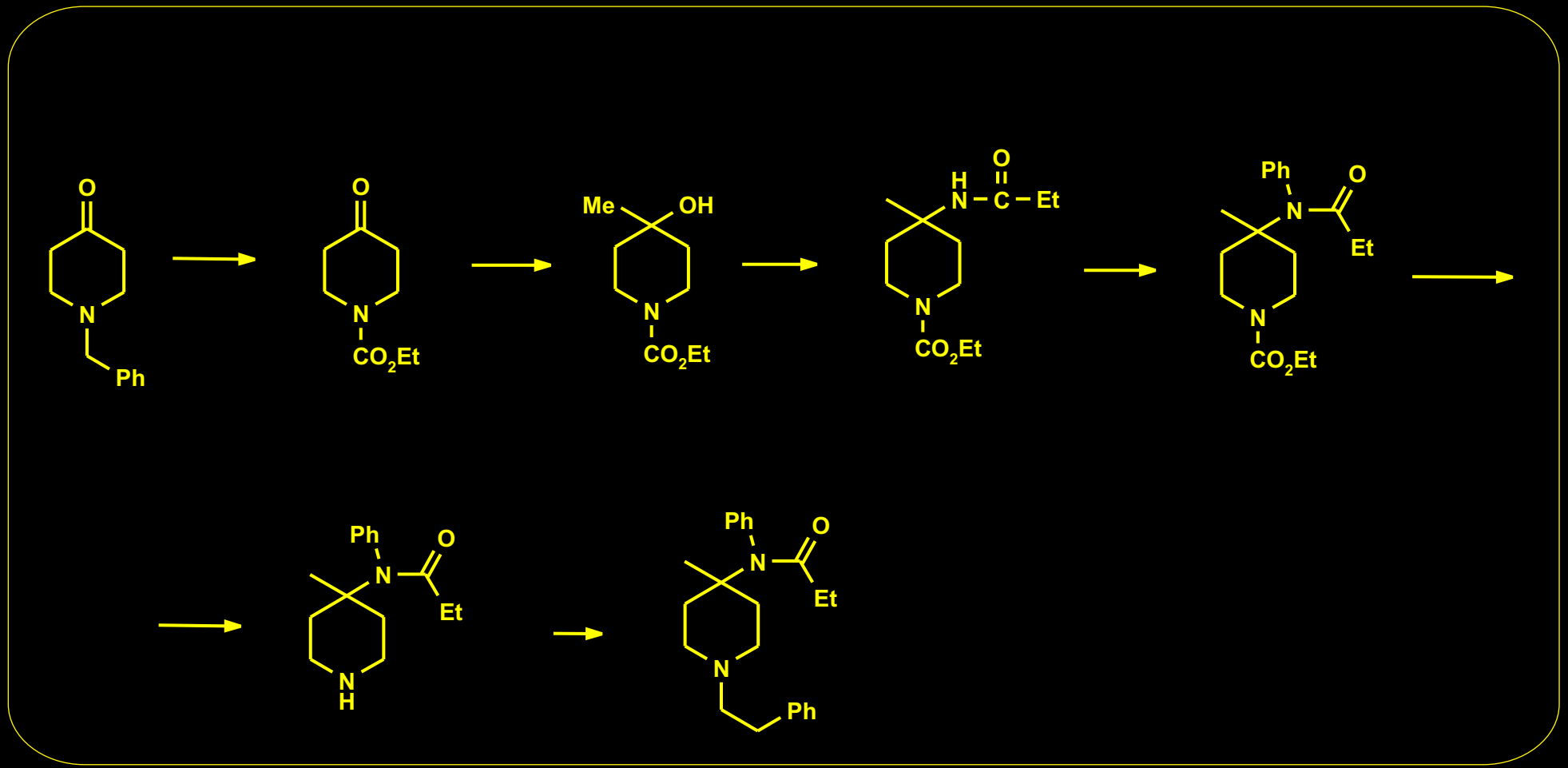


The synthesis and preliminary pharmacological evaluation of the racemic cis and trans 3-alkylfentanyl analogs. Ivanovic, M. D.; Micovic, I. V.; Vuckovic, S.; Prostran, M.; Todorovic, Z.; Kiricojevic, V. D.; Djordjevic, J. B.; Dosen-Micovic, Lj. Faculty of Chemistry, University of Belgrade, Belgrade, Yugoslavia. Journal of the Serbian Chemical Society (2004), 69(7), 511-526.

