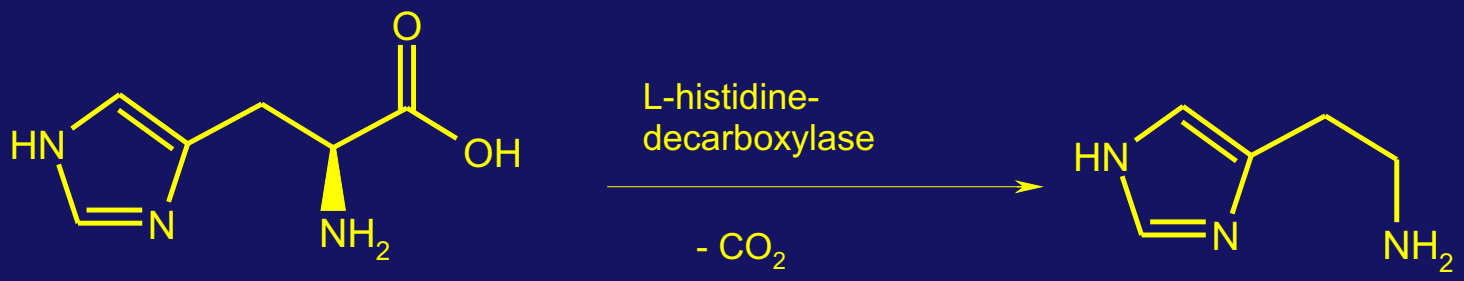
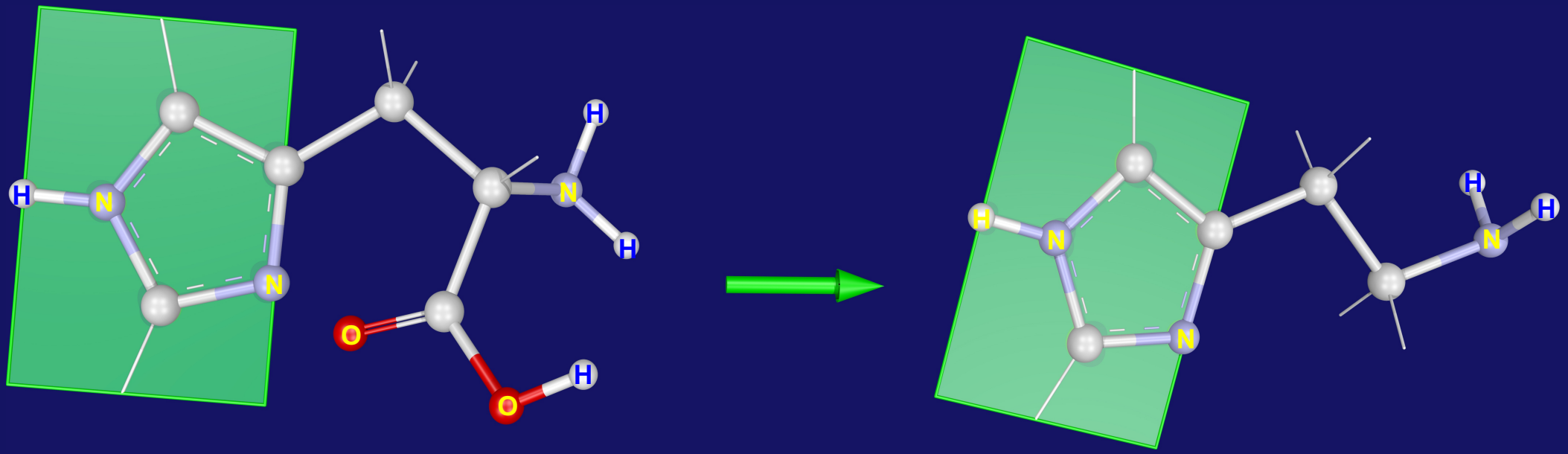
ANTI-HISTAMINICI. HISTAMIN- STRUKTURA, POREKLO I ULOGA

- HISTAMIN[1] POSTAJE U ORGANIZMU DEKARBOKSILACIJOM L-HISTIDINA



Histidine

Histamine



1. The Merck Index Thirteenth Edition; Copyright 2001 by MERCK & Co Inc, USA; Monograph Number: 4739

ANTI-HISTAMINICI. HISTAMIN- STRUKTURA, POREKLO I ULOGA

Monograph Number: 4739
Title: Histamine
CAS Registry Number: 51-45-6
CAS Name: 1*H*-Imidazole-4-ethanamine
Additional Names: 2-(4-imidazolyl)ethylamine; 4-imidazoleethylamine; 5-imidazoleethylamine; □-aminoethylimidazole; □-aminoethylglyoxaline
Molecular Formula: $C_5H_9N_3$
Molecular Weight: 111.14.
Percent Composition: C 54.03%, H 8.16%, N 37.81%
Literature References: Biogenic amine widely distributed in nature; decarboxylation product of histidine, *q.v.* Present in most mammalian tissues; primarily stored in mast cells and basophils. Exhibits multiple biological effects through at least 3 specific receptors. Induces bronchoconstriction and vasodilation; stimulates gastric acid secretion; and acts as a neurotransmitter. Synthesis: A. Windaus, W. Vogt, *Ber.* **40,** 3691 (1907); F. L. Pyman, *J. Chem Soc.* **101,** 530 (1912). Identification as vasodilator: H. H. Dale, P. P. Laidlaw, *J. Physiol.* **41,** 318 (1910). Toxicity data: K. Nagai *et al., Arzneimittel-Forsch.* **17,** 1575 (1967). Diagnostic use in pheochromocytoma: T. Nakai, R. Yamada, *J. Clin. Endocrinol. Met.* **57,** 19 (1983); in airway responsiveness: A. James, G. Ryan, *Respirology* **2,** 97 (1997). Clinical efficacy in combination with interleukin-2, *q.v.,* in treatment of acute myelogenous leukemia: K. Hellstrand *et al., Leuk. Lymphoma* **27,** 429 (1997). Mechanism of antineoplastic activity: *eidem, Acta Oncol.* **37,** 347 (1998). Review of assay methods for determn in plasma: E. Oosting *et al., Clin. Exp. Allergy* **20,** 349-357 (1990). Review of role in allergic disease: M. V. White, *J. Allergy Clin. Immunol.* **86,** 599-605 (1990); in gastric acid secretion: K. J. Obrink, *Scand. J. Gastroenterol.* **26,** Suppl. 180, 4-8 (1991); in homeostatic energy metabolism: T. Sakata *et al., Nutrition* **13,** 403-411 (1997). Review of pharmacology and classification of receptors: S. J. Hill *et al., Pharmacol. Rev.* **49,** 253-278 (1997).
Properties: Deliquescent needles from chloroform, mp 83-84°. bp_{18} 209-210°. Freely sol in water, alcohol, hot chloroform. Practically insol in ether. LD_{50} i.p. in mice: 2020 mg/kg (Nagai).
Melting point: mp 83-84°
Boiling point: bp_{18} 209-210°
Toxicity data: LD_{50} i.p. in mice: 2020 mg/kg (Nagai)

Derivative Type: Dihydrochloride
CAS Registry Number: 56-92-8
Trademarks: Maxamine (Maxim)
Molecular Formula: $C_5H_9N_3.2HCl$
Molecular Weight: 184.07.
Percent Composition: C 32.63%, H 6.02%, N 22.83%, Cl 38.52%
Properties: Prisms from ethanol, mp 244-246°. Freely sol in water, methanol; sol in ethanol.
Melting point: mp 244-246°

Derivative Type: Phosphate
CAS Registry Number: 51-74-1
Molecular Formula: $C_5H_9N_3.2H_3PO_4$
Molecular Weight: 307.13.
Percent Composition: C 19.55%, H 4.92%, N 13.68%, P 20.17%, O 41.67%
Properties: Clear, colorless prisms from water, mp 132-133°. Readily sol in hot water.
Melting point: mp 132-133°

Therap-Cat: Antineoplastic (immunomodulator); diagnostic aid (gastric secretion, pheochromocytoma, bronchial hyperreactivity).

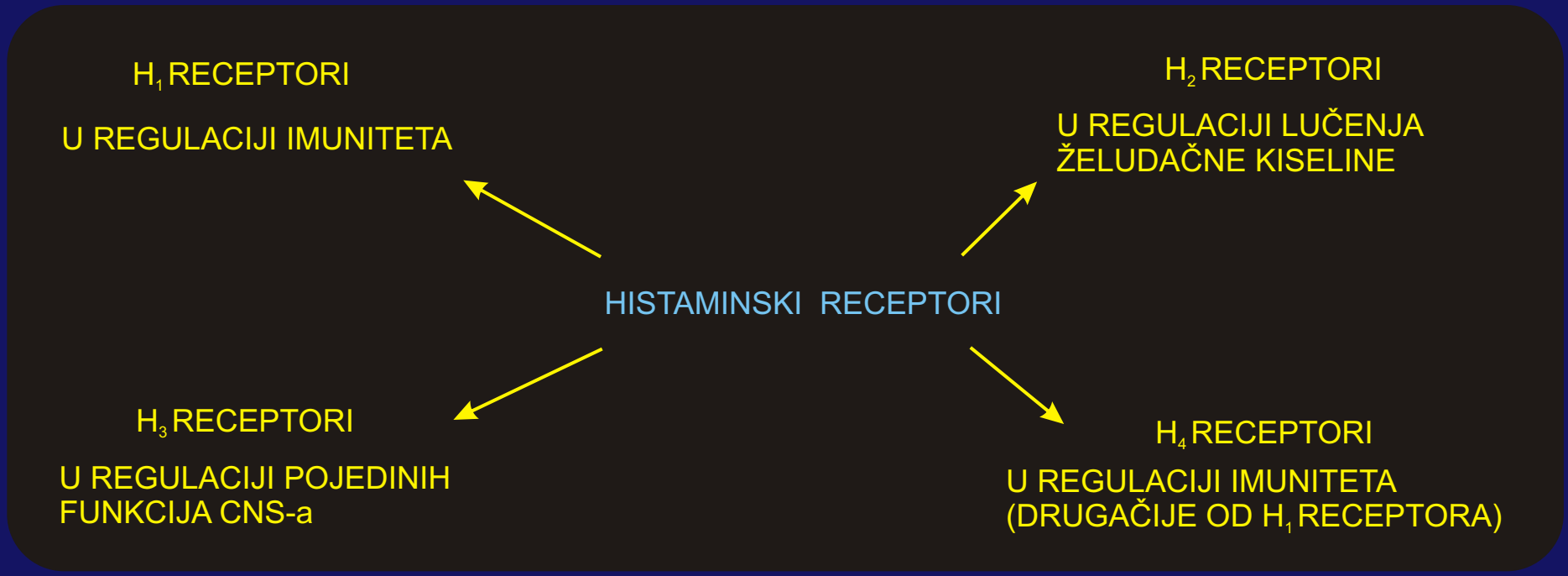
ANTI-HISTAMINICI. HISTAMIN- STRUKTURA, POREKLO I ULOGA[1]

-HISTAMIN JE ŠIROKO RASPROSTRANJEN U GOTOVO SVIM TKVIMA SISARA. IMA ESENCIJALNE I VEOMA RAZLIČITE FUNKCIJE U NORMALNOM FUNKCIONISANJU ORGANIZMA.

