HALUCINOGENI

-OSNOVNA FARMAKOLOŠKA SVOJSTVA I

POJEDINE KLASE OVIH JEDINJENJA

KAKO SE MANIFETSTUJE DEJSTVO HALUCINOGENIH SUPSTANCI NA LJUDSKU PSIHU

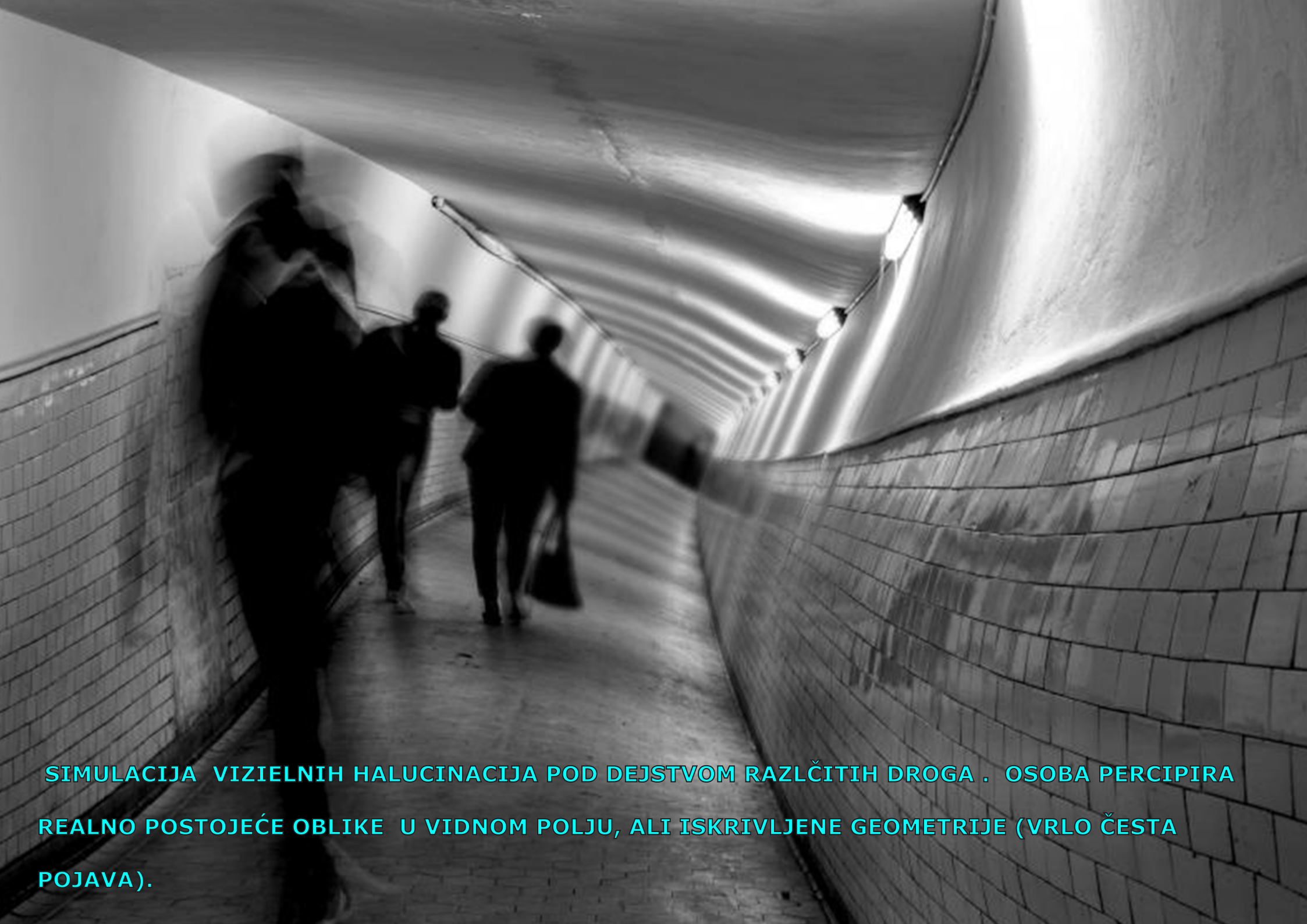
POSTOJE MNOGA JEDINJENJA KOJA, DELUJUĆI NA CNS, PRIVREMENO MENJAJU NORMALNU PERCEPCIJU VIDA, SLUHA I DODIRA. PRI TOME OSOBA (A EVIDENTNO I MNOGI DRUGI ORGANIZMI), OPAŽA OKOLINU NA PROMENJEN, DELIMIČNO ILI POTPUNO NEREALAN NAČIN. ZAVISNO OD PRIRODE TAKVE SUPSTANCE, KAO I DOZE, OVAKVE PROMENE MOGU SE IZUZETNO RAZLIKOVATI I SVOJIM SADRŽAJEM I INTENZITETOM. "BLAŽI" HALUCINOGENI UGLAVNOM MODIFIKUJU NORMALNU VIZUELNU PERCEPCIJU REALNO POSTOJEĆIH PREDMETA U OKOLINI, A TOKOĐE I PERCEPCIJU ZVUKOVA I FIZIČKIH NADRAŽAJA (NPR. DODIRA).

TO UKLJUČUJE OPAŽANJE PREDMETA U PROMENJENIM BOJAMA I IZMENJENOG OBLIKA, DOK SE ZVUKOVI I OSEĆAJ DODIRA MOGU ČINITI VEOMA RAZLIČITIM, U ODNOSU NA ONO ŠTO REALNO JESU.

MEĐUTIM, SNAŽNI HALUCINOGENI, PRE SVEGA LSD, IZAZIVAJU POTPUNE HALUCINACIJE, ŠTO DOVODI DO PRIVIĐANJA OSOBA, PREDMETA I SITUACIJA KOJE ILI NISU PRISUTNE ILI UOPŠTE NE POSTOJE. ČAK I KADA SE OPAŽAJU OBJEKTI KOJI JESU PRISUTNI, NJIHOVI OBLICI MOGU BITI TOLIKO PROMENJENI, DA IH OSOBA POD DEJSTVOM HALUCINOGENA NE PREPOZNAJE KAO TAKVE. KONSEKVENTNO, OVO DOVODI DO POTPUNOG PSIHIČKOG "RASULA", PRAĆENOG NEKONTROLISANIM PONAŠANJEM, ČESTO KRAJNJE OPASNIM I BESMISLENIM FIZIČKIM AKTIVNOSTIMA.

NEOPHODNO JE NAGLASITI DA HALUCINOGENE SUPSTANCE SA BILO KAKVIM, PA I "BLAŽIM" DEJSTVOM NEMAJU NIKAKVU LEGITIMNU, MEDICINSKU PRIMENU, VEĆ SE ISKLJUČIVO ZLOUPOTREBLJAVAJU, ČESTO SA TEŠKIM I DUGOTRAJNIM, PA I FATALNIM POSLEDICAMA. IAKO SE OVO ODNOSI NA SVE HALUCINOGENE SUPSTANCE, TO JE POSEBNO KARAKTERISTIČNO ZA LSD.

SIMULACIJA VIZIELNIH HALUCINACIJA POD DEJSTVOM RAZLČITIH DROGA . OSOBA PERCIPIRA REALNO POSTOJEĆE OBLIKE U VIDNOM POLJU, ALI ISKRIVLJENE GEOMETRIJE (VRLO ČESTA POJAVA).



SIMULACIJA VIZIELNIH HALUCINACIJA POD DEJSTVOM RAZLČITIH DROGA . OSOBA PERCIPIRA REALNO POSTOJEĆE OBLIKE U VIDNOM POLJU, ALI ISKRIVLJENE GEOMETRIJE (VRLO ČESTA POJAVA).

SIMULACIJA VIZIELNIH HALUCINACIJA POD DEJSTVOM RAZLČITIH DROGA . OSOBA PERCIPIRA REALNO POSTOJEĆE OBLIKE U VIDNOM POLJU, ALI ZAMUĆENO (VRLO ČESTA POJAVA).

SIMULACIJA VIZIELNIH HALUCINACIJA POD DEJSTVOM DROGA KAO ŠTO JE PSILOCIBIN I DR.

OSOBA PERCIPIRA REALNO POSTOJEĆE OBLIKE U VIDNOM POLJU, ALI U PROMENJENIM BOJAMA(VRLO ČESTA POJAVA).

SIMULACIJA VIZIELNIH HALUCINACIJA POD DEJSTVOM DROGA KAO ŠTO JE LSD. OSOBA PERCIPIRA PREDMETE, POJAVE ILI OBLIKE KOJI NISU PRISUTNI U VIDNOM POLJU ILI UOPŠTE NE MOGU POSTOJATI (ČESTO SE JAVLJA KOG HALUCINOGENA).

SIMULACIJA VIZIELNIH HALUCINACIJA POD DEJSTVOM DROGA KAO ŠTO JE MESKALIN.

OSOBA PERCIPIRA POTPUNO PROMENJEN ODAZ U OGLEDALU (ČESTO SE JAVLJA KOG HALUCINOGENA).

SIMULACIJA POTPUNOG PSIHIČKOG RASULA (EKSTREMNIH VIZIELNIH HALUCINACIJA) POD DEJSTVOM DROGA KAO ŠTO JE LSD.

IMA BROJNIH MIŠLJENJA DA JE SREDNJOVEKOVNI UMETNIK *Hieronymus Bosch* SLIKAO POD DEJSTVOM HALUCINOGENIH ALKALOIDA, KAO ŠTO JE ERGOT.

MEĐUIM, SAVREMENA NAUČNA SAZNANJA UKAZUJU DA HALUCINOGENE SUPSTANCE NE MOGU DA PODSTAKNU KREATIVNOST, VEĆ SAMO DA JE UNIŠTE.

http://www.bbc.com/culture/story/20160809-hidden-meanings-in-the-garden-of-earthly-delights

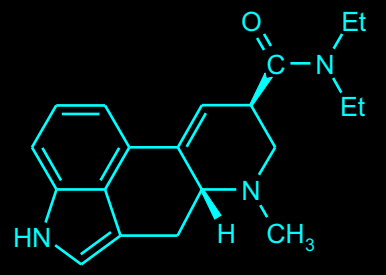
The Artist:
Hieronymus Bosch © 1450–1516)
The Painting:
The Garden of Earthly Delights (catalogue raisonné no. 21)
Dates:
c 1495-1505

POJEDINE KLASE JEDINJENJA KOJA

POKAZUJU HALUCINOGENO DEJSTVO

(često i druge farmakološke efekte)

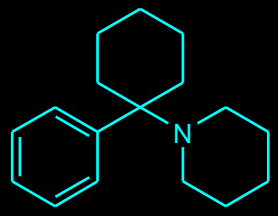
1.



LSD

DERIVATI LISERGINSKE K.

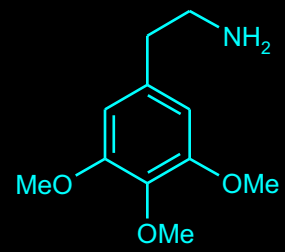
2.



PHENCYCLIDINE

FENCIKLIDINI

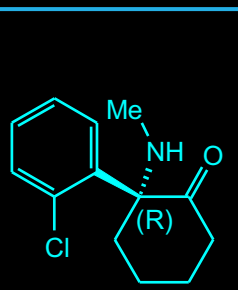
3.



MESCALINE

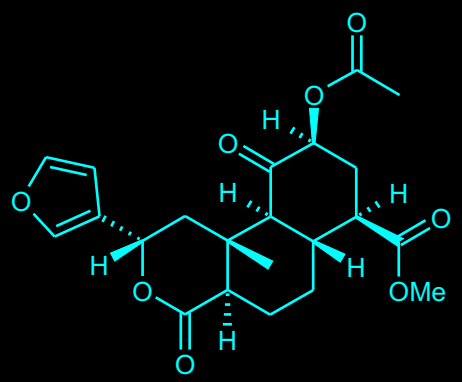
POJEDINI β-FENETILAMINI
(uključujući i neke amfetamine)

4.



(R)-(-) ENANTIOMER

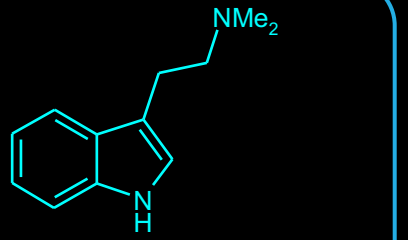
5.



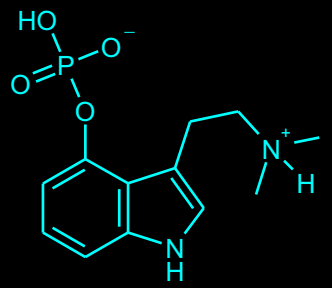
SALVINORIN A

SALVINORINI

6.



N,N DIMETIL TRIPTAMIN



PSILOCYBIN

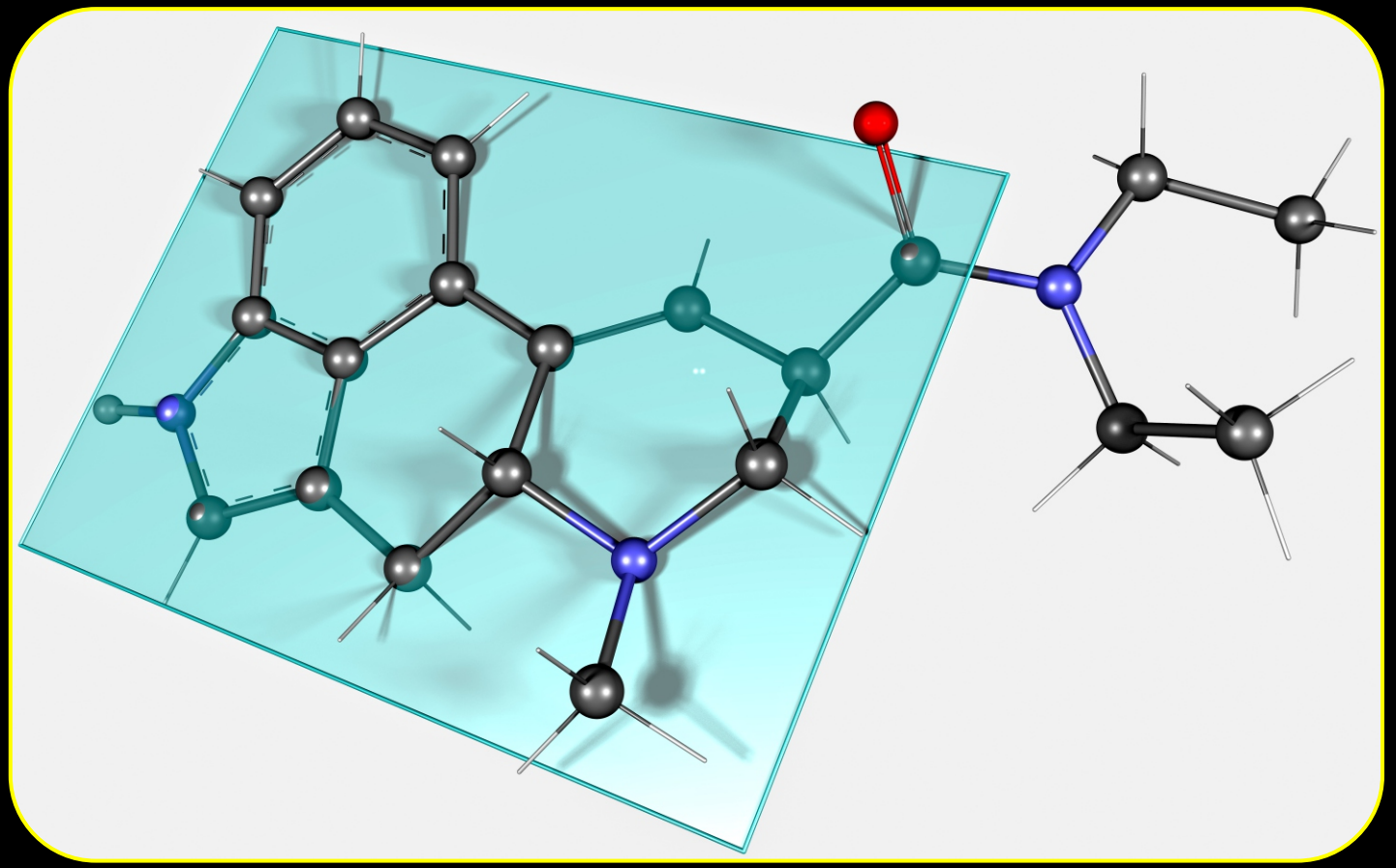
DERIVATI TRIPTAMINA

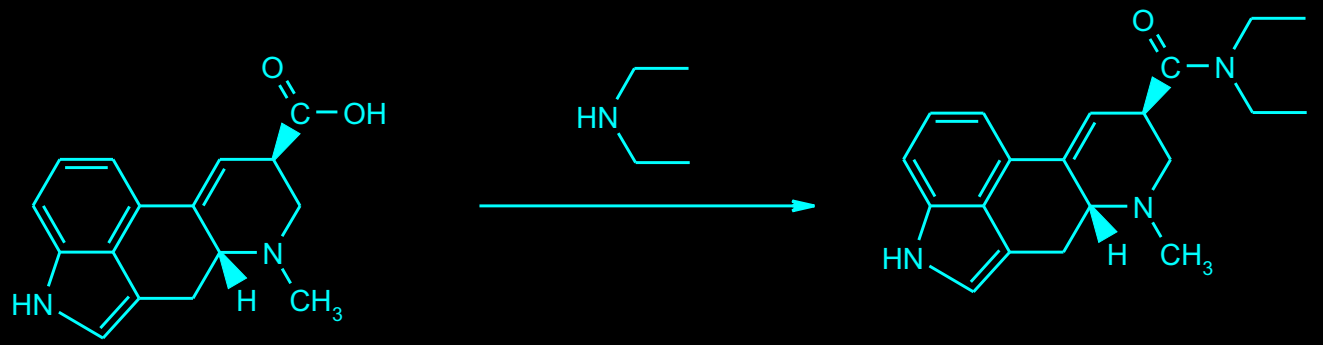
1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

DIETILAMID LISERGINSKE KISELINE, LSD SE PROIZVODI, ISKLJUČIVO ILEGALNO, PARCIJALNOM SINTEZOM, IZ LIZERGINSKE KISELINE, DO KOJE SE DOLAZI IZOLOVANJEM IZ BIOLOŠKOG MATERIJALA – ERGOT GLJIVICA.

OVO JEDINJENJE PREDSTAVLJA DO DANAS NAJJAČI POZNATI (A I NAJOPASNIJI) HALUCINOGEN, AKTIVAN U DOZAMA OD

~0.02 - 0.5 mg (20-500 mg).



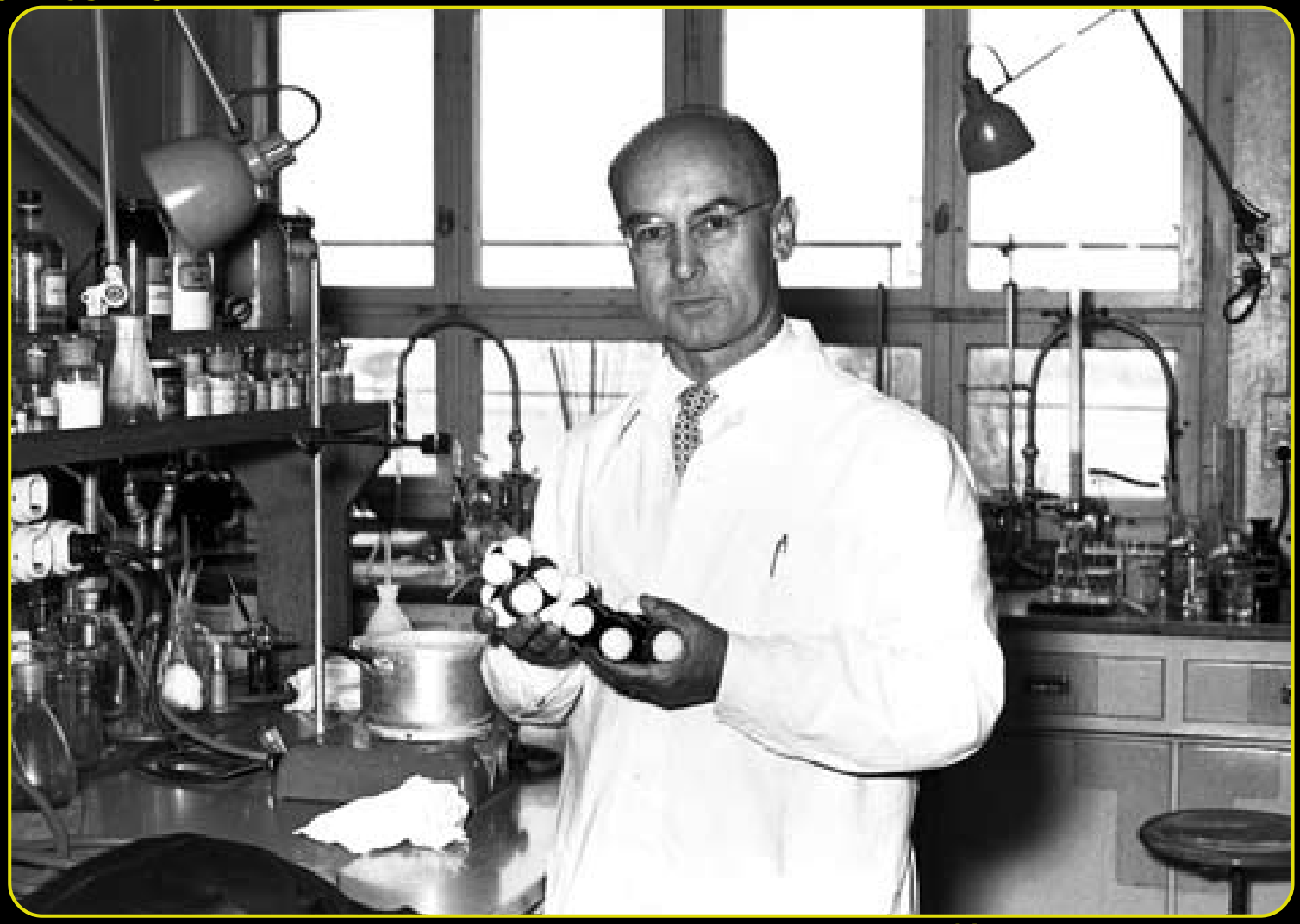


1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

LSD JE PRVI SINTETIZOVAO ALBERT HOFMANN (~1940.), TOKOM LEGITIMNOG ISTRAŽIVANJA ERGOT ALKALOIDA, KAO POTENCIJALNIH LEKOVA.

SLUČAJNO JE, NA SEBI, OTKRIO NJEGOVO HALUCINOGENO DEJSTVO.

KASNIJE SU BROJNI POLU-SINTETIČKI DERIVATI ERGOT ALKALOIDA (NE HALUCINOGENI) NAŠLI ZNAČAJNU PRIMENU U FARMAKOTERAPIJI RAZLIČITIH OBOLJENJA.



Albert Hofmann (11. I 1906 – 29. IV 2008)[1]

1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

IAKO EKSPERIMENTALNA PRIMENA LSD-a NA ŽIVOTINJAMA IMA ODREĐENI NAUČNI ZNAČAJ, NJEGOVO DEJSTVO NA LJUDE JE EKSTREMNO NEGATIVNO I OPASNO. DOLAZI DO TEŠKIH I DUGOTRAJNIH VIZUELNIH HALUCINACIJA, PRAĆENIH NEKONTROLISANIM PONAŠANJEM, ŠTO OSOBU ČINI KRAJNJE OPASNOM PO SEBE I DRUGE (TEŠKE POVREDE, UBISTVA I SAMOUBISTVA).

PORED TOGA, ČESTO SE JAVLJAJU I ZAKASNELA DEJSTVA, TJ. PONOVNI NAPADI HALUCINACIJA, DANIMA, NEDELJAMA PA I GODINAMA POSLE UZIMANJA LSD-a.

OVO UKAZUJE NA DUBOKA, POTENCIJALNO IREVERZIBILNA OŠTEĆENJA MOZGA, DO KOJIH MOŽE DOĆI I PRI JEDNOKRATNOJ UPOTREBI LSD-a.

NAŽALOST, UPRAVO OVAKVO PSIHO-AKTIVNO DEJSTVO MOŽE POJEDINCIMA BITI "INTERESANTNO" TE STOGA POVREMENO, NEKAD I ČESTO, KORISTE LSD.

MNOGO ČEŠĆE, POSEBNO ADOLESCENTI I MLAĐI LJUDI, IZ NEZNANJA I RADOZNALOSTI, BIVAJU NAVEDENI DA PROBAJU OVU DROGU, NESVESNI DA I JEDNOKRATNA UPOTRBA MOŽE BITI FATALNA ILI OSTAVITI TEŠKE POSLEDICE.

LSD SE KRIMINALNO PRODAJE SE U OBLIKU PRAHA, KOJI JE ČESTO VEŠTAČKI OBOJEN, ILI U KAPSULAMA. TAKOĐE SE SREĆE I KAO UPIJAJUĆI PAPIR, IMPREGNIRAN LSD-OM, NA KOME SU ODŠTAMPANE RAZLIČITE, RAZNOBOJNE SLIČICE.

1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

ZAPLENJENI UZORCI LSD-a - VEŠTAČKI OBOJENI PRAH I KAPSULE. STVARNI SADRŽAJ LSD-a JE MINIMALAN (~0.02 - 0.1 mg/KAPSULI), DOK GLAVNINU (>99%) ČINE INERTNI PUNIOCI I KONTAMINANTI.

1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

ZAPLENJENI UZORCI LSD-a - VEŠTAČKI OBOJENI PRAH I KAPSULE. STVARNI SADRŽAJ LSD-a JE MINIMALAN

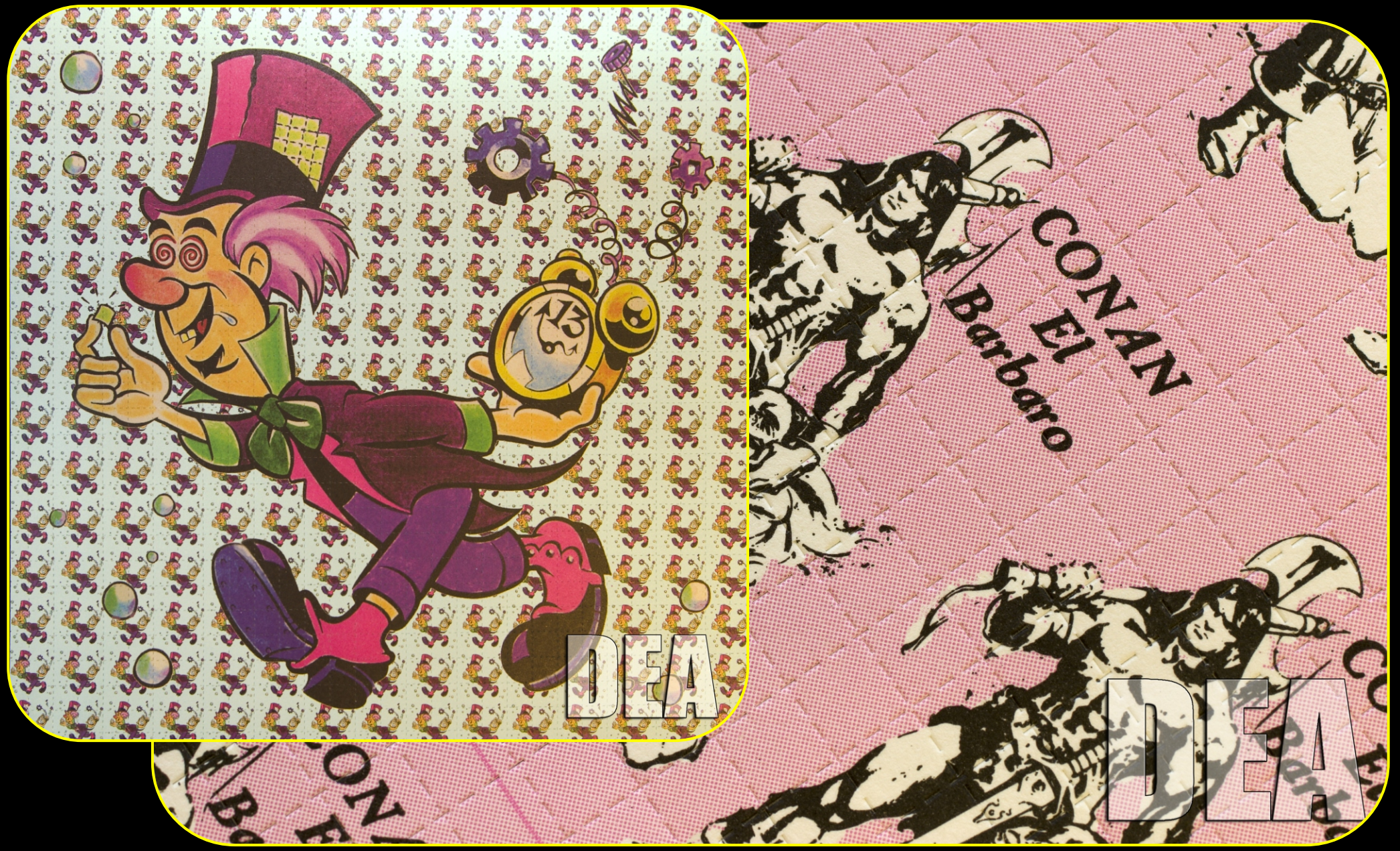
(~0.02 - 0.1 mg/KAPSULA), DOK GLAVNINU MATERIJALA (>99%) ČINE INERTNI PUNIOCI I KONTAMINANTI.

1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

UPIJAJUĆI PAPIR, IMPREGNIRAN LSD-OM, NA KOME SU ODŠTAMPANE RAZLIČITE, RAZNOBOJNE SLIČICE. SVAKI

1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

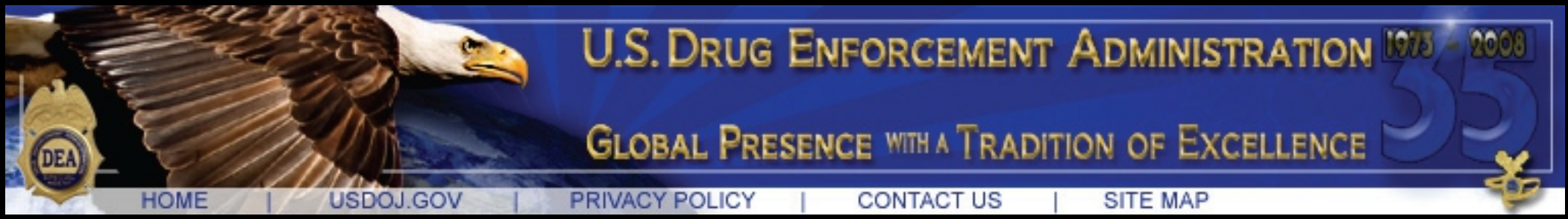
UPIJAJUĆI PAPIR, IMPREGNIRAN LSD-OM, NA KOME SU ODŠTAMPANE RAZLIČITE, RAZNOBOJNE SLIČICE. SVAKI PERFORIRANI KVADRATIĆ ODGOVARA JEDNOJ ORALNOJ DOZI (OBIČNO ~0.02 - 0.1 mg)



1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

MADA PROIZVODNJA I ZLOUPOTREBA LSA-a PREDSTAVLJA OZBILJAN PROBLEM, IPAK JE DALEKO MANJEG OBIMA U POREĐENJU SA HEROINOM, KOKAINOM I AMFETAMINIMA. NAIME, U NOVIJE VREME ŠIRA JAVNOST JE BOLJE UPOZNATA SA EKSTREMNIM RIZICIMA KORIŠĆENJA LSD-A, TAKO DA JE I POTRAŽNJA ZA NJIM MNOGO MANJA NEGO 60-IH GODINA 20. VEKA.

1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD



DEA, INFORMACIJA O PREPARATU, LSD

LSD JE PRVI SINTETIZOVAVO HEMIČAR Albert Hofmann, KOJI JE RADIO UFARMACEUTSKOJ LABORATORIJI SANDOZ KORPORACIJE (ŠVAJCARSKA),1938. ISTRAŽIVAO JE MOGUĆE MEDICINSKE PRIMENE RAZLIČITIH DERIVATA LISERGINSKE KISELINE, JEDINJENJA KOJE POSTAJE U ERGOT GLJIVICI, ČESTOG PARAZITA NA RAŽI. U POTRAZI ZA TERAPIJSKI KORISNIM JEDINJENJIMA, HOFMANN JE SINTETIZOVAO NEKOLIKO DESETINA JEDINJENJA, PARCIJALNOM SINTEZOM IZ LISERGINSKE KISELINE. (1)
LSD SE PRODAJE NA ULICI U OBLIKU TABLETA, KAPSULA A NEKADA I KAO TEČNOST. TO JE SUPSTANCE BEZ BOJE I MIRISA, BLAGO GORKOG UKUSA, KOJA SE OBIČNO UNOSI
ORALNO. ČESTO SE NANOSI NA APSORBUJUĆI PAPIR, KAO ŠTO JE PAPIR ZA UPIJANJE, KOJI JE PERFORIRAN NA MALE ŠARENE KVADRATIĆE, OD KOJIH SVAKI PREDSTAVLJA PO JEDNU DOZU.(2)

STEPEN KONTROLE

LSD JE SUPSTANCA KLASE I (Schedule I) PREMA ZAKONU O KONTROLISANIM SUPSTANCAMA (Controlled Substances Act). SUPSTANCE (DROGE) KLASE I UKLJUČUJU I HEROIN I MDMA (EKSTAZI),
IMAJU VELIKU MOGUĆNOST ZLOUPOTREBE I NEMAJU LEGITIMNU MEDICINSKU PRIMENU.(3) DVA PREKURSORA LSD-a, LISERGINSKA KISELINA I AMID LISERGINSKE KISELINE KLASIFIKOVANI
SU KLASI III (Schedule III). PREKURSORI LSD-a ERGOTAMIN (ergotamine) I ERGONOVIN (ergonovine) NALAZE SE U LISTI I (List I) HEMIKALIJA .(4)

ULIČNI NAZIVI

Acid, blotter acid, window pane, dots, mellow yellow
(Acid, blotter acid, window pane, dots, mellow yellow)

KRATKOROČNI EFEKTI

KRATKOROČNI EFEKTI LSD-a SU NEPREDVIDLJIVI. ZAVISE OD UZETE KOLIČINE, LIČNOSTI KORISNIKA I OKOLNOSTI. PRVI EFEKTI SE JAVLJAJU OBIČNO 30-90 min POSLE UNOŠENJA. DEJSTVO TRAJE TOKOM VIŠE ČASOVA I POSTEPENO PRESTAJE POSLE ~12 h. FIZIOLOŠKI EFEKTI UKLJUČUJU PROŠIRENJE ZENICA, POVIŠENU TELESNU TEMPERATURU, UBRZAN RAD SRCA, POVIŠENI KRVNI PRITISAK, ZNOJENJE, GUBITAK APETITA, NESANICU, SUVA USTA I DRHTANJE. PSIHOLOŠKI EFEKTI SU RAZLIČITI, A PRI VEĆIM DOZAMA SE JAVLJAU PARANOIDNE IDEJE I VIZUELNE HALUCINACIJE.(5)

DUGOROČNI EFEKTI

KORISNICI LSD-a ČESTO DOŽIVLJAVAJU “POVRATNI EFEKAT” (flashbacks), KADA SE POJEDINI EFEKTI DEJSTVA LSD-a IZNENADA JAVLJAJU I DUŽE VREME PO ŽPRESTANKU UZIMANJA SUPSTANCE. PORED TOGA, KOD KORISNIKA SE MOGU JAVITI DUGOTRAJNJA PSIHOTIČNA STANJA (ŠIZOFRENIJA ILI TEŠKA DEPRESIJA). LSD SE NE SMATRA DROGOM KOJA STVARA NAVIKU (TJ. IZRAŽENU PSIHOLOŠKU POTREBU ZA PONOVNIM UZIMANJEM ŠTO JE SLUČAJ KOD KOKAINA ILI AMFETAMINA) NITI IZAZIVA FIZIČKU ZAVISNOST (KAO HEROIN I DR. OPIOIDI). MEĐUTIM, MOŽE SE JAVITI TOLERANCIJA, ŠTO ZNAČI DA SU KORISNIKU POTREBNE SVE
VEĆE DOZE DA BI DOŽIVEO ŽELJENE HALUCINOGENE EFEKTE.(6)

TRENDOVI U PROMETU LSD-a

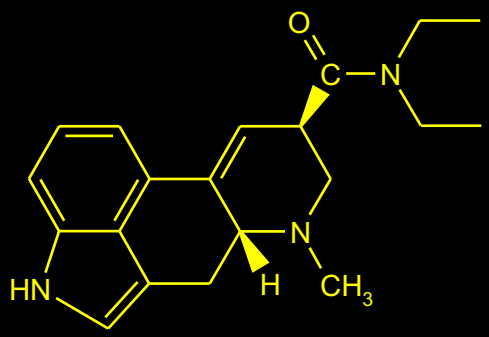
PROMET I ZLOUPOTREBA LSD-a NAGLO JE OPALA POSLE 2000. I
NIJE VEROVATNO DA ĆE U BLIŽOJ BUDUĆNOSTI DOĆI DO PONOVNOG PORASTA.

http://www.usdoj.gov/dea/concern/lsd.html

1. National Institute on Drug Abuse, Research Report: Hallucinogens and Dissociative Drugs, March 2001
2. National Institute on Drug Abuse, InfoFacts: LSD, February 2005
3. National Drug Intelligence Center (NDIC), LSD Fast Facts, May 2003
4. DEA Office of Diversion Control, d-Lysergic Acid Diethylamide
5. National Institute on Drug Abuse, Research Report: Hallucinogens and Dissociative Drugs, March 2001
6. NDIC, LSD Fast Facts, May 2003
7. NDIC,

(SLOBODAN PREVOD SA ENGLESKOG, M. D. IVANOVIĆ)

1. DERIVATI LISERGINSKE KISELINE KAO HALUCINOGENI: LSD

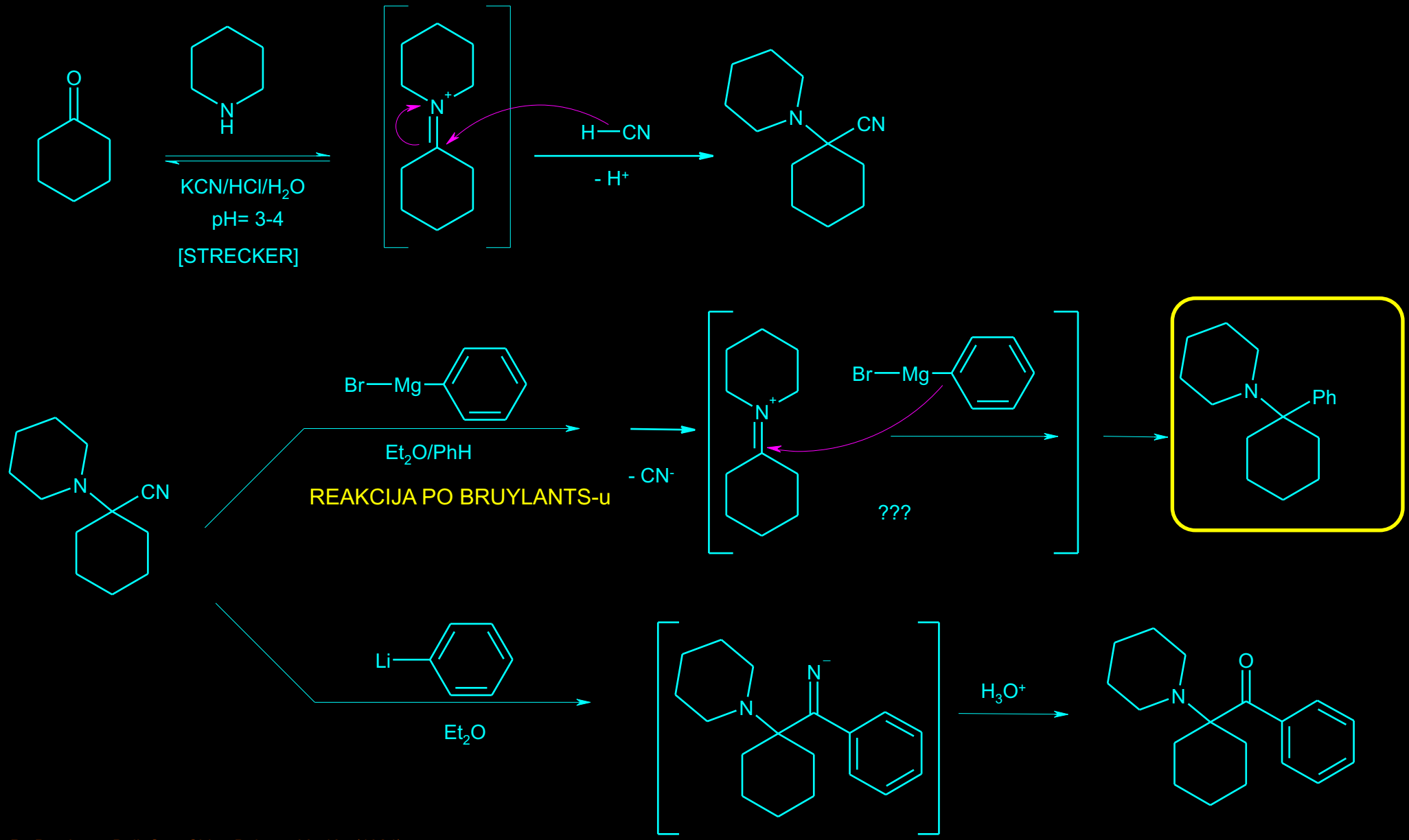


Monograph Number: 5654
Title: Lysergide
CAS Registry Number: 50-37-3
CAS Name: 9,10-Didehydro-*N,N*-diethyl-6-methylergoline-8 -carboxamide
Additional Names: *N,N*-diethyl-D-lysergamide; D-lysergic acid diethylamide; LSD; LSD-25; lysergsäure diethylamid
Molecular Formula: C20H25N3O
Molecular Weight: 323.43.
Percent Composition: C 74.27%, H 7.79%, N 12.99%, O 4.95%
Literature References: Microbial formation by *Claviceps paspali* over the hydroxyethylamide: Arcamone *et al., Proc. Roy. Soc. (London)* 155B, 26 (1961). Partial synthesis: Stoll, Hofmann, *Helv. Chim. Acta* 26, 944 (1943); 38, 421 (1955). Industrial prepn: Pioch, US 2736728; Garbrecht, US 2774763 (both 1956 to Lilly); Patelli, Bernardi, US 3141887 (1964 to Farmitalia). Isotope-labeled LSD: Stoll *et al., Helv. Chim. Acta* 37, 820 (1954). Toxicity data: E. Rothlin, *Ann. N.Y. Acad. Sci.* 66, 668 (1957). *Review:* Hoffer, *Clin. Pharmacol. Ther.* 6, 183 (1965). Book: *The Use of LSD in Psychotherapy and Alcoholism,* H. A. Abramson, Ed. (Bobbs-Merrill, Indianapolis, 1967) 697 pp.
Properties: Pointed prisms from benzene, mp 80-85°. [ ]D20 +17° (c = 0.5 in pyridine). uv max (ethanol): 311 nm (E1%1cm 257). LD50 in mice, rats, rabbits (mg/kg): 46, 16.5, 0.3 i.v. (Rothlin).
Melting point: mp 80-85°
Optical Rotation: [ ]D20 +17° (c = 0.5 in pyridine)
Absorption maximum: uv max (ethanol): 311 nm (E1%1cm 257)
Toxicity data: LD50 in mice, rats, rabbits (mg/kg): 46, 16.5, 0.3 i.v.