NASTAVAK

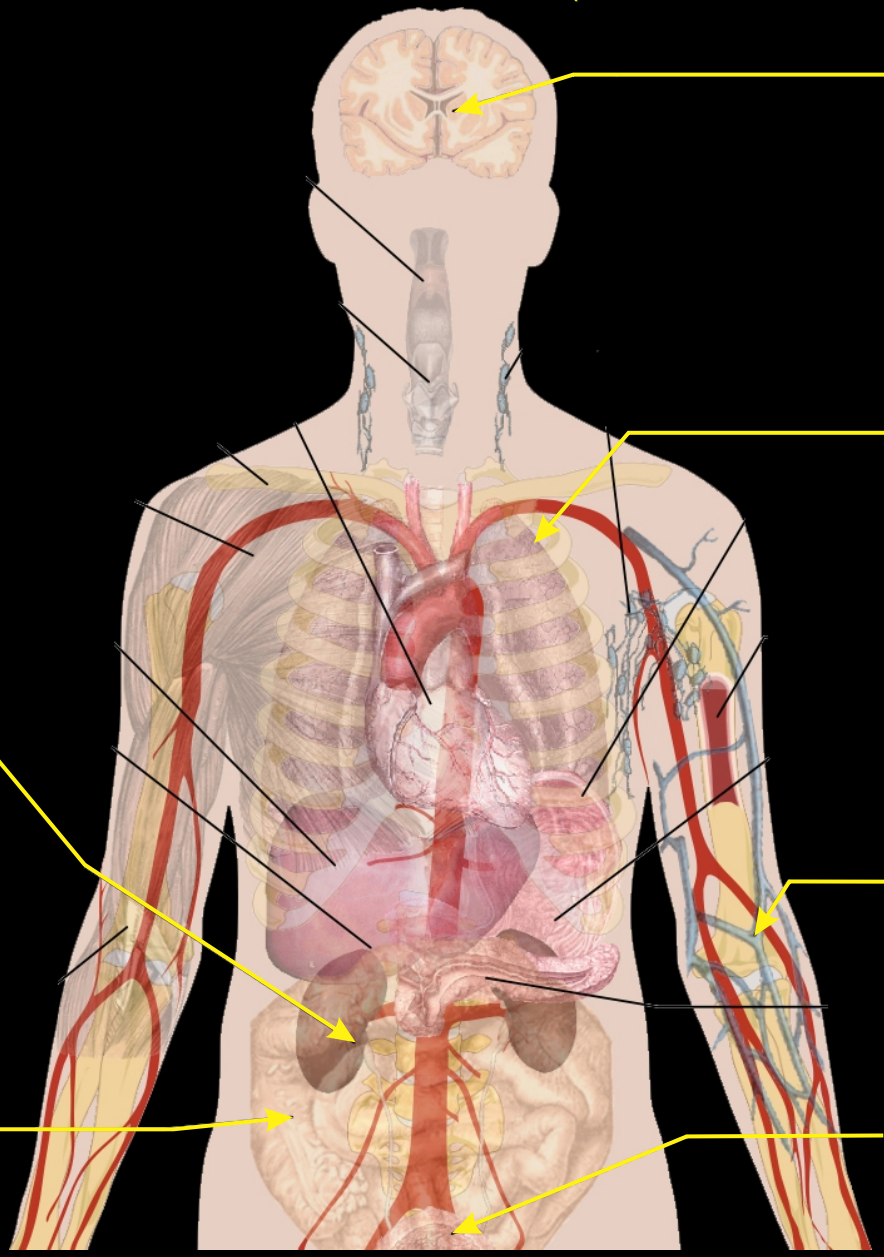

NASTAVAK
NH2
Ph
MeO2C
CO2Me
N
Ph
O
CO2Me
N
Ph
O
N
Ph
N
Ph
O
R
N
Ph
HN
Ph
R
N
Ph
hromatografsko
razdvajanje.
izomera
HN
Ph
R
N
Ph
CIS
+
~40 : 60
HN
Ph
R
N
Ph
TRANS
cis/trans smesa
(razdvojeni)
O
Cl
O
Et
N
Ph
R
N
Ph
CIS
+
Ph
N
O
Et
R
N
Ph
TRANS
(razdvojeni)

PRISTUP SINTEZI 4-METIL FENTANILA (STRUKTURNO BLIZAK KARFENTANILU I ANALOZIMA)



The Synthesis and preliminary pharmacological evaluation of 4-Methyl fentanyl. Micovic, I. V.; Ivanovic, M. D.; Vuckovic, S. M.; Prostran, M.; Dosen-Micovic, L.; Kiricojevic, V. D. Faculty of Chemistry, University of Belgrade, Belgrade, Yugoslavia. Bioorganic & Medicinal Chemistry Letters (2000), 10(17), 2011-2014.

NEKE OD POTENCIJALNIH TERAPIJSKIH PRIMENA ORL1 ANTAGONISTA (ZA SADA NEMA LEKOVA KOJI DELUJU NA OVAJ NAČIN



MOZAK:
-MODULACIJA BOLA,
ANKSIZNOSTI,
DEPRESIJE,

DISAJNI PUTEVI:
-UBLAŽAVANJE KAŠLJA
(ANTITUSIV)