- OVE FUNKCIJE OSTVARUJU SE REVERZIBILNIM VEZIVANJEM HISTAMINA ZA SPECIFIČNE PROTEINSKE MOLEKULE, HISTAMINSKE RECEPTORE, KOJI SE NALAZE U POJEDINIM TKIVIMA.

- DANAS JE POZNATO DA POSTOJE 4 VRSTE OVIH RECEPTORA, OZNAČENIH KAO H_1[2], H_2[3], H_3[4] I H_4[5] IAKO JE NJIHOVA NORMALNA

POJEDINE NORMALNE FIZIOLOŠKE FUNCIJE HISTAMINSKIH RECEPTORA I HISTAMINA



1. **GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS - 11th Ed. (2006)** ; ISBN 0-07-142280-3 ; **CHAPTER 24. HISTAMINE, BRADYKININ, AND THEIR ANTAGONISTS - *Randal A. Skidgel and Ervin G. Erdos***

2.Ash, A.S.F., and Schild, H.O. Receptors mediating some actions of histamine. *Br. J. Pharmacol.,* **1966,** *27*:427-439. ;

3.Black, J.W., Duncan, W.A., Durant, C.J., Ganellin, C.R., and Parsons, E.M. Definition and antagonism of histamine H_2-receptors. *Nature,* **1972,** *236*:385-390;

4.Arrang, J.-M., Garbarg, M., Lancelot, J.-C., *et al.* Highly potent and selective ligands for histamine H_3-receptors. *Nature,* **1987,** *327*:117-123

5.Hough, L.B. Genomics meets histamine receptors: New subtypes, new receptors. *Mol. Pharmacol.,* **2001**, *59*:415-419

HISTAMINSKI RECEPTORI (H_1, H_2, H_3 I H_4)

- PROTEINSKI MOLEKULI KOJI SE NALAZE U ĆELIJSKOM ZIDU POJEDINIH TIPOVA ĆELIJA.

-PRIPADAJU ŠIROJ KLASI POZNATOJ KAO TRANS-MEMBRANSKI RECEPTORI (tj. G-PROTEIN KUPLOVANI RECEPTORI "G PROTEIN-COUPLED RECEPTORS")

- POZNATA JE NJIHOVA AMINO-KISELINSKA SEKVENCA ALI NE I 3D STRUKTURA.

- POSTOJE RAZLIČITI MATEMATIČKI ALGORITMI ZA PREDVIĐANJE MOGUĆE 3D STRUKTURE, POLAZEĆI OD AMINO-KISELINSKE SEKVENCE KAO I POZNATIH 3D STRUKTURA SRODNIH PROTINSKIH MOLEKULA (ADENO-RECEPTOR KAO I BAKTERIJSKI RODOPSIN)

-OVAKO DOBIJENE, HIPOTETIČNE 3D STRUKTURE, MOGU SE KORISTITI ZA "DOCKING" (FORMIRANJE VIRTUELNOG KOMPLEKSA LIGAND - RECEPTOR) I POREĐENJA PRORAČUNATIH VREDNOSTI SA VREDNOSTIMA KOJE SU ODREĐENE EKSPERIMENTALNO (tj. STABILNOST REALNOG KOMPLEKSA LIGAND - RECEPTOR KOJA SE ODREĐUJE *in vitro).*

-KORIŠĆENJE HIPOTETIČNIH 3D STRUKTURA RECEPTORA PRUŽA ZNAČAJNE INFORMACIJE O STRUKTURI I OSOBINAMA AKTIVNOG MESTA RECEPTORA, ALI JE DALEKO MANJE POUZDANO OD REALNIH 3D STRUKTURA (KOJE SE DOBIJAJU RENTGENO-STRUKTURNOM ANALIZOM KRISTALA RECEPTORSKOG PROTEINA).

-MEĐUTIM, TRANS-MEMBRANSKI PROTEINSKI RECEPTORI SE VEOMA TEŠKO IZOLUJU U NATIVNOM 3D OBLIKU I STOGA NJIHOVA 3D STRUKTURA NAJČEŠĆE NIJE ODREĐENA (UZ IZUZETAK NAVEDENOG ADENO-RECEPTORA KAO I BAKTERIJSKOG RODOPSINA)

ANTI-HISTAMINICI- OSNOVNA FARMAKOLOŠKA PODELA

-HISTAMIN KAO LEK NEMA PRIMENU U TERAPIJI. ISKLJUČIVO SE KORISTI KAO DIJAGNOSTIČKO SREDSTVO (U ISPITIVANJU ALERGIJSKIH REAKCIJA)

- ČESTO SE SREĆU POREMEĆAJI METABOLIZMA HISTAMINA: - DOLAZI DO HIPER-PRODUKCIJE I/ILI PREOSETLJIVOSTI ORGANIZMA NA HISTAMIN

- POSLEDICE SU PATOLOŠKA STANJA, OD KOJIH SE NAJČEŠĆE JAVLJAJU RAZLIČITI OBLICI ALERGIJE I PRETERANO LUČENJE ŽELUDAČNE KISELINE

- STOGA JE U TERAPIJSKOM SMISLU, POTREBNO BLOKIRATI DEJSTVO HISTAMINA, NAJČEŠĆE SELEKTIVNOM INHIBICIJOM HISTAMINSKIH RECEPTORA. U TU SVRHU KORISTE SE BROJNI LEKOVI, ANTI-HISTAMINICI, I TO:

H_1 SELEKTIVNI INIBITORI, PROTIV ALERGIJSKIH REAKCIJA I

H_2 SELEKTIVNI INIBITORI, ZA SMANJENJE LUČENJA ŽELUDAČNE KISELINE.

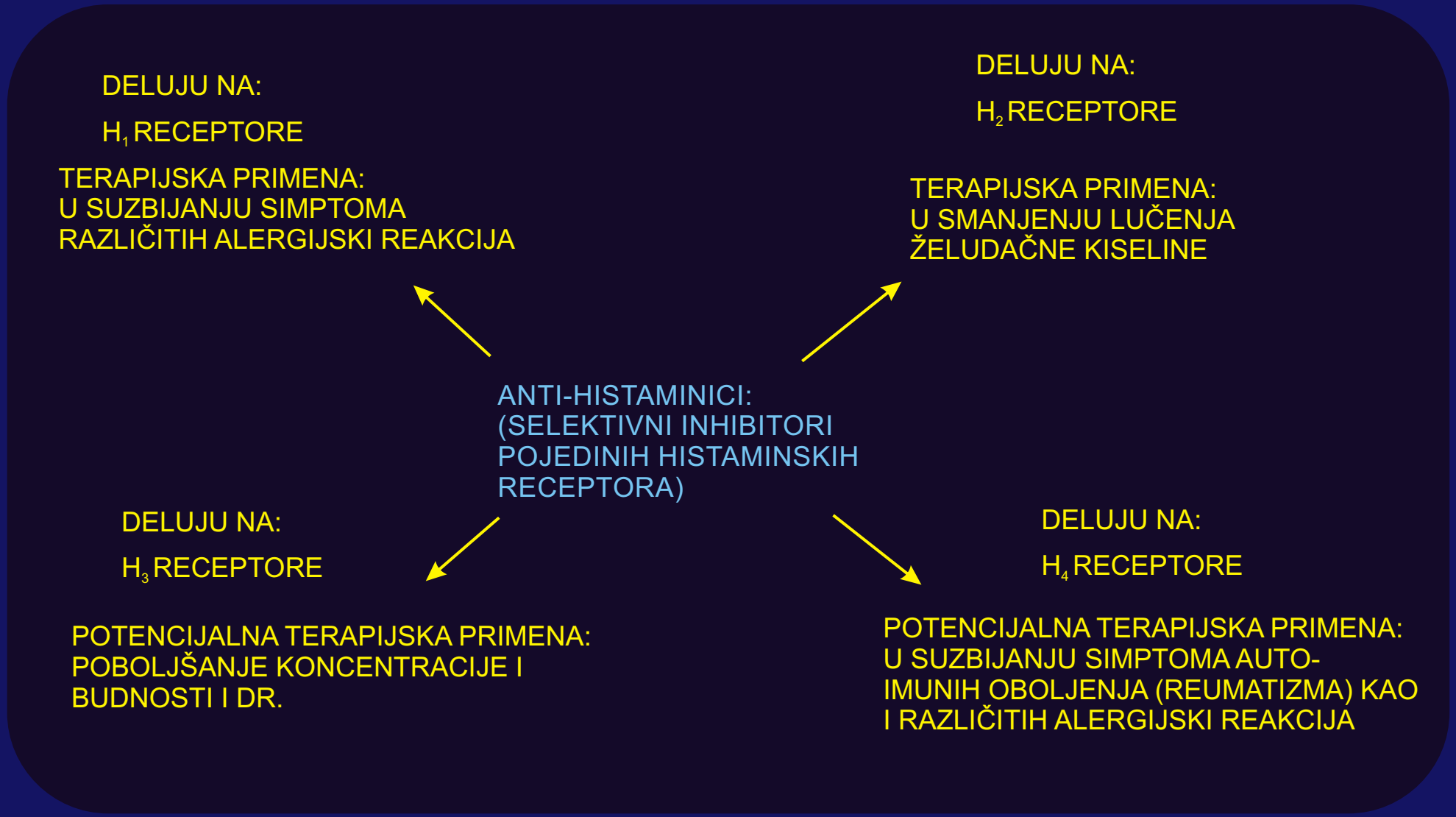
.....

H_3 SELEKTIVNI INIBITORI POSTOJE, ALI ZA SADA NISU U TERAPIJSKOJ PRIMENI. NJIHOVO TERAPIJSKO DEJSTVO SE ISPOLJAVA NA CNS I MOGLO BI DA UKLJUČUJE POBOLJŠANJE KONCENTRACIJE I BUDNOSTI, SUZBIJANJE SIMPTOMA ALZHEIMER-ove BOLESTI I DR.

H_4 SELEKTIVNI INIBITORI SU TAKOĐE POZNATI, A IMAJU POTENCIJAL U TERAPIJI ALERGIJSKIH I AUTO-IMUNIH (REUMATSKIH) OBOLJENJA. MEĐUTIM, NI OVA JEDINJENJA JOŠ UVEK SE NE KORISTE KAO LEKOVI.