Derivative Type: D-Tartrate
Molecular Formula: C46H64N6O10
Molecular Weight: 861.03.
Percent Composition: C 64.17%, H 7.49%, N 9.76%, O 18.58%
Properties: Solvated, elongated prisms from methanol, mp 198-200°. [ ]D20 +30°. Soluble in water.
Melting point: mp 198-200°
Optical Rotation: [ ]D20 +30°

NOTE: This is a controlled substance (hallucinogen): 21 CFR, 1308.11.
Use: In biochemical research as antagonist to serotonin. Has been used experimentally as adjunct in study and treatment of mental disorders.

2. FENCIKLIDINI



1. P . Bruylants, Bull. Soc. Chim. Belgen, 33, 467 (1924)
2. H. Maddor, E. F. Godefroi, and R. F. Parcell, J. Org. Chem., 8, 230 (1962)
3. A. Kalir, H . Edery, Z. Pelah, D. Balderman, Gila Porath, J. Org. Chem., 12, 473 (1969)

2. FENCIKLIDINI

Monograph Number: 7298

Title: Phencyclidine

CAS Registry Number: 77-10-1

CAS Name: 1-(1-Phenylcyclohexyl)piperidine

Additional Names: angel dust; HOG; PCP

Manufacturers' Codes: CI-395

Molecular Formula: C17H25N

Molecular Weight: 243.39.

Percent Composition: C 83.89%, H 10.35%, N 5.75%

Literature References: Prepn: GB 836083 and Godefroi *et al.,* US 3097136 (1960, 1963 to Parke, Davis); V. H. Maddox *et al., J. Med. Chem.* 8, 230 (1965). Pharmacology: G. Chen *et al., J. Pharmacol. Exp. Ther.* 127, 241 (1959); J. C. Munch, *Bull. Narcotics* 26, 9 (1974). Human metabolism: L. K. Wong, K. Biemann, *Biomed. Mass Spectrom.* 2, 204 (1975). Toxicity: K. Bailey *et al., J. Pharm. Pharmacol.* 28, 713 (1976). Extensive bibliography: R. L. Balster, R. S. Pross, *J. Psychedelic Drugs* 10, 1-15 (1978). *Review:* R. E. Garey, *ibid.* 11, 265-275 (1979). Review of neuropharmacology: K. M. Johnson, S. M. Jones, *Ann. Rev. Pharmacol. Toxicol.* 30, 707-750 (1990).

Properties: Colorless crystals, mp 46-46.5°. bp1.0 135-137°. uv max (0.1*N* HCl): 252, 257.5, 262, 268.5 nm (E1%1cm 7.9, 11.2, 13.0, 9.7).

Melting point: mp 46-46.5°

Boiling point: bp1.0 135-137°

Absorption maximum: uv max (0.1*N* HCl): 252, 257.5, 262, 268.5 nm (E1%1cm 7.9, 11.2, 13.0, 9.7)

Derivative Type: Hydrochloride

CAS Registry Number: 956-90-1

Trademarks: Sernyl; Sernylan

Molecular Formula: C17H25N.HCl

Molecular Weight: 279.86.

Percent Composition: C 72.96%, H 9.36%, N 5.01%, Cl 12.67%

Properties: Crystals from 2-propanol, mp 233-235°. uv max (ethanol): 254, 258, 262.5, 269 nm (E1%1cm 7.9, 10.8, 12.7, 10.0). LD50 orally in mice: 76.5 mg/kg (Bailey).

Melting point: mp 233-235°

Absorption maximum: uv max (ethanol): 254, 258, 262.5, 269 nm (E1%1cm 7.9, 10.8, 12.7, 10.0)

Toxicity data: LD50 orally in mice: 76.5 mg/kg (Bailey)

Derivative Type: Hydrobromide

Properties: Crystals, mp 214-218°.

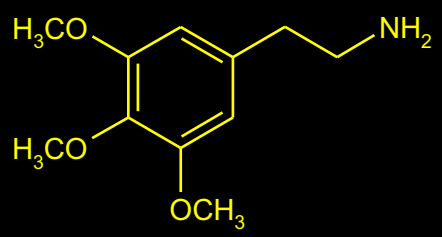
Melting point: mp 214-218°

CAUTION: This is a controlled substance (depressant): 21 CFR, 1308.12. The ethylamine, pyrrolidine and thiophene analogs are controlled substances (hallucinogens): 21 CFR, 1308.11.

Therap-Cat: Anesthetic (intravenous).

Therap-Cat-Vet: Analgesic; anesthetic.

3. POJEDINI β-FENETILAMINI (UKLJUČUJUĆI I NEKE AMFETAMINE)



MESCALINE -HALUCINOGENI ALKALOID AMFETAMINSKE STRUKTURE KOJI SE IZOLUJE IZ MEKSIČKOG KAKTUSA *Lophophora williamsii* ;


Lophophora williamsii

Monograph Number: 5932
Title: MESCALINE
CAS Registry Number: 54-04-6
CAS Name: 3,4,5-Trimethoxybenzeneethanamine
Additional Names: 3,4,5-trimethoxyphenethylamine; mezcaline
Molecular Formula: C11H17NO3
Molecular Weight: 211.26.
Percent Composition: C 62.54%, H 8.11%, N 6.63%, O 22.72%
Literature References: Psychotomimetic alkaloid isolated from ***peyote*** (mescal buttons), the flowering heads of *Lophophora williamsii* (Lemaire) Coult., *Cactaceae.* Isoln: A. Heffter, *Ber.* **29,** 221 (1896). Structure and synthesis: E. Späth, *Monatsh.* **40,** 129 (1919); K. H. Slotta, H. Heller, *Ber.* **63,** 3029 (1930); E. Späth, F. Becke, *Monatsh.* **66,** 327 (1935); M. U. Tsao, *J. Am. Chem. Soc.* **73,** 5495 (1951); K. Banholzer *et al., Helv. Chim. Acta* **35,** 1577 (1952). Novel synthesis: M. N. Aboul-Enein, A. I. Eid, *Acta Pharm. Suec.* **16,** 267 (1979). MS determn: S. P. Jindal, T. Lutz, *Eur. J. Mass Spectrom. Biochem. Med. Environ. Res.* **2,** 117 (1982). Pharmacokinetics in rabbits: C. Van Peteghem *et al., Eur. J. Drug Metab. Pharmacokinet.* **7,** 1 (1982). Mode of action study: M. E. Trulson *et al., Eur. J. Pharmacol.* **96,** 151 (1983). Use in evaluating serotonin S2 antagonists: C. J. E. Niemegeers *et al., Drug Dev. Res.* **3,** 123 (1983). Evaluation of use with chlorpromazine, *q.v.,* in various psychoses: H. C. B. Denber, S. Merlis: *J. Nerv. Ment. Dis.* **122,** 463 (1955). Toxicity data: L. B. Speck, *J. Pharmacol. Exp. Ther.* **119,** 78 (1957); H. F. Hardman *et al., Toxicol. Appl. Pharmacol.* **25,** 299 (1973). *Reviews:* A. R. Patel, *Progress in Drug Research* **vol. 11,** E. Jucker, Ed. (Birkhaüser Verlag, Basel, 1968) pp 11-47; G. J. Kapadia, M. B. E. Fayez, *J. Pharm. Sci.* **59,** 1699-1727 (1970).
Properties: Crystals, mp 35-36°. bp12 180°. Moderately sol in water; sol in alcohol, chloroform, benzene. Practically insol in ether, petr ether. Takes up CO2 from the air and forms a crystalline carbonate. LD50 i.p. in rats: 370 mg/kg (Speck).
Melting point: mp 35-36°
Boiling point: bp12 180°
Toxicity data: LD50 i.p. in rats: 370 mg/kg (Speck)

Derivative Type: Hydrochloride
Molecular Formula: C11H17NO3.HCl
Molecular Weight: 247.72.
Percent Composition: C 53.33%, H 7.32%, N 5.65%, O 19.38%, Cl 14.31%
Properties: Needles, mp 181°. Sol in water, alcohol. LD50 in mice, rats, guinea pigs (mg/kg): 212, 132, 328 i.p. (Hardman).
Melting point: mp 181°
Toxicity data: LD50 in mice, rats, guinea pigs (mg/kg): 212, 132, 328 i.p. (Hardman)

Derivative Type: Sulfate dihydrate
Molecular Formula: (C11H17NO3)2.H2SO4.2H2O
Molecular Weight: 556.63.
Percent Composition: C 47.47%, H 7.24%, N 5.03%, O 34.49%, S 5.76%
Properties: Prisms, mp 183-186°. Sol in hot water, methanol; sparingly sol in cold water, ethanol.
Melting point: mp 183-186°

Derivative Type: Acid sulfate
Molecular Formula: C11H17NO3.H2SO4
Molecular Weight: 309.34.
Percent Composition: C 42.71%, H 6.19%, N 4.53%, O 36.20%, S 10.37%
Properties: Crystals, mp 158°.
Melting point: mp 158°

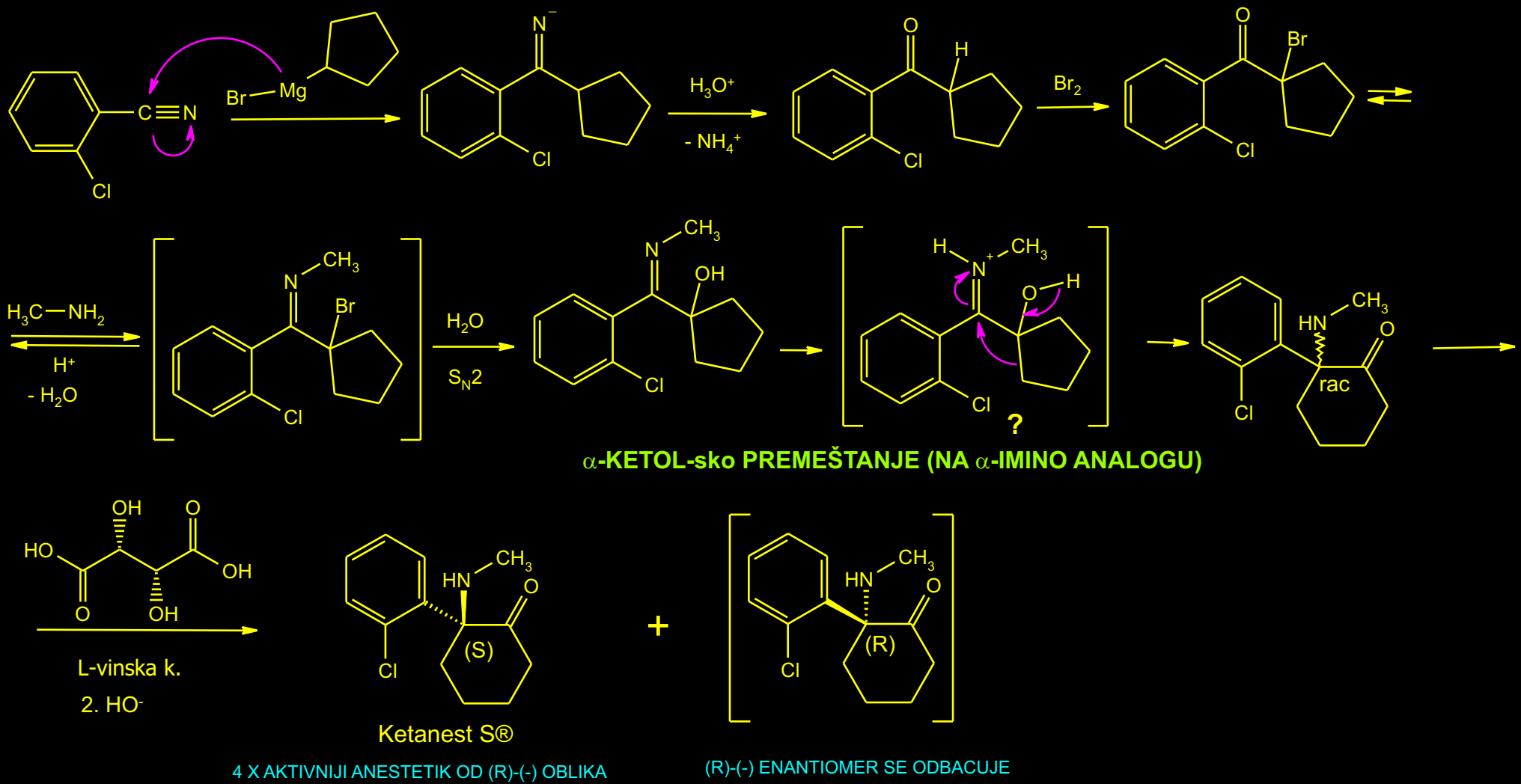
Derivative Type: *N*-Benzoylmescaline
Properties: Needles from aq alc, mp 121°. Very sol in alcohol, ether.
Melting point: mp 121°

Derivative Type: *N*-Methylmescaline
Properties: Occurs naturally, bp 130-140°.
Boiling point: bp 130-140°

Derivative Type: *N*-Acetylmescaline
Properties: Occurs naturally, mp 94°.
Melting point: mp 94°

NOTE: This is a controlled substance (hallucinogen): **21 CFR,** 1308.11.

4. KETAMIN: ANESTETIK, ANALGETIK, ANTIDEPRESANT I HALUCINOGEN



α-KETOL-sko PREMEŠTANJE (NA α-IMINO ANALOGU)

Ketanest S®

4 X AKTIVNIJI ANESTETIK OD (R)-(-) OBLIKA

(R)-(-) ENANTIOMER SE ODBACUJE

1. Tetrahedron: Asymmetry 14 (2003) 2177–2187

2. (R)-(-) MOŽE DA IZAZOVE HALUCINACIJE TOKOM FAZE BUĐENJA: Heinz, T. W. Deutsches A rzteblatt 1999, 96, 2724.

3. (S)-(+) JE 4 X AKTIVNIJI ANESTETIK, A UVEDEN JE U PRIMINU POD NAZIVOM Ketanest S®

4. Ketanest S® DOBIJA SE RAZLAGANJEM RACEMATA KORISTEĆI L-VINSKU KISELINU:

4.1 Steiner, K. Patent WO 97/43244, 1997.
4.2. Russo, T.; Freire, V. Patent WO 01/98265 A2, 2001.

Monograph Number: 5312
Title: Ketamine
CAS Registry Number: 6740-88-1
CAS Name: 2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone
Molecular Formula: C13H16ClNO
Molecular Weight: 237.73.
Percent Composition: C 65.68%, H 6.78%, Cl 14.91%, N 5.89%, O 6.73%
Literature References: Prepn: C. L. Stevens, BE 634208; *idem,* US 3254124 (1963, 1966 both to Parke, Davis). Isoln of optical isomers: T. W. Hudyma *et al.,* DE 2062620 (1971 to Bristol-Myers), *C.A.* 75, 118119x (1971). Clinical pharmacology of racemate and enantiomers: P. F. White *et al., Anesthesiology* 52, 231 (1980). Toxicity: E. J. Goldenthal, *Toxicol. Appl. Pharmacol.* 18, 185 (1971). Enantioselective HPLC determn in plasma: G. Geisslinger *et al., J. Chromatog.* 568, 165 (1991). Comprehensive description: W. C. Sass, S. A. Fusari, *Anal. Profiles Drug Subs.* 6, 297-322 (1977). Review of pharmacology and use in veterinary medicine: M. Wright, *J. Am. Vet. Med. Assoc.* 180, 1462-1471 (1982). Review of pharmacology and clinical experience: D. L. Reich, G. Silvay, *Can. J. Anaesth.* 36, 186-197 (1989); in pediatric procedures: S. M. Green, N. E. Johnson, *Ann. Emerg. Med.* 19, 1033-1046 (1990).
Properties: Crystals from pentane-ether, mp 92-93°. uv max (0.01*N* NaOH in 95% methanol): 301, 276, 268, 261 nm (A1%1cm 5.0, 7.0, 9.8, 10.5). pKa 7.5. pH of 10% aq soln 3.5.
Melting point: mp 92-93°
pKa: pKa 7.5
Absorption maximum: uv max (0.01*N* NaOH in 95% methanol): 301, 276, 268, 261 nm (A1%1cm 5.0, 7.0, 9.8, 10.5)

Derivative Type: Hydrochloride
CAS Registry Number: 1867-66-9
Manufacturers' Codes: CI-581
Trademarks: Ketaject (Bristol-Myers Squibb); Ketalar (Parke-Davis); Ketanarkon (Streuli); Ketanest (Parke-Davis); Ketaset (Am. Home); Ketavet (Gellini); Vetalar (Am. Home)
Molecular Formula: C13H16ClNO.HCl
Molecular Weight: 274.19.
Percent Composition: C 56.95%, H 6.25%, Cl 25.86%, N 5.11%, O 5.84%
Properties: White crystals, mp 262-263°. Soly in water: 20 g/100 ml. LD50 in adult mice, rats (mg/kg): 224 ±4, 229 ±5 i.p. (Goldenthal).
Melting point: mp 262-263°

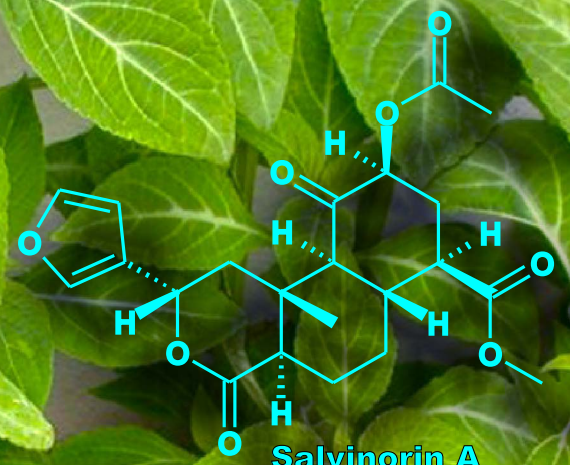
Toxicity data: LD50 in adult mice, rats (mg/kg): 224 ±4, 229 ±5 i.p. (Goldenthal)

NOTE: This is a controlled substance (depressant): 21 CFR, 1308.13.

Therap-Cat: Anesthetic (intravenous).

Therap-Cat-Vet: Anesthetic (intravenous).

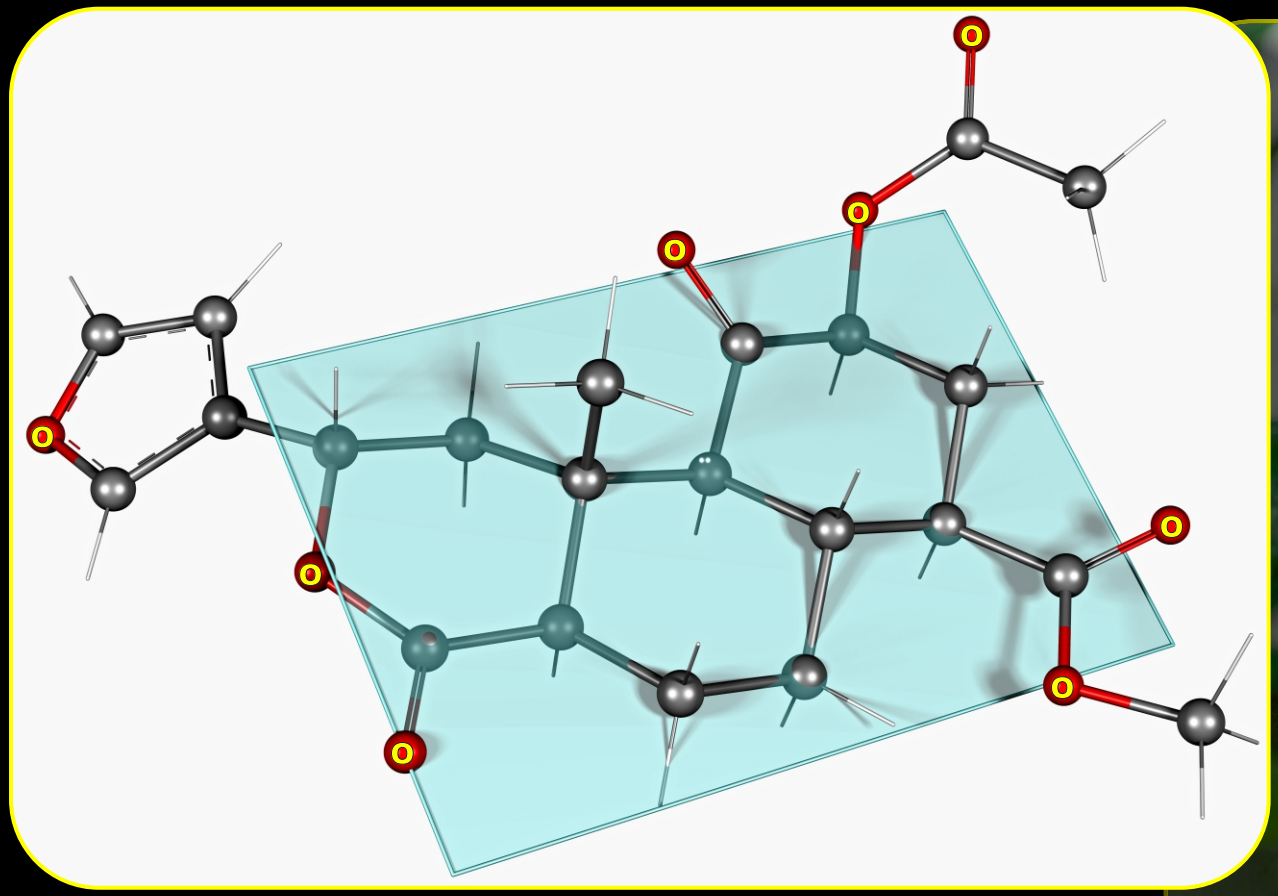
5. SALVINORINI

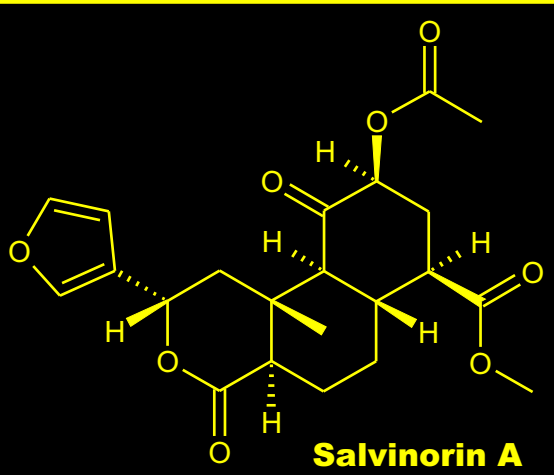


Salvinorin A

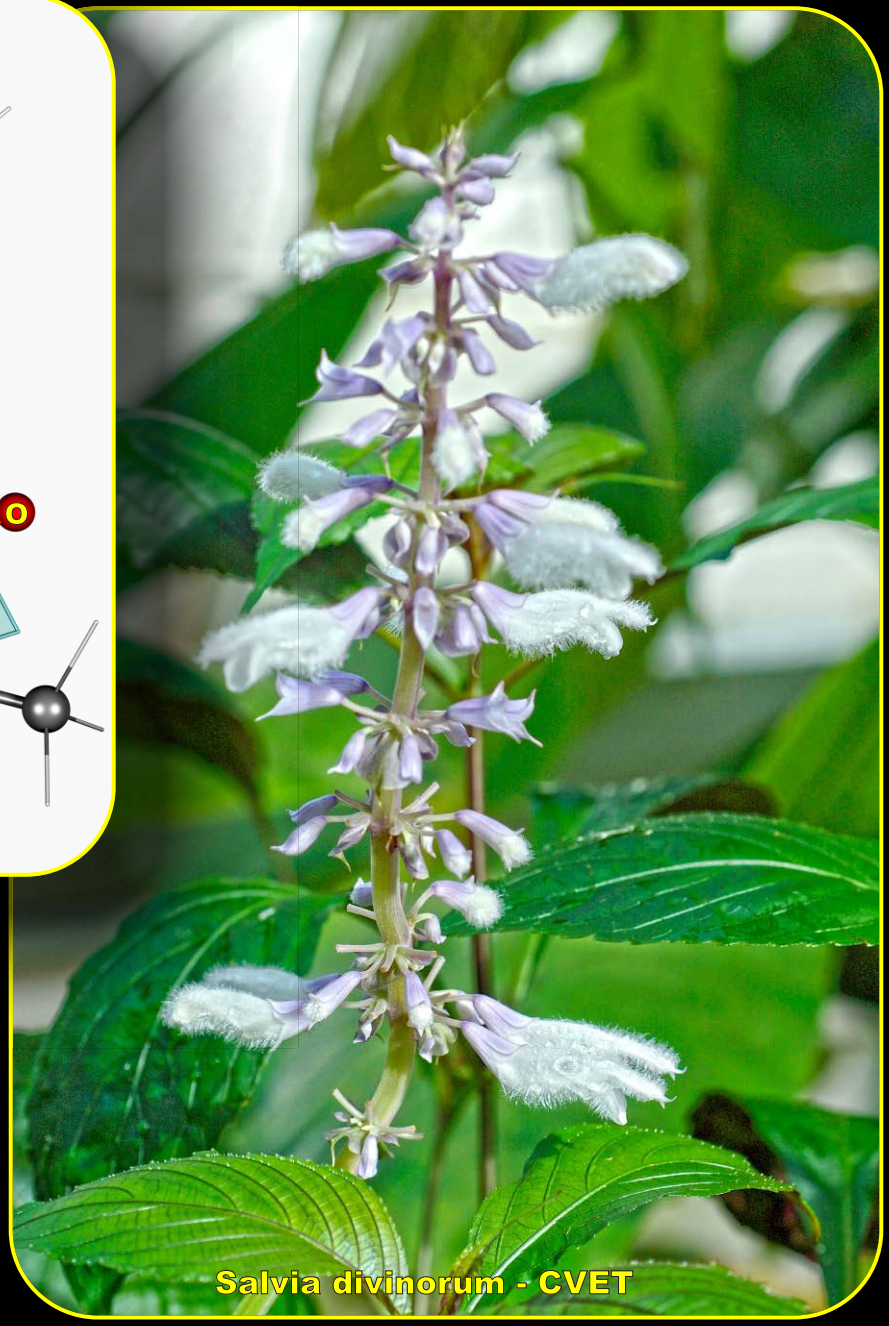
Salvia divinorum - BILJKA SA HALUCINOGENIM DEJSTVOM. NATIVNO RASTE U IZOLOVANIM REGIONIMA KIŠNIH ŠUMA, U OBLASTI SIERRA MAZATECA, OAXACA, MEKSIKO.

5. SALVINORINI





Salvinorin A



5. SALVINORINI

Salvia divinorum JE HALUCINOGENA BILJKA KOJA NATIVNO RASTE U REGIONU *OAXACA*, MEKSIKO. LOKALNO STANOVNIŠTVO JE KORISTI U RELIGIOZNIM OBREDIMA KAO I ZA LEČENJE POJEDINIH OBOLJENJA. GLAVNA AKTIVNA KOMPONENTA JE DITERPEN ***SALVINORIN A***.

SALVINORIN A JE SNAŽAN HALUCINOGEN U LJUIDI, PRI ČEMU SU AKTIVNE DOZE 0.2-0.5 mg. SMATRA SE DA PREDSTAVLJA NAJJAČI POZNATI PRIRODNI HALUCINOGEN (LSD JE JAČI ~10 X ALI JE POLU-SINTETIČKOG POREKLA).

SALVINORIN A JE SNAŽAN AGONIST κ-OPIOIDNIH RECEPTORA (KOP) I PORED TOGA ŠTO NEMA SLIČNOSTI SA DRUGIM POZNATIM KOP AGONISTIMA KAO ŠTO SU CYCLAZOCINE, PENTAZOCINE, KETAZOCINE ILI ARILACETAMID U50,488. MEĐUTIM, VEĆINA κ-OPIOIDNIH AGONISTA ISPOLJAVA HALUCINOGENE EFEKTE (PRETEŽNO VIZUELNOG KARAKTERA), NALIK NA ***SALVINORIN A*** , ZBOG ČEGA JE NJIHOVA TERAPIJSKA PRIMENA MINIMALNA.

SALVINORIN A JE JEDINSTVEN I PO TOME ŠTO ***NIJE ALKALOID*** I ***NE SADRŽI AZOT U BILO KOM OBLIKU***. ZA RAZLIKU OD NJEGA, SVI POZNATI OPIOIDNI AGONISTI ILI ANTAGONISTI (μ, κ, δ, ORL) SADRŽE AZOT I TO U BAZNOM OBLIKU (KAO AMIN).

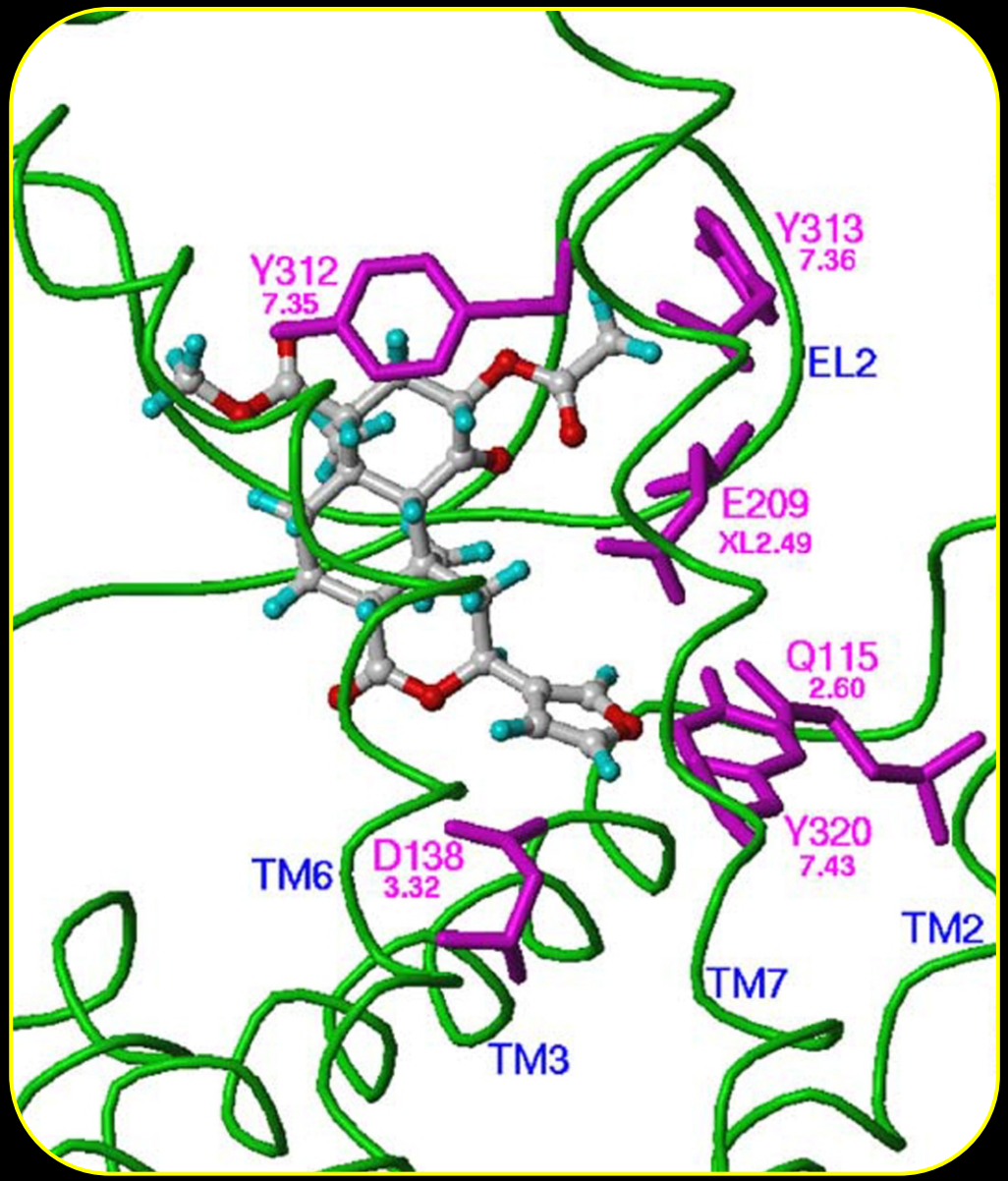
KOLIKO JE POZNATO,***SALVINORIN A*** NE ISPOLJAVA HALUCINOGENA SVOJSTVA PREKO 5-HT_{2A} RECEPTORA, KAO ŠTO JE TO SLUČAJ SA KLASIČNIM HALUCINOGENIMA (LSD, MESCALINE, PSILOCIN I DR.)

ZBOG HALUCINOGENIH SVOJSTAVA, ***SALVINORIN A*** SE NE MOŽE KORISTI U TERAPIJI (NPR. ANALGEZIJI). MEĐUTIM, MOGUĆE JE DA ĆE NEKI DERIVATI/ANALOZI OVE SUPSTANCE, AKO POKAŽU POVOLJAN FARMAKOLOŠKI PROFIL, IPAK NAĆI TERAPIJSKU PRIMENU.

IZ TOG RAZLOGA, PARCIJALNE HEMIJSKE MODIFIKACIJE ***SALVINORIN-a A*** KAO I TOTALNE SINTEZE NJEGOVIH ANALOGA, PREDSTAVLJAJU ZNAČAJAN CILJ SAVREMENE ORGANSKE SINTEZE.

5. SALVINORINI

TAKOĐE, ***SALVINORIN A*** JE I PREDMET TEORIJSKIH PROUČAVANJA, POSEBNO MODELOVANJA KOMPLEKSA LIGAND (***SALVINORIN A***)-κ-OPIOIDNI RECEPTOR (SLIKA PRIKAZUJE DEO TAKVOG TEORIJSKI MODELOVANOG KOMPLEKSA.