BUBREZI:
-POBOLJŠANO IZLUČIVANJE
TEČNOSTI

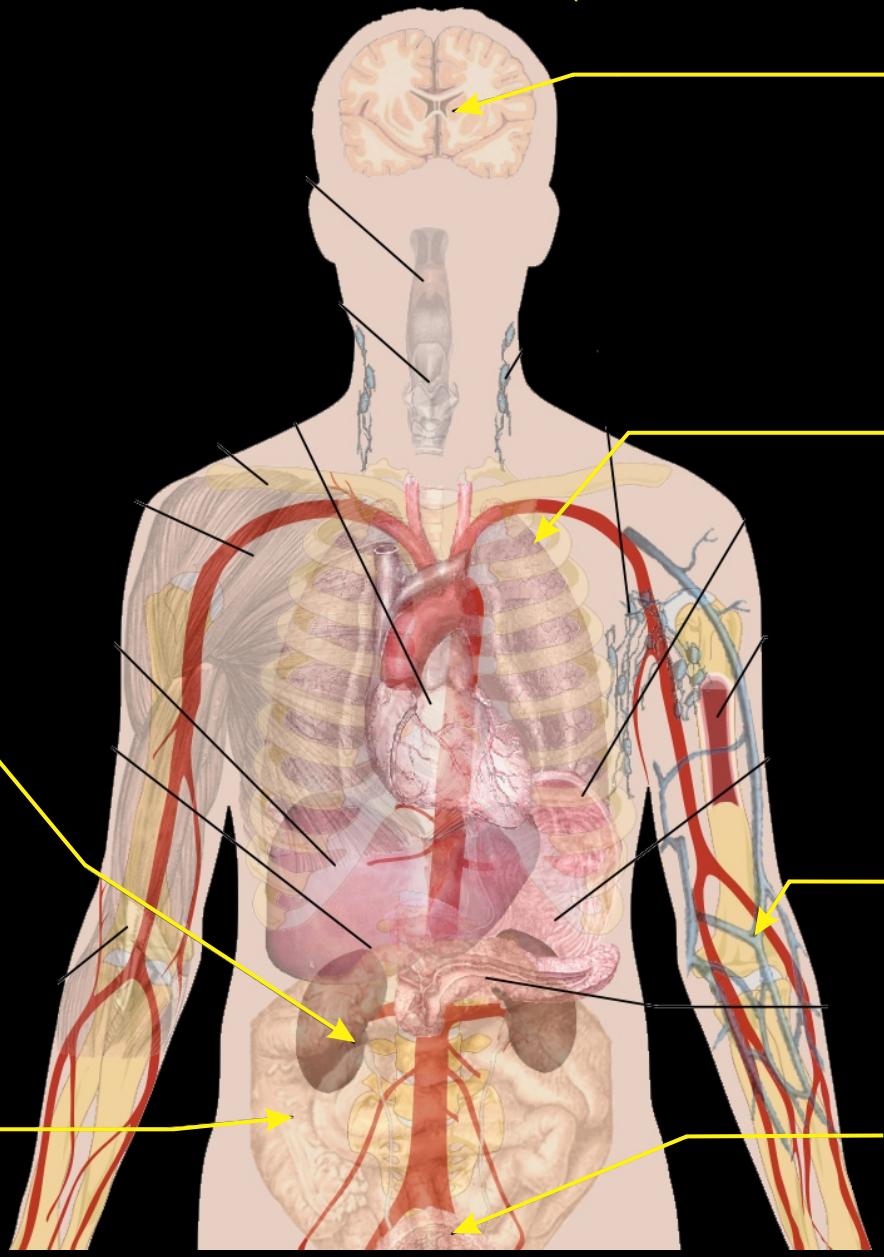
KRVNI SUDOVI:
-HIPERTENZIJA,
MOŽDANI UDAR

DIGESTIVNI TRAKT:
-REGULACIJA
POREMEĆAJA
VARENJA

BEŠIKA:
UBLAŽAVANJE HIPER-AKTIVNOSTI
BEŠIKE

NAPOMENA: ELKTRONSKO PRETRAŽIVANJE I OBRADU LITERTATURNIH PODATAKA (SCIFINDER I KOBSON), KOJI SE ODNOSE NA STRUKTURE, SINTEZE I OSOBINE ORL1 ANTAGONISTA IZVRŠILI SU M.D.IVANOVIĆ I S. STEPANOVIĆ TOKOM 2010-2011 g. (Stepan Stepanović, Diplomski Rad: "Ispitivanje i optimizacija pojedinih faza u sintezi ORL1 antagonista J-113397 i njegovih analoga", Hemijski fakultet Univerziteta u Beogradu, setembar 2011, Biblioteka Hemijskog fakulteta).

NEKE OD POTENCIJALNIH TERAPIJSKIH PRIMENA ORL1 ANTAGONISTA (ZA SADA NEMA LEKOVA KOJI DELUJU NA OVAJ NAČIN



MOZAK:
-MODULACIJA BOLA,
ANKSIZNOSTI,
DEPRESIJE,

DISAJNI PUTEVI:
-UBLAŽAVANJE KAŠLJA
(ANTITUSIV)

BUBREZI:
-POBOLJŠANO IZLUČIVANJE
TEČNOSTI

KRVNI SUDOVI:
-HIPERTENZIJA,
MOŽDANI UDAR

DIGESTIVNI TRAKT:
-REGULACIJA
POREMEĆAJA
VARENJA

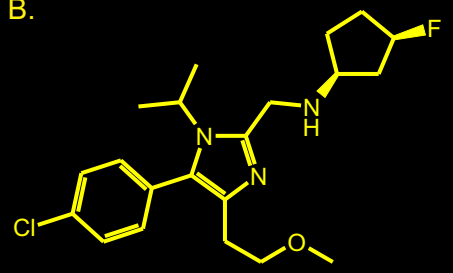
BEŠIKA:
UBLAŽAVANJE HIPER-AKTIVNOSTI
BEŠIKE

NAPOMENA: ELKTRONSKO PRETRAŽIVANJE I OBRADU LITERTATURNIH PODATAKA (SCIFINDER I KOBSON), KOJI SE ODNOSE NA STRUKTURE, SINTEZE I OSOBINE ORL1 ANTAGONISTA IZVRŠILI SU M.D.IVANOVIĆ I S. STEPANOVIĆ TOKOM 2010-2011 g. (Stepan Stepanović, Diplomski Rad: "Ispitivanje i optimizacija pojedinih faza u sintezi ORL1 antagonista J-113397 i njegovih analoga", Hemijski fakultet Univerziteta u Beogradu, setembar 2011, Biblioteka Hemijskog fakulteta).

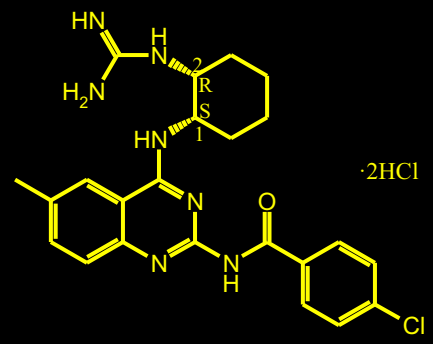
VAŽNIJE KLASE ORL1 ANTAGONISTA ILUSTROVANE SA PO JEDNOM STRUKTUROM

A.

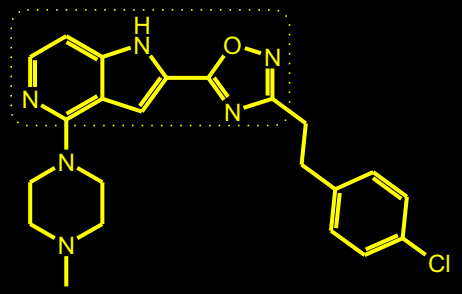
B.



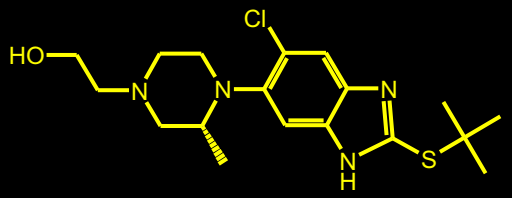
Y. Sugimoto et al. *Bioorg. Med. Chem. Lett.* 19 (**2009**) 4611–4616



G.