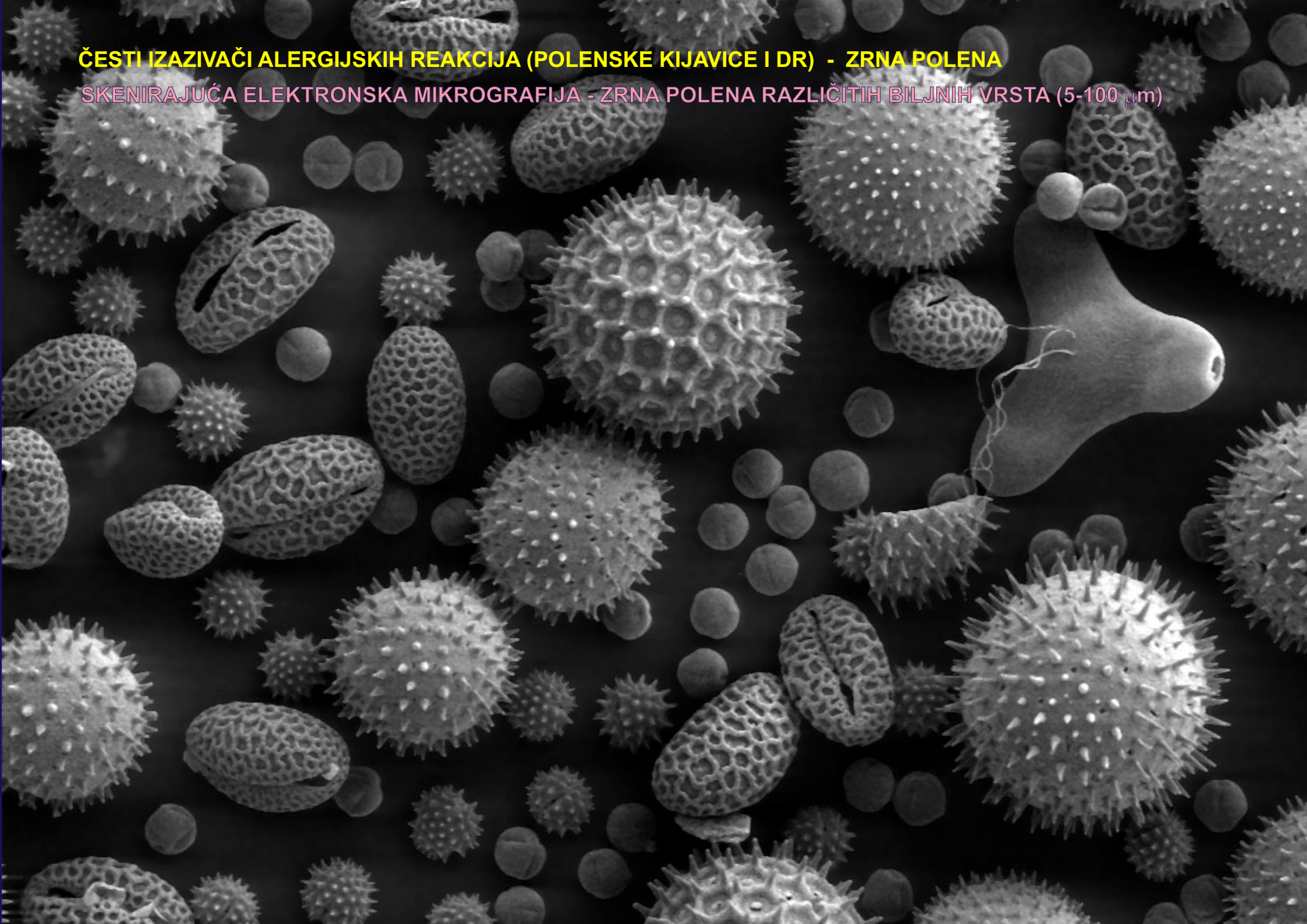
ANTI-HISTAMINICI- OSNOVNA FARMAKOLOŠKA PODELA

OSNOVNA FARMAKOLOŠKA PODELA ANTI-HISTAMINSKIH PREPARATA



ALERGIJE - NEKE EGZOGENE SUPSTANCE KOJE MOGU IZAZVATI PATOLOŠKI IMUNI ODGOVOR ORGANIZMA

ČESTI IZAZIVAČI ALERGIJSKIH REAKCIJA (POLENSKE KIJAVICE I DR) - ZRNA POLENA


ČESTI IZAZIVAČI ALERGIJSKIH REAKCIJA (POLENSKE KIJAVICE I DR) - ZRNA POLENA
SKENIRAJUĆA ELEKTRONSKA MIKROGRAFIJA - ZRNA POLENA RAZLIČITIH BILJNIH VRSTA (5-100 μm)

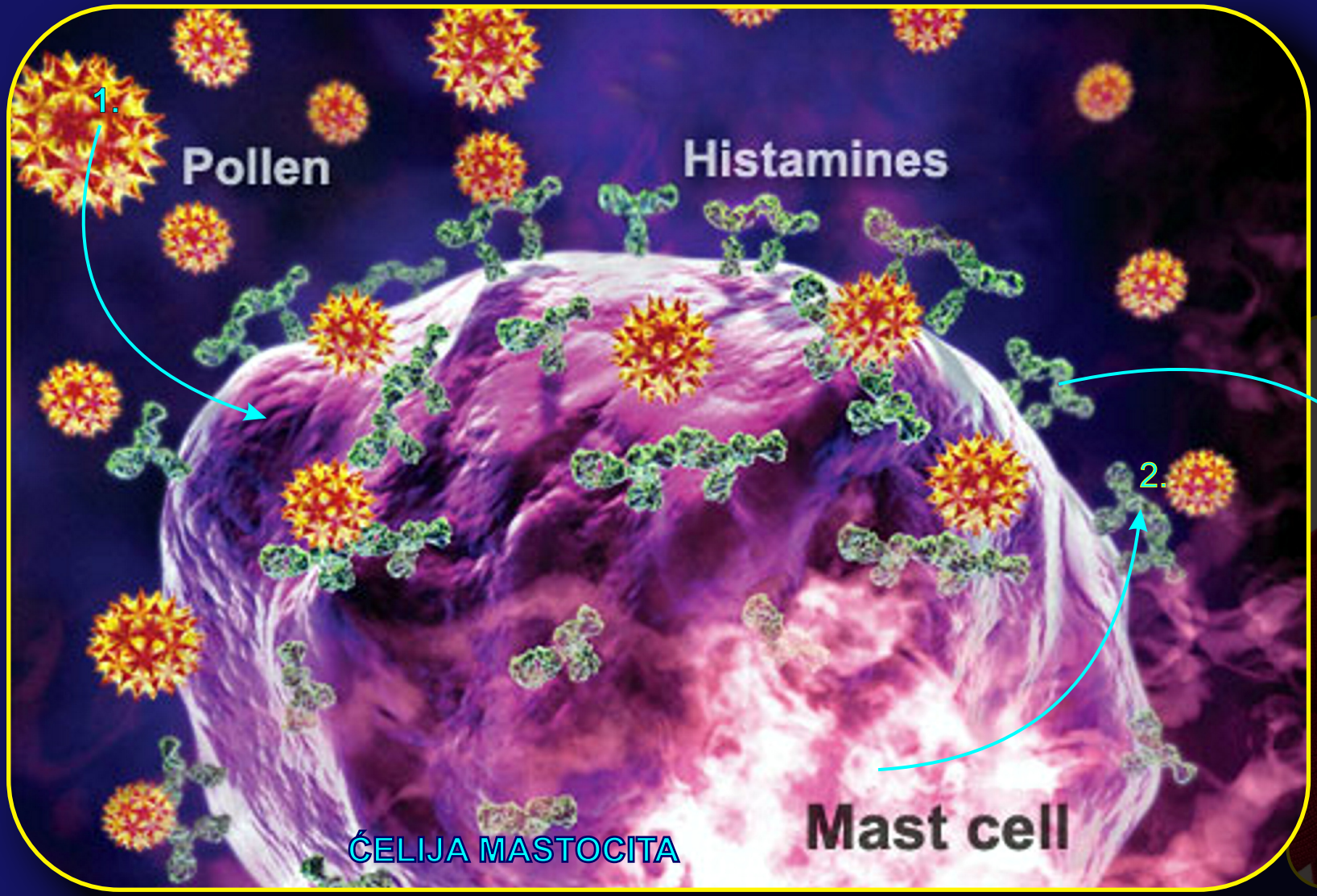
ČESTI IZAZIVAČI ALERGIJSKIH REAKCIJA (POLENSKE KIJAVICE I DR) - ZRNA POLENA U TREPLJASTOM TKIVU DISAJNIH PUTEVA (SKENIRAJUĆA ELEKTRONSKA MIKROGRAFIJA, DIGITALNO PROIZVOLJNO OBOJENA

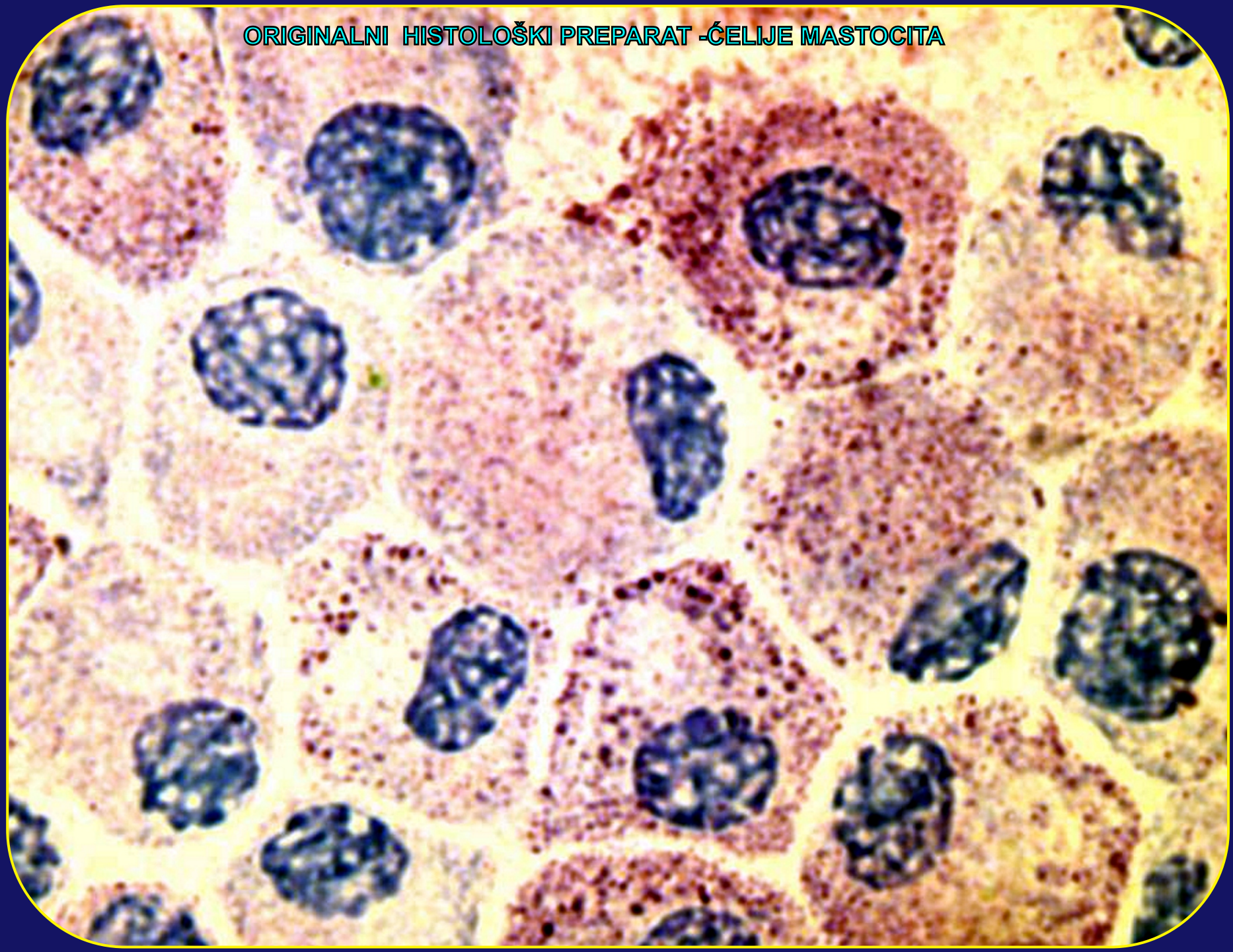
KRAJNJE POJEDNOSTAVLJENI MEHANIZAM ALERGIJSKE REAKCIJE -

1. ČESTICE POLENA INTERAGUJU SA POSEBNIM ĆELIJAMA - MASTOCITIMA, UNUTAR KOJIH SE NALAZI HISTAMIN.