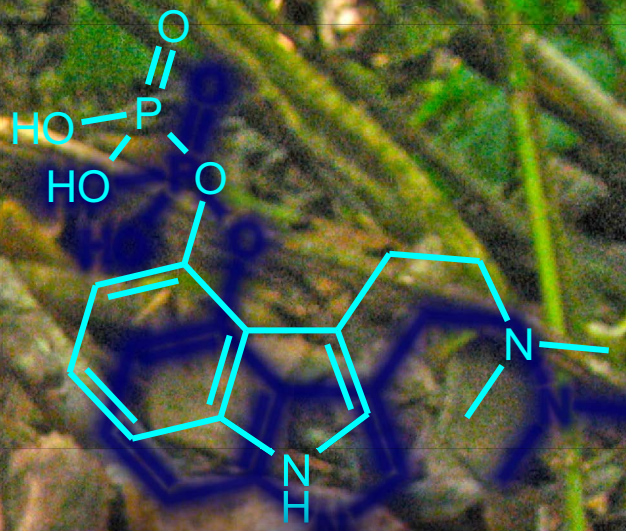


1. A. Lozama, C. W. Cunningham, M. J. Caspers, J. T. Douglas, C. M. Dersch, R. B. Rothman, T. E. Prisinzano;"Opioid Receptor Probes Derived from Cycloaddition of the Hallucinogen Natural Product Salvinorin A"; ***J. Nat. Prod. 2011, 74, 718–726***

2. D. L. McGovern , P. D. Mosier, B. L. Roth, R. B. Westkaemper; "CoMFA analyses of C-2 position Salvinorin A analogs at the kappa-opioid receptor provides insights into epimer selectivity" ***Journal of Molecular Graphics and Modelling 28 (2010) 612***

6. DERIVATI TRIPTAMINA: PSILOCIBIN

Psilocybe zapotecorum



AKTIVNA KOMPONENTA:

ALKALOID *PSILOCYBIN*.

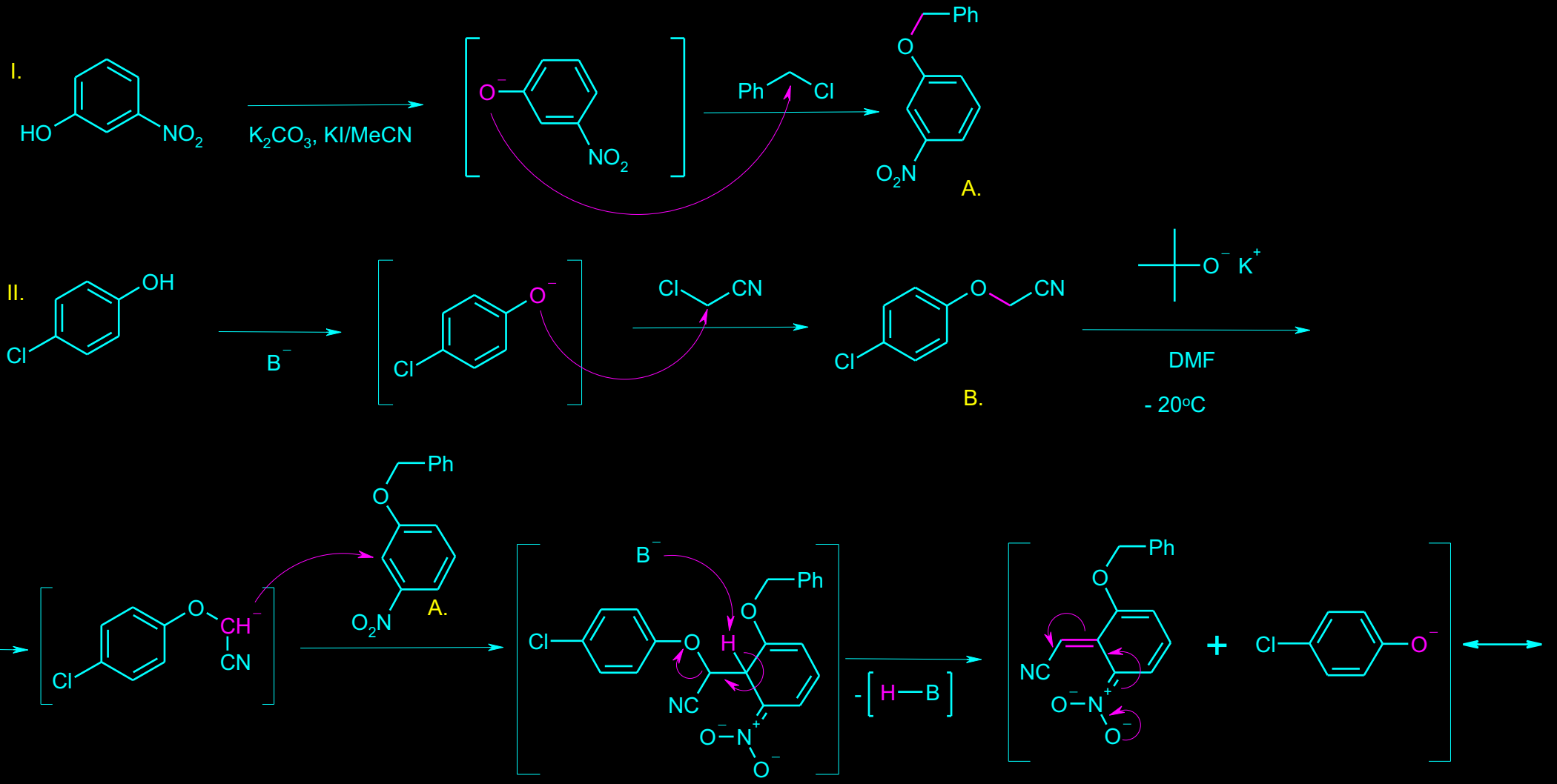
EFEKTIVNE DOZE:
-10-50 mg ŠTO ODGVARA KOLIČINI OD NEKOLIKO GRAMA OSUŠENIH PEČURAKA, ZAVISNO OD VRSTE, KVALITETA I DR.

-IZAZIVA RAZNOVRSNE HALUCINACIJE TOKOM VIŠE ČASOVA

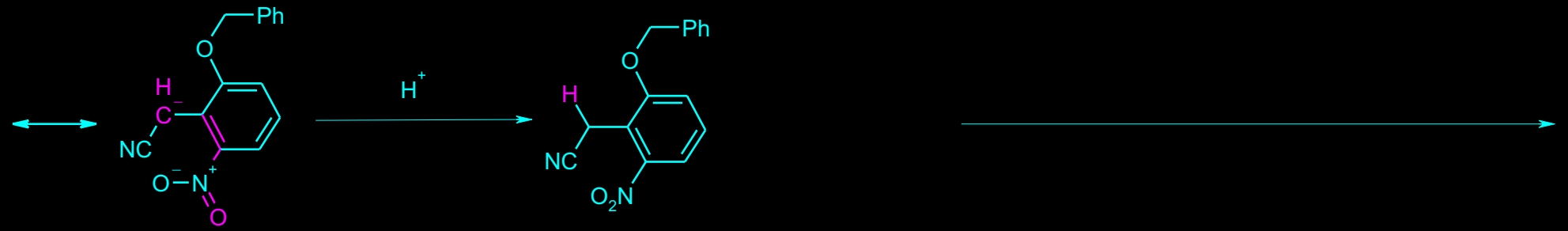
WIKIPEDIA

6. DERIVATI TRIPTAMINA: PSILOCIBIN

SINTEZA AKTIVNE KOMPONENTE PEČURAKA *PSILOCYBE - ALKALOIDA PSILOCYBIN-a*

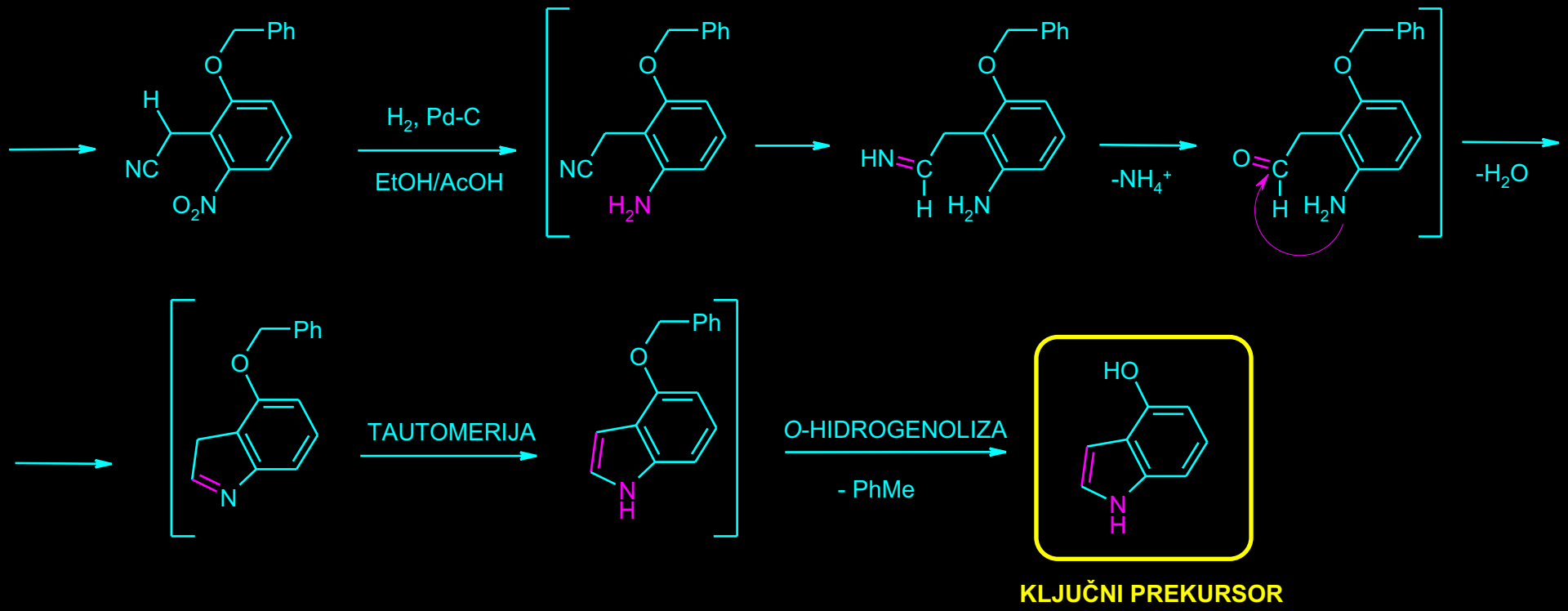


MEHANIZAM: INDIREKTNA NUKLEOFILNA SUPSTITUCIJA VODONIKA “VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN”



6. DERIVATI TRIPTAMINA: PSILOCIBIN

SINTEZA AKTIVNE KOMPONENTE PEČURAKA *PSILOCYBE - ALKALOIDA PSILOCYBIN-a* (nastavak)



KLJUČNI PREKURSOR

SINTEZA KLJUČNOG PREKURSORA:

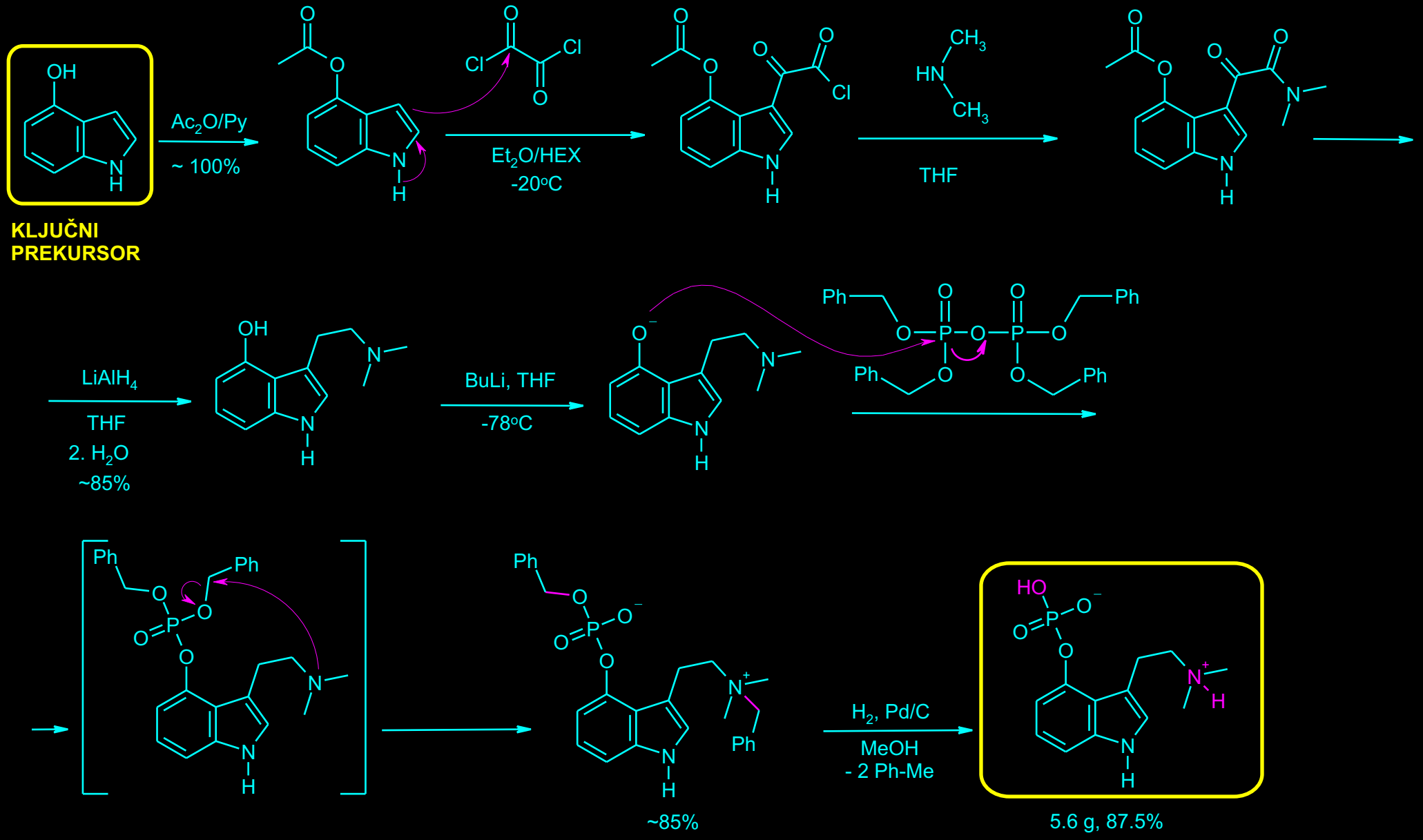
1. European Journal of Medicinal Chemistry 44 (2009) 809
2. M. Makosza, W. Danikiewicz, K. Wojciechowski, Liebigs Ann. Chem.(1988) 203

MEHANIZAM INDIREKTNE NUKLEOFILNE SUPSTITUCIJE VODONIKA:

1. Michael B. Smith, Jerry March *MARCH'S ADVANCED ORGANIC CHEMISTRY*, str. 914-915 2007 by John Wiley & Sons, Inc.
2. Stahly, G.P.; Stahly, B.C.;Maloney, J.R. J. Org. Chem. 1988, 53, 690.

6. DERIVATI TRIPTAMINA: PSILOCIBIN

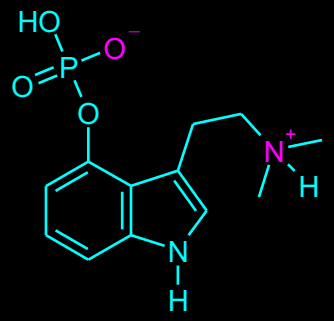
SINTEZA AKTIVNE KOMPONENTE PEČURAKA *PSILOCYBE - ALKALOIDA PSILOCYBIN-a* (nastavak)



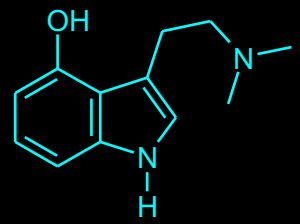
O. Shirota, W. Hakamata, Y. Goda; **Concise Large-Scale Synthesis of Psilocin and Psilocybin, Principal Hallucinogenic Constituents of "Magic Mushroom",** *J. Nat. Prod.* **2003,** *66,* 885

6. DERIVATI TRIPTAMINA: PSILOCIBIN

Monograph Number: 8017
Title: Psilocybin
CAS Registry Number: 520-52-5
CAS Name: 3-[2-(Dimethylamino)ethyl]-1*H*-indol-4-ol dihydrogen phosphate ester
Additional Names: *O*-phosphoryl-4-hydroxy-*N,N*-dimethyltryptamine
Trademarks: Indocybin (Sandoz)
Molecular Formula: $C_{12}H_{17}N_2O_4P$
Molecular Weight: 284.25.
Percent Composition: C 50.70%, H 6.03%, N 9.86%, O 22.51%, P 10.90%
Literature References: The major of two hallucinogenic components of Teonanácatl, the sacred mushroom of Mexico, the other component being psilocin, *q.v.* from the fruiting bodies of *Psilocybe mexicana* Heim, *Agaricaceae:* Hofmann *et al., Experientia* **14,** 107 (1958); Heim *et al., Helv. Chim. Acta* **42,** 1557 (1959); Heim *et al.,* **DE 1087321** (1960 to Sandoz). Structure: Hofmann *et al., Experientia* **14,** 397 (1958). Synthesis: Hofmann, Troxler, **US 3075992** (1963 to Sandoz). Crystal structure: H. P. Weber, T. J. Petcher, *J. Chem. Soc., Perkin Trans. II* **1974,** 942. Converted to psilocin *in vivo.* Toxicity data: E. Usdin, D. H. Efron, *Psychotropic Drugs and Related Compounds* (National Institute of Mental Health, Rockville, Md., 2nd ed., 1972) p 138. *Reviews:* Hofmann, *Proc. 1st Int. Congr. Neuro-Pharm., Rome* **1958,** 446; Cerletti, *Deut. Med. Wochenschr.* **84,** 2317 (1959); Hofmann, *Bull. Narcotics* **23,** 3 (1971).
Properties: Crystals from boiling water, mp 220-228°; from boiling methanol, mp 185-195°. uv max (methanol): 220, 267, 290 nm (log 4.6, 3.8, 3.6). pH 5.2 in 50% aq ethanol. Sol in 20 parts boiling water, 120 parts boiling methanol; difficultly sol in ethanol. Practically insol in chloroform, benzene. LD_{50} in mice, rats, rabbits (mg/kg): 285, 280, 12.5 i.v. (Usdin, Efron).
Melting point: mp 220-228°; mp 185-195°
Absorption maximum: uv max (methanol): 220, 267, 290 nm (log 4.6, 3.8, 3.6)
Toxicity data: LD_{50} in mice, rats, rabbits (mg/kg): 285, 280, 12.5 i.v. (Usdin, Efron)
NOTE: This is a controlled substance (hallucinogen): **21 CFR,** 1308.11.
Therap-Cat: Psychomimetic.



Monograph Number: 8016
Title: Psilocin
CAS Registry Number: 520-53-6
CAS Name: 3-[2-(Dimethylamino)ethyl]-1*H*-indol-4-ol
Additional Names: 4-hydroxy-*N,N*-dimethyltryptamine; psilocyn
Molecular Formula: $C_{12}H_{16}N_2O$
Molecular Weight: 204.27.
Percent Composition: C 70.56%, H 7.89%, N 13.71%, O 7.83%
Literature References: The minor hallucinogenic component of Teonanácatl, the sacred mushroom of Mexico. Isolated in trace amounts from the fruiting bodies of *Psilocybe mexicana* Heim, *Agaricaceae:* Hofmann *et al., Experientia* **14,** 107 (1958); Heim *et al., Helv. Chim. Acta* **42,** 1557 (1959). Prepn: Heim *et al.,* **DE 1087321** (1960 to Sandoz). Synthetic precursor of psilocybin: Hofmann, Troxler, **US 3075992** (1963 to Sandoz). Psilocin, the 4-hydroxy analog of psilocybin, is formed by metabolic dephosphorylation of psilocybin and is the active species in the central nervous system: Horita, Weber, *Toxicol Appl. Pharmacol.* **4,** 730 (1962). Crystal structure: T. J. Petcher, H. P. Weber, *J. Chem. Soc. Perkin Trans. II* **1974,** 946. *Review:* Hofmann, *Bull. Narcotics* **23,** 3 (1971).
Properties: Plates from methanol, mp 173-176°. Amphoteric substance. Unstable in soln, esp. akaline soln. Very slightly sol in water. uv max: 222, 260, 267, 283, 293 nm (log 4.6, 3.7, 3.8, 3.7, 3.6).
Melting point: mp 173-176°
Absorption maximum: uv max: 222, 260, 267, 283, 293 nm (log 4.6, 3.7, 3.8, 3.7, 3.6)
NOTE: This is a controlled substance (hallucinogen): **21 CFR,** 1308.11.



IPAK, IMA I DALEKO OPASNIJIH PEČURAKA NEGO ŠTO SU *PSILOCYBE*....KAO ŠTO SU ONE IZ RODA *Amanita*

Amanita bisporigera

Amanita phaloides

DODATAK

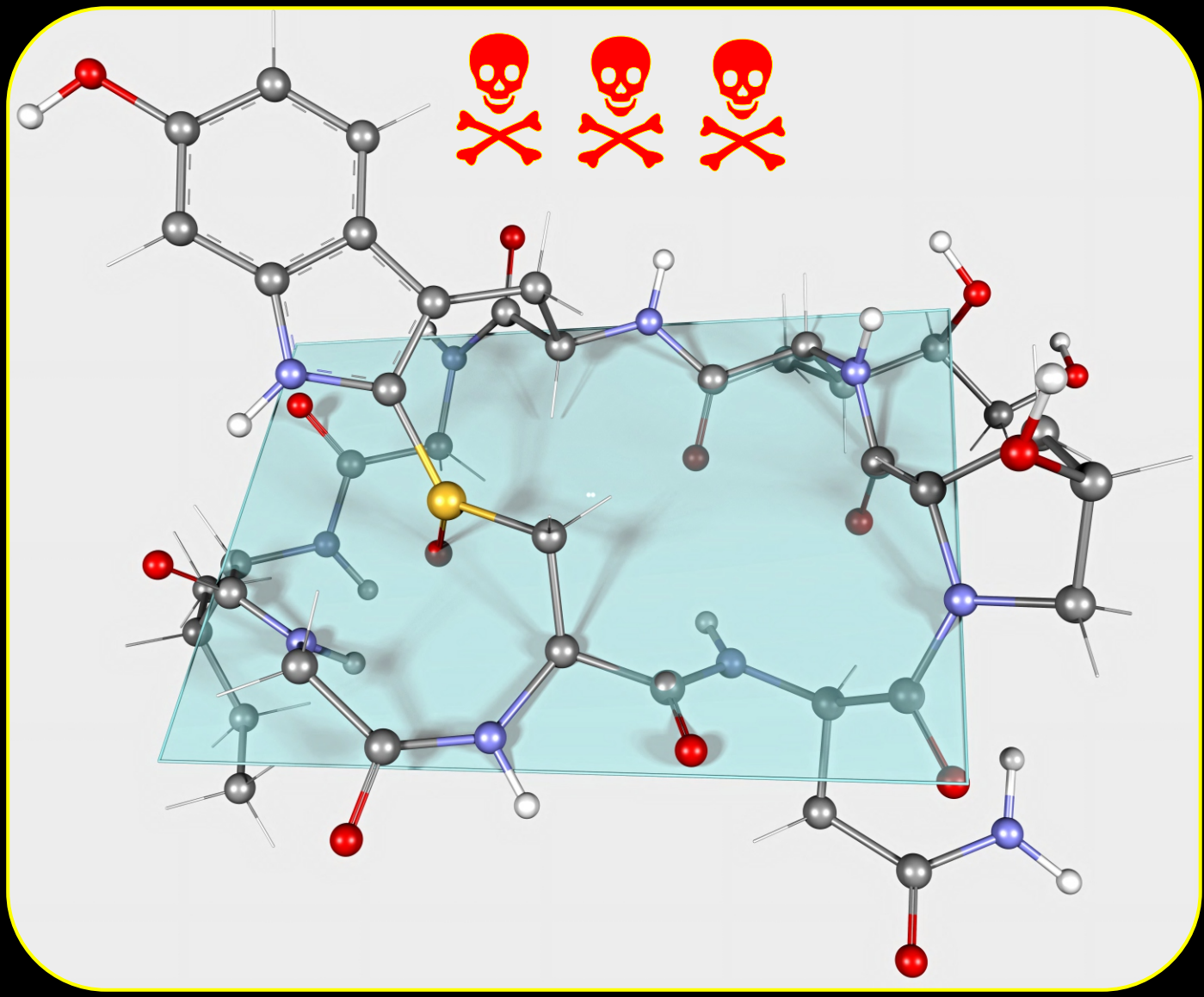
...jer Amanita PEČURKE SADRŽE CIKLIČNI OLIGOPEPTID AMANITIN.

-LETALNA DOZA ZA ODRASLU OSOBU MOŽE BITI ~5-10mg, ČESTO I PORED INTENZIVNOG LEČENJA.

-AMANITIN DELUJE TEK ~ 10 h POSLE KONZUMIRANJA, A UNIŠTAVA TKIVO JETRE I DRUGIH ORGANA.

-PO PRAVILU, NE KONZUMIRATI PEČURKE KOJE RASTU DIVLJE, VEĆ SAMO ONE KOJE SE GAJE VEŠTAČKI.

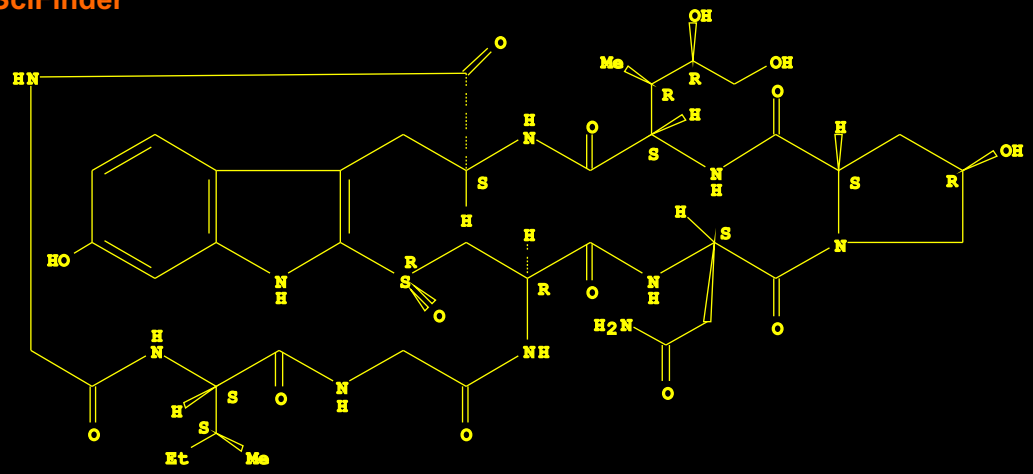
-TROVANJE OTROVNIM PEČURKAMA NEMA NIKAKVE VEZE SA TROVANJEM JESTIVIM PEČURKAMA, KOJE, KAO I DRUGA HRANA, MOGU DA SE “POKVARE” DEJSTVOM SAPROFITSKIH BAKTERIJA. TROVANJA “POKVARENIM” PEČURKAMA OBIČNO SU NEUPOREDIVO BLAŽA.



DODATAK

AMANITIN - REFERENCE

SciFinder



Registry Number: 23109-05-9

Formula: C39 H54 N10 O14 S

CA Index Name: α-Amanitin

Other Names: 9,18-(Iminoethaniminoethaniminoethaniminomethano)pyrrolo[1',2':8,9][1,5,8,11,14]thiatetraazacyclooctadecino[18,17-b]indole, cyclic peptide deriv.; Cyclo[L-asparaginyl-4-hydroxy-L-prolyl-(R)-4,5-dihydroxy-L-isoleucyl-6-hydroxy-2-mercapto-L-tryptophylglycyl-L-isoleucylglycyl-L-cysteinyl], cyclic (4 8)-sulfide, (R)-S-oxide; -Amanitine; -Amatoxin

Sequence Length: 8

References: ~817

MERCK INDEX

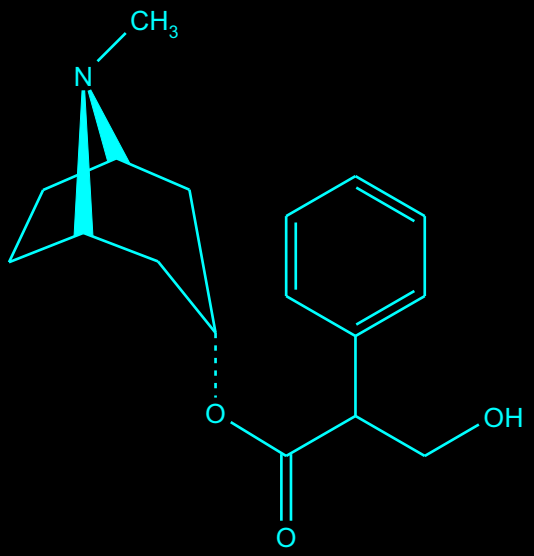
Monograph Number: 370
Title: Amanitin
CAS Registry Number: 11030-71-0
Literature References: Group 1 mushroom toxin from the poisonous mushroom *Amanita phalloides* (Fr.) Secr., *Agaricaceae.* Inhibits protein synthesis of mammalian cells. Comprised of –, –, -amanitin and ***amanin***. -Amanitin is the major poisonous constituent of *A. phalloides;* it is 10-20 times more toxic than phalloidin, *q.v.* Isoln of - and -amanitin: Wieland, *Ann.* **564,** 152 (1949). Prepn of -amanitin from -amanitin: Wieland, Boehringer, *ibid.* **635,** 178 (1960). Structure: Wieland, *Pure Appl. Chem.* **9,** 145 (1964); Wieland, Gebert, *Ann.* **700,** 157 (1967). Review of chemistry and toxicology of the toxins of *Amanita phalloides:* Wieland, Wieland, *Pharmacol. Rev.* **11,** 87-107 (1959); T. Wieland, *Fortschr. Chem. Org. Naturst.* **25,** 214-250 (1967); T. Wieland, H. Faulstich, *Crit. Rev. Biochem.* **5,** 185-260 (1978). Book: H. Faulstich *et al., Amanita Toxins and Poisoning: International Amanita Symposium* (Lubrecht & Cramer, Heidelberg, 1980) 246 pp.
Derivative Type: -Amanitin
CAS Registry Number: 23109-05-9
Molecular Formula: $C_{39}H_{54}N_{10}O_{14}S$
Molecular Weight: 918.98.
Percent Composition: C 50.97%, H 5.92%, N 15.24%, O 24.37%, S 3.49%
Properties: Needles from methanol, mp 254-255°. $[\ ]_{D20}$ +191°. uv max: 302 nm. LD_{50} i.p. in albino mice: 0.1 mg/kg (Wieland, Wieland).
Melting point: mp 254-255°
Optical Rotation: $[\ ]_{D20}$ +191°
Absorption maximum: uv max: 302 nm
Toxicity data: LD_{50} i.p. in albino mice: 0.1 mg/kg (Wieland, Wieland)
Derivative Type: -Amanitin
CAS Registry Number: 21150-22-1
Molecular Formula: $C_{39}H_{53}N_9O_{15}S$
Molecular Weight: 919.97.
Percent Composition: C 50.92%, H 5.81%, N 13.70%, O 26.09%, S 3.49%
Properties: Needles from methanol, mp 300°. uv max: 302 nm. Sol in water, methanol, ethanol, aqueous butanol. LD_{50} i.p. in albino mice: 0.4 mg/kg (Wieland, Wieland).
Melting point: mp 300°
Absorption maximum: uv max: 302 nm
Toxicity data: LD_{50} i.p. in albino mice: 0.4 mg/kg (Wieland, Wieland)
CAUTION: Highly toxic. Following a characteristic asymptomatic period of 6-15 hrs, potential symptoms of intoxication due to ingestion include violent gastroenteritis; fever, tachycardia, hyperglycemia, dehydration, electrolyte imbalance; liver dysfunction and necrosis; renal failure; may be fatal. *See Clinical Toxicology of Commercial Products,* R. E. Gosselin *et al.,* Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section II, p 246; M. J. Ellenhorn, D. G. Barceloux, *Medical Toxicology: Diagnosis and Treatment of Human Poisoning* (Elsevier, New York, 1988) pp 1331-1338.
Use: As a tool in molecular biology.

ATROPA BELLADONNA

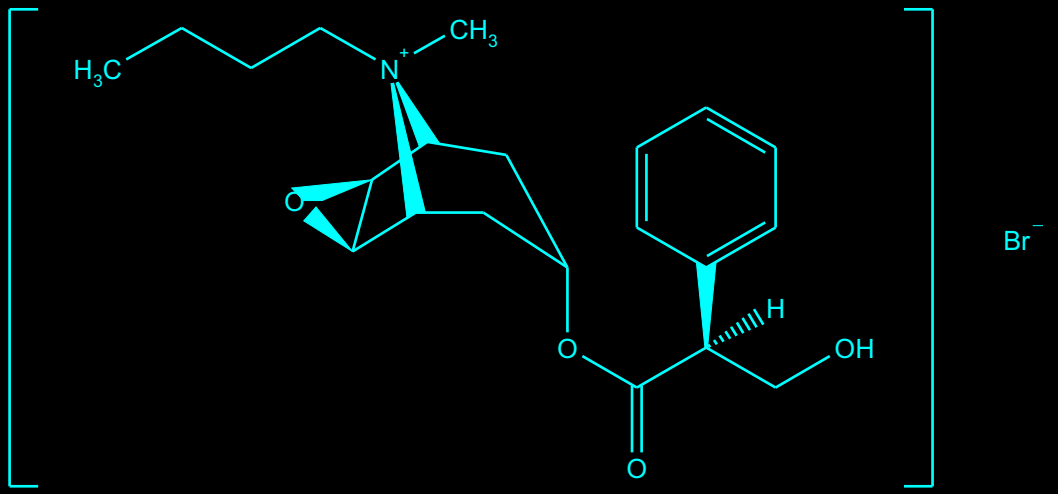
Franz Eugen Köhler, Köhler's Medizinal-Pflanzen

PLOD

TROPANSKI ALKALOIDI

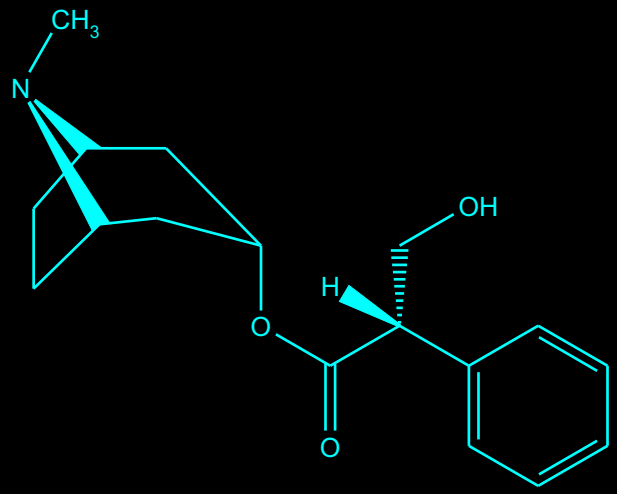


ATROPINE



SCOPOLAMINE

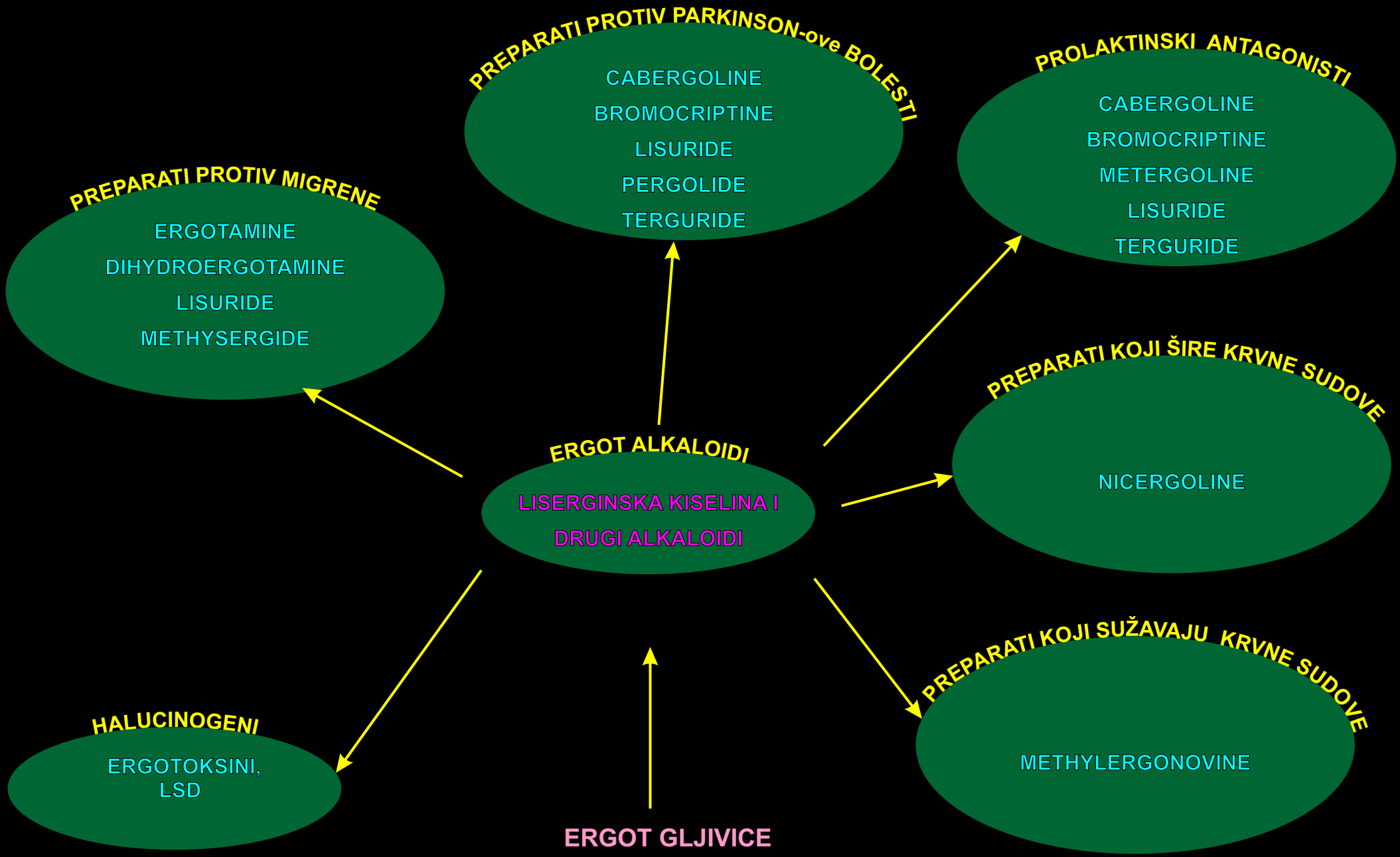
(PROTIVOTROV KOD
ORGANOFOSFORNIH
NERVNIH OTROVA)