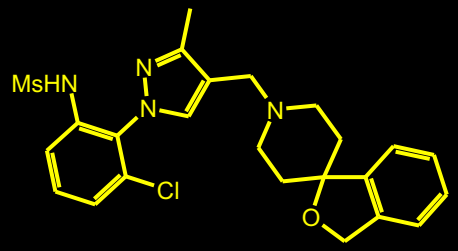


Y. Sugimoto et al. Bioorg. Med. Chem. Lett. 16 (**2006**) 3569–3573

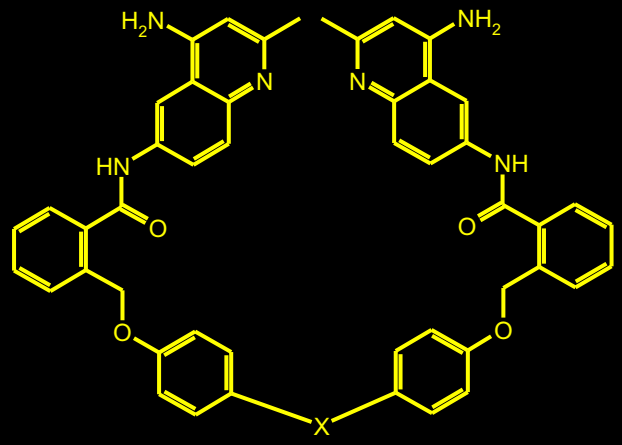


O. Okamoto et al. *Bioorg. Med. Chem. Lett.* 18 (**2008**) 3282–3285

E.



T. Yoshizumi et al. *Bioorg. Med. Chem. Lett.* 18 (**2008**) 3778–3782



X= -CH=N-$(CH_2)_n$-N=CH-;

X= -CH_2-NH-$(CH_2)_n$-NH-CH_2-

M.R. Del Giudice et al. *European Journal of Medicinal Chemistry* 46 (**2011**) 1207-1221

Synthesis I. I. Jevtić et al. Paper

Synthesis of Orthogonally Protected (±)-3-Amino-4-anilidopiperidines and (±)-3-*N*-Carbomethoxyfentanyl

Ivana I. Jevtić[a]
Ljiljana I. Došen-Mićović[a]
Evica R. Ivanović[b]
Nina M. Todorović[c]
Milovan D. Ivanović*[a]

[a] Faculty of Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia
misai@chem.bg.ac.rs
[b] Faculty of Agriculture, University of Belgrade, Nemanjina 6, 11080 Belgrade-Zemun, Serbia
[c] Institute of Chemistry, Technology and Metallurgy, Center of Chemistry, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia

Received: 03.02.2017
Accepted after revision: 08.03.2017
Published online: 03.04.2017
DOI: 10.1055/s-0036-1588985; Art ID: ss-2017-t0070-op

Abstract The synthesis of orthogonally protected *cis*- and *trans*-3-amino-4-anilidopiperidine derivatives has been accomplished in six steps, starting from readily accessible 4-piperidone derivatives. The last three steps, i.e., N-acylation, Hofmann rearrangement, and carbamate cleavage, involved separated (±)-*cis* and (±)-*trans* intermediates. Complete retention of configuration was observed at position 3 of the piperidine ring. Specifically protected positions 1 and 3 at the piperidine scaffold allow for selective deprotection and introduction of diverse substituents at the respective nitrogen sites. The orthogonally protected anilidopiperidines open avenues to potentially pharmacologically active compounds, including opioids and various bivalent ligands for G protein-coupled receptors. In addition, a prototype of a novel class of fentanyl derivatives, possessing a 3-amino group, was synthesized by using the same approach.

Key words heterocycles, rearrangement, acylation, protecting groups, diastereoselectivity

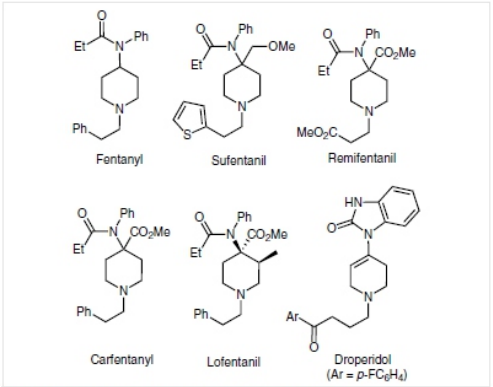


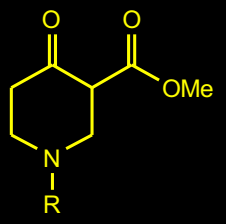
Figure 1 Representative 4-anilidopiperidine drugs

4-Anilidopiperidines represent an important class of pharmacologically active compounds.[1,2] Several of the compounds are highly potent opioid analgesics in clinical use, including fentanyl, sufentanil, alfentanil, lofentanil, and remifentanil,[3] and carfentanil is a veterinary drug used to sedate wild animals[2c,4] (Figure 1). Isotopically ^{11}C-labeled carfentanil, however, is a useful tool in opioid receptor research.[2c] Other structurally related 4-anilidopiperidines, devoid of opioid activity, are therapeutically significant drugs, including antipsychotics (droperidol, pimozide), antiemetics (domperidone), antiarrhythmics (lorcainide), antidiarrheals (zaldaride), and others.[3]

SAR studies established various structural features that are significant for the opioid activity of 4-anilidopiperidines.[5,6] For example, the 1-*N*-phenethyl group is responsible for the highest activity compared with other 1-*N*-groups,[1] whereas substituents in the 3-position of the piperidine ring can significantly increase or decrease the opioid activity, depending on the size, relative and absolute stereochemistry, and possibly the chemical properties. Thus, (+)-*cis*-3-methyl fentanyl is ca. 120 times more potent than the (–)-enantiomer and 16–19 times more potent than both the (±)-*trans*-diastereomer and fentanyl.[7] Voluminous 3-alkyl groups reduce the activity,[5,8] and a 3-carbomethoxy function confers potency similar to that of fentanyl[9a,10] while 3-hydroxy,[11,12] 3-methoxy,[13] and 3-fluorine[14] substituents were not evaluated pharmacologically.