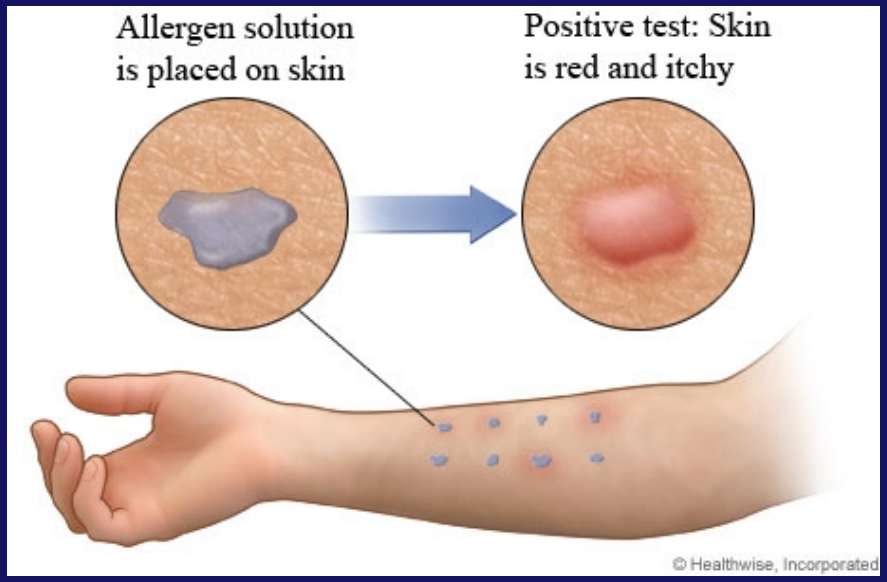
2. KAO POSLEDICA IMUNE REAKCIJE , DOLAZI DO OSLOBAĐANJA HISTAMINA, ČIME POČINJE "LANČANA REAKCIJA" U ORGANIZMU.

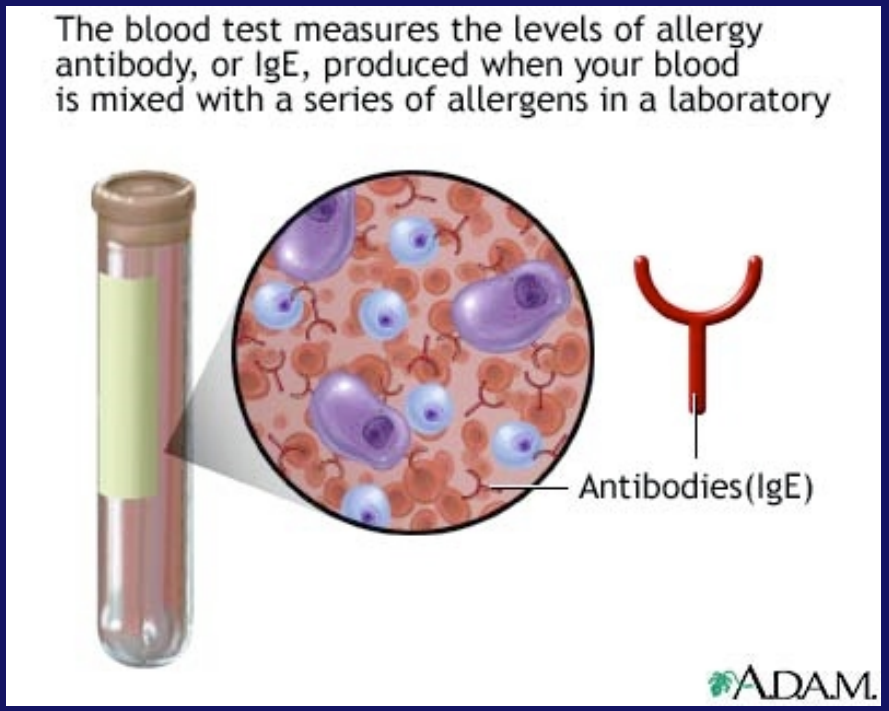
3. KRAJNJI REZULTAT JE ALERGIJSKA KIJAVICA, NADRAŽAJ OČIJU, KAŠALJ, EVENTUALNO REAKCIJE NA KOŽI I DR.