HYOSCYAMINE

ERGOT GLJIVICE I FARMAKOLOŠKA PRIMENA DERIVATA ERGOT ALKALOIDA

FARMAKOLOŠKO DEJSTVO JEDINJENJA DOBIJENIH PARCIJALNOM SINTEZOM IZ PRIRODNIH ERGOT ALKALOIDA

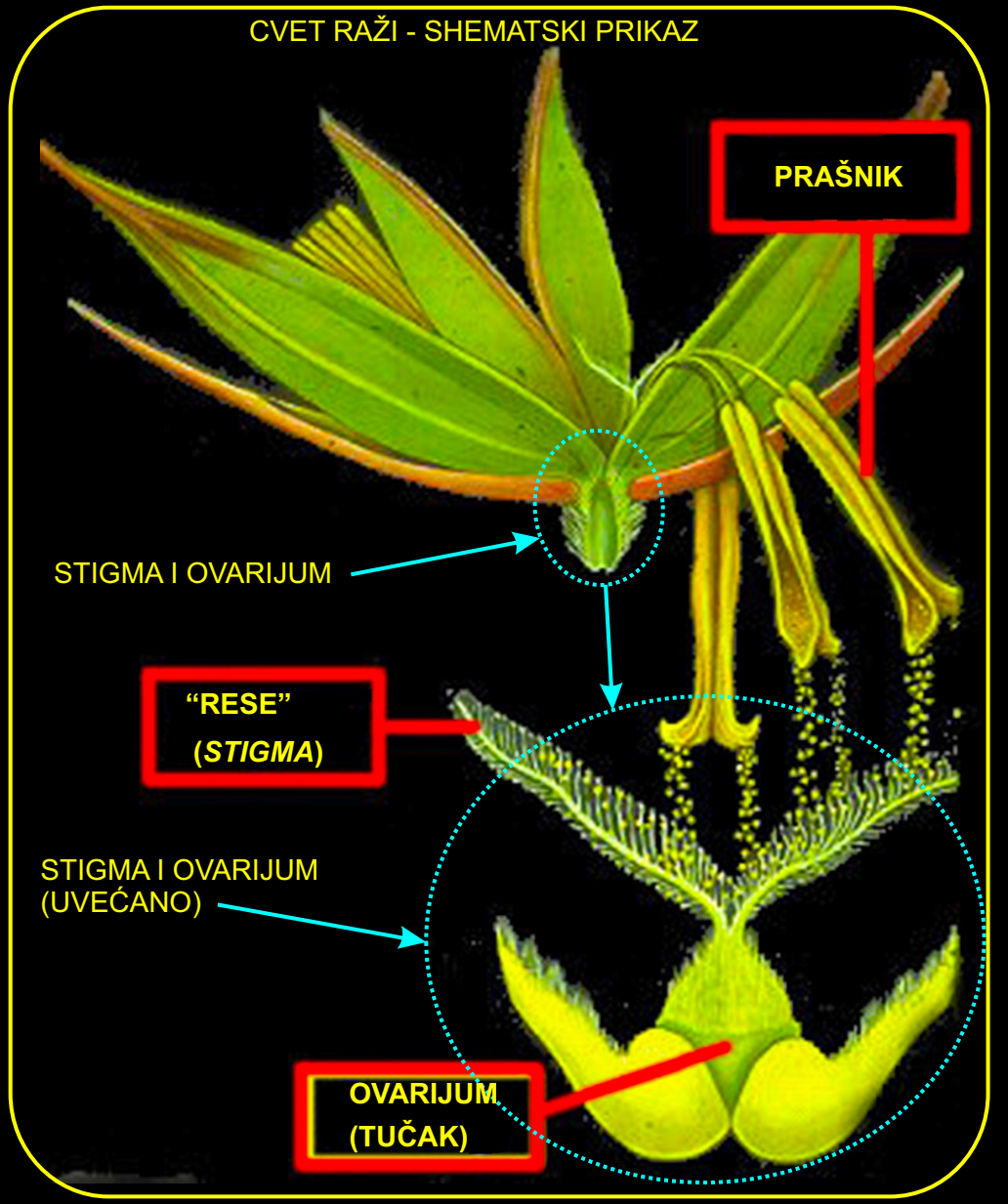


ERGOT GLJIVICE I FARMAKOLOŠKA PRIMENA DERIVATA ERGOT ALKALOIDA

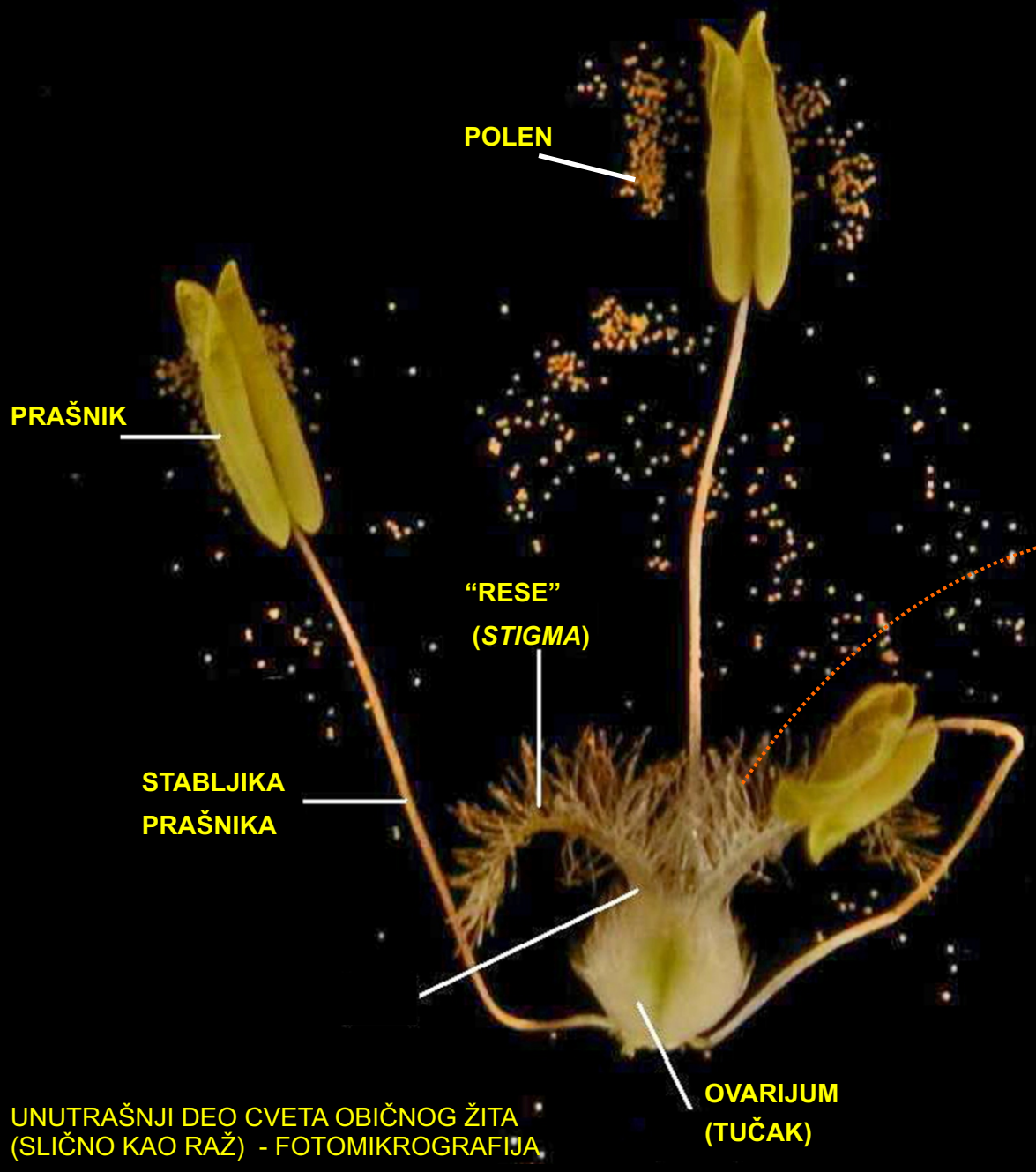
RAZLIČITE VRSTE ERGOT GLJIVICA (KAO NPR. *Claviceps purpurea*) RAZMNOŽAVAJU SE KAO PARAZITI NA VIŠIM BILJNIM VRSTMA, UGLAVNOM ŽITARICAMA. INFEKCIJI SU POSEBNO PODLOŽNI RAŽ I JEČAM.

SLIKE PRIKAZUJU NORMALAN IZGLED CVETA RAŽI.

CVET RAŽI

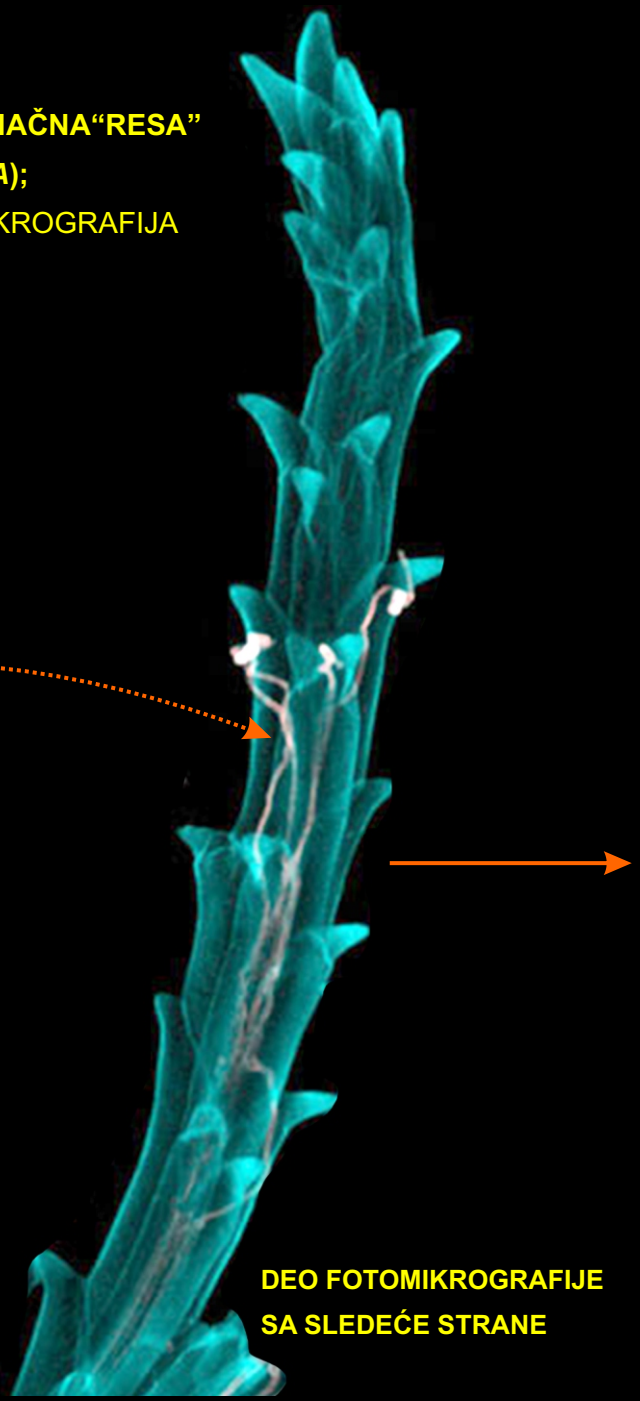


INFEKCIJA POČINJE TAKO ŠTO VLAKNASTA SPORA GLJIVICE ULAZI U OVARIJUM (TUČAK) CVETA KROZ “RESICE” (*STIGMA*), NA ISTI NAČIN KAO ŠTO ULAZI I ZRNO POLENA PRILIKOM OPRAŠIVANJA.



UNUTRAŠNJI DEO CVETA OBIČNOG ŽITA
(SLIČNO KAO RAŽ) - FOTOMIKROGRAFIJA

POJEDINAČNA“RESA”
(*STIGMA*);
FOTOMIKROGRAFIJA



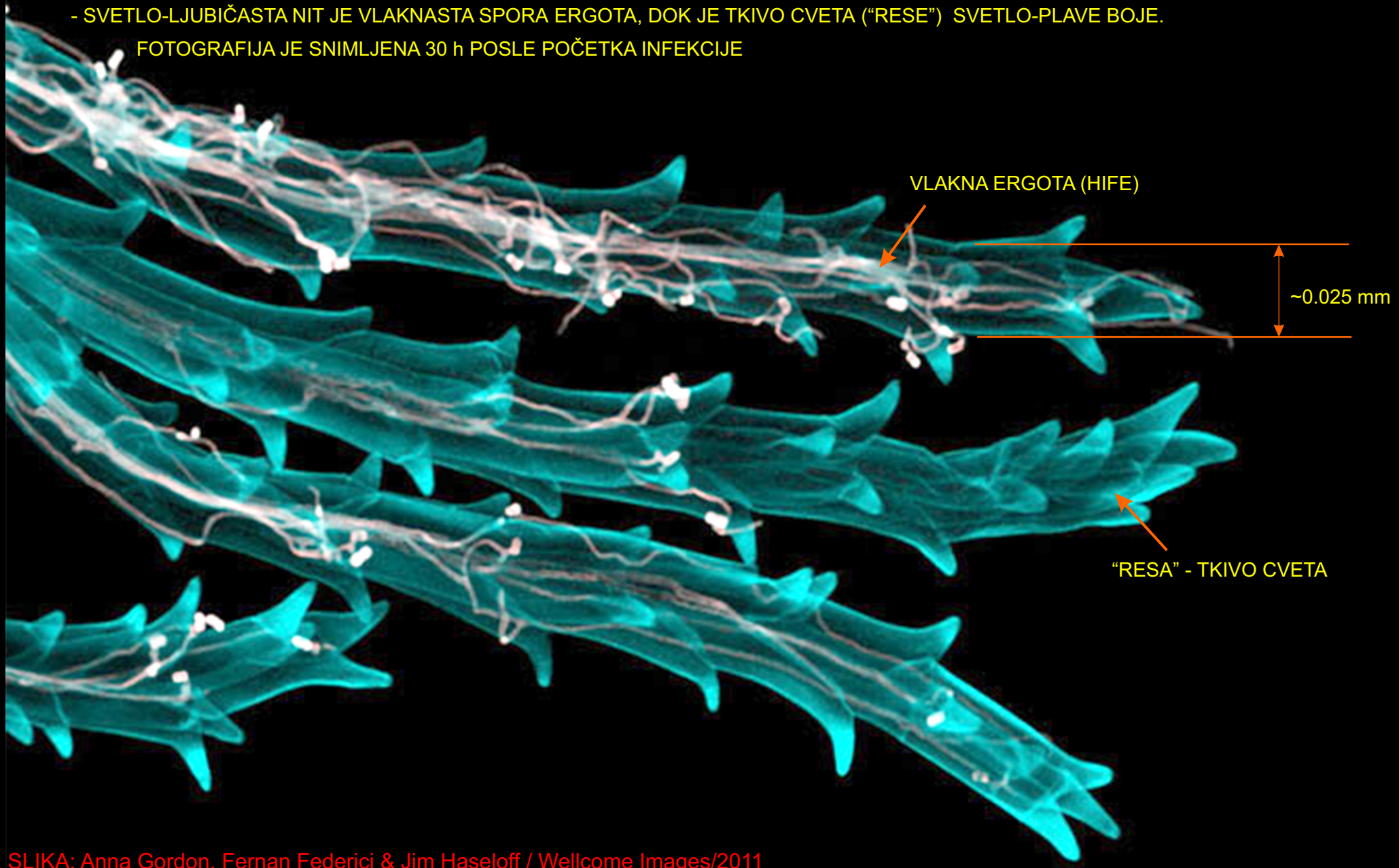
DEO FOTOMIKROGRAFIJE
SA SLEDEĆE STRANE

RANA FAZA INFEKCIJE ERGOT GLJIVICOM CVETA OBIČNOG ŽITA KROZ ”RESE” OVARIJUMA

-FLUORESCENTNA MIKROSKOPSKA FOTOGRAFIJA PRIKAZUJE KAKO VLAKNASTE SPORE ERGOTA (HIFE), RASTU KROZ ISTO TKIVO CVETA (“RESE”) KROZ KOJE NORMALNO RASTE I VLAKNO IZ ZRNA POLENA TOKOM OPRAŠIVANJA.

- SVETLO-LJUBIČASTA NIT JE VLAKNASTA SPORA ERGOTA, DOK JE TKIVO CVETA (“RESE”) SVETLO-PLAVE BOJE.

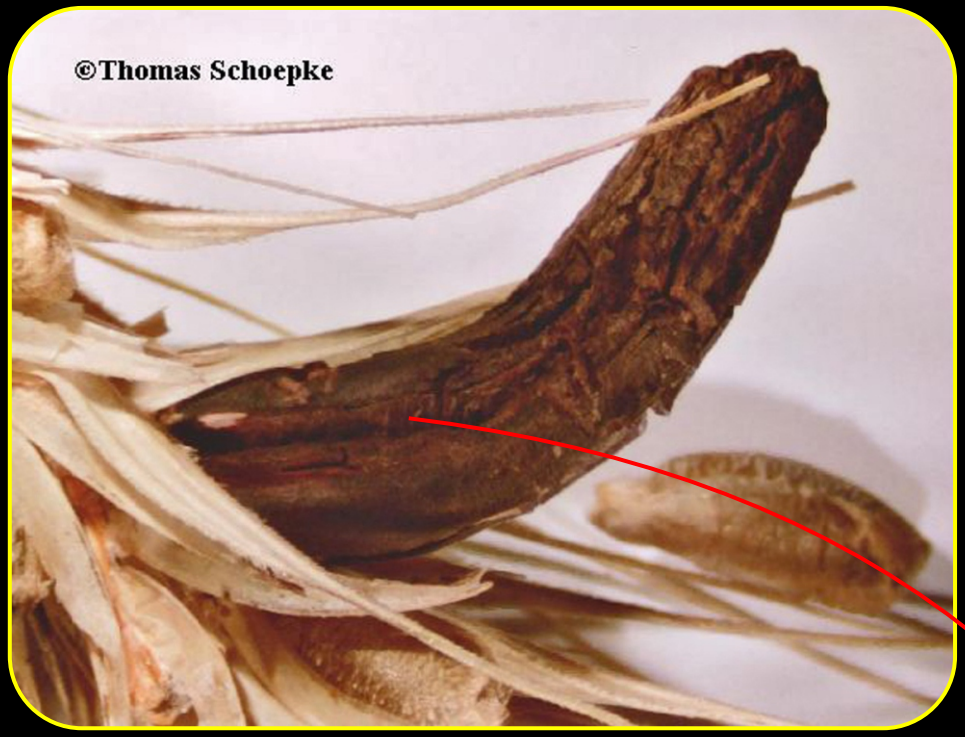
FOTOGRAFIJA JE SNIMLJENA 30 h POSLE POČETKA INFEKCIJE



SLIKA: Anna Gordon, Fernan Federici & Jim Haseloff / Wellcome Images/2011

U OVARIJUMU (TUČKU) SPORA ERGOTA POČINJE DA SE RAZVIJA I RASTE, ANALOGNO NORMALNOM SEMENU, KORISTEĆI TKIVO CVETA NAMENJENO ISHRANI SEMENA. FORMIRA SE ABNORMALNO, BELO MEKO TKIVO (*sphacelia*) KAO I LEPLJIVE KAPI KOJE SE CEDE SA ZARAŽENIH CVETOVA. KOD NEKIH VRSTA ERGOT GLJIVICA, TE LEPLJIVE KAPI SADRŽE SEKUNDARNE, ASEKSUALNE SPORE, KOJE TAKOĐE MOGU BITI IZVOR INFEKCIJE.

DALJIM RAZVOJEM, TKIVO GLJIVICE OČVRSNE, I DOBIJA IZGLED TAMNOG ZRNA U KLASU. POSTALA TVOREVINA OZNAČAVA SE KAO SKLEROCIJUM (*sclerotium*) I UPRAVO U NJOJ DOLAZI DO BIOSINTEZE ERGOT ALKALOIDA.

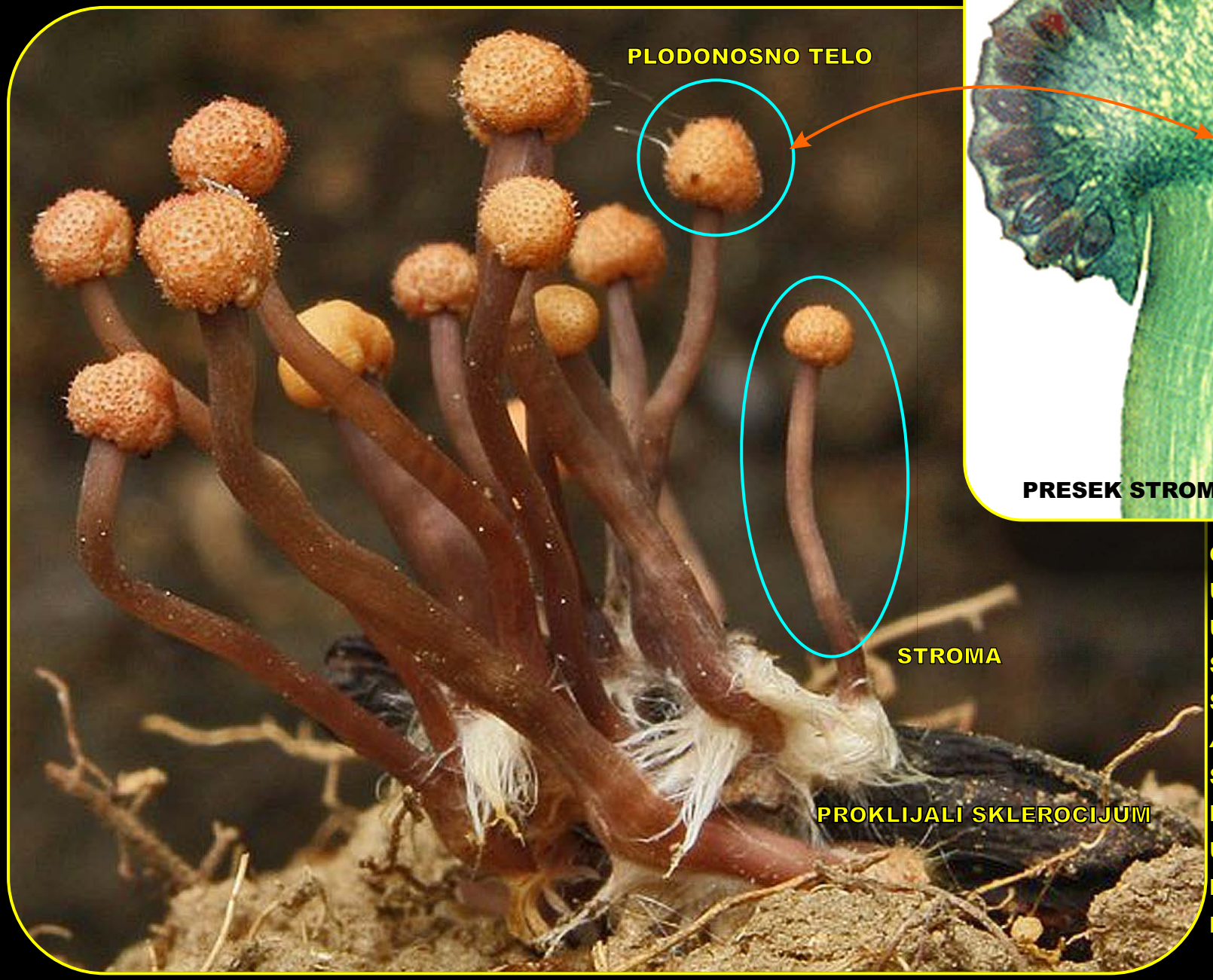


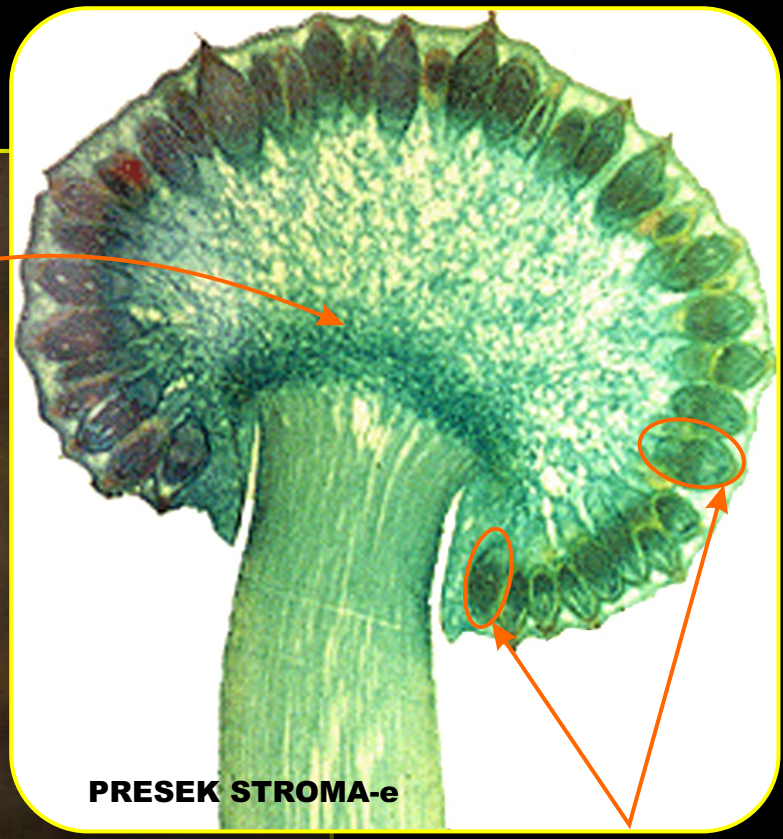
ZRELI SKLEROCIJUM PADA NA TLO I OSTAJE LATENTAN DO SLEDEĆEG PROLEĆA (ODN. DO NOVOG KIŠNOG PERIODA U TROPSKIM KRAJEVIMA). TADA POČINJE DA KLIJA, FORMIRAJUĆI IZRASLINE VEOMA SLIČNE MALIM PEČURKAMA KOJE SE OZNAČAVAJU KAO ***STROMA***.

"GLAVA"

STROMA-e NAZIVA SE PLODONOSNO TELO (OVO JE SEKSUALNA FAZA RAZMNOŽAVANJA ERGOT GLJIVICA).

SLOŽENA STRUKTURA *STROMA*-e



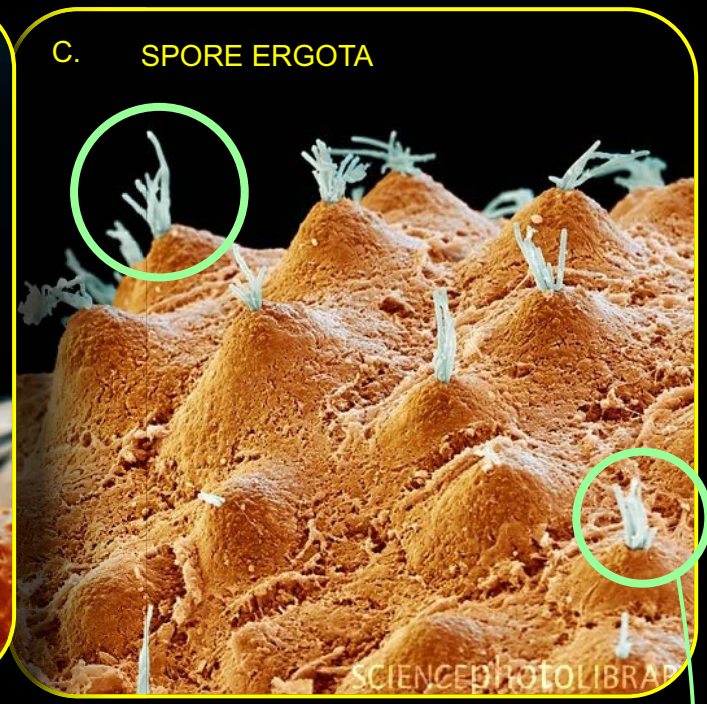


OVALNE STRUKTURE (*ASCI*), UNUTAR PLODONOSNOG TELA, U KOJIMA SE FORMIRAJU SPORE ERGOTA.

SPORE SE OZNAČAVAJU KAO *ASCOSPORE*, A POSTAJU U SEKSUALNOJ FAZI RAZMNOŽAVANJA ERGOTA.

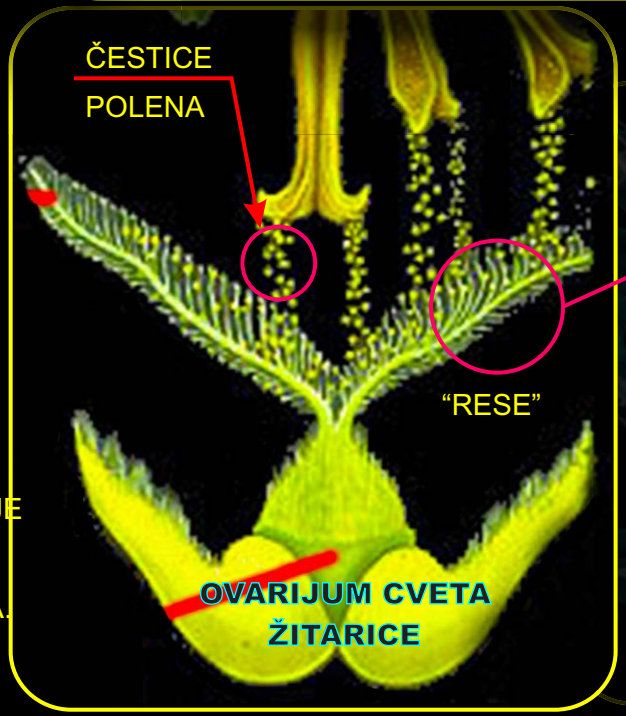
UPRAVO SU OVE SPORE INFEKTIVNI AGENS KOJI INFICIRA CVETOVE ŽITARICA.

ZATVARANJE CIKLUSA INFEKCIJE ŽITARICA GLJIVICOM ERGOTA

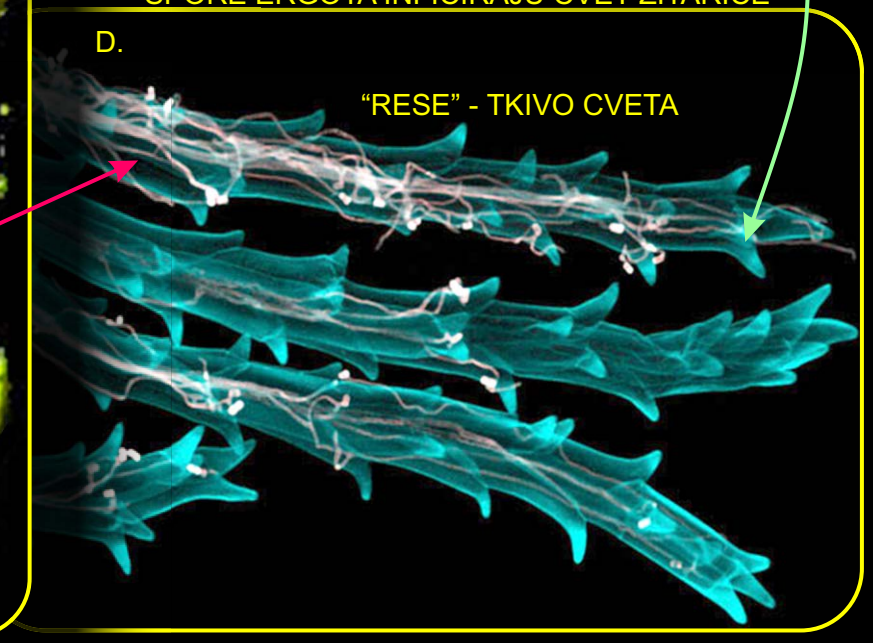


SLIKE ***A***, ***B*** I ***C***: SKENIRAJUĆE ELEKTRONSKE MIKROGRAFIJE (SEM), PROIZVOLJNO DIGITALNO OBOJENE.
A. PROKLIJALI SKLEROCIJUM ERGOTA
B. PLODONOSNO TELO "GLAVA" STROMA-e IZ KOJE IZBIJAJU SPORE
C. UVEĆANA SLIKA B: SPORE ERGOTA

SLIKA ***D***: SPORE ERGOTA PRODIRU U OVARIJUM CVETA ŽITARICE KROZ "RESE", ČIME SE CIKLUS INFEKCIJE ZATVARA. OSLOBAĐANJE SPORA ERGOTA SINHRONIZOVANO JE SA PERIODOM CVETANJA ŽITARICA.



SPORE ERGOTA INFICIRAJU CVET ŽITARICE



ERGOT GLJIVICE: TOKSIČNOST I FARMAKOLOŠKA PRIMENA DERIVATA ERGOT ALKALOIDA

FARMAKOLOŠKO DEJSTVO NATIVNE SMESE ERGOT ALKALOIDA POKAZUJE VISOKU AKUTNU TOKSIČNOST, A UKLJUČUJE IZAZIVANJE VIZUELNIH HALUCINACIJA, POREMEĆAJE KRVOTOKA I FUNKCIONISANJA KARDIO-VASKULARNOG SISTEMA, GANGRENE, KOMATOZNA STANJA I SMRT.

MEĐUTIM, POSTOJANJE ERGOT GLJIVICA NIJE BILO POZNATO DO 19. VEKA, VEĆ SE SMATRALO DA POMENUTI SKLEROCIUM PREDSTAVLJA NORMALNI, SASTAVNI DEO ŽITARICA. STOGA SE OD USEVA ZARAŽENIH OVIM PARAZITOM, PROIZVODILO BRAŠNO I HLEB, ČIJIM JE KONZUMIRANJEM DOLAZILO DO ČESTIH I MASOVNIH TROVANJA STANOVNIŠTVA.

"BOLEST", TADA NEPOZNATOG POREKLA, DANAS JE POZNATA KAO ERGOTIZAM.

Photo: University of Calgary

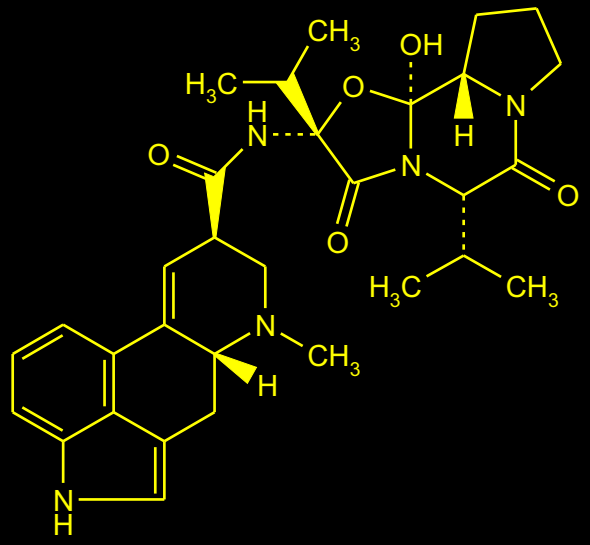
ERGOT GLJIVICE: TOKSIČNOST I FARMAKOLOŠKA PRIMENA DERIVATA ERGOT ALKALOIDA

http://www.ryebelt.com/1449.html?&L=1

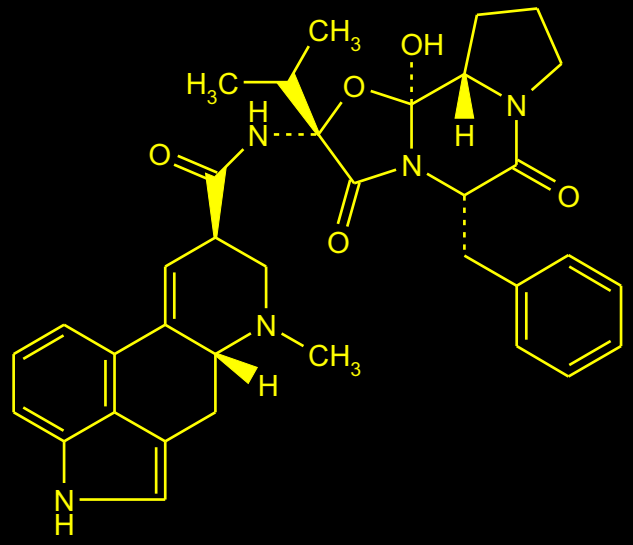
ERGOT GLJIVICE: TOKSIČNOST I FARMAKOLOŠKA PRIMENA DERIVATA ERGOT ALKALOIDA

https://www.grainews.ca/2015/03/23/a-small-dose-of-ergot-is-harmful/

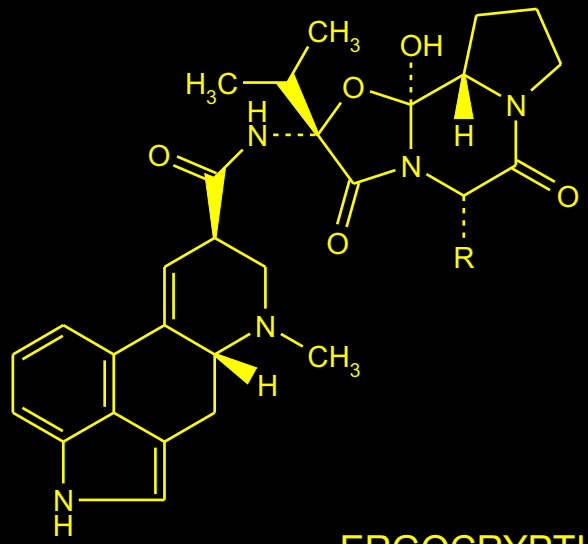
PRIRODNI DERIVATI LISERGINSKE KISELINE ČIJA SMESA JE POZNATA KAO ERGOTOKSIN (ERGOCORNINE, ERGOCRISTINE i ERGOCRYPTINE)



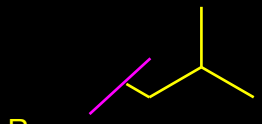
ERGOCORNINE



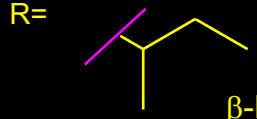
ERGOCRISTINE



ERGOCRYPTINE



α-Ergocryptine



β-Ergocryptine

PRIRODNI DERIVATI LISERGINSKE KISELINE ČIJA SMESA JE POZNATA KAO ERGOTOKSIN (ERGOCORNINE, ERGOCRISTINE i ERGOCRYPTINE)

Monograph Number: 3678

Title: ERGOCORNINE
CAS Registry Number: 564-36-3
CAS Name: (5)-12 -Hydroxy-2 ,5 -bis(1-methylethyl)ergotaman-3 ,6 ,18-trione
Molecular Formula: $C_{31}H_{39}N_5O_5$
Molecular Weight: 561.67.
Percent Composition: C 66.29%, H 7.00%, N 12.47%, O 14.24%
Literature References: Natural ergot alkaloid derived from lysergic acid; a member of the ergotoxine group. Isoln from ergot: Stoll, Hofmann, *Helv. Chim. Acta* **26,** 1570 (1943). Structure: Stoll *et al., ibid.* **34,** 1544 (1951). Separation and purification: Stoll, Hofmann, **US 2447214** (1948 to Sandoz). Synthesis: Stadler *et al., Helv. Chim. Acta* **52,** 1549 (1969).
Properties: Solvated, polyhedra from methanol, dec 181° (contains 1 mole methanol). [ ]$_{D20}$ -110° (pyridine); -175° (chloroform). uv max (methanol): 311 nm (log 3.91). Soluble in acetone, chloroform, ethyl acetate; slightly sol in ethyl and methyl alcohol. Nearly insol in water.
Optical Rotation: [ ]$_{D20}$ -110° (pyridine); -175° (chloroform)
Absorption maximum: uv max (methanol): 311 nm (log 3.91)

Derivative Type: Ergocornine phosphate
Properties: Crystals, dec 190-195°.