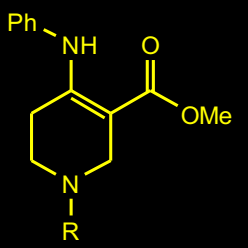
4-Anilidopiperidines with 3-amino groups are practically unknown, reflecting synthetic difficulties.[15] It seems likely though, that polar and basic amino groups, which can form hydrogen bonding and/or ionic interactions, may significantly influence pharmacological activity in a manner

This is a copy of the author's personal reprint



10a, R=Benzyl,
10b, R=2-Phenetyl

1.4 equiv $PhNH_2$
AcOH, r.t., 24h

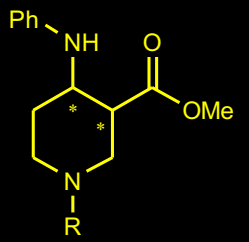


11a, 75%
11b, 77%

1.5 equiv $NaBH_3CN$
2.7 equiv AcOH
MeOH, r.t., 24h

cis/trans: 1:1

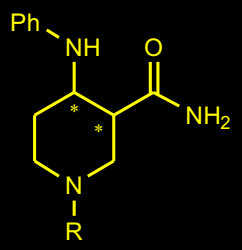
chromatography
(optional)



(±) *cis* **12a**, 43%
(±) *trans* **12a**, 45%
(±) *cis* **12b**, 46%,
(±) *trans* **12b**, 47%

4.0 equiv $HCONH_2$,
2.0 equiv, LiH
DMF or DMSO,
r.t., 16 h

(epimerisation)
chromat
ography



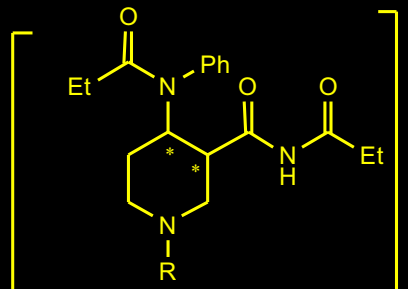
(±) *cis* **13a**, 41%,
(±) *trans* **13a**, 48%
(±) *cis* **13b**, 38%
(±) *trans* **13b**, 45%

1. 6.0 equiv EtCOCl,
2.5 equiv Et_3N

DMF, r.t., 24 h;

2. 7-9 M
NH_3/MeOH
r.t., 6h

retention of
configuration



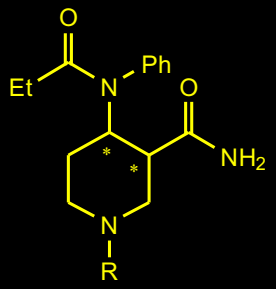
main product

(±) *cis* **15a**
(±) *trans* **15a**
(±) *cis* **15b**
(±) *trans* **15b**

~>80%

1) NH_3/MeOH

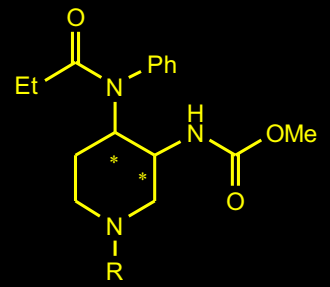
2) Separation of **14**
by chromatography



(±) *cis* **6**, 64%,
(±) *trans* **6**, 66%
(±) *cis* **8**, 62%
(±) *trans* **8**, 69%

9.0 equiv NBA,
25.0 equiv $LiOH{\cdot}H_2O$
MeOH, r.t., 48 h

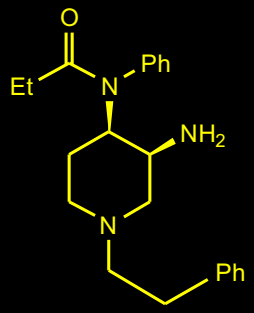
retention of
configuration



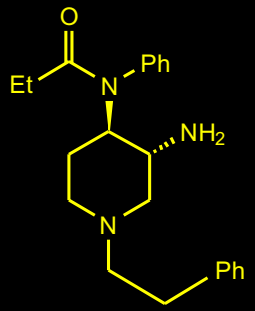
(±) *cis* **16a**, 68%,
(±) *trans* **16a,** 72%
(±) *cis* **16b,** 64%,
(±) *trans* **16b,** 74%