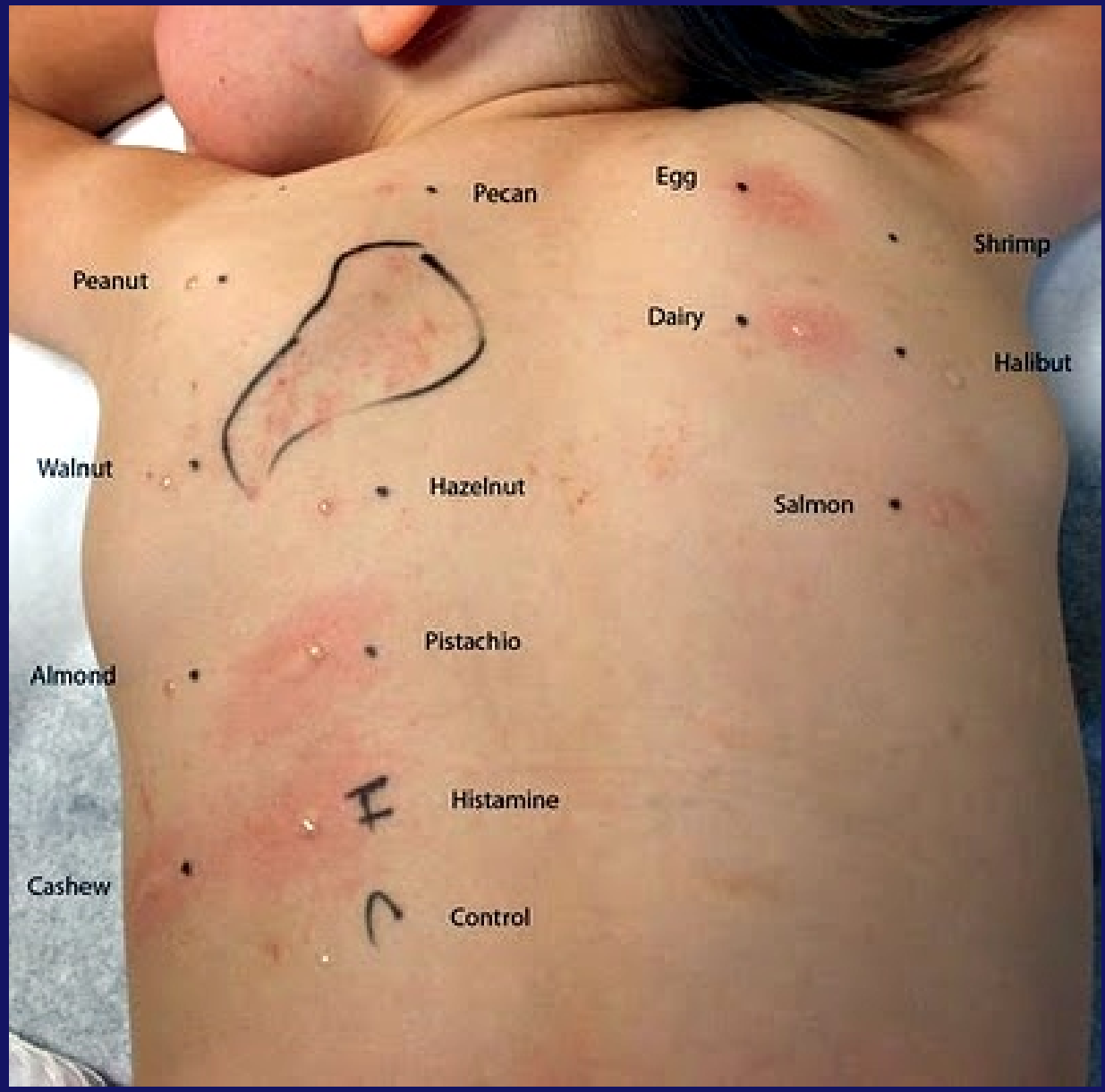



ORIGINALNI HISTOLOŠKI PREPARAT -ĆELIJE MASTOCITA

IZGLED ALERGIJSKE REAKCIJE NA KOŽI - ALERGOTESTOVI



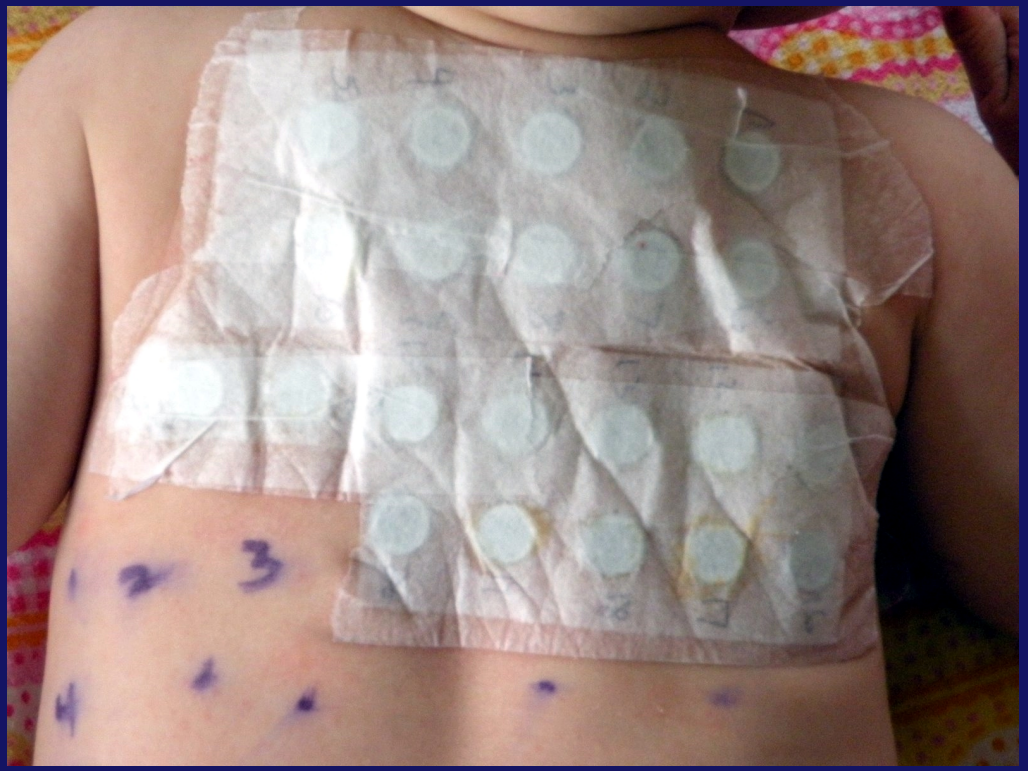


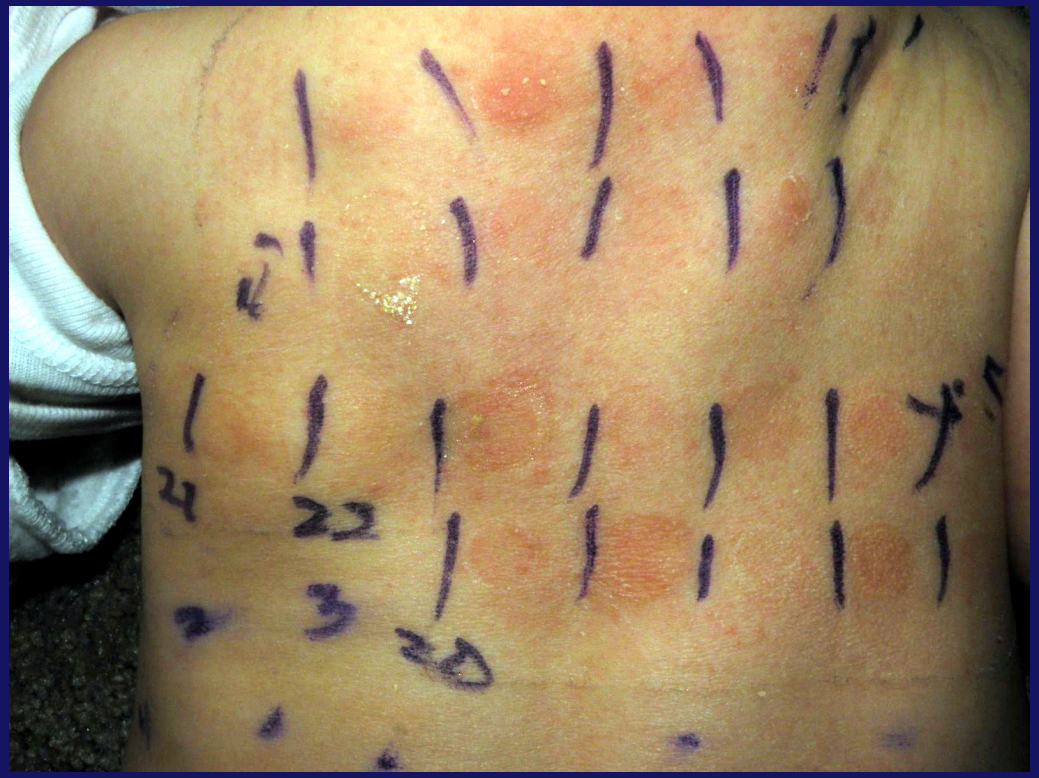


IZGLED ALERGIJSKE REAKCIJE NA KOŽI - ALERGOTESTOVI

KORIŠĆENJE FLASTERA SA ODGOVARAJUĆIM ALERGENIMA (HISTAMIN, RAZNE VRSTE POLENA I DR.) -SLIKA 1

REAKCIJA NA KOŽI POSLE UKLANJANJA FLASTERA - SLIKA 2

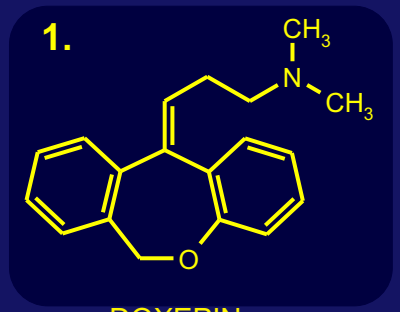




STRUKTURNA PODELA H_1 ANTI-HISTAMINSKIH PREPARATA

SVAKA KLASA ILUSTROVANA JE JEDNIM PRIMEROM

1.



DOXEPIN

DIBENZOXEPIN-ski TRICIKLICI

2.

Diphenhydramine

ALKIL-AMINO-ETRI

3.

Pyrilamine

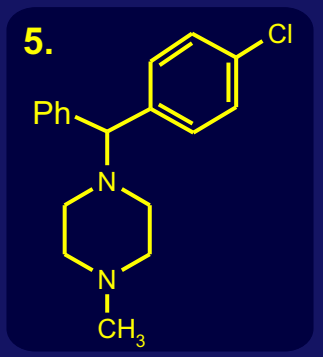
ETILEN-DIAMINI

4.

Chlorpheniramine

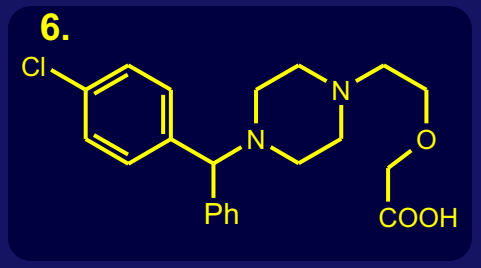
ALKIL-AMINI

5.



Chlorcyclizine

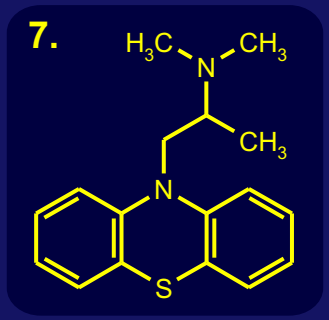
6.



Cetirizine

PIPERAZINI **II** GENERACIJE

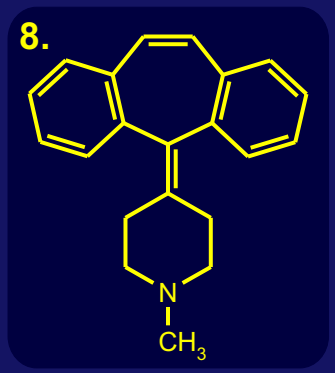
7.



Promethazine

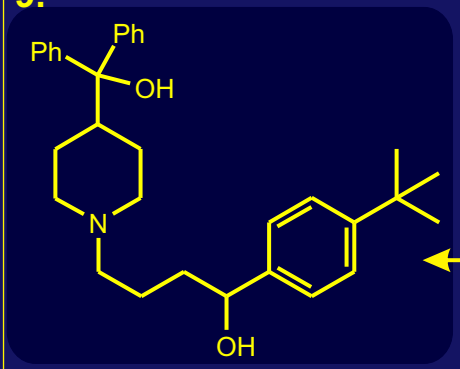
FENOTIAZINI

8.



Cyproheptadine

9.



Terfenadine

1. H_1 ANTI-HISTAMINSKI PREPARATI - DIBENZOXEPIN-ski TRICIKLIČNI ANTI-HISTAMINICI I ANTI-DEPRESANTI

Monograph Number: 3469

Title: **Doxepin**

CAS Registry Number: 1668-19-5

CAS Name: 3-Dibenz[*b,e*]oxepin-11(6*H*)-ylidene-*N,N*-dimethyl-1-propanamine

Additional Names: *N,N*-dimethyldibenz[*b,e*]oxepin-□11(6*H*),□-propylamine; 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[*b,e*]oxepin

Manufacturers' Codes: P-3693A

Molecular Formula: $C_{19}H_{21}NO$

Molecular Weight: 279.38.

Percent Composition: C 81.68%, H 7.58%, N 5.01%, O 5.73%

Literature References: Prepn of mixture of *cis*- and *trans*-isomers: K. Stach, F. Bickelhaupt, *Monatsh.* **93,** 896 (1962); F. Bickelhaupt *et al., ibid.* **95,** 485 (1964); **NL 6407758**; K. Stach, **US 3438981** (1965, 1969 both to Boehringer Mann.); and separation and activity of isomers: B. M. Bloom, J. R. Tretter, **BE 641498**; *eidem,* **US 3420851** (1964, 1969 both to Pfizer). Pharmacology: A. Ribbentrop, W. Schaumann, *Arzneimittel-Forsch.* **15,** 863 (1965). Metabolism in animals: D. C. Hobbs, *Biochem. Pharmacol.* **18,** 1941 (1969). Determn in plasma by GC/MS: T. P. Davis *et al., J. Chromatog.* **273,** 436 (1983); by HPLC: T. Emm, L. J. Lesko, *ibid.* **419,** 445 (1987). Clinical study in depression: K. Rickels *et al., Arch. Gen. Psychiat.* **42,** 134 (1985). Comparative clinical trial with cimetidine, *q.v.,* in treatment of ulcer: R. K. Shrivastava *et al., Clin. Ther.* **7,** 181 (1985). Review of pharmacology and therapeutic efficacy: R. M. Pinder *et al., Drugs* **13,** 161 (1977).

Properties: Oily liq consisting of a mixture of *cis*- and *trans*-isomers. $bp_{0.03}$ 154-157°, $bp_{0.2}$ 260-270°. LD_{50} in mice, rats (mg/kg): 26, 16 i.v.; 79, 182 i.p.; 135, 147 orally (Ribbentrop, Schaumann).

Boiling point: $bp_{0.03}$ 154-157°; $bp_{0.2}$ 260-270°

Toxicity data: LD_{50} in mice, rats (mg/kg): 26, 16 i.v.; 79, 182 i.p.; 135, 147 orally (Ribbentrop, Schaumann)

Derivative Type: Hydrochloride

CAS Registry Number: 1229-29-4

Trademarks: Adapin (Lotus); Aponal (Boehringer, Mann.); Curatin (Pfizer); Quitaxon (Boehringer, Mann.); Sinequan (Pfizer)

Molecular Formula: $C_{19}H_{21}NO.HCl$

Molecular Weight: 315.84.

Percent Composition: C 72.25%, H 7.02%, N 4.43%, O 5.07%, Cl 11.22%

Properties: Crystals, mp 184-186°, 188-189°.

Melting point: mp 184-186°, 188-189°

Derivative Type: Maleate

Properties: Crystals, mp 161-164°, 168-169°.

Melting point: mp 161-164°, 168-169°

Derivative Type: *trans*-Form hydrochloride

CAS Registry Number: 3607-18-9

Properties: mp 192-193°.

Melting point: mp 192-193°

Derivative Type: *cis*-Form hydrochloride

CAS Registry Number: 25127-31-5

Additional Names: Cidoxepin hydrochloride

Manufacturers' Codes: P-4599

Properties: Crystals, mp 209-210.5°.