Derivative Type: Ergocornine ethanesulfonate
Properties: Crystals, dec 209°.

Therap-Cat: *See* Ergot.

Monograph Number: 3680

Title: ERGOCRISTINE
CAS Registry Number: 511-08-0
CAS Name: 12 -Hydroxy-2 -(1-methylethyl)-5 -(phenylmethyl)ergotaman-3 ,6 ,18-trione
Molecular Formula: $C_{35}H_{39}N_5O_5$
Molecular Weight: 609.71.
Percent Composition: C 68.95%, H 6.45%, N 11.49%, O 13.12%
Literature References: Natural ergot alkaloid derived from lysergic acid; a member of the ergotoxine group. Isoln from ergot: Stoll, Burckhardt, *Z. Physiol. Chem.* **250,** 1 (1937); Stoll, Hofmann, *Helv. Chim. Acta* **26,** 1570 (1943). Structure: Stoll *et al., ibid.* **34,** 1544 (1951). Separation and purification: Stoll, Hofmann, **US 2447214** (1948 to Sandoz). Synthesis: Stadler *et al., Helv. Chim. Acta* **52,** 1549 (1969).
Properties: Orthorhombic crystals with $2C_6H_6$ from benzene. mp 155-157° (dec) (solvent-free base). [ ]$_{D20}$ -183° (chloroform). Very sol in ethyl and methyl alcohol, acetone, chloroform, ethyl acetate. Slightly sol in ether. Practically insol in water, petr ether.
Melting point: mp 155-157° (dec) (solvent-free base)
Optical Rotation: [ ]$_{D20}$ -183° (chloroform)

Derivative Type: Ergocristine phosphate
Properties: Crystals, dec 195°.

Derivative Type: Ergocristine ethanesulfonate
Properties: Crystals, dec 207°.

PRIRODNI DERIVATI LISERGINSKE KISELINE ČIJA SMESA JE POZNATA KAO ERGOTOKSIN (ERGOCORNINE**,** ERGOCRISTINE **i** ERGOCRYPTINE**)**

Monograph Number: 3682
Title: ERGOCRYPTINE
Additional Names: Ergokryptine
Molecular Formula: C32H41N5O5
Molecular Weight: 575.70.
Percent Composition: C 66.76%, H 7.18%, N 12.16%, O 13.90%
Literature References: Two closely related isomers of the ergotoxine group which differ in the peptide portion of the molecule; -ergocryptine yielding L-leucine upon hydrolysis, -ergocryptine yielding L-isoleucine. The ergocryptine discussed in the literature prior to 1967 is now referred to as -ergocryptine. Isoln from ergot: Stoll, Hofmann, *Helv. Chim. Acta* **26,** 1570 (1943). Structure: Stoll *et al., ibid.* **34,** 1544 (1951). Separation and purification: Stoll, Hofmann, **US 2447214** (1948 to Sandoz). Separation of -ergocryptine from -ergocryptine: Schlientz *et al., Experientia* **23,** 991 (1967); *see also eidem, Pharm. Acta Helv.* **43,** 497 (1968). Synthesis of - and -ergocryptine: Stadler *et al., Helv. Chim. Acta* **52,** 1549 (1969).

Derivative Type: -Ergocryptine
CAS Registry Number: 511-09-1
CAS Name: (5)-12 -Hydroxy-2 -(1-methylethyl)-5 -(2-methylpropyl)ergotaman-3 ,6 ,18-trione
Properties: Solvated prisms from acetone, benzene, methanol. With MeOH of crystn, mp 212° (dec). [ ]D20 -120° (pyridine); -198° (chloroform). uv max (methanol): 241, 312.5 nm (log 4.31, 3.95).
Freely sol in alcohol, chlorofom. Almost insol in water.
Melting point: mp 212° (dec)
Optical Rotation: [ ]D20 -120° (pyridine); -198° (chloroform)
Absorption maximum: uv max (methanol): 241, 312.5 nm (log 4.31, 3.95)

Derivative Type: -Ergocryptine
CAS Registry Number: 20315-46-2
CAS Name: [5 (*S*)]-12 -Hydroxy-2 -(1-methylethyl)-5 -(1-methylpropyl)ergotaman-3 ,6 ,18-trione
Properties: Rectangular plates from benzene, mp 173° (dec). [ ]D20 -98° (c = 0.5 in pyridine); -179° (c = 0.5 in chloroform). uv max (methanol): 312 (log 3.93).
Melting point: mp 173° (dec)
Optical Rotation: [ ]D20 -98° (c = 0.5 in pyridine); -179° (c = 0.5 in chloroform)
Absorption maximum: uv max (methanol): 312 (log 3.93)

Therap-Cat: *See* Ergot.

ERGOT GLJIVICE I FARMAKOLOŠKA PRIMENA DERIVATA ERGOT ALKALOIDA

PORED TOKSIČNOSTI, POJEDINI ERGOT ALKALOIDI IMAJU I ZNAČAJAN I RAZNOVRSTAN TERAPIJSKI POTENCIJAL. INTENZIVNO SU ISTRAŽIVANI, POSEBNO OD 30-IH GODINA 20. VEKA.

TOTALNE HEMIJSKE SINTEZE ERGOT ALKALOIDA SU POTPUNO AKADEMSKOG KARAKTERA, JER BI CENA SINTETIČKIH FINALNIH PROIZVODA BILA MNOGOSTRUKO VEĆA U ODNOSU NA ISTA JEDINJENJA BIOGENOG POREKLA.

SVI SAVREMENI PREPARATI NA BAZI ERGOT ALKALOIDA SU POLU-SINTETIČKOG POREKLA, A DOBIJAJU SE PARCIJALNOM HEMIJSKOM SINTEZOM IZ PRIRODNE, (+) LISERGINSKE KISELINE. KAO PREKURSORI, POREDLISERGINSKE KISELINE, KORISTE SE I DRUGI ERGOT ALKALOIDI.

IZUZETAK JE ERGOTAMIN, KOJI JE NEMODIFIKOVANI ERGOT ALKALOID.

STANDARDNI NAČIN KULTIVACIJE ERGOT GLJIVICA JE U OBLIKU PARAZITSKIH KULTURA, KADA SE POJEDINE PARCELE POSEBNIH SOJEVA ŽITARICA SISTEMATSKI INFICIRAJU SPORAMA ERGOT GLJIVICA. NA OVAJ NAČIN MOGUĆE JE DOBITI 1000-2000 kg SKLEROCIJUMA /ha ODN. 8-10kg ALKALOIDA/ha.

MEĐUTIM, U NOVIJE VREME, ERGOT ALKALOIDI (UGLAVNOM (+) LISERGINSKA KISELINA I NJENI JEDNOSTAVNI DERIVATI) SE PRETEŽNO DOBIJAJU GAJENJEM ERGOT GLJIVICA NA POSEBNIM HRANLJIVIM PODLOGAMA, ŠTO JE POZNATO KAO SAPROFITSKA KULTIVACIJA. ZBOG SLOŽENOG ŽIVOTNOG CIKLUSA ERGOT GLJIVICA I NIZA DRUGIH FAKTORA, OVAKVE FERMENTATIVNE METODOLOGIJE SU VEOMA KOMPLEKSNE I ZAHTEVAJU STALNU KONTROLU PROCESA (ČESTO DOLAZI DO PRESTANKA BIOSINTEZE ALKALOIDA).

Appl Microbiol Biotechnol (2001) 57:593–605; **P. Tudzynski · T. Correia · U. Keller;** "Biotechnology and genetics of ergot alkaloids"; DOI 10.1007/s002530100801

RAST GLIVICE ERGOTA NA HRANLJIVOJ PODLOZI (SAPROFITSKA KULTIVACIJA) ČVRSTE, MRKE STRUKTURE SU TKIVO SKLEROCIJUMA (NIJE NAVEDENO GDE JE FOTOGRAFIJA SNIMLJENA NITI DRUGI RELEVANTNI PODACI)

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SE KORISTE U TERAPIJI MIGRENE

MIGRENE - KRATAK OPIS

-NEUROLOŠKI POREMEĆAJ/OBOLJENJE KOJI KARAKTERIŠE UMERENA DO EKSTREMNO JAKA GLAVOBOLJA I MUČNINA.

-NEŠTO ČEŠĆE SE SREĆE KOD ŽENA NEGO KOD MUŠAKARACA.

-POSTOJI VIŠE OBLIKA MIGRENE, KAO ŠTO SU OBIČNE (BEZ VIZUALNIH POREMEĆAJA), SA AUROM (SA VIZUALNIM POREMEĆAJIMA) I DR.

-MIGRENOZNI BOL TIPIČNO ZAHVATA SAMO JEDNU POLOVINU GLAVE, IMA PULSIRAJUČI KARAKTER, A UKLJUČUJE MUČNINU, POVRAĆANJE, PREOSETLJIVOST NA SVETLOST (FOTOFOBIJA) KAO I NA ZVUKOVE.

-KOD ZNATNOG BROJA OSOBA KOJE PATE OD MIGRENE ISPOLJAVAJU SE RAZLIČITI POREMEĆAJI VIDA KOJI NEPOSREDNO PRETHODE NAPADU MIGRENE - AURA.

-NAPADI MIGRENE MOGU SE JAVLJATI OD 1-2 GODIŠNJE DO VIŠE PUTA MESEČNO, SA POJEDINAČNIM TRJAJANJEM OD NEKOLIKO ČASOVA DO NEKOLIKO DANA. INTENZITET I DRUGE MANIFESTACIJE NAPADA MOGU BITI BITI VRLO RAZLIČITI, ŠTO JE INDIVIDUALNOG KARAKTERA.

-U NEKIM SLUČAJEVIMA POSTOJI INCIJATOR (”TRIGGER”) KAO ŠTO JE STRES, NEISPAVANOST, POJEDINI HEMIJSKI PREPARATI.

- MIGRENOZNE GLAVOBOLJE SU ŠIROKO RASPROSTRANJENI POREMEĆAJ, SA OZBILJNIM ZDRAVSTVENIM I SOCIO-EKONOMSKIM POSLEDICAMA (OSOBE TOKOM NAPADA MIGRENE OBIČNO NISU RADNO SPOSOBNE).

- STATITISTIČKE STUDIJE SU POKAZALE DA PACIJENTI KOJI BOLUJU OD MIGRENA IMAJU ZNATNO POVIŠEN RIZIK OD MOŽDANOG UDARA TOKOM SVOG ŽIVONOG VEKA.

-OSNOVNI UZROK MIGRENE NIJE POZNAT, A VERUJE SE DA JE GENETSKI USLOVLJEN POREMEĆAJ SEROTONERGIČKOG KONTROLNOG SISTEMA (ABNORMALNO FUNKCIONISANJE POJEDINIH TIPOVA SEROTONINSKIH RECEPTORA). POSEBNO SU ZNAČAJNI SEROTONINSKIH SUB-TIPOVI RECEPTORA (5-$HT_{1B/1D}$), ČIJI AGONISTI SNAŽNO UBLAŽAVAJU NAPADE MIGRENE (LEKOVI IZ KATEGORIJE TRIPTANA)

-RANIJE SU VIŠE KORIŠĆENI LEKOVI NA BAZI ERGOT ALKALOIDA, KOJI SE KORISTE I U NOVIJE VREME, MADA U MANJOJ MERI.

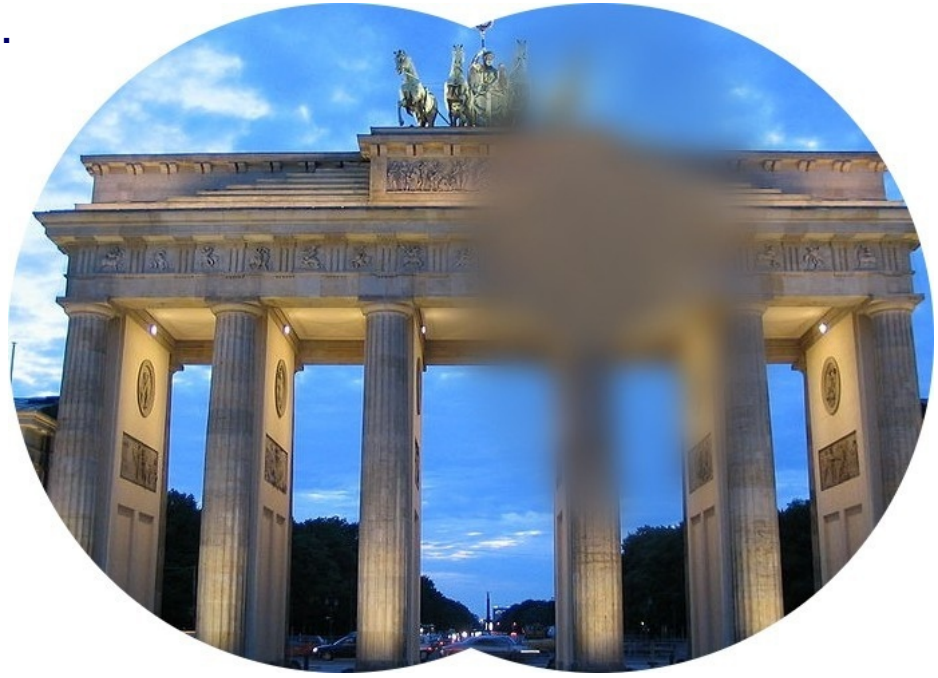
-TAKOĐE SE POVREMENO PRIMENJUJU I CEREBRO-VASKULARNI HIRURŠKI ZAHVATI, KOJI U IZVESNIM, TEŽIM SLUČAJEVIMA, POKAZJU POTPUNI USPEH (TRAJNO NESTAJENJE MIGRENOZNIH NAPADA).

SIMULIRANI IZGLED RAZLIČITIH MIGRENOZNIH “AURA” KOJE ČESTO PRETHODE NAPADU MIGRENE

A.

B.

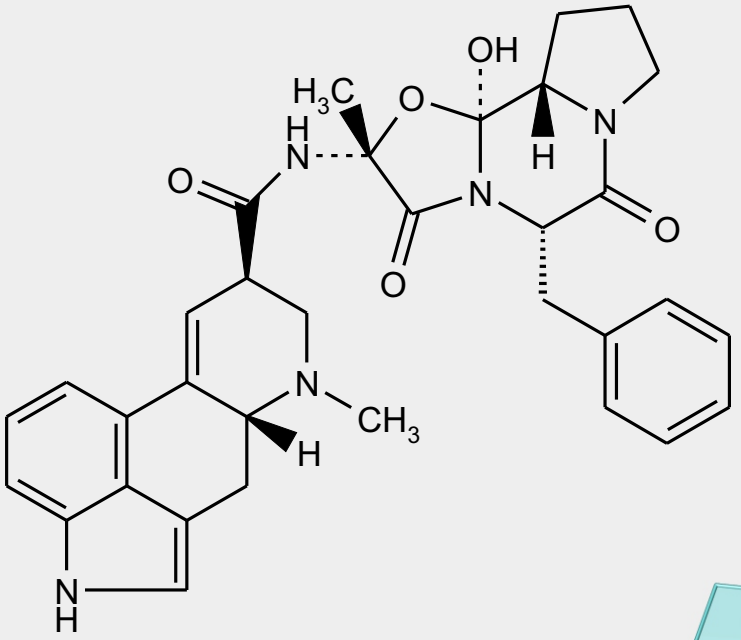
C.

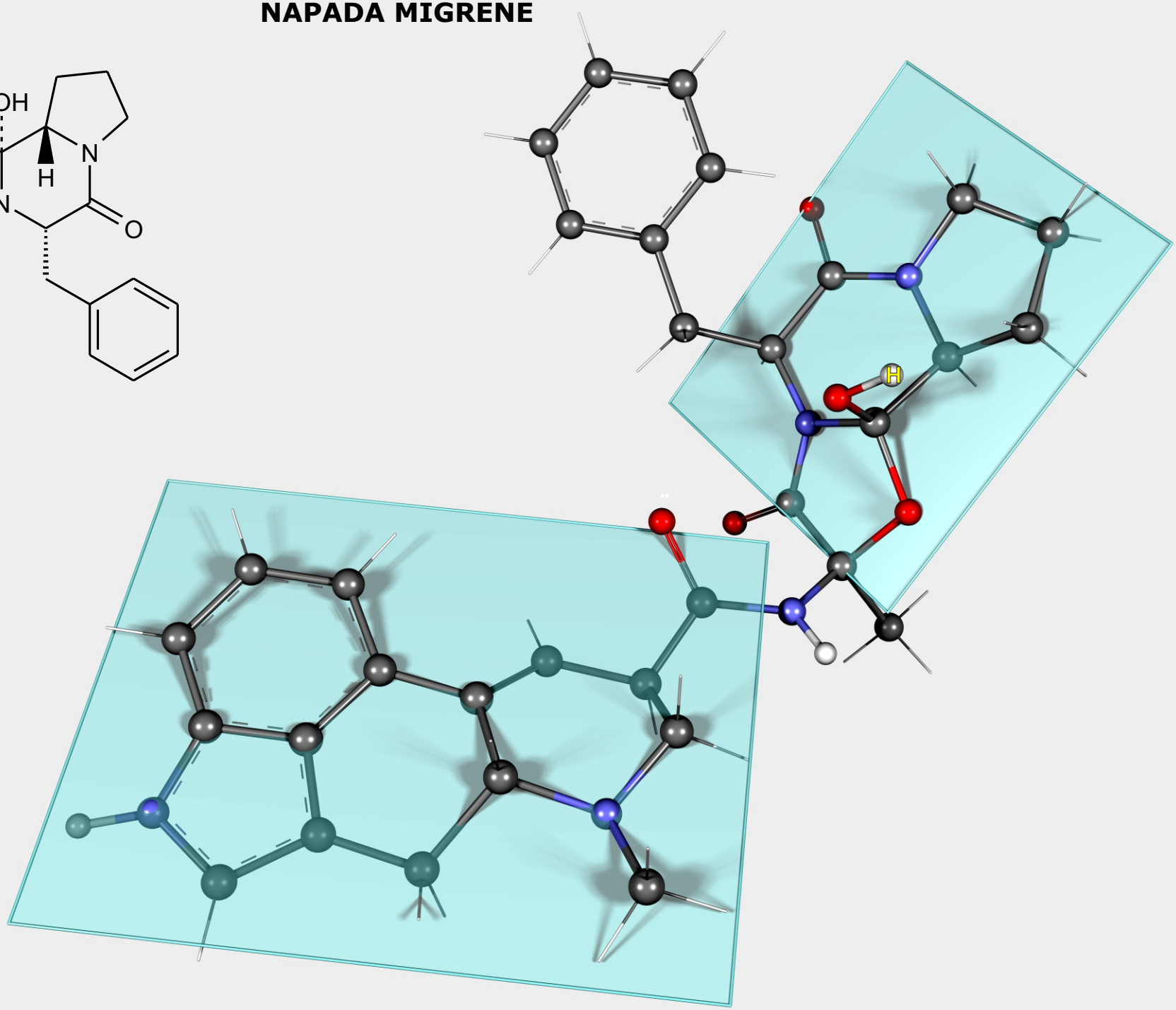


D.

WIKIPEDIA

ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU NAPADA MIGRENE

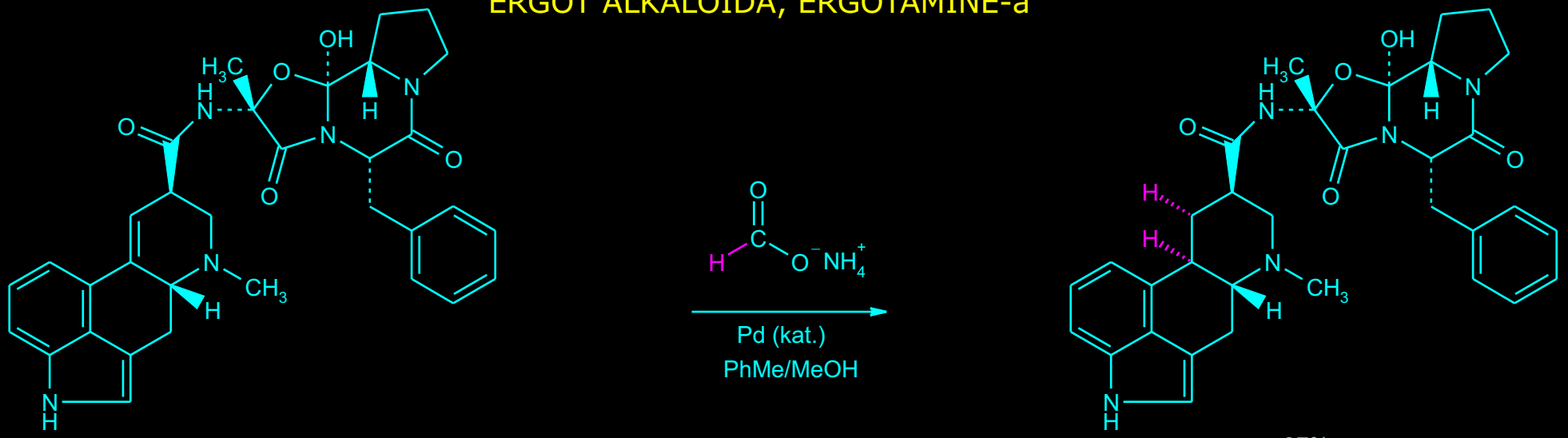




ERGOTAMIN - PRIRODNI ALKALOID IZ ERGOT GLJIVICA

ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU NAPADA MIGRENE

1. SINTEZA DIHYDROERGOTAMINE-a PRENOSNOM KATALITIČKOM HIDROGENIZACIJOM IZ PRIRODNOG ERGOT ALKALOIDA, ERGOTAMINE-a

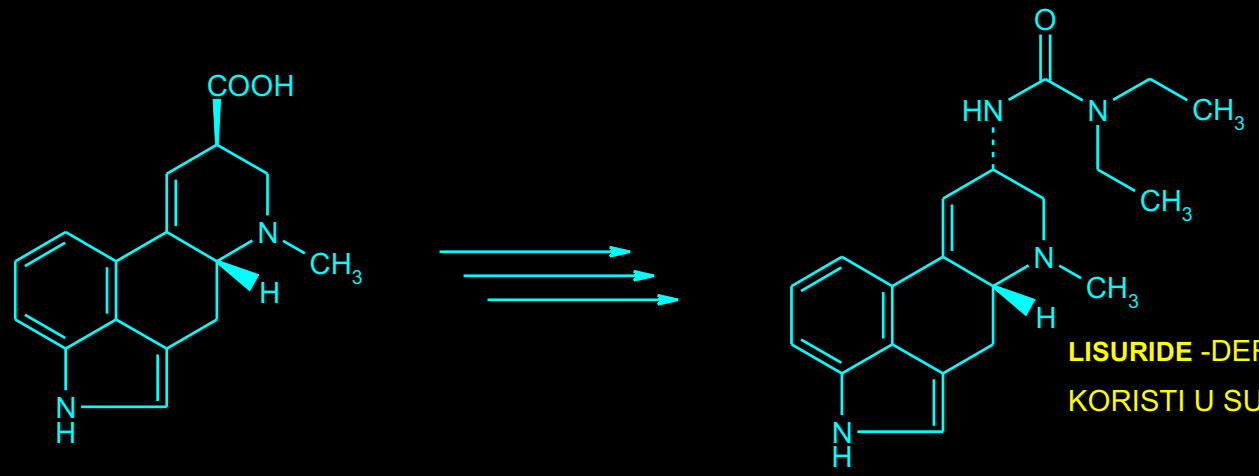


Czech Rep., 287080, 16 Aug 2000 (ČEŠKI PATENT, PREMA SCIFINDER-u)

97%

DIHYDROERGOTAMINE

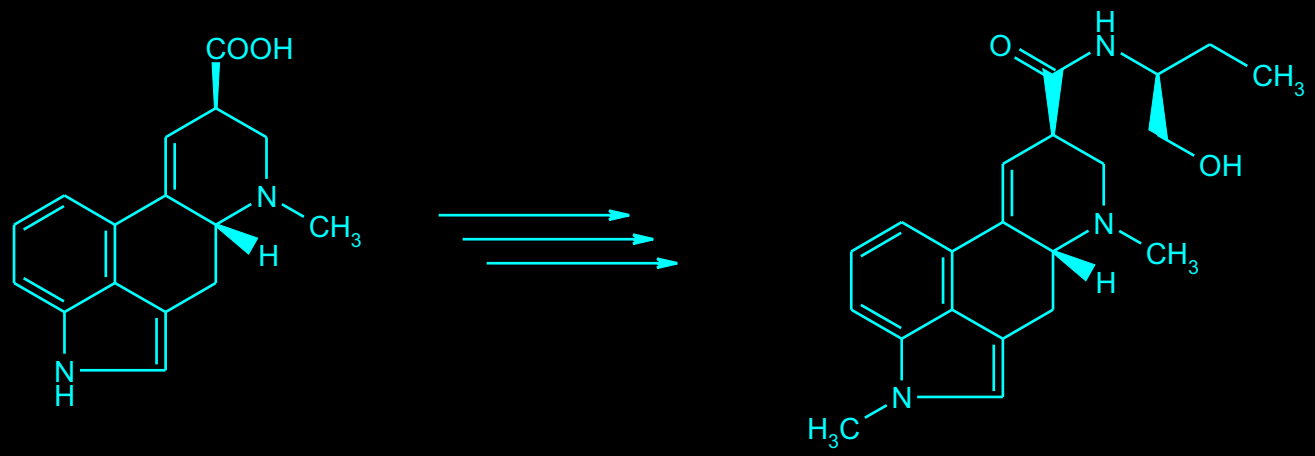
2.



LISURIDE -DERIVAT LISERGINSKE KISELINE KORISTI U SUZBIJANJU NAPADA MIGRENE

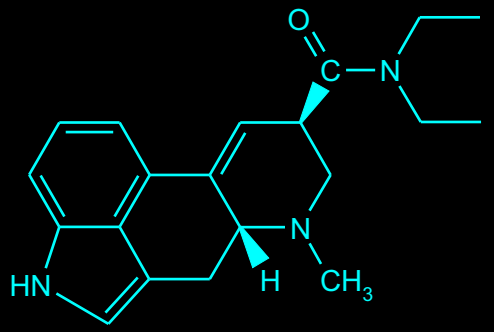
ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU NAPADA MIGRENE

3.



METHYSERGIDE

MALE STRUKTURNE VARIJACIJE MOGU DA POTPUNO IZMENE FARMAKOLOŠKO DEJSTO



LSD

ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU NAPADA MIGRENE

Monograph Number: 3696
Title: Ergotamine
CAS Registry Number: 113-15-5
CAS Name: (5)-12 -Hydroxy-2 -methyl-(phenylmethyl)ergotaman-3 ,6 ,18-trione
Molecular Formula: $C_{33}H_{35}N_5O_5$
Molecular Weight: 581.66.
Percent Composition: C 68.14%, H 6.06%, N 12.04%, O 13.75%
Literature References: Vasoconstrictor found in ergot of Central Europe. Extraction procedure: Stoll, *Helv. Chim. Acta* **28,** 1283 (1945). Pharmacology: E. Rothlin, *Schweiz. Med. Wochenschrift* **76,** 1254 (1946). Structure: Stoll *et al., ibid.* **34,** 1544 (1951). Total synthesis: Hofmann *et al., Experientia* **17,** 206 (1961). Stereochemistry: Hofmann *et al., ibid.* **46,** 2306 (1963). Comprehensive description: B. Kreilgard, *Anal. Profiles Drug Subs.* **6,** 113-159 (1977). LC determn in tablets: U. R. Cieri, *J. Assoc. Off. Anal. Chem.* **70,** 538 (1987); GC/MS determn in plasma: N. Feng *et al., J. Chromatog.* **575,** 289 (1992). Bioavailablity and efficacy in migraine: V. Ala-Hurula, *Headache* **22,** 167 (1982). Review of clinical pharmacokinetics and treatment of headache: V. L. Perrin, *Clin. Pharmacokinet.* **10,** 334-352 (1985). Review of teratogenic risk: G. V. Raymond, *Teratology* **51,** 344-347 (1995).
Properties: Elongated prisms from benzene. Very hygroscopic. Darkens and dec on exposure to air, heat and light. Dec 212-214°. [ ]$_{D20}$ -160° (chloroform). Sol in about 70 parts methanol, 150 parts acetone, 300 parts alcohol; freely sol in chloroform, pyridine, glacial acetic acid; moderately sol in ethyl acetate; slightly in benzene. Almost insol in water, petr ether. LD_{50} in mice, rats, rabbits (mg/kg): 62, 80, 3 i.v.; in cats: 11 s.c. (Rothlin).
Optical Rotation: [ ]$_{D20}$ -160° (chloroform)
Toxicity data: LD_{50} in mice, rats, rabbits (mg/kg): 62, 80, 3 i.v.; in cats: 11 s.c. (Rothlin)

Derivative Type: Hydrochloride
Molecular Formula: $C_{33}H_{35}N_5O_5.HCl$
Molecular Weight: 618.13.
Percent Composition: C 64.12%, H 5.87%, N 11.33%, O 12.94%, Cl 5.74%
Properties: Rectangular plates from 90% alc, mp 212° (dec). Sol in water-alcohol mixtures; sparingly in water or alcohol.
Melting point: mp 212° (dec)

Derivative Type: Tartrate
CAS Registry Number: 379-79-3
Trademarks: Ergate (Vernleigh); Ergomar (Lotus); Ergostat (Parke-Davis); Ergotartrat (Rosch & Handel); Ergoton-A (Azusa); Gynergen (Novartis); Lingraine (Sanofi-Winthrop)
Molecular Formula: $(C_{33}H_{35}N_5O_5)_2.C_4H_6O_6$
Molecular Weight: 1313.41.
Percent Composition: C 64.01%, H 5.83%, N 10.66%, O 19.49%
Properties: Solvated crystals, e.g. the dimethanolate, heavy rhombic plates from methanol, mp 203° (dec). [ ]$_{D25}$ -125 to -155° (c = 0.4 in chloroform). One gram dissolves in 500 ml water or 500 ml alc. *Protect from light and heat.*
Melting point: mp 203° (dec)
Optical Rotation: [ ]$_{D25}$ -125 to -155° (c = 0.4 in chloroform)

Therap-Cat: Antimigraine.

Ph Eur monograph 0224

$(C_{33}H_{35}N_5O_5)_2,C_4H_6O_6$ 1313 *379-79-3*

Action and use
Used in treatment of migraine.

Preparation
Ergotamine Sublingual Tablets

Ph Eur
DEFINITION

Ergotamine tartrate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of bis[(6a*R*,9*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b- hydroxy-2-methyl-3,6-dioxo-octahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide] tartrate, calculated with reference to the dried substance. It may contain two molecules of methanol of crystallisation.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, slightly hygroscopic, slightly soluble in alcohol. Aqueous solutions slowly become cloudy owing to hydrolysis; this may be prevented by the addition of tartaric acid.

IDENTIFICATION .....

ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU NAPADA MIGRENE

Monograph Number: 3196
Title: DIHYDROERGOTAMINE
CAS Registry Number: 511-12-6
CAS Name: 9,10-Dihydro-12 -hydroxy-2 -methyl-5 -(phenylmethyl)ergotaman-3 ,6 ,18-trione
Molecular Formula: $C_{33}H_{37}N_5O_5$
Molecular Weight: 583.68.
Percent Composition: C 67.91%, H 6.39%, N 12.00%, O 13.71%
Literature References: -Adrenergic blocker with selective venoconstrictor properties. Also binds to serotonin $5HT_1$-receptors. Prepn from ergotamine: Stoll, Hofmann, *Helv. Chim. Acta* **26,** 2070 (1943). Clinical pharmacology: H. de Marées *et al., Eur. J. Clin. Pharmacol.* **30,** 685 (1986). Neurotransmitter receptor binding study: B. G. McCarthy, S. J. Peroutka, *Headache* **29,** 420 (1989). Clinical trials in migraine: P. Winner *et al., ibid.* **33,** 471 (1993); D. Ziegler *et al., Neurology* **44,** 447 (1994).
Properties: Strongly refractive prisms from dil acetone, contg 2 mols acetone and 2 mols water of crystn. mp 239°. [ ]$_{D20}$ -64°; [ ]$_{20546}$ -79° (c = 0.5 in pyridine). Insol in water. Sparingly sol in methanol, ethanol, chloroform, benzene.
Melting point: mp 239°
Optical Rotation: [ ]$_{D20}$ -64°; [ ]$_{20546}$ -79° (c = 0.5 in pyridine)

Derivative Type: Tartrate
Trademarks: Divegal (Waldheim)
Molecular Formula: $(C_{33}H_{37}N_5O_5)_2.C_4H_6O_6$
Molecular Weight: 1317.44.
Percent Composition: C 63.82%, H 6.12%, N 10.63%, O 19.43%
Properties: Six-sided plates from methanol, dec 210-215°.

Derivative Type: Methanesulfonate
CAS Registry Number: 6190-39-2
Additional Names: Dihydroergotamine mesylate
Trademarks: Agit (Sanofi Winthrop); Angionorm (Farmasan); Dergotamine (Abbott); DET MS (Rentschler); D.H.E. 45 (Novartis); Diergo (Novartis); Dihydergot (Novartis); Dirgotarl (Horita); Endophleban (Rentschler); Ergomimet (Klinge); Ergont (Desitin); Ergotonin (Streuli); Ikaran (Fabre); Migranal (Novartis); Orstanorm (Novartis); Séglor (Sanofi Winthrop); Tonopres (Boehringer, Ing.); Verladyn (Verla)
Molecular Formula: $C_{33}H_{37}N_5O_5.CH_3SO_3H$
Molecular Weight: 679.79.
Percent Composition: C 60.07%, H 6.08%, N 10.30%, O 18.83%, S 4.72%
Properties: Large prisms from 95% alc. mp 230-235°. Moderately sol in water.
Melting point: mp 230-235°

Ph Eur monograph 0551)

$C_{34}H_{41}N_5O_8S$ 680 *6190-39-2*

Action and use
Used in treatment of migraine.
Ph Eur
DEFINITION
(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-methyl-3,6- dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10, 10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulphonate. \

Content
98.0 per cent to 101.0 per cent (dried substance).

PRODUCTION
The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

CHARACTERS

Appearance
White or almost white, crystalline powder or colourless crystals.

Solubility
Slightly soluble in water, sparingly soluble in methanol, slightly soluble in alcohol.

IDENTIFICATION
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ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU NAPADA MIGRENE

Monograph Number: 5540
Title: **LISURIDE**
CAS Registry Number: 18016-80-3
CAS Name: *N* -[(8)-9,10-didehydro-6-methylergolin-8-yl]-*N,N*-diethylurea
Additional Names: 9-(3,3-diethylureido)-4,6,6a,7,8,9-hexahydro-7-methylindolo[4,3-*f,g*]quinoline; 1,1-diethyl-3-(D-6-methylisoergolen-8-yl)urea; *N*-(D-6-methyl-8-isoergolenyl)-*N,N*-diethylurea; methylergol carbamide; lysuride
Molecular Formula: C20H26N4O
Molecular Weight: 338.45.
Percent Composition: C 70.97%, H 7.74%, N 16.55%, O 4.73%
Literature References: Dopamine D2-receptor agonist. Prepn: V. Zikan, M. Semonsky, *Coll. Czech. Chem. Commun.* **25,** 1922 (1960); *eidem, Pharmazie* **23,** 147 (1968). Pharmacology and toxicity: Z. Votava, I. Lamplova, *Physiol. Bohemoslov.* **12,** 37 (1963), *C.A.* **59,** 9221d (1963).
Properties: Crystals from benzene, mp 186°. [ ]D20 +313° (c = 0.60 in pyridine).
Melting point: mp 186°
Optical Rotation: [ ]D20 +313° (c = 0.60 in pyridine)

Derivative Type: Maleate
CAS Registry Number: 19875-60-6
Trademarks: Apodel (Meiji); Cuvalit (Schering AG); Dopergin (Schering AG); Eunal (Schering); Lysenyl (Spofa); Revanil (Roche)
Molecular Formula: C20H26N4O.C4H4O4
Molecular Weight: 454.52.
Percent Composition: C 63.42%, H 6.65%, N 12.33%, O 17.60%
Properties: Prisms from ethanol, mp 200° (dec). [ ]D20 +288° (c = 0.5 in methanol). uv max (methanol): 313 nm. LD50 i.v. in mice: 14.4 mg/kg (Votava, Lamplova).
Melting point: mp 200° (dec)
Optical Rotation: [ ]D20 +288° (c = 0.5 in methanol)
Absorption maximum: uv max (methanol): 313 nm
Toxicity data: LD50 i.v. in mice: 14.4 mg/kg (Votava, Lamplova)

Therap-Cat: Antimigraine; prolactin inhibitor; antiparkinsonian.

ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU NAPADA MIGRENE

Monograph Number: 6158
Title: METHYSERGIDE
CAS Registry Number: 361-37-5
CAS Name: (8)-9,10-Didehydro-*N*-[(1*S*)-1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8-carboxamide
Additional Names: *N*-[1-(hydroxymethyl)propyl]-1-methyl-D-lysergamide; 1-methylmethylergonovine; 1-methyl-*d*-lysergic acid butanolamide; 1-methyl-*d*-lysergic acid (+)-1-hydroxy-2-butylamide
Manufacturers' Codes: UML-491
Molecular Formula: $C_{21}H_{27}N_3O_2$
Molecular Weight: 353.46.
Percent Composition: C 71.36%, H 7.70%, N 11.89%, O 9.05%
Literature References: Serotonin receptor antagonist. Prepn: **GB 854569** (1960); A. Hofmann, F. Troxler, **US 3113133** (1963 to Sandoz). Comparative pharmacology: Z. Votava *et al., Arzneimittel-Forsch.* **16,** 220 (1966); P. N. Chambers, P. B. Marshall, *J. Pharm. Pharmacol.* **19,** 65 (1967). Mechanism of action: D. A. Curran *et al., Res. Clin. Stud. Headache* **1,** 74 (1967); J. E. Hardebo *et al., Neurology* **28,** 64 (1978); S. W. J. Lamberts, R. M. Mac Leod, *Endocrinology* **103,** 287 (1978).
Properties: Crystals, mp 194-196°. $[\alpha]_{D20}$ -45° (c = 0.5 in pyridine).
Melting point: mp 194-196°
Optical Rotation: $[\alpha]_{D20}$ -45° (c = 0.5 in pyridine)

Derivative Type: Tartrate
Molecular Formula: $C_{46}H_{60}N_6O_{10}$
Molecular Weight: 857.00.
Percent Composition: C 64.47%, H 7.06%, N 9.81%, O 18.67%
Properties: Crystals, sparingly sol in water.