Me_3Si-I

then H_2O



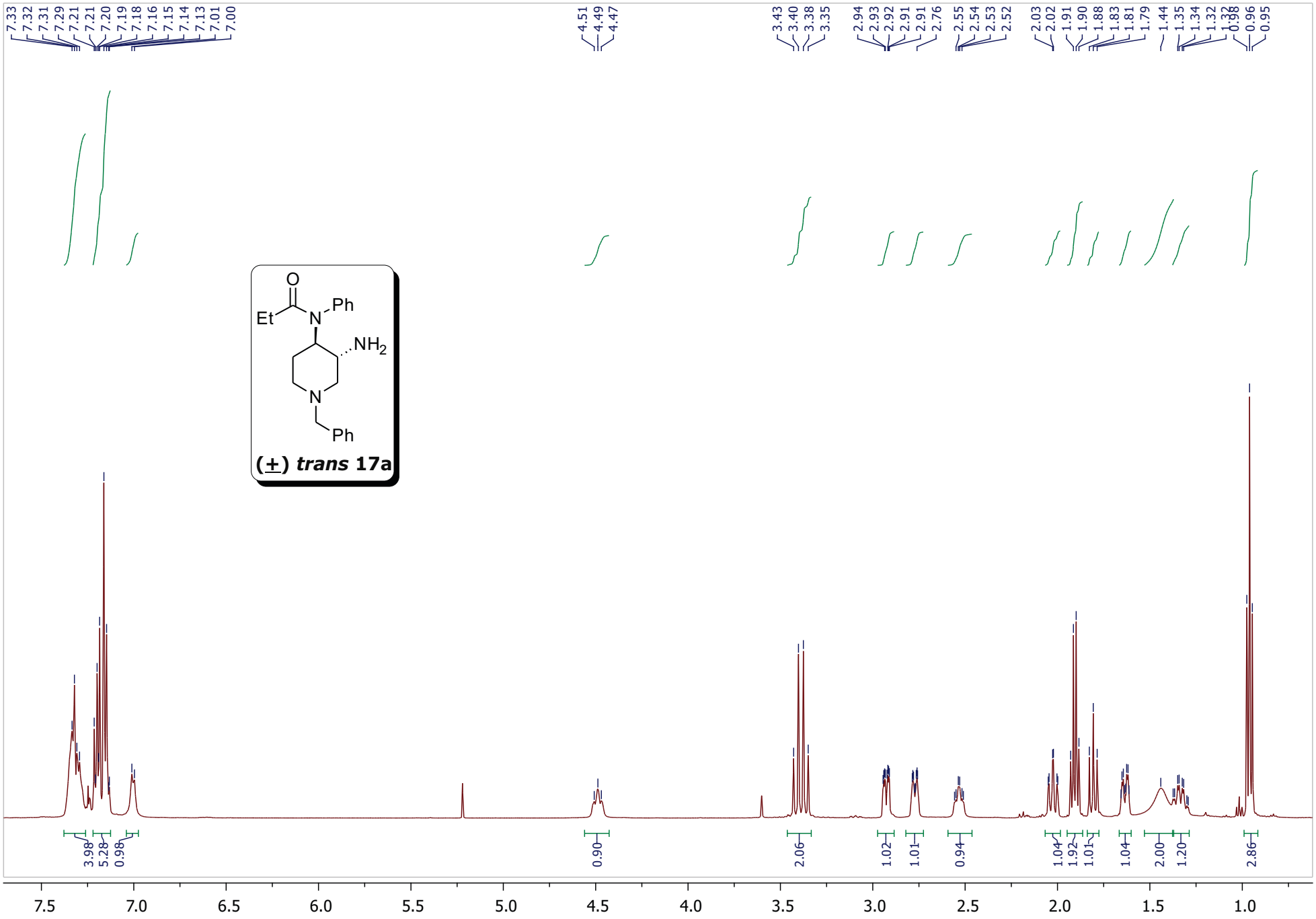
or



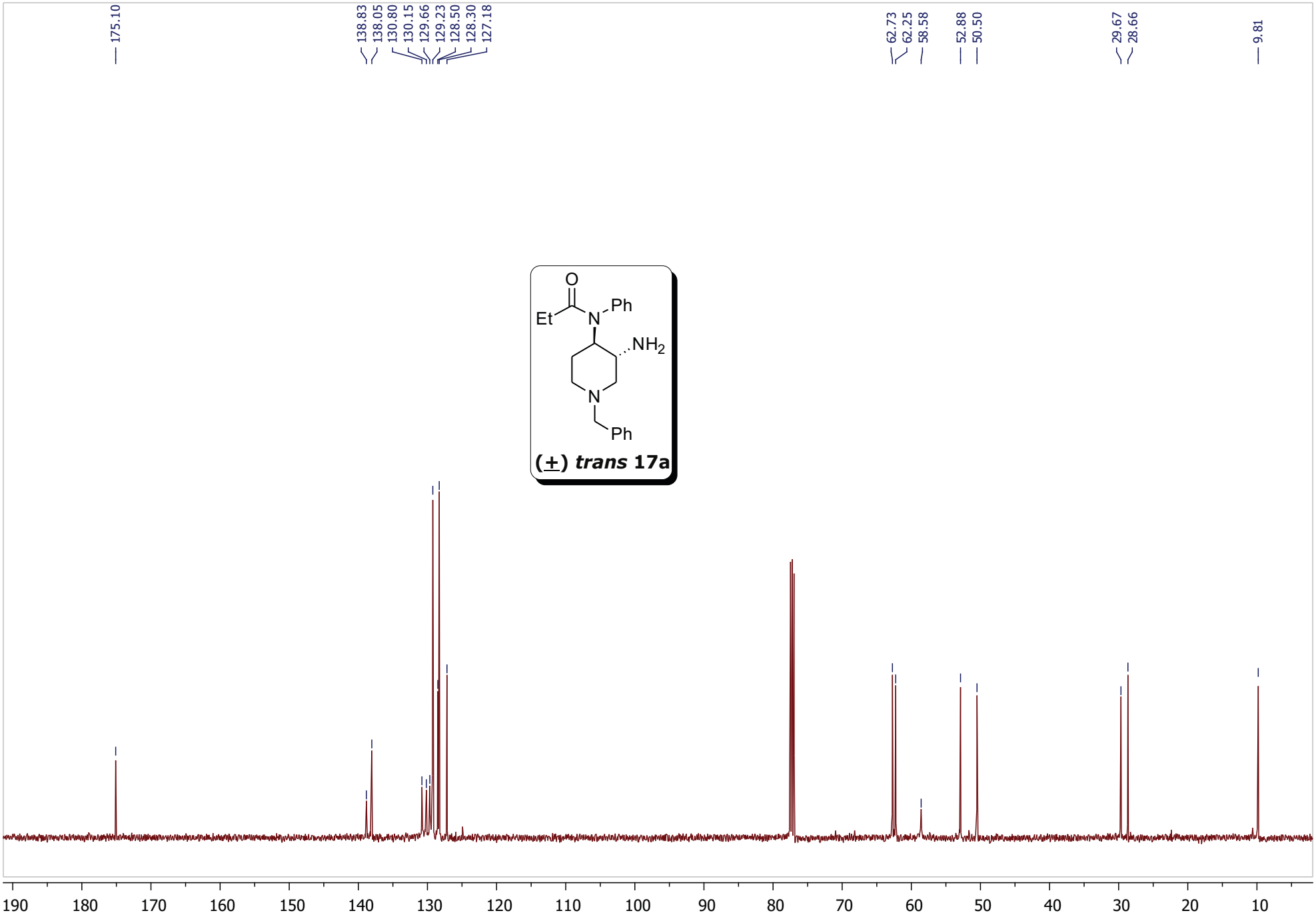
further elaboration

OTHER
DERIVATIVES

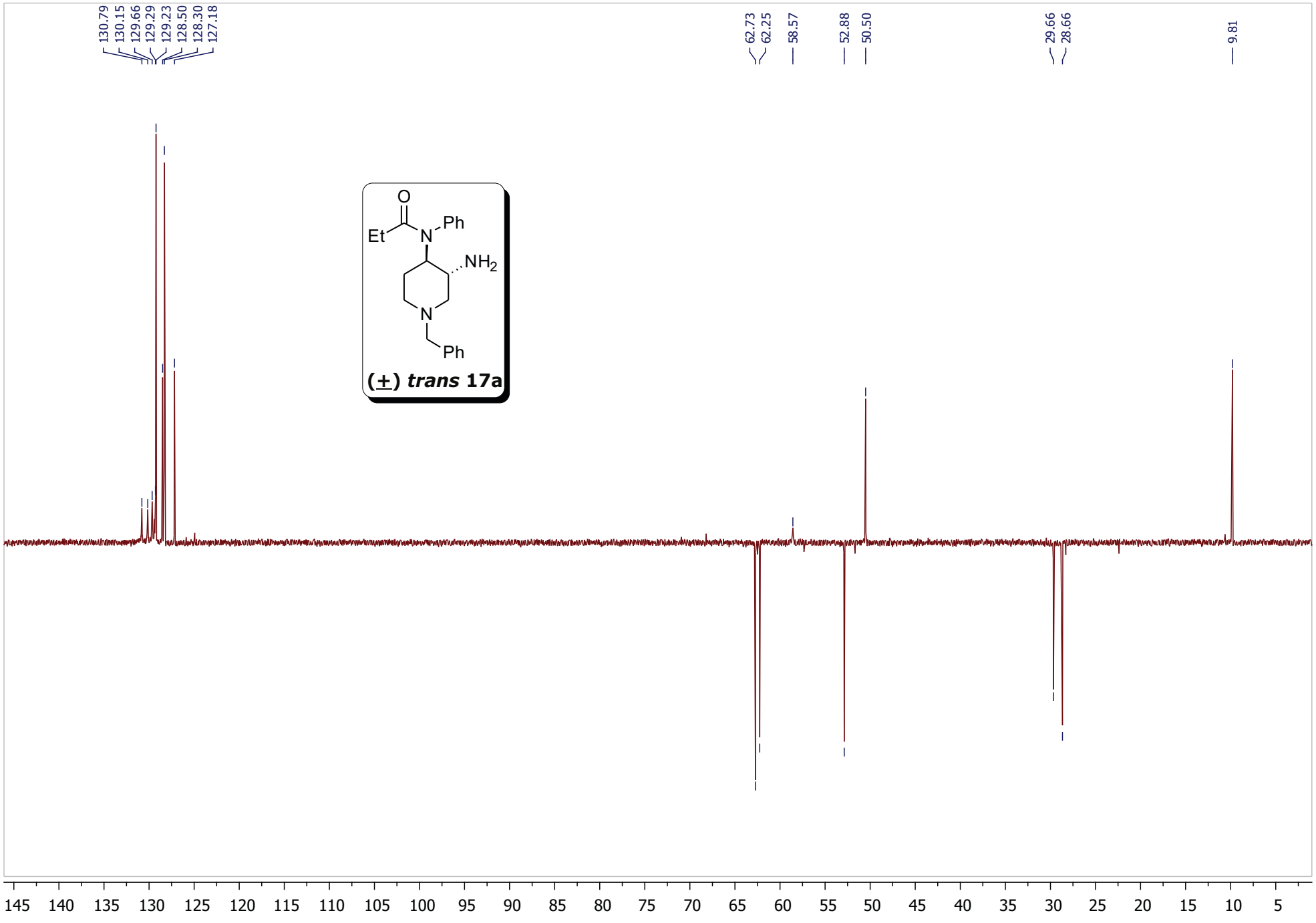
^{1}H NMR (500 MHZ,DMSO-d6, 75 °C)



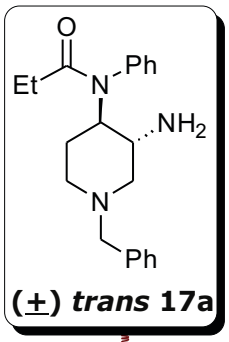
^{13}C NMR (126 MHZ,DMSO-d6, 75 °C)



DEPT (126 MHZ,DMSO-d6, 75 °C)

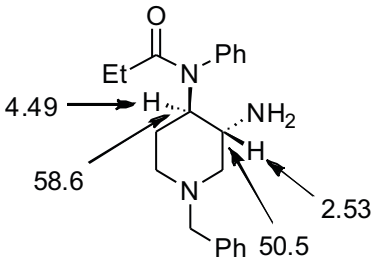


HSQC (DMSO-d6, 75 °C)