Melting point: mp 209-210.5°

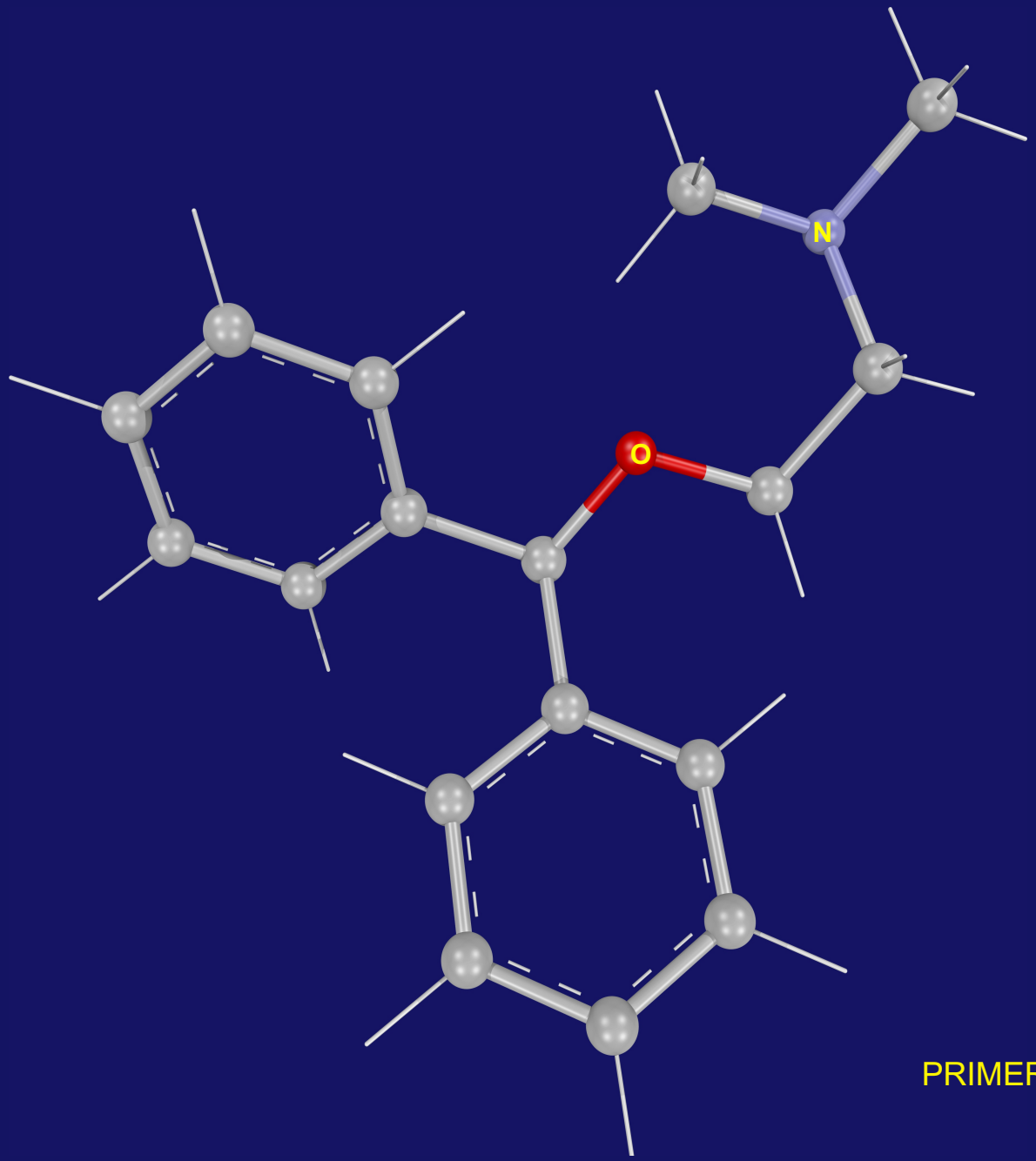
Therap-Cat: Antidepressant.

Therap-Cat-Vet: Antipruritic.

DOXEPIN JE LEK KOJI SPADA U KATEGORIJU TRICIKLIČNIH ANTI-DEPRESANATA I PRIMENJUJE SE U SUZBIJANJU SIMPTOMA DEPRESIJE. MEĐUTIM, TAKOĐE JE I VEOMA SNAŽAN H_1 ANTAGONIST. IPAK, RETKO SE PRIMENJUJE KAO ANTI-ALERGETIK JER IZAZIVA IZRAŽENE SPOREDNE EFEKTE KAO ŠTO JE POSPANOST.

INTERESANTNO JE DA OVAJ LEK DALEKO BOLJE PODNOSE PACIJENTI KOJI PATE OD DEPRESIJE NEGO ONI KOJI NISU DEPRESIVNI. KOD NE-DEPRESIVNIH PACIJENATA, ČAK I VRLO MALE DOZE (~20 mg), ČESTO IZAZIVAJU DEZORIJENTACIJU I MENTALNU KONFUZIJU.

2. H_1 ANTI-HISTAMINSKI PREPARATI - ALKIL-AMINO-ETRI



≡

PRIMER: DIPHENHYDRAMINE

2. H_1 ANTI-HISTAMINSKI PREPARATI - ALKIL-AMINO-ETRI - DIPHENHYDRAMINE

Monograph Number: 3341
Title: Diphenhydramine

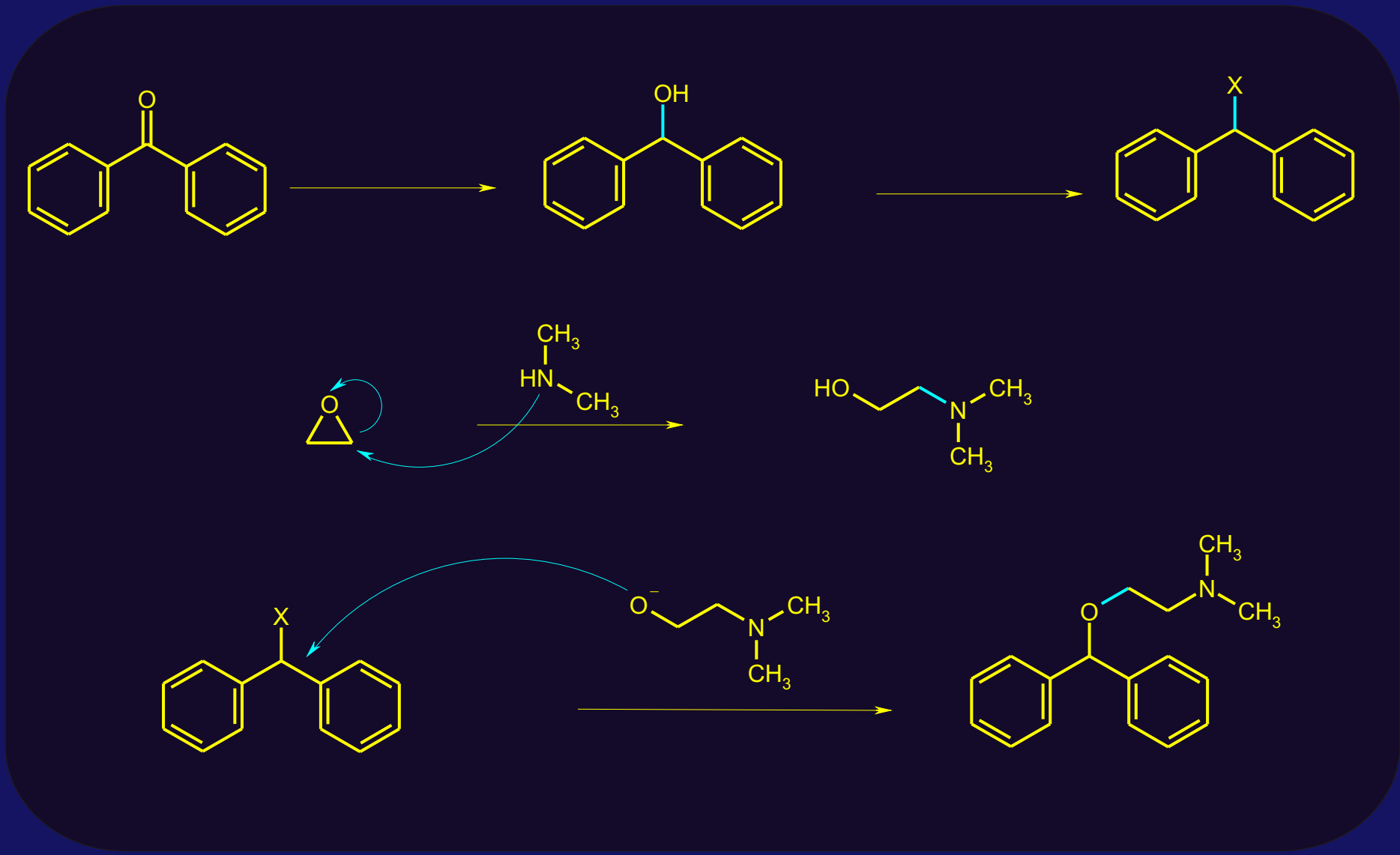
CAS Registry Number: 58-73-1
CAS Name: 2-Diphenylmethoxy-*N,N*-dimethylethanamine
Additional Names: 2-(benzhydryloxy)-*N,N*-dimethylethylamine; □-dimethylaminoethyl benzhydryl ether; *O*-benzhydryldimethylaminoethanol; □-dimethylaminoethanol diphenylmethyl ether; □-(2-dimethylaminoethoxy)diphenylmethane; benzhydramine
Molecular Formula: C17H21NO
Molecular Weight: 255.35.
Percent Composition: C 79.96%, H 8.29%, N 5.49%, O 6.27%
Literature References: Prepn: Rieveschl, Jr., **US 2421714**; **US 2427878** (both 1947 to Parke, Davis), *cf.* **US 2397799** (1946). Toxicity: Gruhzit, Fisken, *J. Pharmacol. Exp. Ther.* **89,** 227 (1947). Comprehensive description of the hydrochloride: I. J. Holcomb, S. A. Fusari, *Anal. Profiles Drug Subs.* **3,** 173-232 (1974).
Properties: bp2.0 150-165°.
Boiling point: bp2.0 150-165°

Derivative Type: Hydrochloride
CAS Registry Number: 147-24-0
Trademarks: Alledryl; Allergina (De Angeli); Amidryl; Bagodryl; Bax (McKesson); Benadryl (Parke-Davis); Benocten (Medinova); Benzantin; Dibondrin (Montavit); Dihydral (SCS); Diphantine; Dolestan (Much); Fenylhist (Mallard); Halbmond (Much); Histacyl (Streuli); Noctomin (Medichemie); S 8 (Chefaro); Sedopretten (Schoening); Sekundal-D (Rorer); Syntedril; Wehydryl (Hauck)
Molecular Formula: C17H21NO.HCl
Molecular Weight: 291.82.
Percent Composition: C 69.97%, H 7.60%, N 4.80%, O 5.48%, Cl 12.15%
Properties: Crystals from abs alcohol + ether, mp 166-170°. Bitter taste. Slowly darkens on exposure to light. Stable under ordinary conditions. One gram dissolves in 1 ml water, 2 ml alcohol, 2 ml chloroform, 50 ml acetone. Very slightly sol in benzene, ether. pH of 1% aq soln about 5.5. The aq soln forms a pink precipitate with satd Reinecke's salt soln. LD50 orally in rats: 500 mg/kg (Gruhzit, Fisken).
Melting point: mp 166-170°
Toxicity data: LD50 orally in rats: 500 mg/kg (Gruhzit, Fisken)

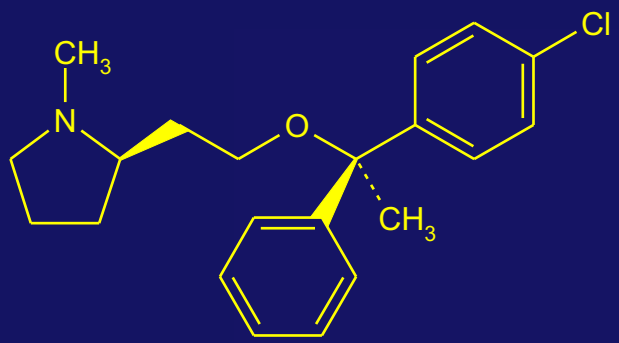
Derivative Type: Compd with *p*-sulfonamide benzoate
CAS Registry Number: 60539-06-2
Trademarks: Neobenadol
Literature References: Prepn: U. Iwase *et al.,* **JP 64 243** (1964 to Taisho), C.A. **60,** 10700a (1964).