Derivative Type: Dimaleate
Properties: Dec ~165°. Sol in methanol, less sol in water (1:250). Practically insol in abs ethanol.

Derivative Type: Hydrogen maleate
CAS Registry Number: 129-49-7
Additional Names: Methysergide maleate
Trademarks: Deseril (Novartis); Désernil (Novartis); Sansert (Novartis)
Molecular Formula: $C_{21}H_{27}N_3O_2.C_4H_4O_4$
Molecular Weight: 469.53.
Percent Composition: C 63.95%, H 6.65%, N 8.95%, O 20.45%

Therap-Cat: Antimigraine.

Ph Eur monograph

Methysergide Maleate

$C_{21}H_{27}N_3O_2,C_4H_4O_4$ 469.5 *129-49-7*

ACTION AND USE
Prophylaxis of migraine.
Preparation
Methysergide Tablets
DEFINITION

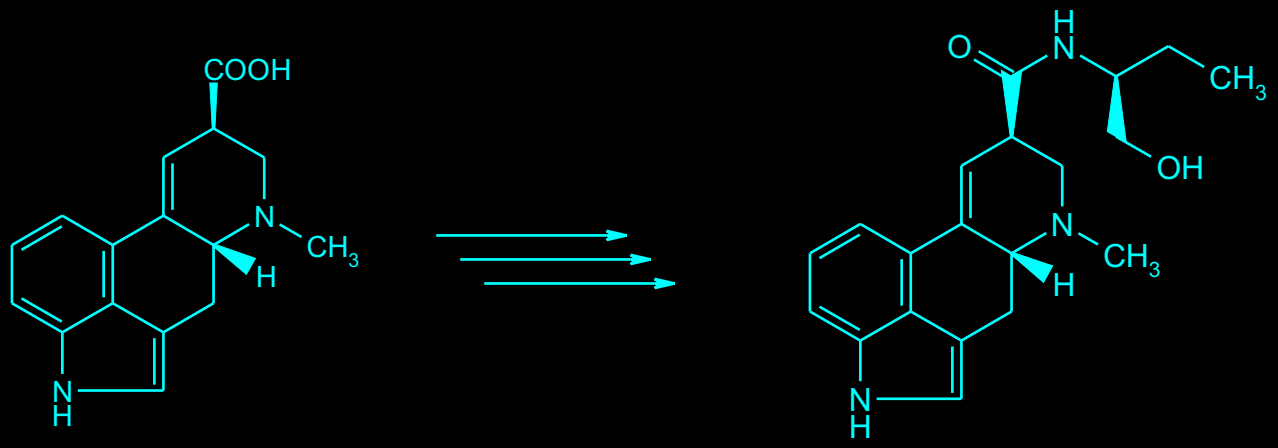
Methysergide Maleate is (1*RS*)-*N*-[1-(hydroxymethyl)propyl]-1-methyl-D-lysergamide hydrogen maleate. It contains not less than 98.0% and not more than 101.0% of $C_{21}H_{27}N_3O_2,C_4H_4O_4$, calculated with reference to the dried substance.

CHARACTERISTICS
A white or almost white, crystalline powder which may have a yellow or pink tinge.

Slightly soluble in *water* and in *methanol* ; practically insoluble in *chloroform* and in *ether* .

IDENTIFICATION.....

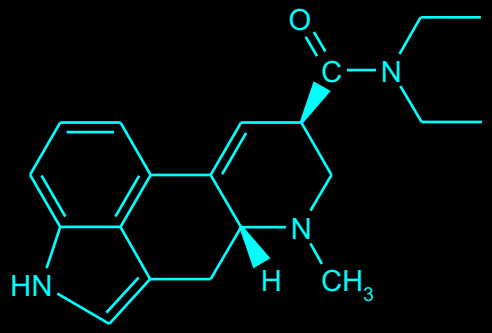
ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU PATOLOŠKIH GINEKOLOŠKIH KRVARENJA



METHYLERGONOVINE

MALE STRUKTURNE VARIJACIJE MOGU DA POTPUNO IZMENE

FARMAKOLOŠKO DEJSTO



LSD

ERGOT ALKALOIDI I NJIHOVI POLU-SINTETIČKI DERIVATI KOJI SE KORISTE U SUZBIJANJU PATOLOŠKIH GINEKOLOŠKIH KRVARENJA

Monograph Number: 6095
Title: METHYLERGONOVINE
CAS Registry Number: 113-42-8
CAS Name: (8)-9,10-Didehydro-*N*-[(1*S*)-1-(hydroxymethyl)propyl]-6-methylergoline-8-carboxamide
Additional Names: *N*-[-(hydroxymethyl)propyl]-D-lysergamide; D-lysergic acid (+)-butanolamide-(2); *d*-lysergic acid-*d*-1-hydroxybutylamide-2; methylergometrine; methylergobasine
Molecular Formula: C20H25N3O2
Molecular Weight: 339.43.
Percent Composition: C 70.77%, H 7.42%, N 12.38%, O 9.43%
Literature References: Semisynthetic ergot alkaloid; metabolite of methysergide, *q.v*. Prepn: A. Stoll, A. Hofmann, US 2265207 (1941 to Sandoz); *eidem, Helv. Chim. Acta* 26, 944 (1943). HPLC determn in plasma: H. T. Smith, N. C. Molinaro, *J. Chromatog.* 424, 416 (1988). Clinical trial in prevention of cluster headache: L. Mueller *et al., Headache* 37, 437 (1997). Review of pharmacology and clinical use in obstetrics and gynecology: A. N. de Groot *et al., Drugs* 56, 523-535 (1998).
Properties: Shiny crystals from benzene, mp 172° (some decompn). [ ]D20 -45° (c = 0.4 in pyridine). Sparingly sol in water. Freely sol in alcohol, acetone.
Melting point: mp 172° (some decompn)
Optical Rotation: [ ]D20 -45° (c = 0.4 in pyridine)

Derivative Type: Maleate
CAS Registry Number: 57432-61-8
Trademarks: Basofortina (Novartis); Methergin (Novartis); Methergine (Novartis); Metenarin (Teikoku Zoki); Methylergobrevin (Asta Medica); Ryegonovin (HMR); Spametrin-M (Yamanouchi Seiyaku)
Molecular Formula: C20H25N3O2.C4H4O4
Molecular Weight: 455.50.
Percent Composition: C 63.28%, H 6.42%, N 9.23%, O 21.07%
Properties: White to pinkish-tan microcryst powder; odorless; bitter taste. Slightly sol in water, alcohol; very slightly sol in chloroform, ether.

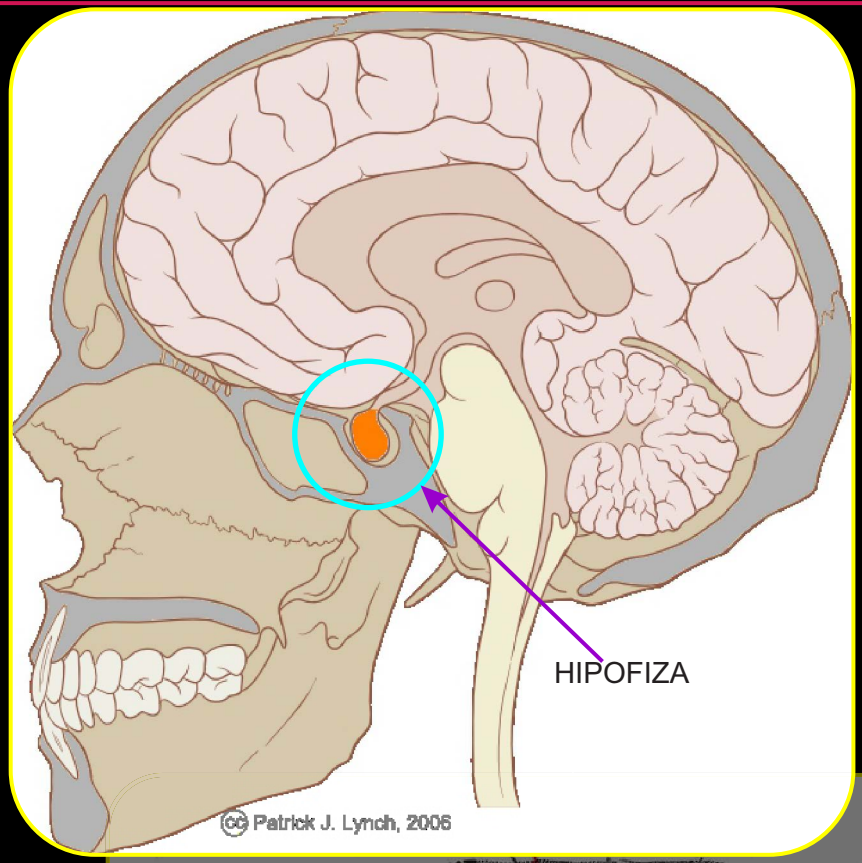
Therap-Cat: Oxytocic.

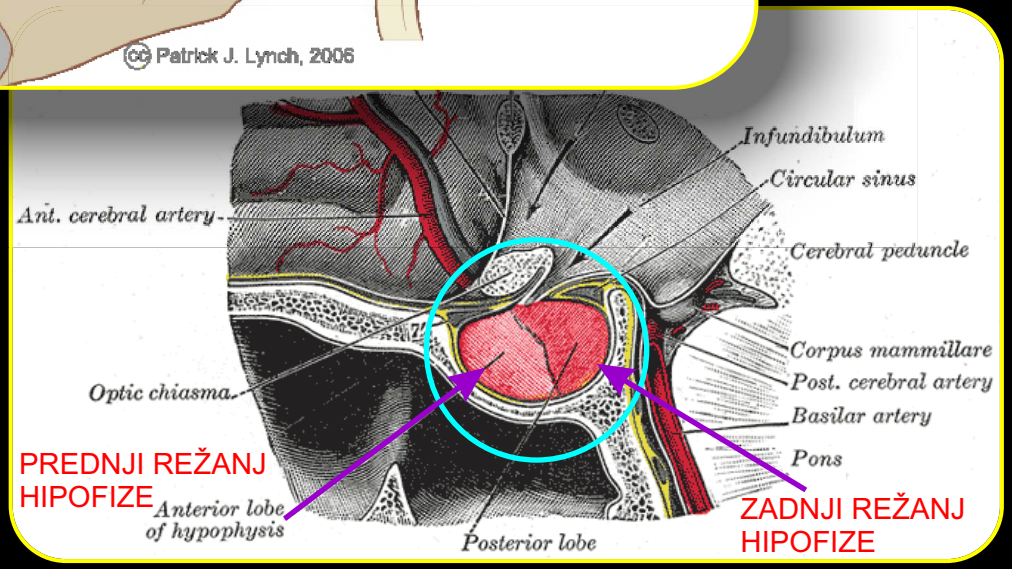
DODATAK

PROLAKTIN

-JEDAN OD BROJNIH PEPTIDNIH HORMONA KOJE SE LUČI U PREDNJEM REŽNJU HIPOFIZE
-LJUDSKI PROLAKTIN IMA 199 AMINO-KISELINA (~23 000 D)
-BITAN JE ZA ODRŽAVANJE TRUDNOĆE. U TOM PERIODU NJEGOVA KONCENTRACIJA SE MNOGOSTRUKO POVEĆAVA
-TAKOĐE JE POVEĆANA I TOKOM DOJENJA
-U MUŠKARACA, NORMALAN NIVO PROLAKTINA JE NIZAK
-RECEPTORI PROLAKTINA PRISUTNI SU U BROJNIM TKIVIMA, KAO ŠTO SU NEKI REGIONI MOZGA, JETRA, TESTISI, OVARIJUM, PROSTATA I IMUNI SISTEM
-KONSEKVENTNO, PROLAKTIN VEROVATNO IMA BROJNE, NORMALNE FIZIOLOŠKE FUNKCIJE, KOJE UGLAVNOM NISU POZNATE.

-SAM PROLAKTIN NEMA PRIMENU U TERAPIJI
-HIPERPRODUKCIJA PROLAKTINA (OSIM U TRUDNOĆI) PREDSTAVLJA RELATIVNO ČEST ENDOKRINI POREMEĆAJ
-NEGATIVNE POSLEDICE HIPERPRODUKCIJE PROLAKTINA SU ZNAČAJNE U OBA POLA, A NAJBITNIJA JE SMANJENA PLODNOST ODN. NEPLODNOST. (POREMEĆAJ JE REVERZIBILAN, A LEČI SE SNIŽENJEM KONCENTRACIJE PROLAKTINA)
- HIPERPRODUKCIJA PROLAKTINA SE SUZBIJA RAZLIČITIM TERAPIJSKIM POSTUPCIMA, A NAJČEŠĆE LEKOVIMA.





CHAPTER 55. PITUITARY HORMONES AND THEIR HYPOTHALAMIC RELEASING HORMONES - *Keith L. Parker and Bernard P. Schimmer*

DODATAK

PARKINSONOVA BOLEST

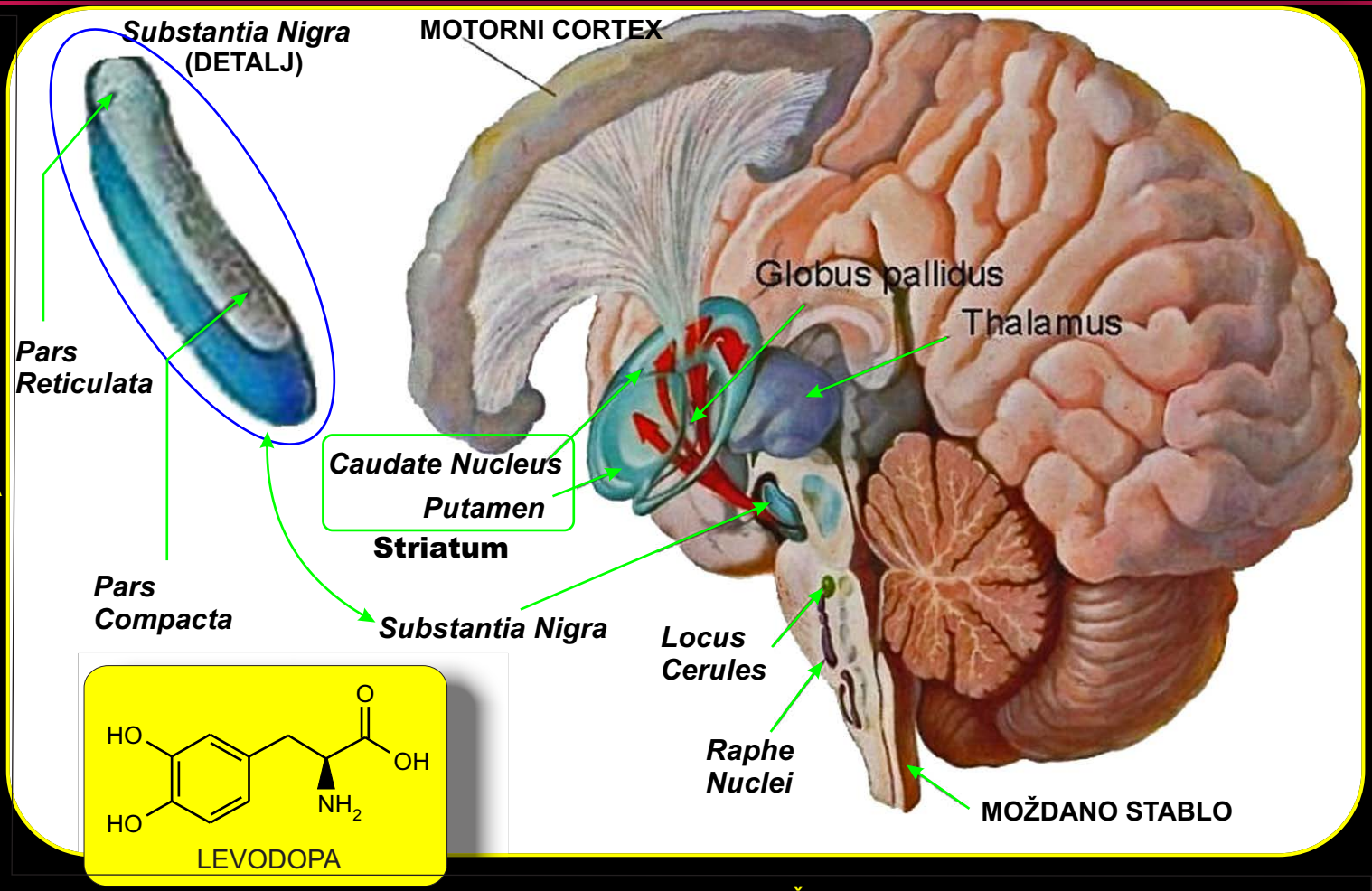
NEIZLEČIVO I PROGRESIVNO NEUROLOŠKO OBOLJENJE KOJE SE PRETEŽNO JAVLJA U STARIJIH OSOBA, A KARAKTERIŠU GA ČETIRI GLAVNE ODLIKE:

1. USPORENO I OTEŽANO KRETANJE
2. RIGIDITET MIŠIĆA
3. DRHTANJE TELA TOKOM MIROVANJA
4. POREMEĆENO ODRŽAVANJE RAVNOTEŽE TOKOM KRETANJA

-HISTOPATOLOŠKI (AUTOPSIJOM) KONSTATUJE SE GUBITAK PIGMENTISANIH DOPAMINERGIČKIH NEURONA (*substantia nigra pars compacta*) KAO I POJAVA INTRACELULARNIH STRUKTURA (LEWY-jeva TELA)

-BEZ LEČENJA, TOKOM PERIODA OD 5-10 GODINA, DOLAZI DO NEMOGUĆNOSTI KRETANJA, PARALIZE I SMRTI

-PRIMENOM LEKOVA, PROCES SE OBIČNO VEOMA USPORAVA, PACIJENTI ŽIVE DALEKO DUŽE I SIMPTOMI SU MANJE IZRAŽENI. U NOVIJE VREME IZVODE SE EKSPERIMENTI I SA MATIČNIM ĆELIJAMA, RADI EVENTUALNE REGENERACIJE OŠTEĆENIH NEURONA. IAKO SU POSTIGNUTI IZVESNI REZULTATI, MOGUĆA PRIMENA U TERAPIJI JE JOŠ (VRLO?) DALEKO.



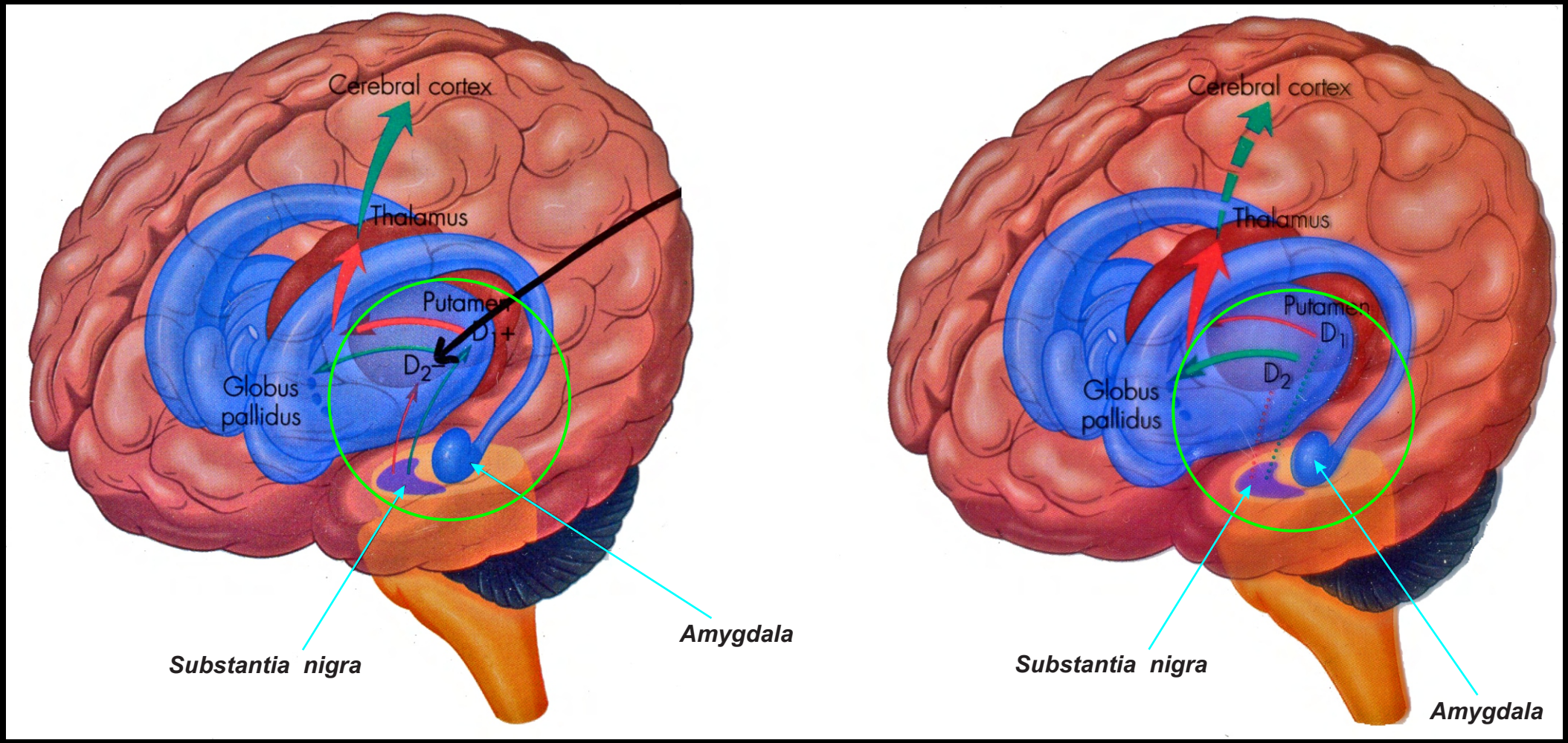
-OSNOVNI UZROK OBOLJENJA NIJE POZNAT

-U SAVREMENOJ TERAPIJI SE KORISTE KOMBINACIJE RAZLIČITIH LEKOVA, (POSEBNO LEVODOPA), POJEDINI DERIVATI ERGOT ALKALOIDA I DRUGI PREPARATI.

CHAPTER 20. TREATMENT OF CENTRAL NERVOUS SYSTEM DEGENERATIVE DISORDERS - *David G. Standaert and Anne B. Young*

PARKINSONOVA BOLEST -nastavak

Substantia nigra i PARKINSON-ovo OBOLJENJE



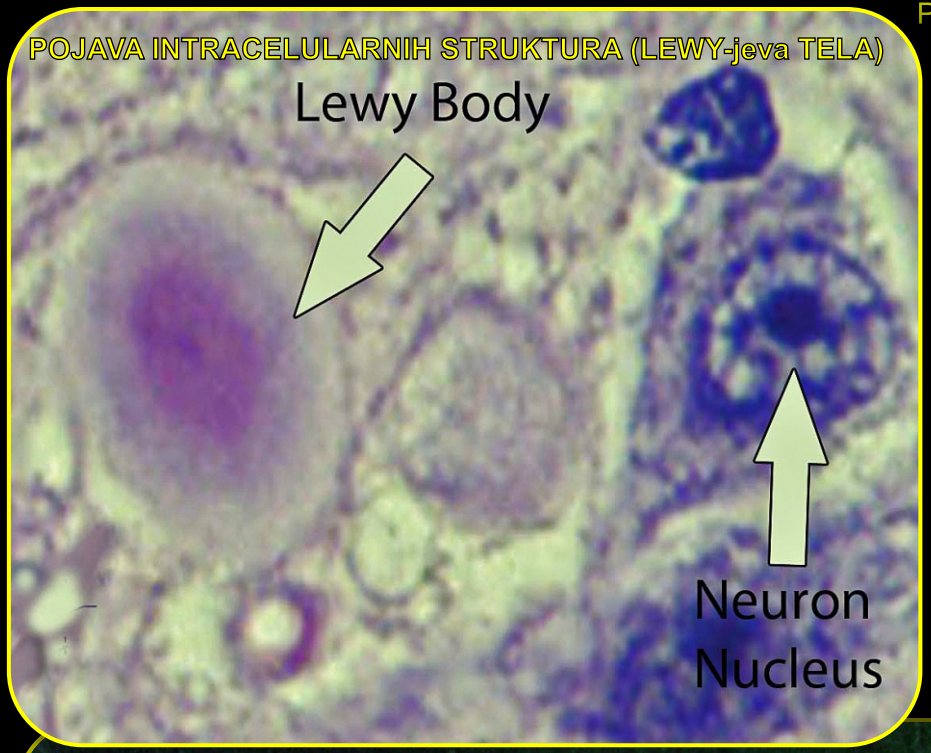
A. NORMALAN MOZAK

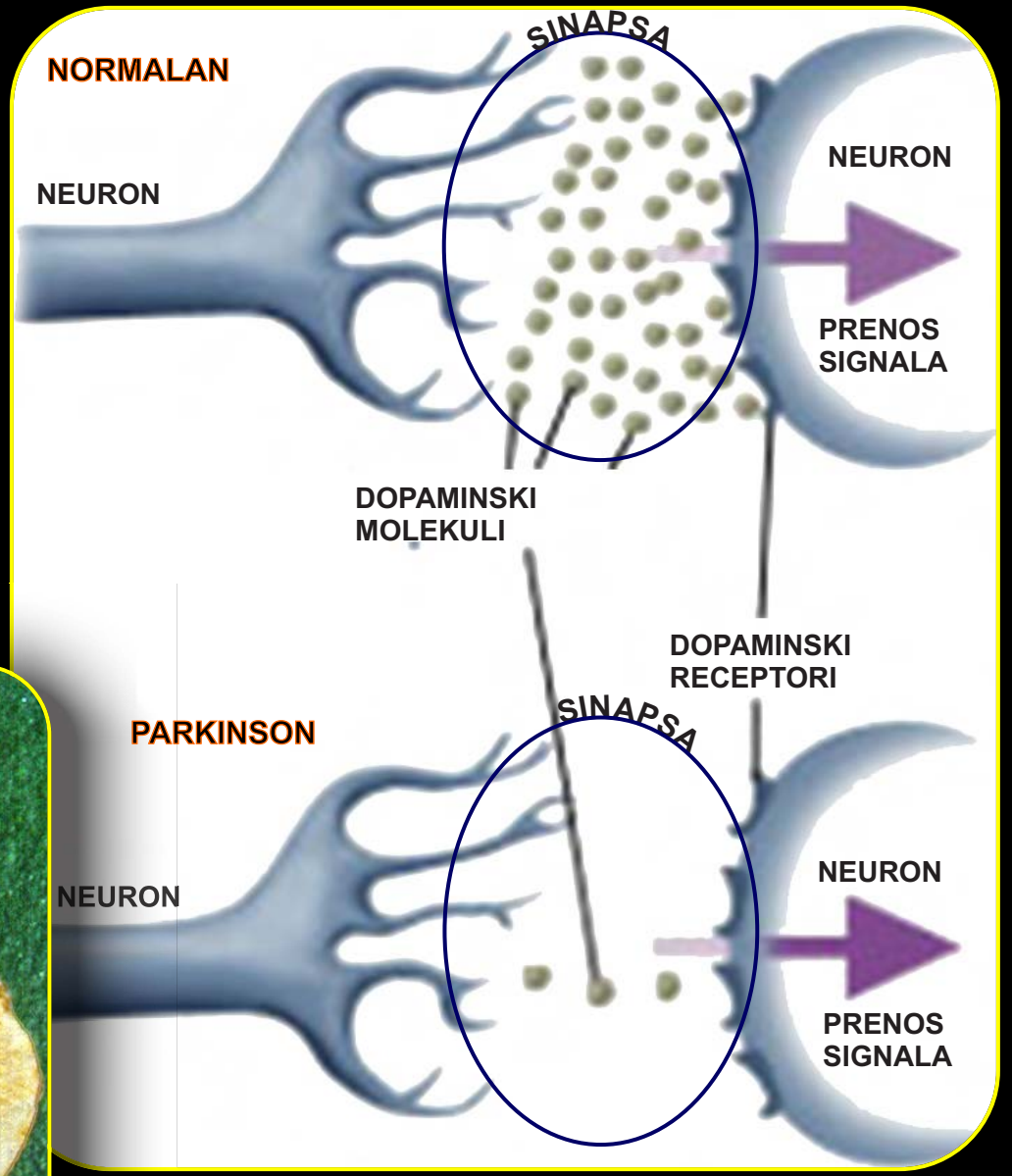
B. OBOLELI MOZAK
OSLABLJENI PROTOK SIGNALA IZ REGIONA
Substantia nigra PREMA D_1 I D_2 RECEPTORIMA

Based on "Parkinson's Disease and the Basal Ganglia: Lessons from the Laboratory and from Neurosurgery," by T. Wichmann, J. L. Vitek, and M. R. DeLong, 1995, *The Neuroscientist*, 1, 236–244.

DODATAK

PARKINSONOVA BOLEST -nastavak

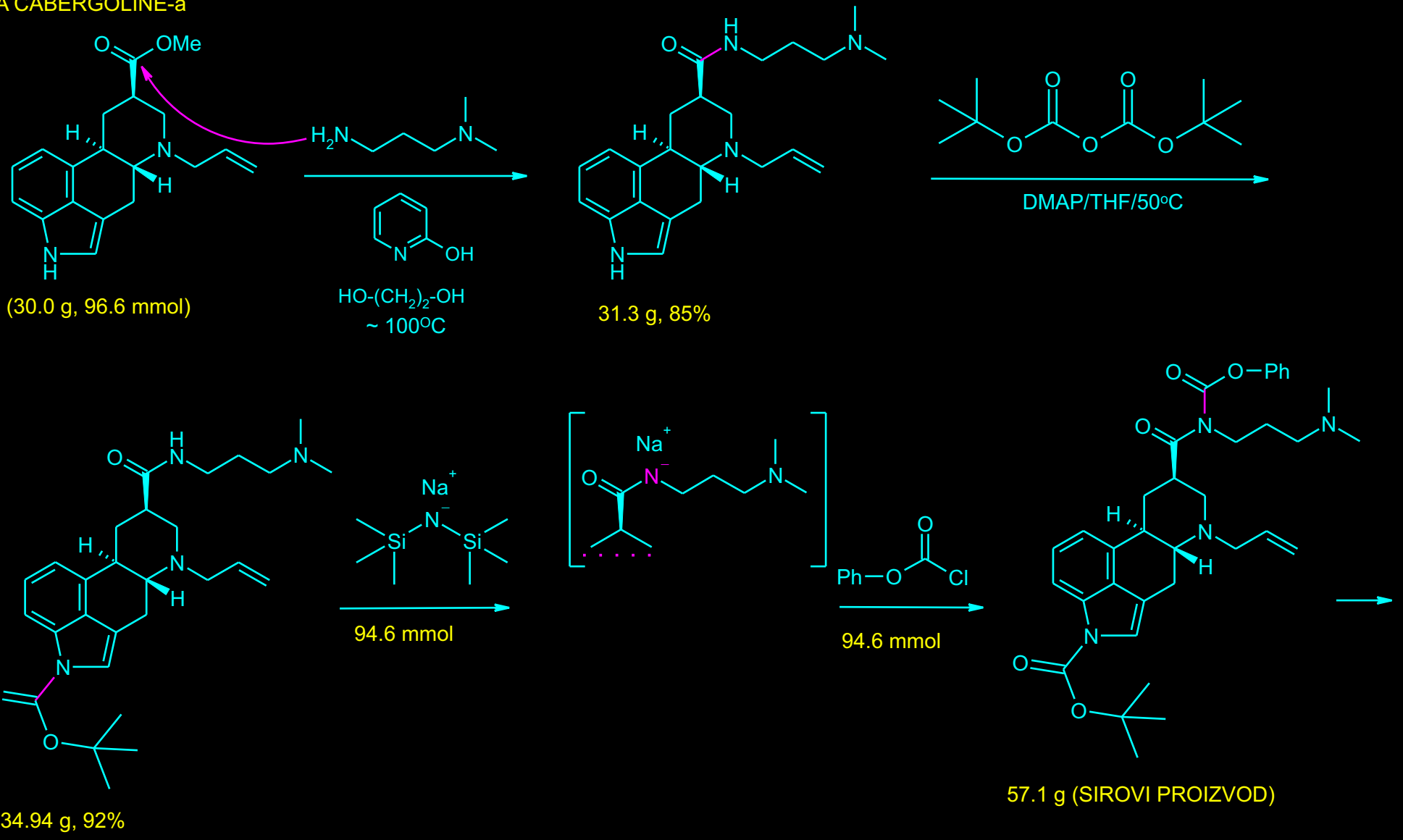




PRENOS NERVNOG SIGNALA
PREKO DOPAMINSKIH RECEPTORA

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJANJU SIMPTOME PARKINSONOVE BOLESTI

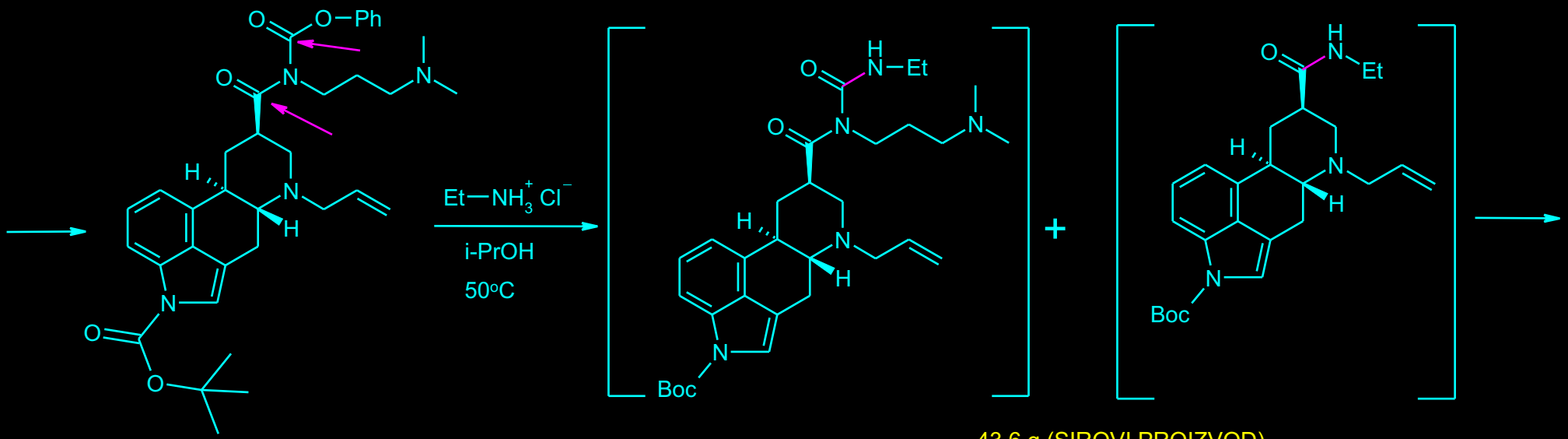
SINTEZA CABERGOLINE-a

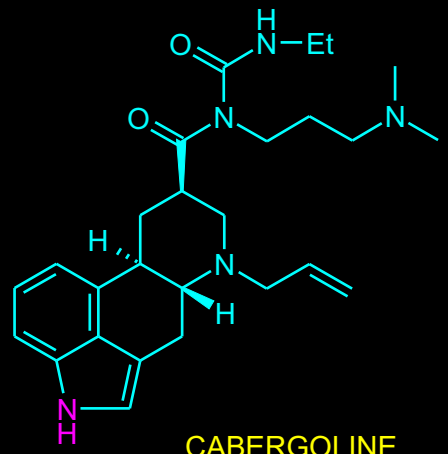


Andrew M. Anderson, and Peter G. M. Wuts; "A Practical Synthesis of Cabergoline"; Scott W. Ashford, Kevin E. Henegar, *J. Org. Chem. 2002, 67, 7147-7150*

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJANJU SIMPTOME PARKINSONOVE BOLESTI

SINTEZA CABERGOLINE-a (NASTAVAK)

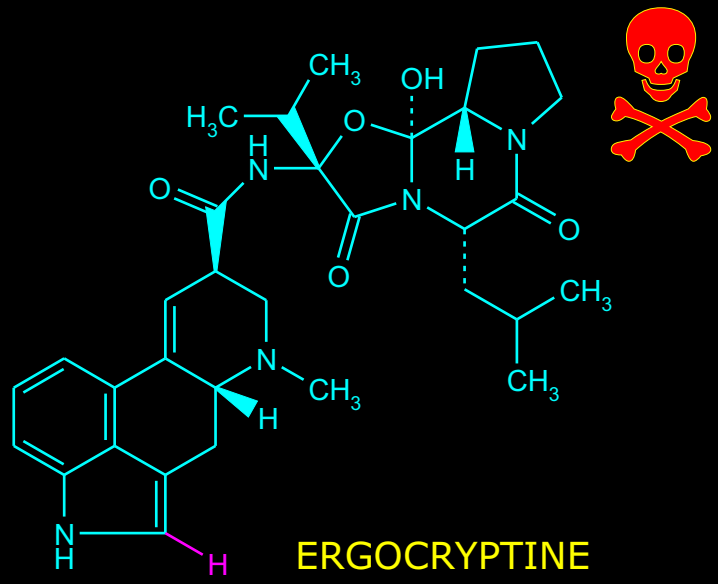




CABERGOLINE

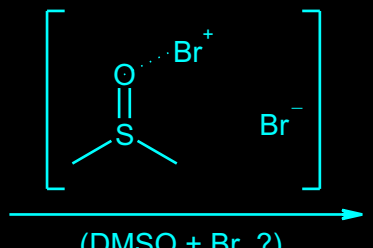
~ 94%

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJANJU SIMPTOME PARKINSONOVE BOLESTI



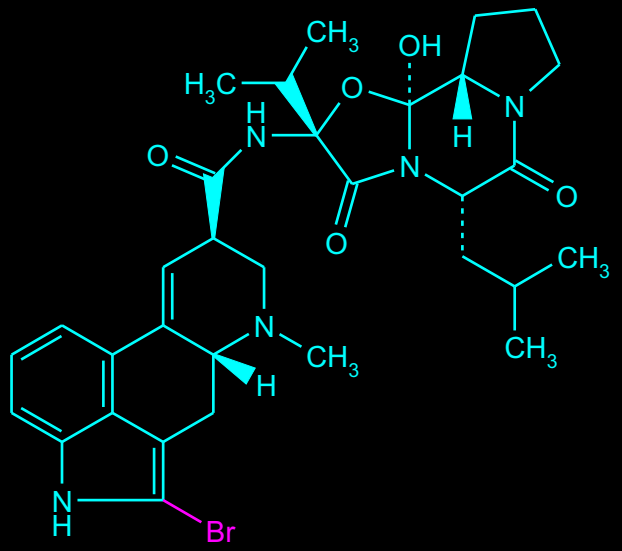
ERGOCRYPTINE

OTROV



(DMSO + Br_2 ?)