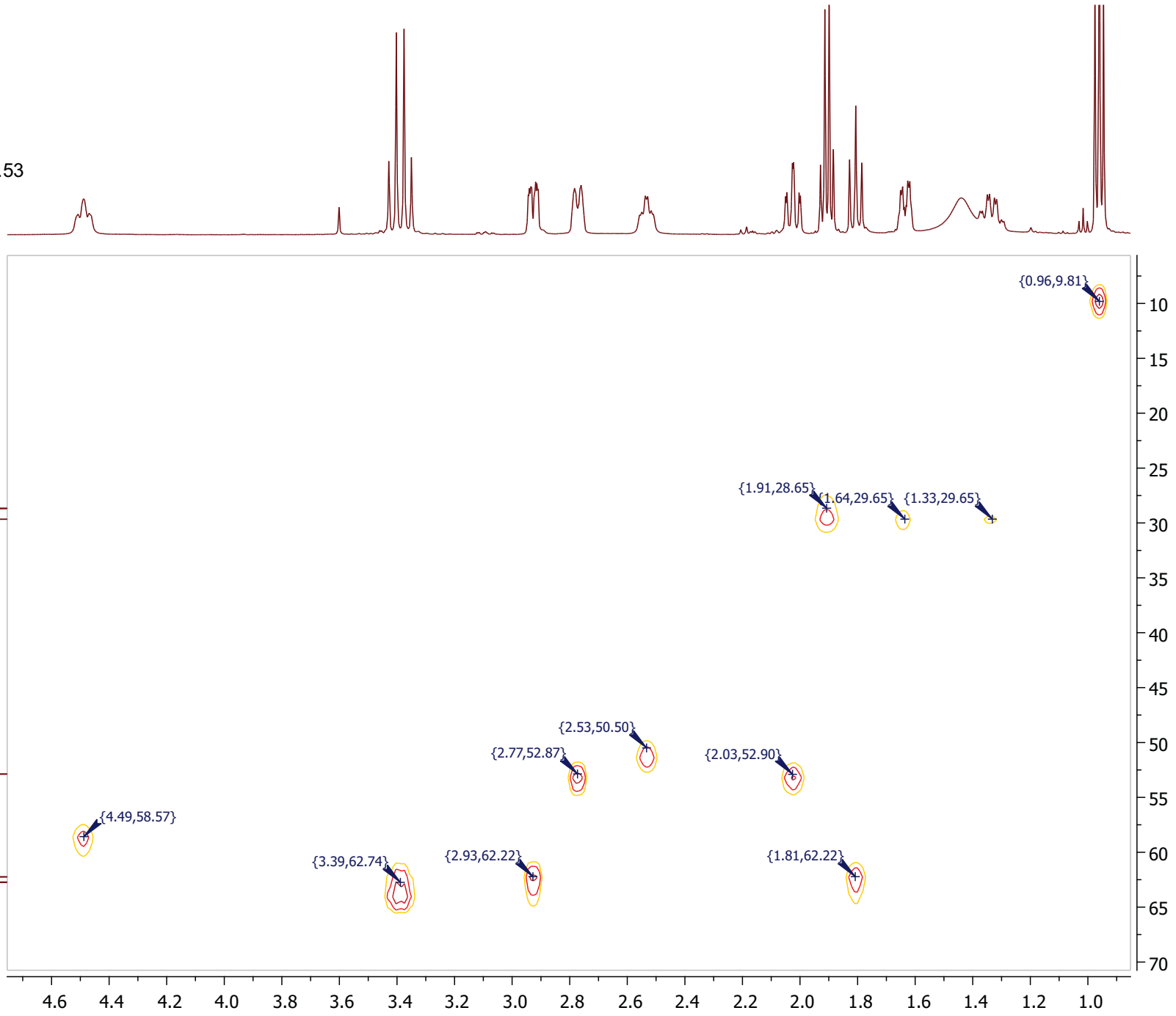


(±) *trans* 17a

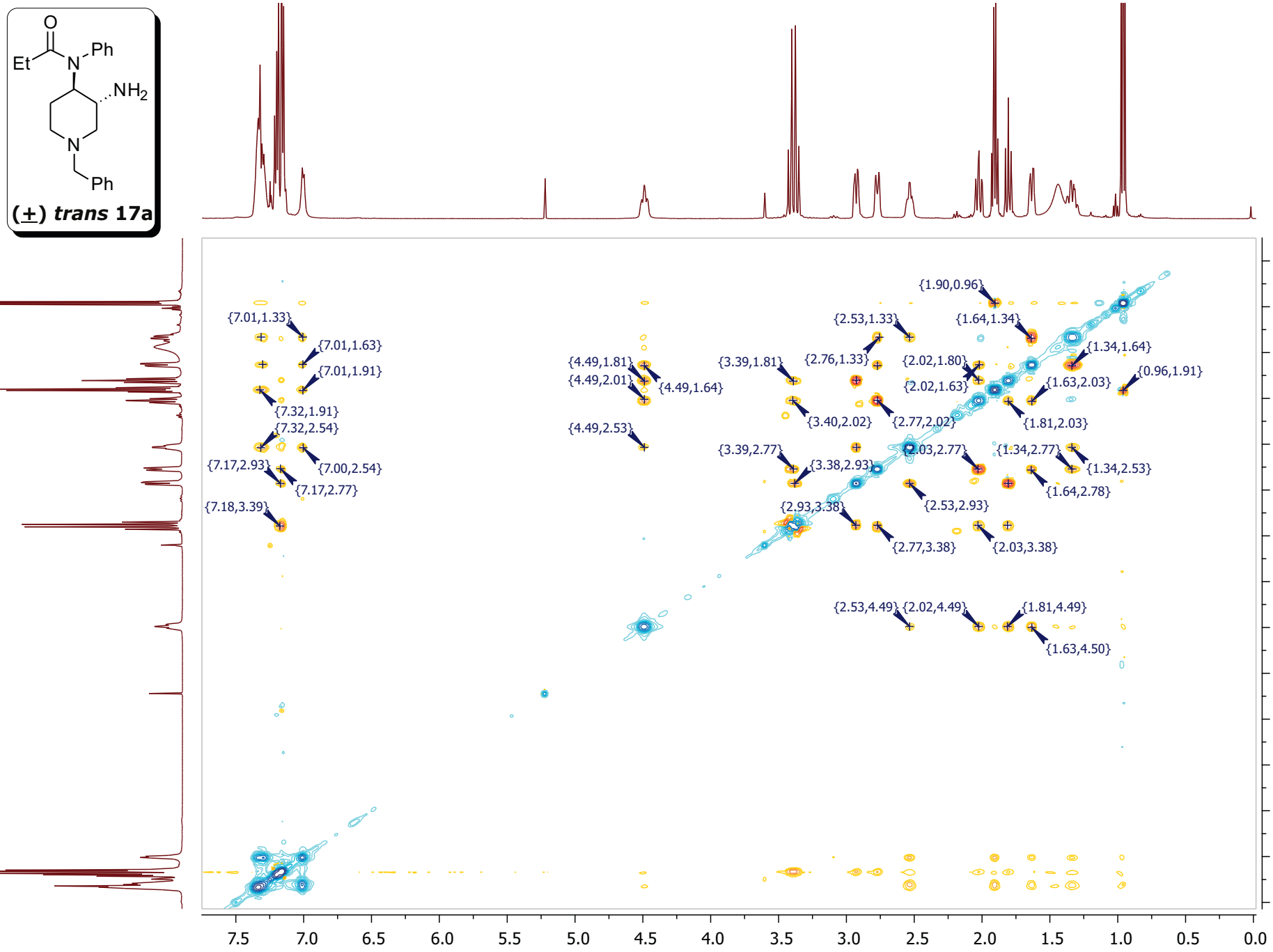
HSQC (expanded, 4.6 - 0.9 δ, DMSO-d6, 75 °C)



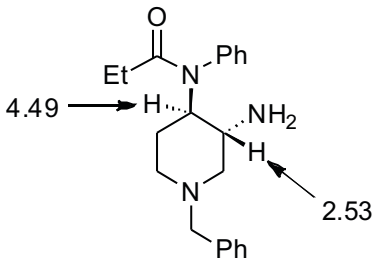
(±) *trans* 17a



NOESY (DMSO-d6, 75 °C)



NOESY (expanded, 5.2 - 0.6 δ, DMSO-d6, 75 °C)



(±) *trans* 17a