Therap-Cat: Antihistaminic.
Therap-Cat-Vet: Antihistaminic. Also in motion sickness.

H_1 ANTI-HISTAMINSKI PREPARATI - ALKIL-AMINO-ETRI. PRIMER: SINTEZA DIPHENHYDRAMINE-a



H_1 ANTI-HISTAMINSKI PREPARATI - ALKIL-AMINO-ETRI. PRIMER: CLEMASTINE

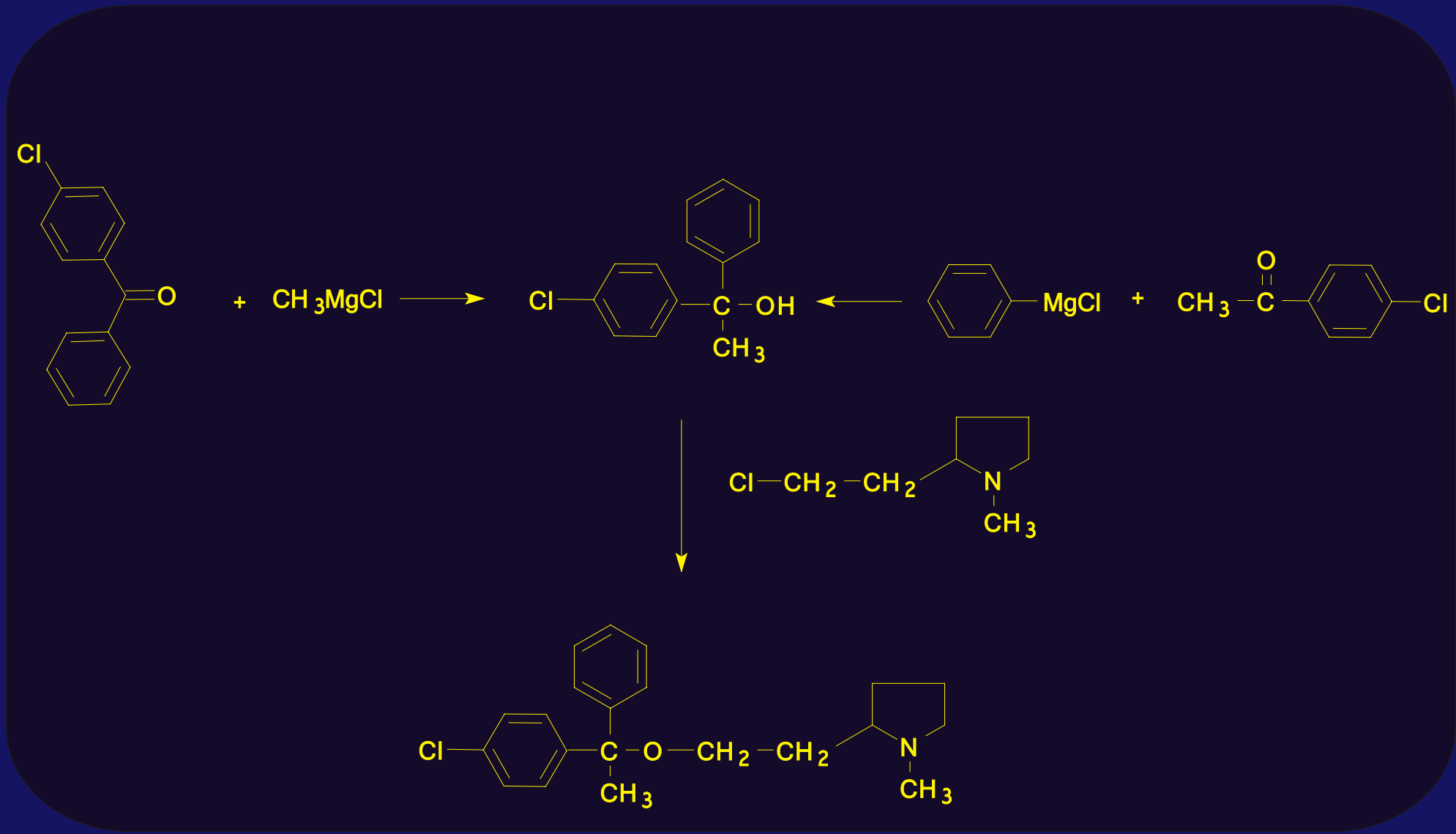


Monograph Number: 2367
Title: Clemastine
CAS Registry Number: 15686-51-8
CAS Name: (2R)-2-[2-[(1R)-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine
Additional Names: (+)-2-[2-[(p-chloro-α-methyl-α-phenylbenzyl)oxy]ethyl]-1-methylpyrrolidine; 1-methyl-2-[2-(α-methyl-p-chlorobenzhydryloxy)ethyl]pyrrolidine; 1-methyl-2-[2-(methyl-p-chlorodiphenylmethyloxy)ethyl]pyrrolidine; meclastine
Molecular Formula: C21H26ClNO
Molecular Weight: 343.90.
Percent Composition: C 73.34%, H 7.62%, Cl 10.31%, N 4.07%, O 4.65%
Literature References: Prepn: GB 942152 (1963 to Sandoz). Synthesis and abs config: A. Ebnöther, H. P. Weber, Helv. Chim. Acta 59, 2462 (1976). Pharmacology and toxicology of the hydrogen fumarate: Weidmann et al., Boll. Chim. Farm. 106, 467 (1967).
Properties: Free base, bp0.02 154°. nD22 1.5582. [α]D20 +33.6° (ethanol).
Boiling point: bp0.02 154°
Optical Rotation: [α]D20 +33.6° (ethanol)
Index of refraction: nD22 1.5582

Derivative Type: Hydrogen fumarate
CAS Registry Number: 14976-57-9
Manufacturers' Codes: HS-592
Trademarks: Aloginan (Tobishi); Alphamin (SS Pharm.); Anhistan (Nippon Zoki); Fuluminol (Tatsumi); Inbestan (Maruko); Kinotomin (Toa Eiyo); Lacretin (Tokyo Tanabe); Lecasol (Kaken); Maikohis (Nichiiko); Mallermin-F (Taiyo); Marsthine (Towa Yakuhin); Masletine (Sioe); Piloral (Nippon Kayaku); Reconin (Toyama); Tavegil (Novartis); Tavegyl (Novartis); Tavist (Novartis); Telgin-G (Takeda); Trabest (Hoei); Xolamin (Sanko)
Molecular Formula: C25H30ClNO5
Molecular Weight: 459.97.
Percent Composition: C 65.28%, H 6.57%, Cl 7.71%, N 3.05%, O 17.39%
Properties: mp 177-178°. [α]D21 +16.9° (methanol). LD50 in mice, rats (mg/kg): 730, 3550 orally; 43, 82 i.v. (Weimann).
Melting point: mp 177-178°
Optical Rotation: [α]D21 +16.9° (methanol)
Toxicity data: LD50 in mice, rats (mg/kg): 730, 3550 orally; 43, 82 i.v. (Weimann)

Therap-Cat: Antihistaminic.

H_1 ANTI-HISTAMINSKI PREPARATI - ALKIL-AMINO-ETRI. PRIMER: SINTEZA CLEMASTINE-a



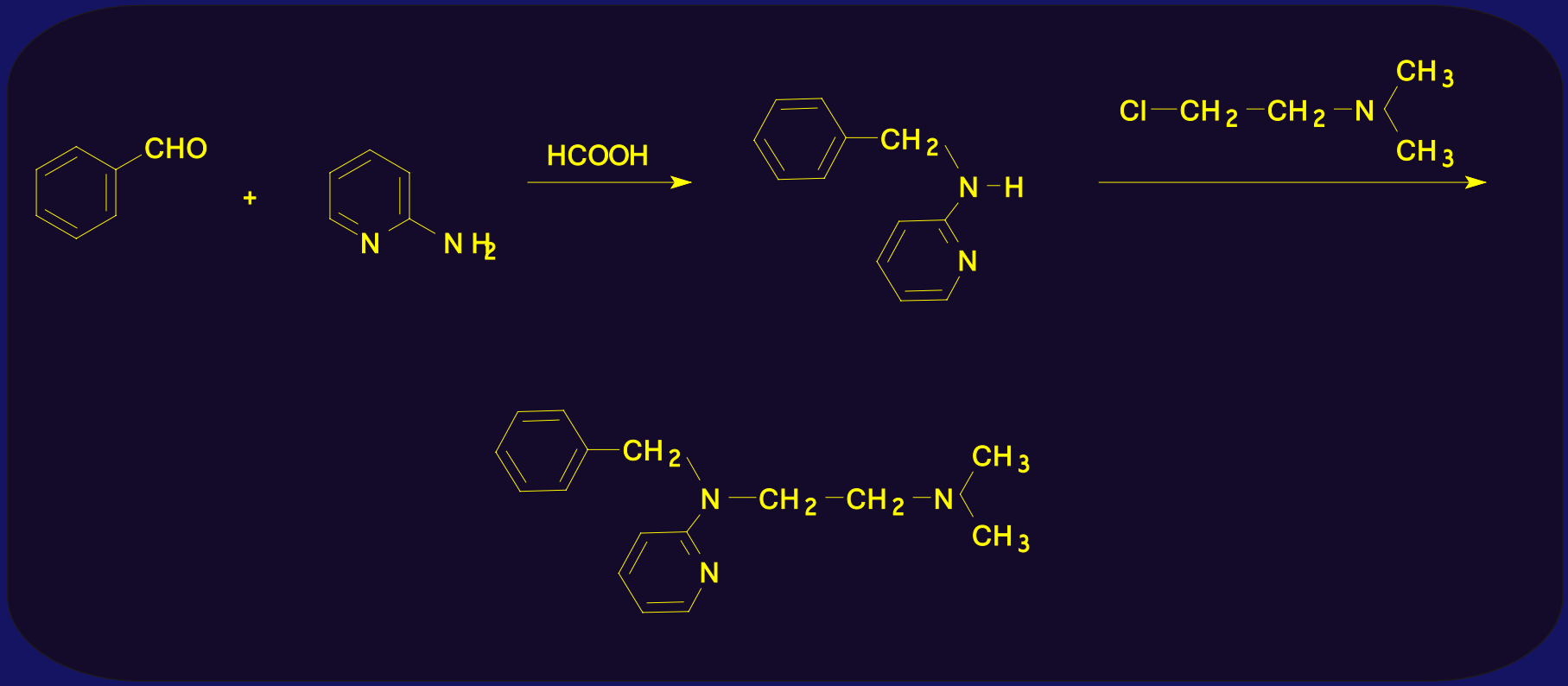
Monograph Number: 9809
Title: Tripelennamine
CAS Registry Number: 91-81-6
CAS Name: N,N-Dimethyl-N′-(phenylmethyl)-N′-2-pyridinyl-1,2-ethanediamine
Additional Names: 2-[benzyl(2-dimethylaminoethyl)amino]pyridine; N-benzyl-N′,N′-dimethyl-N-(2-pyridyl)ethylenediamine; N,N-dimethyl-N′-benzyl-N′-(α-pyridyl)ethylenediamine; α-dimethylaminoethyl-2-pyridylbenzylamine; α-dimethylaminoethyl-2-pyridylaminotoluene
Molecular Formula: C16H21N3
Molecular Weight: 255.36.
Percent Composition: C 75.26%, H 8.29%, N 16.46%
Literature References: Prepn: C. P. Huttrer et al., J. Am. Chem. Soc. 68, 1999 (1946); C. Djerassi et al., US 2406594 (1946 to Ciba); R. J. Horclois, US 2502151 (1950 to Rhône-Poulenc). Crystal structure: M. Parvez, Acta Crystallogr. C43, 1408 (1987). Toxicity studies: D. P. Waller et al., Clin. Toxicol. 16, 17 (1980). Comprehensive description: H. G. Piskorik, Anal. Profiles Drug Subs. 14, 108-133 (1985).
Properties: Yellow oil. Amine odor. bp0.1 138-142°, bp1.7 185-190°, bp20 193-205°. nD25 1.5759-1.5765. Miscible with water.
Boiling point: bp0.1 138-142°; bp1.7 185-190°; bp20 193-205°
Index of refraction: nD25 1.5759-1.5765