DMSO



93%

BROMOCRIPTINE

LEK

Synthetic Communications, 19(20), 3415-30; 1989 (PREMA SCIFINDER-u)

I DRUGE SLIČNE METODE ZA ELEKTROFILNO BROMOVANJE INDOLSKOG PRSTENA:

Russ., 2274640, 20 Apr 2006

Pol., 161874, 31 Aug 1993

Collection of Czechoslovak Chemical Communications, 57(3), 565-72; 1992

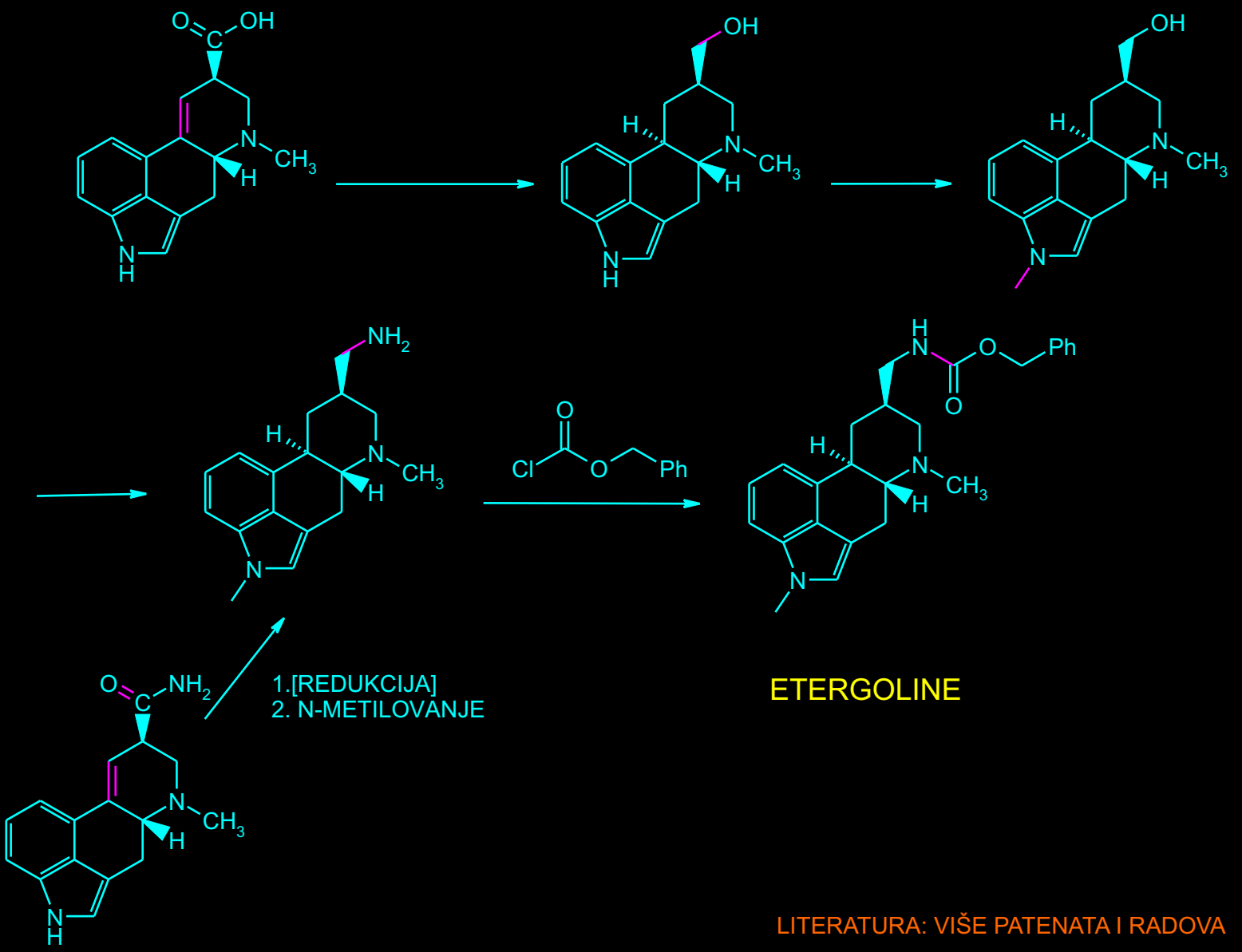
Czech., 272370, 15 Jan 1991

Czech., 250972, 14 May 1987

US Patent 3,752,814 (1973)

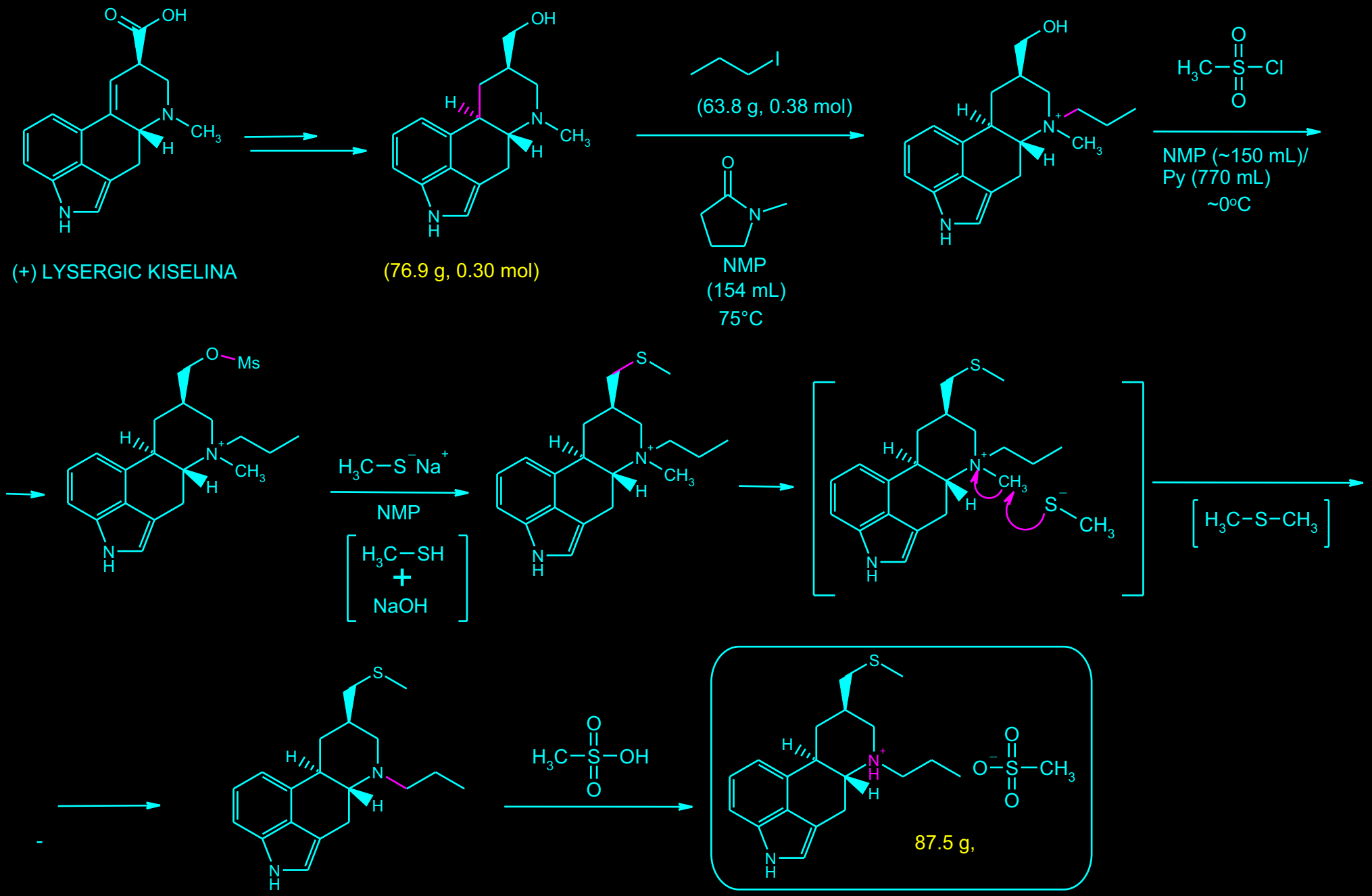
PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJANJU SIMPTOME PARKINSONOVE BOLESTI

SINTEZA ETERGOLINE-a.



LITERATURA: VIŠE PATENATA I RADOVA

SINTEZA PERGOLIDA BEZ IZOLOVANJA INTERMEDIJERA (”**ONE-POT SYNTHESIS**”)

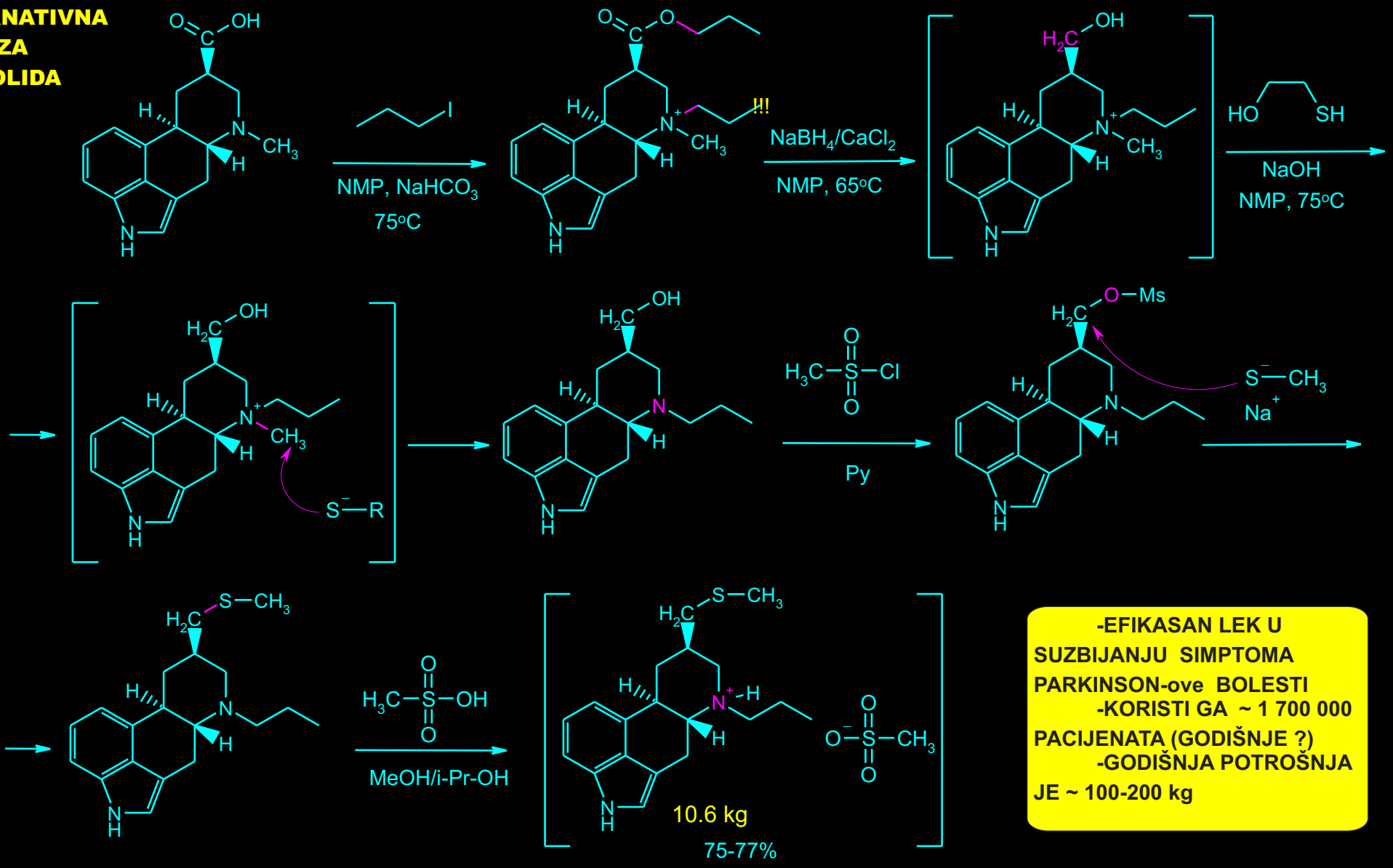


Organic Process Research & Development 1997, 1, 77-80; **Integration of a Highly Selective Demethylation of a Quaternized Ergoline into a One-Pot Synthesis of Pergolide**
Jerry W. Misner,* Joseph H. Kennedy, and W. Scott Biggs

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE

PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJANJU SIMPTOME PARKINSONOVE BOLESTI

ALTERNATIVNA SINTEZA PERGOLIDA

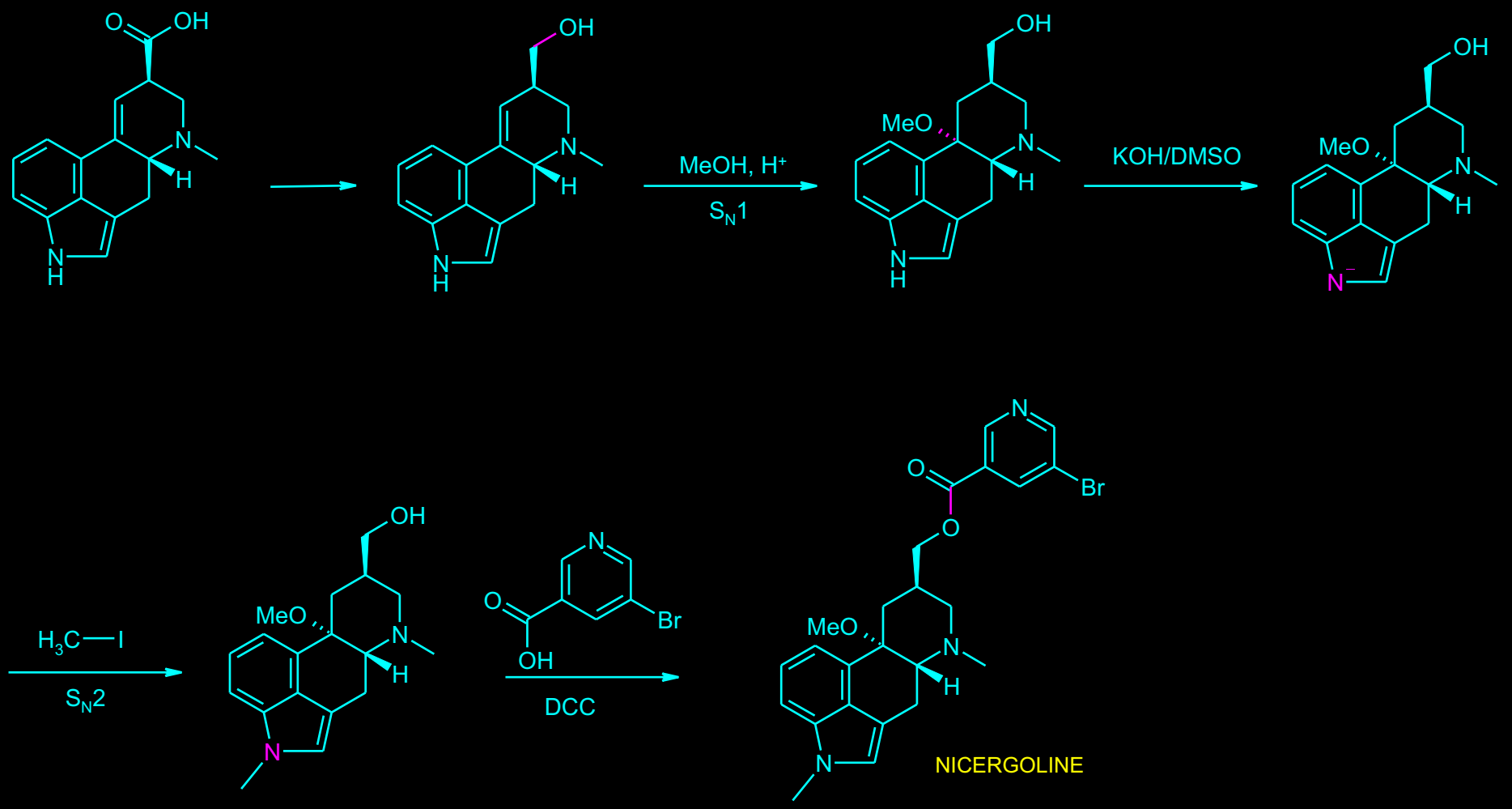


-EFIKASAN LEK U SUZBIJANJU SIMPTOMA PARKINSON-ove BOLESTI
-KORISTI GA ~ 1 700 000 PACIJENATA (GODIŠNJE ?)
-GODIŠNJA POTROŠNJA JE ~ 100-200 kg

Organic Process Research & Development 2006, 10, 198-202; **Development of a Practical High-Yield Industrial Synthesis of Pergolide Mesylate.** Walter Cabri,* Jacopo Roletto, Sara Olmo, Piera Fonte, Paolo Ghetti, Simonetta Songia, Elio Mapelli,Marco Alpegiani, and Paolo Paissoni

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJANJU SIMPTOME PARKINSONOVE BOLESTI

SINTEZA NICERGOLINE-a



Faming Zhuanli Shenqing Gongkai Shuomingshu, 101781296, 21 Jul 2010; KINESKI PATENT PREMA SCIFINDER-u

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJSJU SIMPTOME PARKINSONOVE BOLESTI

Monograph Number: 1601
Title: CABERGOLINE
CAS Registry Number: 81409-90-7
CAS Name: *(8)-N*-[3-(Dimethylamino)propyl]-*N*-[(ethylamino)carbonyl]-6-(2-propenyl)ergoline-8-carboxamide
Additional Names: 1-ethyl-3-(3 -dimethylaminopropyl)-3-(6 -allylergoline-8 -carbonyl)urea; 1-[(6-allylergoline-8 -yl)carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea
Manufacturers' Codes: FCE-21336
Trademarks: Cabaser (Pharmacia & Upjohn); Dostinex (Pharmacia & Upjohn)
Molecular Formula: C26H37N5O2
Molecular Weight: 451.60.
Percent Composition: C 69.15%, H 8.26%, N 15.51%, O 7.09%
Literature References: Dopamine D2-receptor agonist. Prepn: P. Salvati *et al.,* BE 888243; *eidem,* US 4526892 (1981, 1985 both to Farmitalia Carlo Erba). Prepn and bioactivity: E. Brambilla *et al., Eur. J. Med. Chem.* 24, 421 (1989). Clinical pharmacology: C. Ferrari *et al., J. Clin. Endocrinol. Metab.* 63, 941 (1986). Veterinary trial as abortifacient in dogs: K. Post *et al., Theriogenology* 29, 1233 (1988). Clinical evaluation to prevent puerperal lactation: G. B. Melis *et al., Obstet. Gynecol.* 71, 311 (1988); in hyperprolactinemic disorders: C. Ferrari *et al., J. Clin. Endocrinol. Metab.* 68, 1201 (1989). Clinical trial in Parkinson's disease: J. T. Hutton *et al., Neurology* 46, 1062 (1996).
Properties: White crystals from diethyl ether, mp 102-104°. LD50 orally in male mice: >400 mg/kg (Brambilla).
Melting point: mp 102-104°
Toxicity data: LD50 orally in male mice: >400 mg/kg (Brambilla)

Derivative Type: Diphosphate
CAS Registry Number: 85329-89-1
Molecular Formula: C26H37N5O2.2H3PO4
Molecular Weight: 647.59.
Percent Composition: C 48.22%, H 6.69%, N 10.81%, O 24.71%, P 9.57%
Properties: mp 153-155°.
Melting point: mp 153-155°

Therap-Cat: Prolactin inhibitor; antiparkinsonian.

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJSJU SIMPTOME PARKINSONOVE BOLESTI

Monograph Number: 1400
Title: BROMOCRIPTINE
CAS Registry Number: 25614-03-3
CAS Name: (5)-2-Bromo-12 -hydroxy-2 -(1-methylethyl)-5 -(2-methylpropyl)ergotaman-3 ,6 ,18-trione
Additional Names: 2-bromoergocryptine; 2-bromo- -ergokryptin
Manufacturers' Codes: CB-154
Molecular Formula: $C_{32}H_{40}BrN_5O_5$
Molecular Weight: 654.61.
Percent Composition: C 58.71%, H 6.16%, Br 12.21%, N 10.70%, O 12.22%
Literature References: Dopamine receptor agonist; derivative of the ergotoxin group of ergot alkaloids. Prepn: E. Flückiger *et al.,* **DE 1926045**; *eidem,* **US 3752814** (1969, 1973 both to Sandoz). Pharmacology: E. Flückiger, H. R. Wagner, *Experientia* **24,** 1130 (1968); E. Del Pozo *et al., Schweiz. Med. Wochenschr.* **103,** 847 (1973). Relationship of stereochemistry and biological activity: H. P. Weber, *Adv. Biochem. Psychopharmacol.* **23,** 25 (1980); N. Camerman, A. Camerman, *Mol. Pharmacol.* **19,** 517 (1981). Long term clinical trial in Parkinson's disease: T. Nakanishi *et al., Eur. Neurol.* **32,** Suppl. 1, 9 (1992). Clinical effect on body weight and glucose tolerance in obesity: A. H. Cincotta, A. H. Meier, *Diabetes Care* **19,** 667 (1996). Comprehensive description: D. A. Giron-Forest, W. D. Schönleber, *Anal. Profiles Drug Subs.* **8,** 47-81 (1979). Review of pharmacology, toxicology and therapeutic uses: D. Parkes, *Advan. Drug Res.* **12,** 247-344 (1977); of therapeutic applications in endocrine and neurological diseases: K. Y. Ho, M. O. Thorner, *Drugs* **36,** 67-82 (1988).
Properties: Crystals from methyl ethyl ketone-isopropyl ether, mp 215-218° (dec). [ ]$_{D20}$ -195° (c = 1 in methylene chloride).
Melting point: mp 215-218° (dec)
Optical Rotation: [ ]$_{D20}$ -195° (c = 1 in methylene chloride)

Derivative Type: Methanesulfonate
CAS Registry Number: 22260-51-1
Manufacturers' Codes: CB-154 mesylate
Trademarks: Parlodel (Novartis); Pravidel (Novartis)
Molecular Formula: $C_{32}H_{40}BrN_5O_5.CH_3SO_3H$
Molecular Weight: 750.71.
Percent Composition: C 52.80%, H 5.91%, Br 10.64%, N 9.33%, O 17.05%, S 4.27%
Properties: Crystals from methyl ethyl ketone, mp 192-196° (dec). [ ]$_{D20}$ +95° (c = 1 in methanol-methylene chloride). Soly at 25° (mg/ml): methanol 910; ethanol 23.0; water 0.8; chloroform 0.45; benzene <0.1; hexane <0.1. pKa 4.90. LD_{50} in mice, rats, rabbits (mg/kg): 190, 72, 12.5 i.v. (Parkes).
Melting point: mp 192-196° (dec)
pKa: pKa 4.90
Optical Rotation: [ ]$_{D20}$ +95° (c = 1 in methanol-methylene chloride)
Toxicity data: LD_{50} in mice, rats, rabbits (mg/kg): 190, 72, 12.5 i.v. (Parkes)

Therap-Cat: Prolactin inhibitor; antiparkinsonian.

Ph Eur monograph 0596

$C_{32}H_{40}BrN_5O_5S,CH_4SO_3$ 751 *22260-51-1*

Action and use

Dopamine agonist.

Preparations

Bromocriptine Capsules

Bromocriptine Tablets

Ph Eur

DEFINITION

Bromocriptine mesilate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of (6a*R*,9*R*)-5-bromo-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-(2-methylpropyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9- carboxamide monomethanesulphonate, calculated with reference to the dried substance.

PRODUCTION

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

CHARACTERS

A white or slightly coloured, fine crystalline powder, very sensitive to light, practically insoluble in water, freely soluble in methanol, soluble in alcohol, sparingly soluble in methylene chloride.

The identification, tests and assay are to be carried out as rapidly as possible, protected from light.

IDENTIFICATION .....

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJSJU SIMPTOME PARKINSONOVE BOLESTI

Monograph Number: 5962

Title: METERGOLINE

CAS Registry Number: 17692-51-2

CAS Name: [[(8)-1,6-Dimethylergolin-8-yl]methyl]carbamic acid phenylmethyl ester

Additional Names: D-8 -[(carbobenzoxyamino)methyl]-1,6-dimethyl-10 -ergoline; D-*N*-carbobenzoxydihydro-1-methyllysergamine I; D-8 -[(carboxyamino)methyl]-1,6-dimethylergoline I benzyl ester; D-*N*-carboxydihydro-1-methyllysergamine I benzyl ester; D-[(4,6,6a,7,8,9,10,10a-octahydro-4,7-dimethyl-10a -indolo[4,3-*fg*]quinolin-9 -yl)methyl]carbamic acid benzyl ester; methergoline

Trademarks: Liserdol (Farmitalia); Contralac (Virbac)

Molecular Formula: C25H29N3O2

Molecular Weight: 403.52.

Percent Composition: C 74.41%, H 7.24%, N 10.41%, O 7.93%

Literature References: Serotonin 5HT-receptor antagonist. Prepn: Bernardi *et al., Gazz. Chim. Ital.* **94,** 936 (1964); Camerino *et al.,* **US 3238211** (1966 to Farmitalia). Pharmacology: C. Beretta *et al., Nature* **207,** 421 (1965). Metabolic studies: Arcamone *et al., Boll. Chim. Farm.* **110,** 704 (1971). Mode of action study: L. Krulich *et al., Endocrinology* **108,** 1115 (1981). Clinical antiprolactin activity: F. Scapin *et al., Eur. J. Clin. Pharmacol.* **22,** 181 (1982); A. Caballero *et al., J. Reprod. Med.* **32,** 115 (1987).

Properties: Crystals from benzene + ether, mp 146-149°. [ ]D28 -7 ±2°. uv max: 291 nm (E1%1cm 165). Very sol in pyridine; sol in alc, acetone, chloroform. Practically insol in benzene, ether, water. LD50 in mice (mg/kg): 85 i.p., 430 orally; in rats (mg/kg): >800 orally (Beretta).

Melting point: mp 146-149°

Optical Rotation: [ ]D28 -7 ±2°

Absorption maximum: uv max: 291 nm (E1%1cm 165)

Toxicity data: LD50 in mice (mg/kg): 85 i.p., 430 orally; in rats (mg/kg): >800 orally (Beretta)

Therap-Cat: Prolactin inhibitor.

Therap-Cat-Vet: Prolactin inhibitor.

PRIRODNI I POLU-SINTETIČKI DERIVATI LISERGINSKE KISELINE KOJI SPREČAVAJU PREKOMERNO LUČENJE PROLAKTINA (HORMONA HIPOFIZE); TAKOĐE SUZBIJSJU SIMPTOME PARKINSONOVE BOLESTI

Monograph Number: 7240
Title: Pergolide
CAS Registry Number: 66104-22-1
CAS Name: (8)-8-[(Methylthio)methyl]-6-propylergoline
Additional Names: D-6-*n*-propyl-8 -methylmercaptomethylergoline
Manufacturers' Codes: LY-141B
Molecular Formula: C19H26N2S
Molecular Weight: 314.50.
Percent Composition: C 72.56%, H 8.33%, N 8.91%, S 10.20%
Literature References: Dopaminergic agonist that also decreases plasma prolactin concentrations. Prepn: E. C. Kornfeld, N. J. Bach, **US 4166182** (1979 to Lilly). Dopaminergic effects in rats: R. W. Fuller *et al., Life Sci.* **24,** 375 (1979); T. T. Yen *et al., ibid.* **25,** 209 (1979). Clinical pharmacology: L. Lemberger, R. E. Crabtree, *Science* **205,** 1151 (1979). Pharmacological evaluation as antiparkinson agent: W. C. Koller, *Neuropharmacology* **19,** 831 (1980). Clinical study in galactorrhea: J. T. Callaghan *et al., Life Sci.* **28,** 95 (1981); in hyperprolactinemia: S. Francks *et al., Lancet* **2,** 659 (1981); in treatment of pituitary tumors secreting prolactin or growth hormone: D. L. Kleinberg *et al., N. Engl. J. Med.* **309,** 704 (1983). Clinical studies in Parkinson's disease: J. Jankovic, J. Orman, *Adv. Neurol.* **45,** 551 (1986); C. W. Olanow, M. J. Alberts, *ibid.* 555. Comprehensive description: D. J. Sprankle, E. C. Jensen, *Anal. Profiles Drug Subs. Excip.* **21,** 375-413 (1992).
Properties: Solid, mp 206-209°.
Melting point: mp 206-209°

Derivative Type: Mesylate

CAS Registry Number: 66104-23-2
Manufacturers' Codes: LY-127809
Trademarks: Celance (Lilly); Permax (Lilly); Nopar (Lilly)
Molecular Formula: C19H26N2S.CH3SO3H
Molecular Weight: 410.60.
Percent Composition: C 58.50%, H 7.36%, N 6.82%, S 15.62%, O 11.69%
Properties: Crystals, mp 225° (dec); also reported as 258-260° (Sprankle, Jensen). uv max (water): 279 nm (6385); (methanol): 280 nm (6980); (dehydrated ethanol): 281 nm (6993). D20 between -18.0° and -23.0° (c = 10 mg/ml in DMF). pKa (66% DMF) 7.8. Sparingly sol in DMF, methanol; slightly sol in water, 0.01*N* HCl, chloroform, acetonitrile, dichloromethane, dehydrated ethanol; very slightly sol in acetone. Practically insol in 0.1*N* NaOH, 0.1*N* HCl, ether. Partition coefficient at 25° (chloroform/water): 6.14 (pH 2.19); 119.6 (pH 4.02).
Melting point: mp 225° (dec); also reported as 258-260° (Sprankle, Jensen)
pKa: pKa (66% DMF) 7.8
Optical Rotation: D20 between -18.0° and -23.0° (c = 10 mg/ml in DMF)
Log P: Partition coefficient at 25° (chloroform/water): 6.14 (pH 2.19); 119.6 (pH 4.02)
Absorption maximum: uv max (water): 279 nm (6385); (methanol): 280 nm (6980); (dehydrated ethanol): 281 nm (6993)

Therap-Cat: Antiparkinsonian.

Monograph Number: 6521

Title: NICERGOLINE

CAS Registry Number: 27848-84-6

CAS Name: (8)-10-Methoxy-1,6-dimethylergoline-8-methanol 5-bromo-3-pyridinecarboxylate (ester)

Additional Names: 1-methyllumilysergol 8-(5-bromonicotinate) 10-methyl ether; 4,6,6a,7,8,9,10,10a-octahydro-10a -methoxy-4,7-dimethylindolo[4,3-*fg*]quinoline-9-methanol 5-bromonicotinate; 8 -[(5-bromonicotinoyloxy)methyl]-1,6-dimethyl-10 -methoxyergoline; nicotergoline; nimergoline; MNE

Manufacturers' Codes: FI-6714

Trademarks: Cergodum (Duncan); Circo-Maren (Krewel); Dilasenil (Celtia); Duracebrol (Durachemie); Ergotop (Kwizda); Ergobel (Hormosan); Memoq (Gödecke); Nicergolent (Ramon); Sermion (Farmitalia); Vasospan (Exa)

Molecular Formula: $C_{24}H_{26}BrN_3O_3$

Molecular Weight: 484.39.

Percent Composition: C 59.51%, H 5.41%, Br 16.50%, N 8.68%, O 9.91%

Literature References: Prepn: Bernardi *et al.,* **US 3228943**; Temperilli, **DE 2112273** (1966, 1971, both to Farmitalia); Arcari *et al., Experientia* **28,** 819 (1972). Series of articles on pharmacology, clinical studies, tolerability: *Arzneimittel-Forsch.* **29,** 1213-1316 (1979). Toxicity study: B. W. Neumann, F. Lauschner, *ibid.* 1206. Hemodynamic effects in the dog: *ibid.* **31,** 1693 (1981). Use in acute myocardial infarction with diastolic hypertension: E. Triulzi *et al., Farmaco Ed. Prat.* **36,** 449 (1981).

Properties: mp 136-138°. LD_{50} in male mice, rats (mg/kg): 860, 2800 orally; 46, 43 i.v. (Neumann, Lauschner).

Melting point: mp 136-138°

Toxicity data: LD_{50} in male mice, rats (mg/kg): 860, 2800 orally; 46, 43 i.v. (Neumann, Lauschner)

Therap-Cat: Vasodilator (cerebral, peripheral).

(Ph Eur monograph 1998)

$C_{24}H_{26}BrN_3O_3$ 484.4 *27848-84-6*

Action and use

Vasodilator.

Ph Eur

DEFINITION

[(6a*R*,9*R*,10a*S*)-10a-Methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate.

Content

99.0 per cent to 101.0 per cent (anhydrous and solvent-free substance).

CHARACTERS

Appearance

Fine to granular, white or yellowish powder.

Solubility

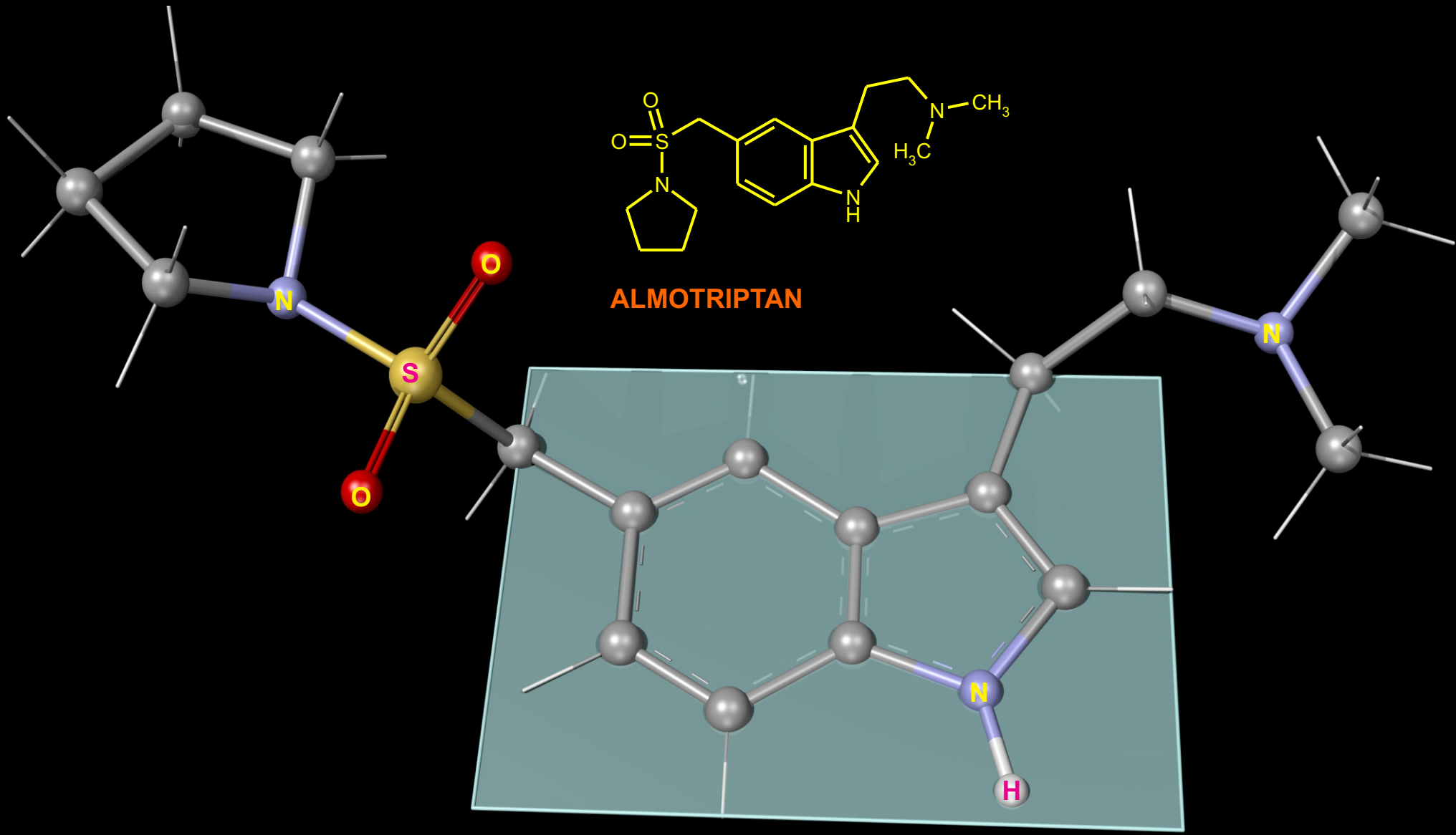
Practically insoluble in water, freely soluble in methylene chloride, soluble in alcohol.

It shows polymorphism.

IDENTIFICATION...

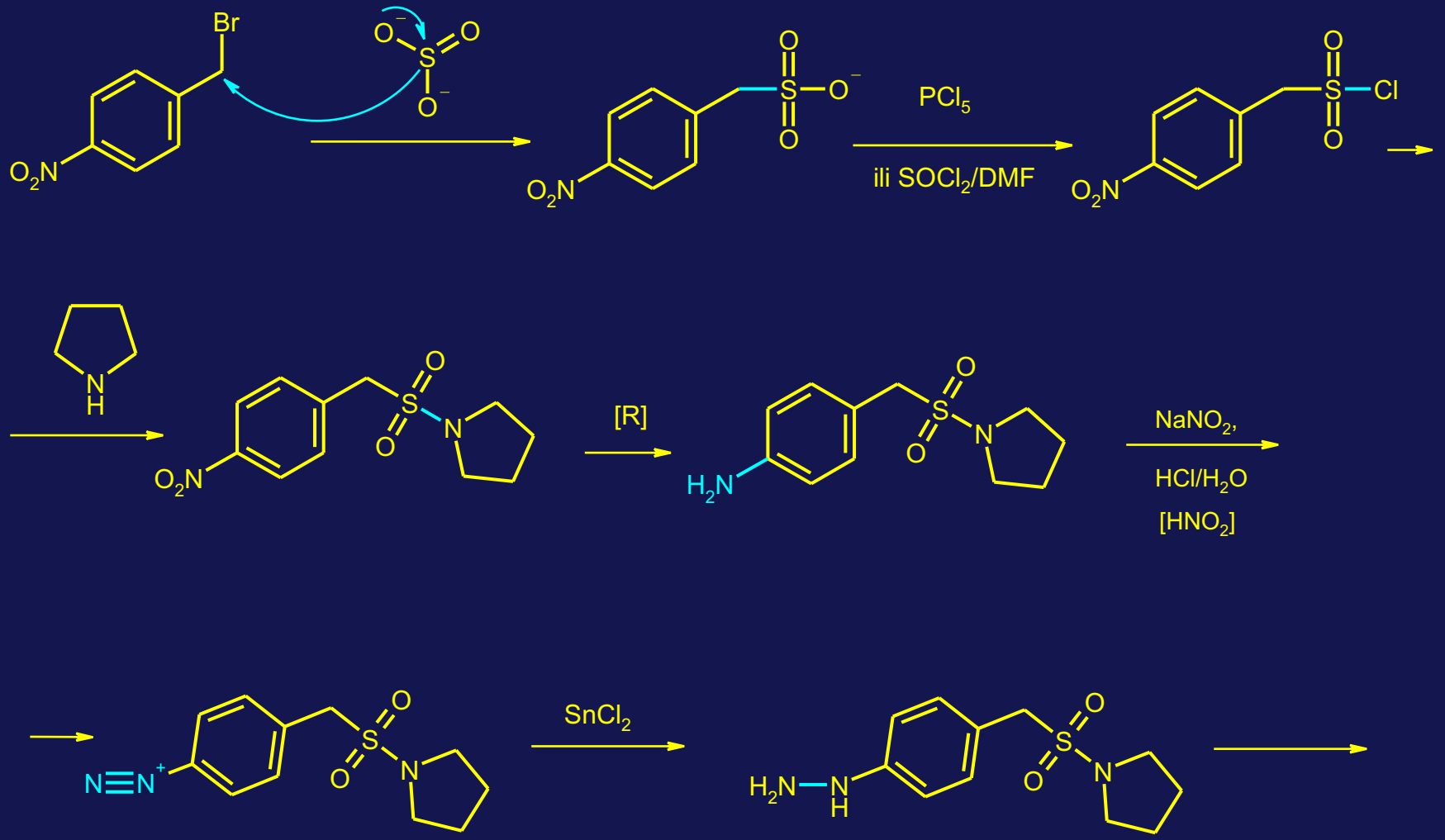
PREPARATI NOVE GENERACIJE ZA SUZBIJANJE SIMPTOMA MIGRENE - TRIPTANI

TRIPTANI: STRUKTURA I LITERATURA



PREPARATI PROTIV MIGRENE - TRIPTANI: SINTEZE

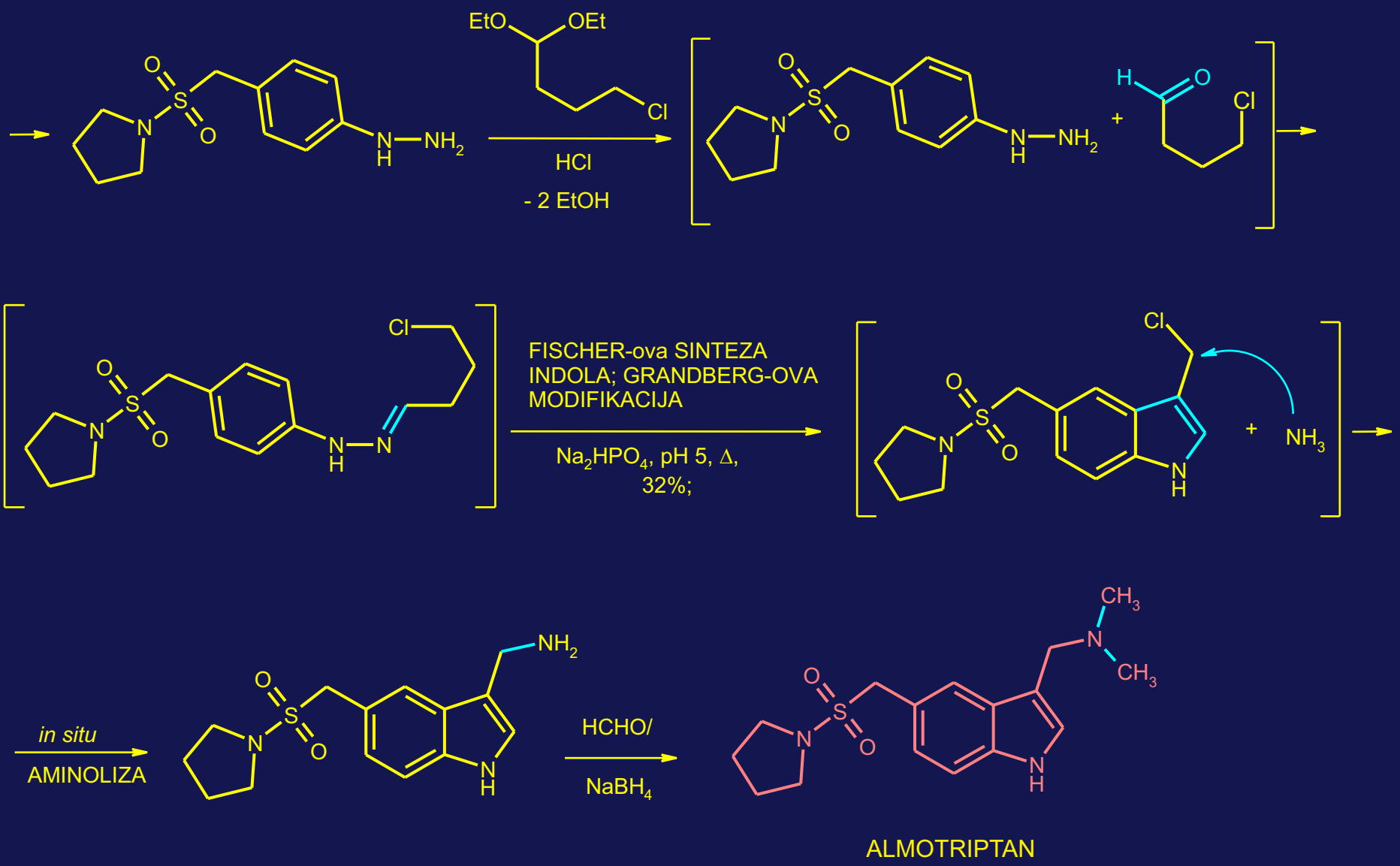
ALMOTRIPTAN



J. Bosch et al. / Tetrahedron 57 (2001) 1041-1048

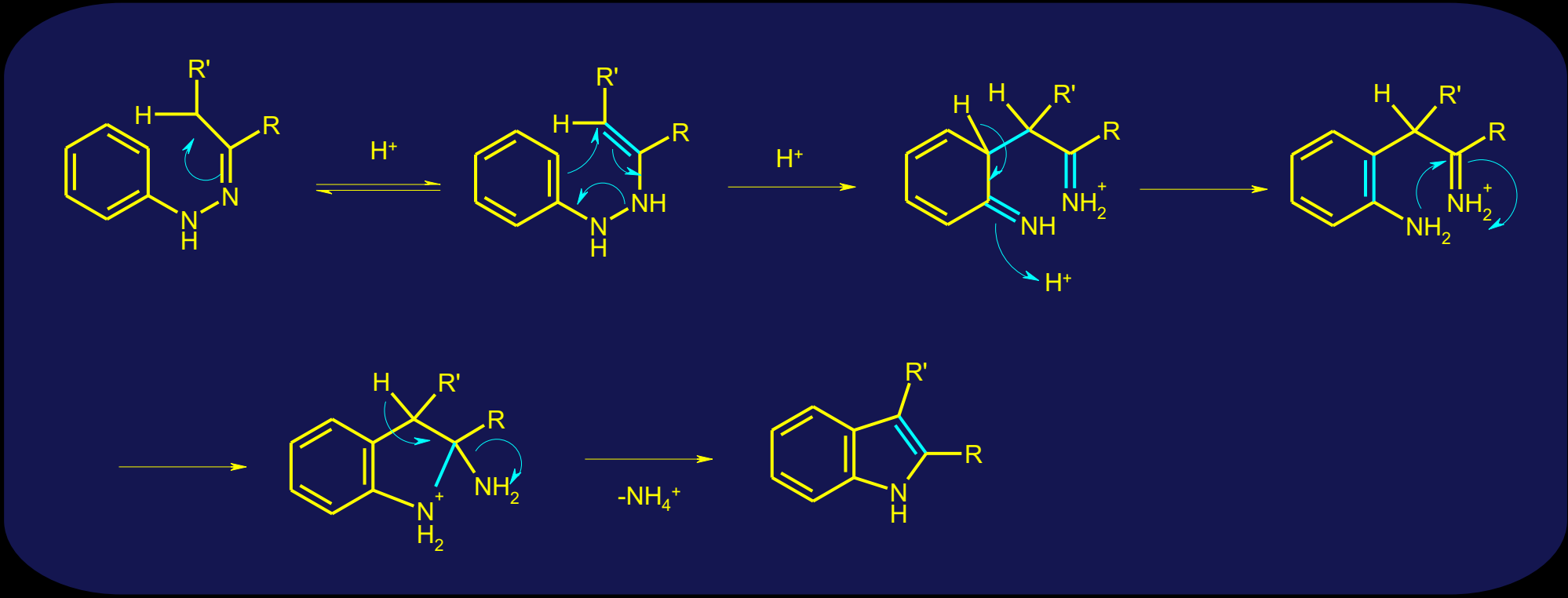
PREPARATI PROTIV MIGRENE - TRIPTANI: SINTEZE

ALMOTRIPTAN - nastavak



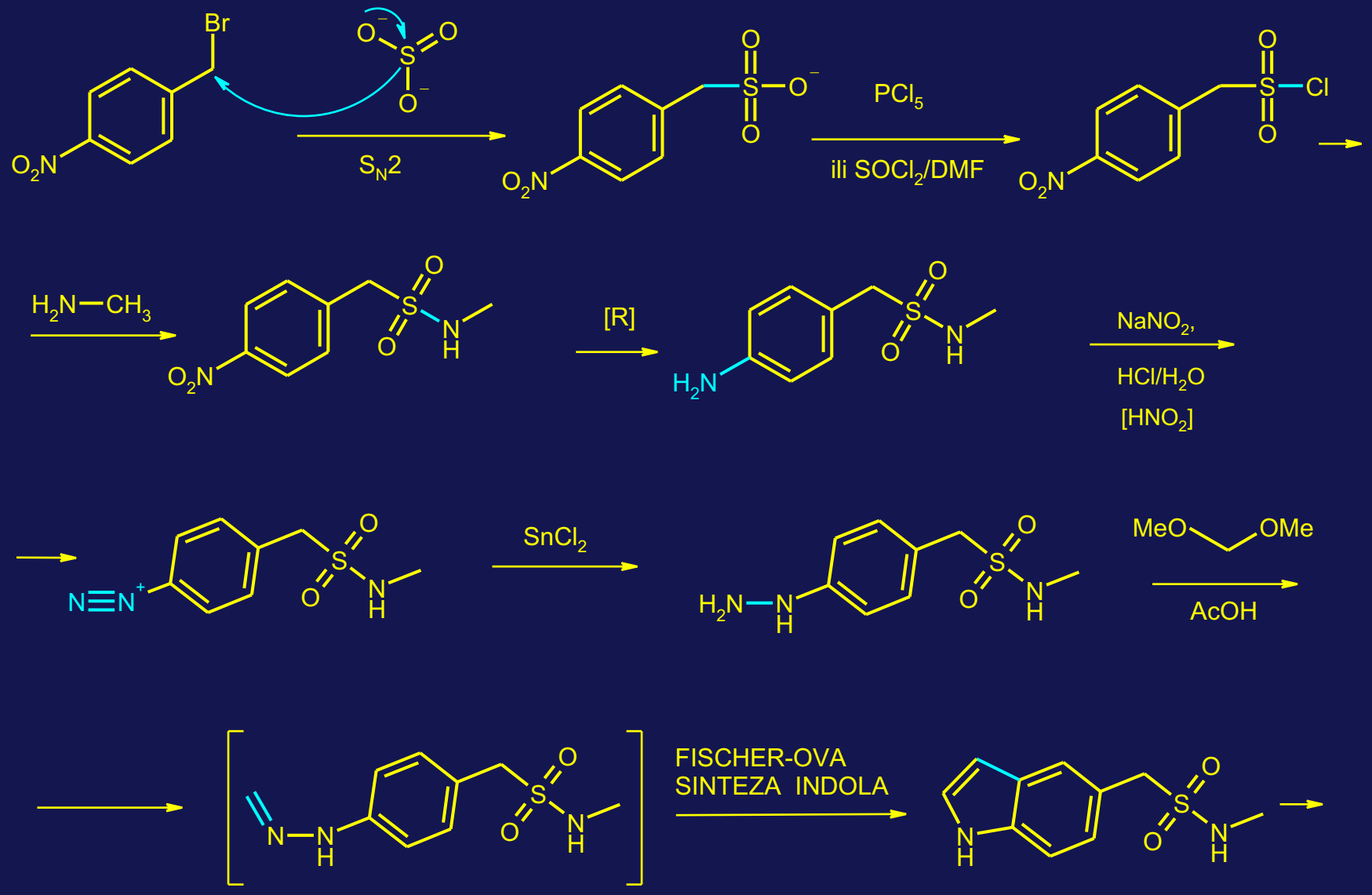
J. Bosch et al. / Tetrahedron 57 (2001) 1041-1048

MEHANIZAM FISCHER-ove SINTEZE INDOLA - [3,3]-SIGMATROPNO PREMEŠTANJE



PREPARATI PROTIV MIGRENE - TRIPTANI: SINTEZE

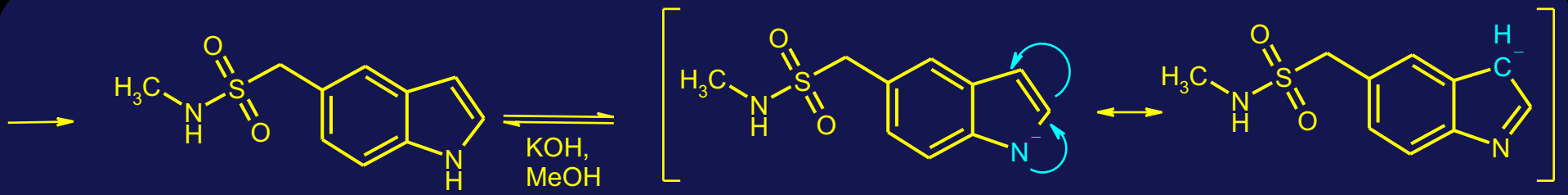
NARATRIPTAN

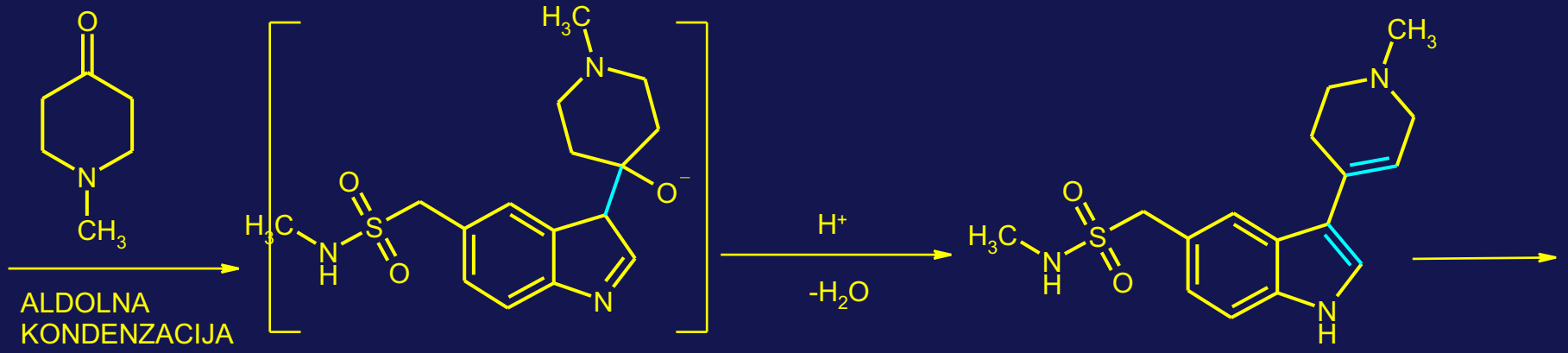


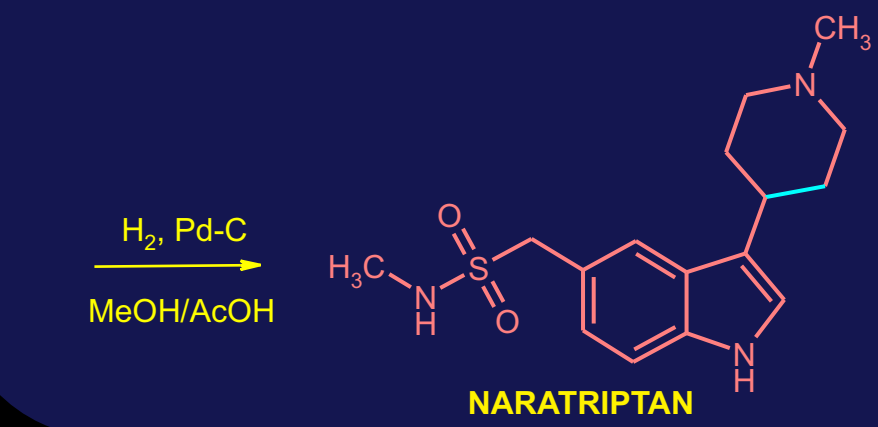
1. Organic Process Research & Development 2009, 13, 468; 2. U.S. Patent 4,997,841, 1991

PREPARATI PROTIV MIGRENE - TRIPTANI: SINTEZE

NARATRIPTAN - nastavak



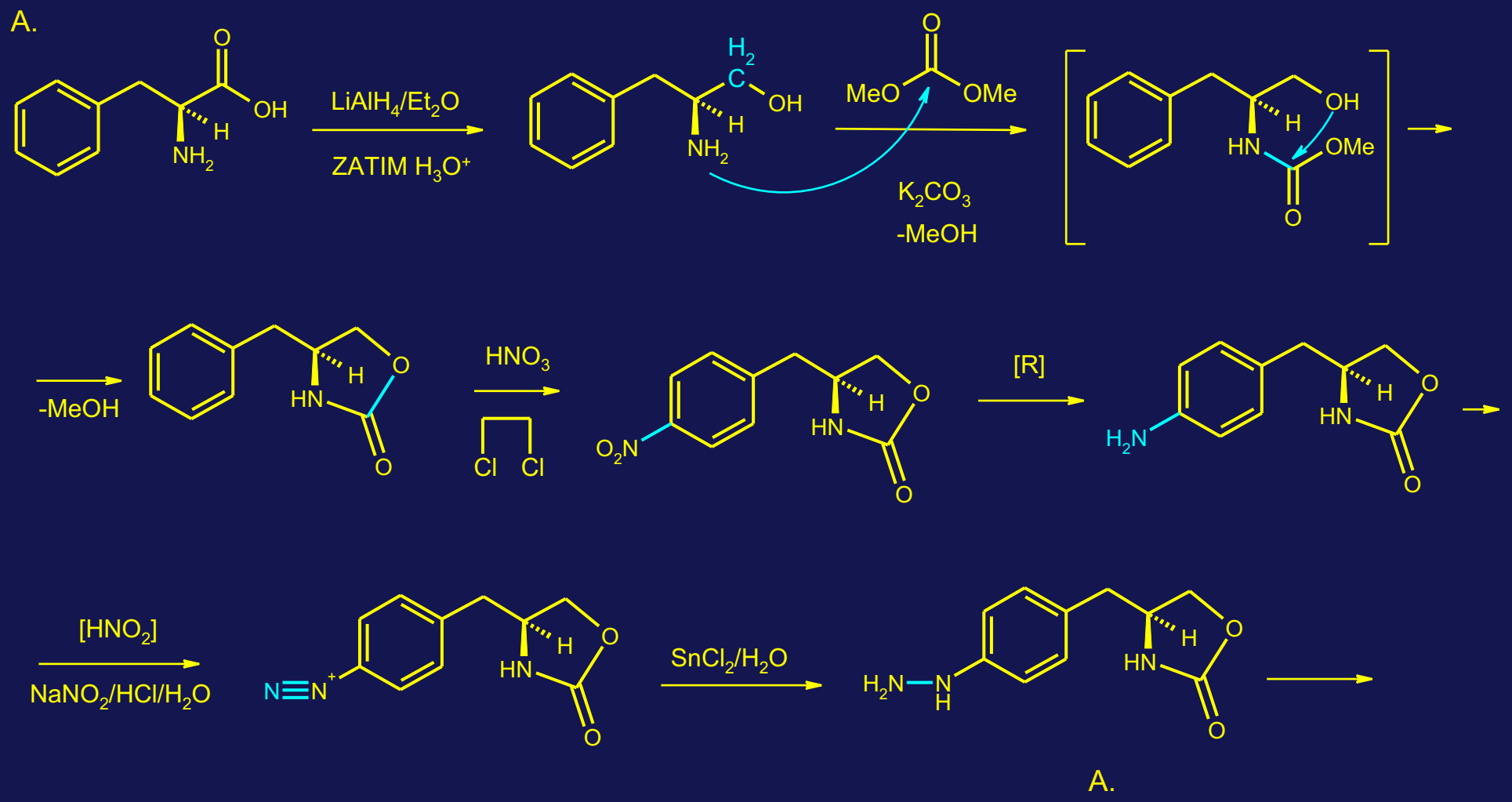




NARATRIPTAN

PREPARATI PROTIV MIGRENE - TRIPTANI: SINTEZE

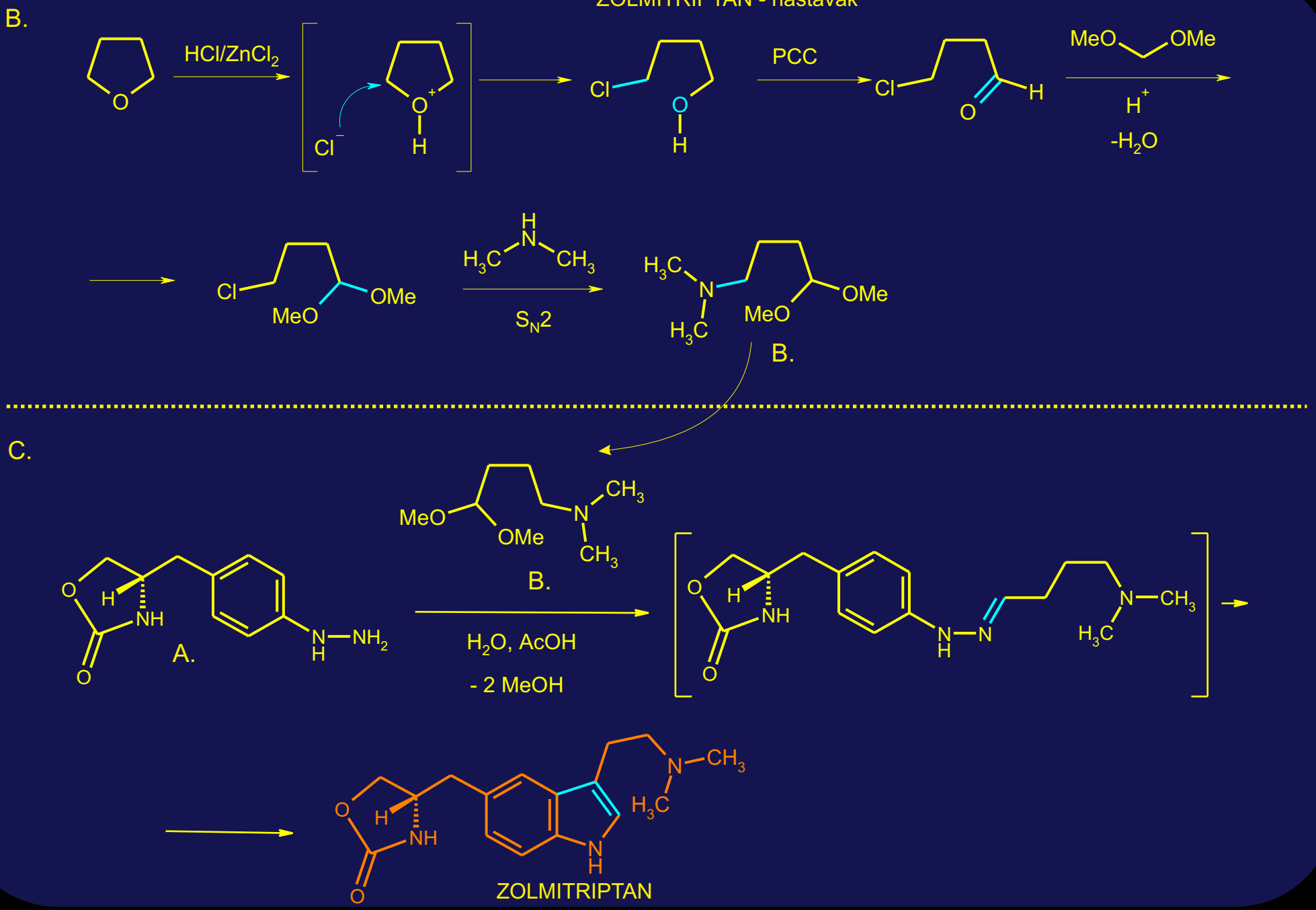
ZOLMITRIPTAN



PCT Int. Appl., 2009044211, 09 Apr 2009; Bioorganic Chemistry 30 (2002) 315

PREPARATI PROTIV MIGRENE - TRIPTANI: SINTEZE

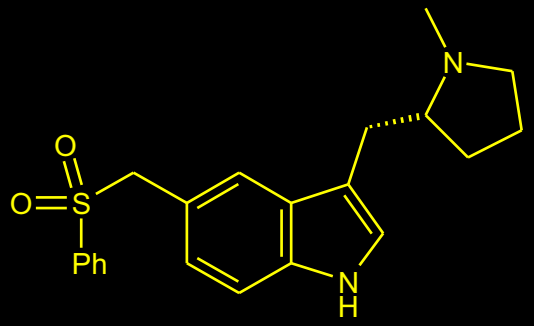
ZOLMITRIPTAN - nastavak



NOVI PREPARATI PROTIV MIGRENE - TRIPTANI: STRUKTURA I LITERATURA

Monograph Number: 301
Title: ALMOTRIPTAN
CAS Registry Number: 154323-57-6
CAS Name: 1-[[[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]sulfonyl]pyrrolidine
Additional Names: 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine
Manufacturers' Codes: LAS-31416
Molecular Formula: C17H25N3O2S
Molecular Weight: 335.47.
Percent Composition: C 60.87%, H 7.51%, N 12.53%, O 9.54%, S 9.56%
Literature References: Serotonin 5HT1B/1D-receptor agonist. Prepn: D. F. Forner *et al.,* **WO 94 2460**; *eidem*, **US 5565447** (1994, 1996 both to Almirall). Clinical pharmacokinetics: J. C. Fleishaker *et al., Clin. Pharmacol. Ther.* **67**, 498 (2000). *Review*: F. Kamali, *Curr. Opin. CPNS Invest. Drugs* **2**, 197-202 (2000).
Derivative Type: Maleate
CAS Registry Number: 181183-52-8
Manufacturers' Codes: PNU-180638E
Trademarks: Almogran (Almirall); Axert (Pharmacia & Upjohn)
Molecular Formula: C17H25N3O2S.C4H6O5
Molecular Weight: 469.56.
Percent Composition: C 53.72%, H 6.65%, N 8.95%, O 23.85%, S 6.83%
Therap-Cat: Antimigraine.

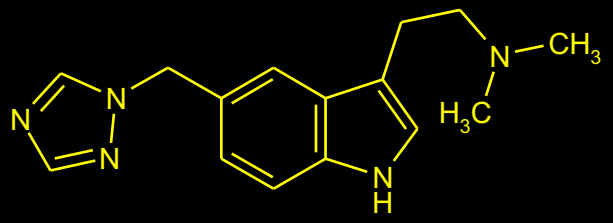
Monograph Number: 3577
Title: ELETRIPTAN
CAS Registry Number: 143322-58-1
CAS Name: 3-[[(2*R*)-1-Methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonyl)ethyl]-1*H*-indole
Additional Names: 5-[2-(benzenesulfonyl)ethyl]-3-(1-methylpyrrolidin-2(*R*)-ylmethyl)-1*H*-indole
Manufacturers' Codes: UK-116044
Trademarks: Relpax (Pfizer)
Molecular Formula: C22H26N2O2S
Molecular Weight: 382.53.
Percent Composition: C 69.08%, H 6.85%, N 7.32%, O 8.36%, S 8.38%
Literature References: Serotonin 5-HT1B/1D receptor agonist. Prepn: J. E. Macor, M. J. Wythes, **WO 92 06973**; *eidem,* **US 5545644** (1992, 1996 both to Pfizer). Pharmacology: E. Willems *et al., Arch. Pharmacol.* **358,** 212 (1998). Affinity and specificity of receptor binding: C. Napier *et al., Eur. J. Pharmacol.* **368,** 259 (1999). Clinical trial in comparison with sumatriptan, *q.v.*: P. J. Goadsby *et al., Neurology* **54,** 156 (2000). Review of pharmacokinetics, and clinical efficacy: A. Bardsley-Elliot, S. Noble, *CNS Drugs* **12,** 325-333 (1999).
Therap-Cat: Antimigraine.



NOVI PREPARATI PROTIV MIGRENE - TRIPTANI: STRUKTURA I LITERATURA

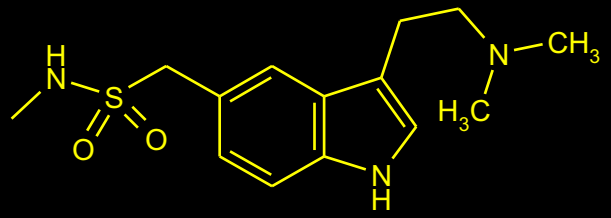
Monograph Number: 6446
Title: NARATRIPTAN
CAS Registry Number: 121679-13-8
CAS Name: *N*-Methyl-3-(1-methyl-4-piperidinyl)-1*H*-indole-5-ethanesulfonamide
Molecular Formula: C17H25N3O2S
Molecular Weight: 335.47.
Percent Composition: C 60.87%, H 7.51%, N 12.53%, O 9.54%, S 9.56%
Literature References: Serotonin 5-HT1B/1D receptor agonist. Prepn: A. W. Oxford *et al.,* **EP 303507**; *eidem,* **US 4997841** (1989, 1991 both to Glaxo). Pharmacology and receptor binding study: H. E. Connor *et al., Cephalalgia* **17,** 145 (1997). Determn in plasma and pharmacokinetics in rabbits: B. D. Duléry *et al., J. Pharm. Biomed. Anal.* **15,** 1009 (1997). Clinical trial in migraine: H. Havanka *et al., Clin. Ther.* **22,** 970 (2000).
Properties: Crystals from ethyl acetate, mp 170-171°.
Melting point: mp 170-171°
Derivative Type: Hydrochloride
CAS Registry Number: 143388-64-1
Manufacturers' Codes: GR-85548A
Trademarks: Amerge (Glaxo Wellcome); Naramig (Glaxo Wellcome)
Molecular Formula: C17H25N3O2S.HCl
Molecular Weight: 371.93.
Percent Composition: C 54.90%, H 7.05%, N 11.30%, O 8.60%, S 8.62%, Cl 9.53%
Properties: Microcrystals, mp 237-239°.**Melting point:** mp 237-239°
Therap-Cat: Antimigraine.

Monograph Number: 8324
Title: RIZATRIPTAN
CAS Registry Number: 144034-80-0
CAS Name: *N,N*-Dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine
Additional Names: 3-[2-(dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)indole; *N,N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3yl]ethylamine
Molecular Formula: C15H19N5
Molecular Weight: 269.34.
Percent Composition: C 66.89%, H 7.11%, N 26.00%
Literature References: Selective serotonin 5-HT1D receptor agonist; structurally derived from tryptamine. Prepn: R. Baker *et al.,* **EP 497512**; *eidem,* **US 5298520** (1992, 1994 both to Merck Sharp & Dohme); and binding characteristics: L. J. Street *et al., J. Med. Chem.* **38,** 1799 (1995). Synthesis: C. Chen *et al., Tetrahedron Letters* **35,** 6981 (1994). Clinical pharmacokinetics: H. Cheng *et al., Biopharm. Drug Dispos.* **17,** 17 (1996). LC-MS determn in plasma: D. A. McLoughlin *et al., J. Chromatog. A* **726,** 115 (1996). Multicenter clinical trial in treatment of migraine: W. H. Visser *et al., Arch. Neurol.* **53,** 1132 (1996).
Properties: mp 120-121°.**Melting point:** mp 120-121°
Derivative Type: Benzoate
CAS Registry Number: 145202-66-0
Manufacturers' Codes: MK-0462; MK-462
Trademarks: Maxalt (Merck & Co)
Molecular Formula: C15H19N5.C6H5COOH
Molecular Weight: 391.47.
Percent Composition: C 67.50%, H 6.44%, N 17.89%, O 8.17%
Properties: mp 178-180°.
Melting point: mp 178-180°
Therap-Cat: Antimigraine.



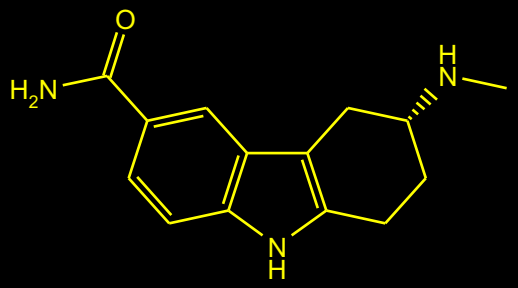
NOVI PREPARATI PROTIV MIGRENE - TRIPTANI: STRUKTURA I LITERATURA

Monograph Number: 9088
Title: SUMATRIPTAN
CAS Registry Number: 103628-46-2
CAS Name: 3-[2-(Dimethylamino)ethyl]-*N*-methyl-1*H*-indole-5-methanesulfonamide
Manufacturers' Codes: GR-43175
Molecular Formula: $C_{14}H_{21}N_3O_2S$
Molecular Weight: 295.41.
Percent Composition: C 56.92%, H 7.17%, N 14.22%, O 10.83%, S 10.85%
Literature References: Serotonin $5HT_1$-receptor agonist. Prepn: M. D. Dowle, I. H. Coates, **DE 3320521**; *eidem,* **US 4816470**; A. W. Oxford, **GB 2162522** (1983, 1989, 1986 all to Glaxo). Receptor binding studies: P. P. A. Humphrey *et al., Brit. J. Pharmacol.* **94,** 1123 (1988); P. Schoeffter, D. Hoyer, *Arch. Pharmacol.* **340,** 135 (1989). LC-MS determn in plasma: J. Oxford, M. S. Lant, *J. Chromatog.* **496,** 137 (1989). Clinical evaluations in migraine: A. Doenicke *et al., Lancet* **1,** 1309 (1988); Subcutaneous Sumatriptan International Study Group, *N. Engl. J. Med.* **325,** 316 (1991); in acute cluster headache: Sumatriptan Cluster Headache Study Group, *ibid.* 322. Review of pharmacology and clinical experience: S. J. Peroutka, *Headache* **30** (Suppl. 2), 554-560 (1990).
Properties: mp 169-171°. **Melting point:** mp 169-171°
Derivative Type: Succinate
CAS Registry Number: 103628-48-4
Manufacturers' Codes: GR-43175C
Trademarks: Imigran (Glaxo); Imitrex (Glaxo Wellcome); Imiject (Glaxo Wellcome)
Molecular Formula: $C_{14}H_{21}N_3O_2S.C_4H_6O_4$
Molecular Weight: 413.49.
Percent Composition: C 52.29%, H 6.58%, N 10.16%, O 23.22%, S 7.75%
Properties: mp 165-166°.
Melting point: mp 165-166°
Therap-Cat: Antimigraine.



Monograph Number: 10241
Title: ZOLMITRIPTAN
CAS Registry Number: 139264-17-8
CAS Name: (4*S*)-4-[[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-2-oxazolidinone
Additional Names: (*S*)-*N,N*-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-3-yl]ethylamine
Manufacturers' Codes: 311C90; BW-311C90
Trademarks: Zomig (Zeneca)
Molecular Formula: $C_{16}H_{21}N_3O_2$
Molecular Weight: 287.36.
Percent Composition: C 66.87%, H 7.37%, N 14.62%, O 11.14%
Literature References: Serotonin $5HT_{1D}$-receptor agonist. Prepn: A. D. Robertson *et al.,* **WO 91 18897** (1991 to Wellcome Foundation); *eidem,* **US 5466699** (1995 to Burroughs Wellcome). Structure-activity and receptor binding study: R. C. Glen *et al., J. Med. Chem.* **38,** 3566 (1995). Pharmacology: P. J. Goadsby, L. Edvinsson, *Headache* **34,** 394 (1994). Clinical pharmacokinetics: E. Seaber *et al., Brit. J. Clin. Pharmacol.* **41,** 141 (1996). Clinical trial in migraine: S. J. Tepper *et al., Curr. Med. Res. Opin.* **15,** 254 (1999).
Properties: White crystals from isopropanol as the 0.9 isopropanolate hemihydrate, mp 139-141°. [ ]$_{D22}$ -5.79° (c = 0.5 in methanol). pKa 9.64. Stable; nonhygroscopic. Soly in aq soln at neutral pH: >20 mg/ml.
Melting point: mp 139-141°
pKa: pKa 9.64
Optical Rotation: [ ]$_{D22}$ -5.79° (c = 0.5 in methanol)
Therap-Cat: Antimigraine.

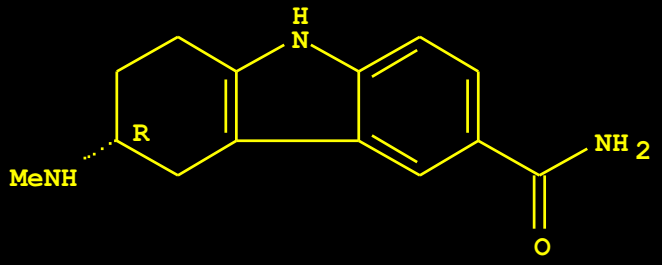
NOVI PREPARATI PROTIV MIGRENE - TRIPTANI: STRUKTURA I LITERATURA



(R)-Frovatriptan;
Frova

Registry Number: 158747-02-5

Absolute stereochemistry. Rotation (+).



Formula: $C_{14}H_{17}N_3O$

CA Index Name: 1H-Carbazole-6-carboxamide, 2,3,4,9-tetrahydro-3-(methylamino)-, (3R)-

Other Names: 1H-Carbazole-6-carboxamide, 2,3,4,9-tetrahydro-3-(methylamino)-, (R)-; (R)-Frovatriptan; Frova Frovatriptan; Migard; Miguard; SB 209509

References: ~235