Derivative Type: Hydrochloride
CAS Registry Number: 154-69-8
Trademarks: Dehistin (EGYT); Azaron (Chefaro); Pyribenzamine (Ciba-Geigy); PBZ (Ciba-Geigy); Vetibenzamina (Ciba-Geigy)
Molecular Formula: C16H21N3.HCl
Molecular Weight: 291.83.
Percent Composition: C 65.85%, H 7.60%, N 14.40%, Cl 12.15%
Properties: Crystals from ethyl acetate + methanol, mp 192-193°. Bitter taste, produces temporary numbness of the tongue. uv max (water): 244, 305 (ε 14470, 4780). One gram dissolves in 0.77 ml water, in 6 ml alcohol, in 6 ml chloroform, in about 350 ml acetone. Practically insol in benzene, ether, ethyl acetate. About neutral to litmus. pH of aq soln contg 25 mg/ml: 6.71; 50 mg/ml: 6.67; 100 mg/ml: 5.56. LD50 in mice (mg/kg): 47 i.p. (Walker).
Melting point: mp 192-193°
Absorption maximum: uv max (water): 244, 305 (ε 14470, 4780)
Toxicity data: LD50 in mice (mg/kg): 47 i.p. (Walker)

Derivative Type: Citrate
CAS Registry Number: 6138-56-3
Molecular Formula: C16H21N3.C6H8O7
Molecular Weight: 447.48.
Percent Composition: C 59.05%, H 6.53%, N 9.39%, O 25.03%
Properties: Crystals, mp 106-110°. Less bitter than the hydrochloride. Freely sol in water, alcohol. Very slightly sol in ether. Practically insol in benzene, chloroform. 1% aq soln has a pH of 4.25.
Melting point: mp 106-110°

Therap-Cat: Antihistaminic.
Therap-Cat-Vet: Antihistaminic.

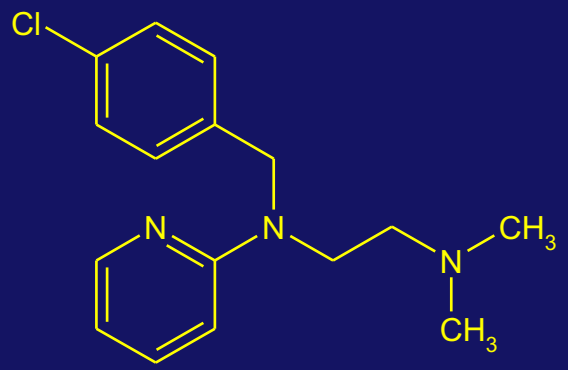
H_1 ANTI-HISTAMINSKI PREPARATI - ETILEN-DIAMINI. PRIMER: SINTEZA **TRIPELENNAMINE**-a



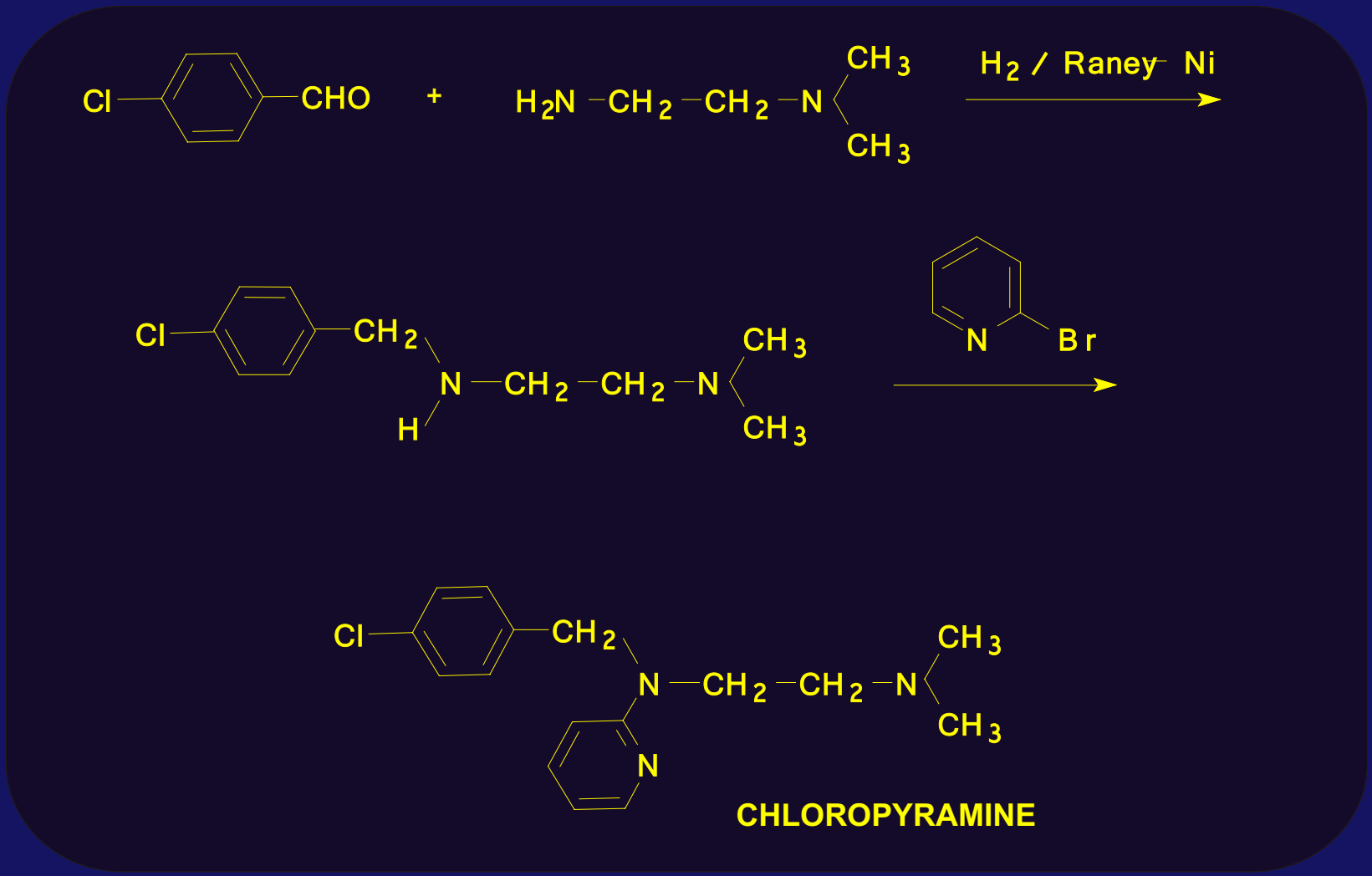
Monograph Number: 2181
Title: Chloropyramine
CAS Registry Number: 59-32-5
CAS Name: N-[(4-Chlorophenyl)methyl]-N′,N′-dimethyl-N-2-pyridinyl-1,2-ethanediamine
Additional Names: 2-[(p-chlorobenzyl)[2-(dimethylamino)ethyl]amino]pyridine; N-dimethylaminoethyl-N-p-chlorobenzyl-α-aminopyridine; N,N-dimethyl-N′-(p-chlorobenzyl)-N′-(2-pyridyl)ethylenediamine; halopyramine
Trademarks: Chloropyribenzamine (Polfa)
Molecular Formula: C16H20ClN3
Molecular Weight: 289.81.
Percent Composition: C 66.31%, H 6.96%, Cl 12.23%, N 14.50%
Literature References: Prepn: Phillips, Cates, US 2607778 (1952 to Merck & Co.); Howard, US 2569314 (1951 to Am. Cyanamid); CH 264754; CH 266234; CH 266235 (1950); GB 651596 (1951) (all to Geigy).
Properties: Light yellow, viscous, oily liquid. Pungent odor. bp0.2 154-155°.
Boiling point: bp0.2 154-155°

Derivative Type: Hydrochloride
CAS Registry Number: 6170-42-9
Trademarks: Alegan S (Ind. Med.); Synopen (Geigy); Synpen (Geigy)
Molecular Formula: C16H20ClN3.HCl
Molecular Weight: 326.27.
Percent Composition: C 58.90%, H 6.49%, Cl 21.73%, N 12.88%
Properties: Crystals from acetone, mp 172-174°.
Melting point: mp 172-174°

Therap-Cat: Antihistaminic.



H_1 ANTI-HISTAMINSKI PREPARATI - ETILEN-DIAMINI. PRIMER: SINTEZA **CHLOROPYRAMINE**-a



Monograph Number: 2198
Title: Chlorpheniramine
CAS Registry Number: 132-22-9
CAS Name: □ -(4-Chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine
Additional Names: 2-[p-chloro-□ -(2-dimethylaminoethyl)benzyl]pyridine; 1-(p-chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane; 1-(p-chlorophenyl)-1-(2-pyridyl)-3-N,N-dimethylpropylamine; 3-(p-chlorophenyl)-3-(2-pyridyl)-N,N-dimethylpropylamine; □ -(4-chlorophenyl)-□ -(2-pyridyl)propyldimethylamine; chlorprophenpyridamine; chlorphenamine
Trademarks: Haynon (R. P. Drugs)
Molecular Formula: C16H19ClN2
Molecular Weight: 274.80.
Percent Composition: C 69.93%, H 6.97%, Cl 12.90%, N 10.19%
Literature References: Synthesis: Sperber et al., US 2567245, US 2676964 (1951, 1954, both to Schering). Prepn of d-form: L. A. Walter, US 3061517 (1962 to Schering). Solutions: Foley, Ilavsky, US 2766174 (1956 to Schering). Pharmacology: F. E. Roth, W. M. Govier, J. Pharmacol. Exp. Ther. 124, 347 (1958). Toxicity data: R. B. Smith et al., Toxicol. Appl. Pharmacol. 28, 240 (1974). Comprehensive description: C. G. Eckhart, T. McCorkle, Anal. Profiles Drug Subs. 7, 43-80 (1978).
Properties: Oily liquid, bp1.0 142°.
Boiling point: bp1.0 142°

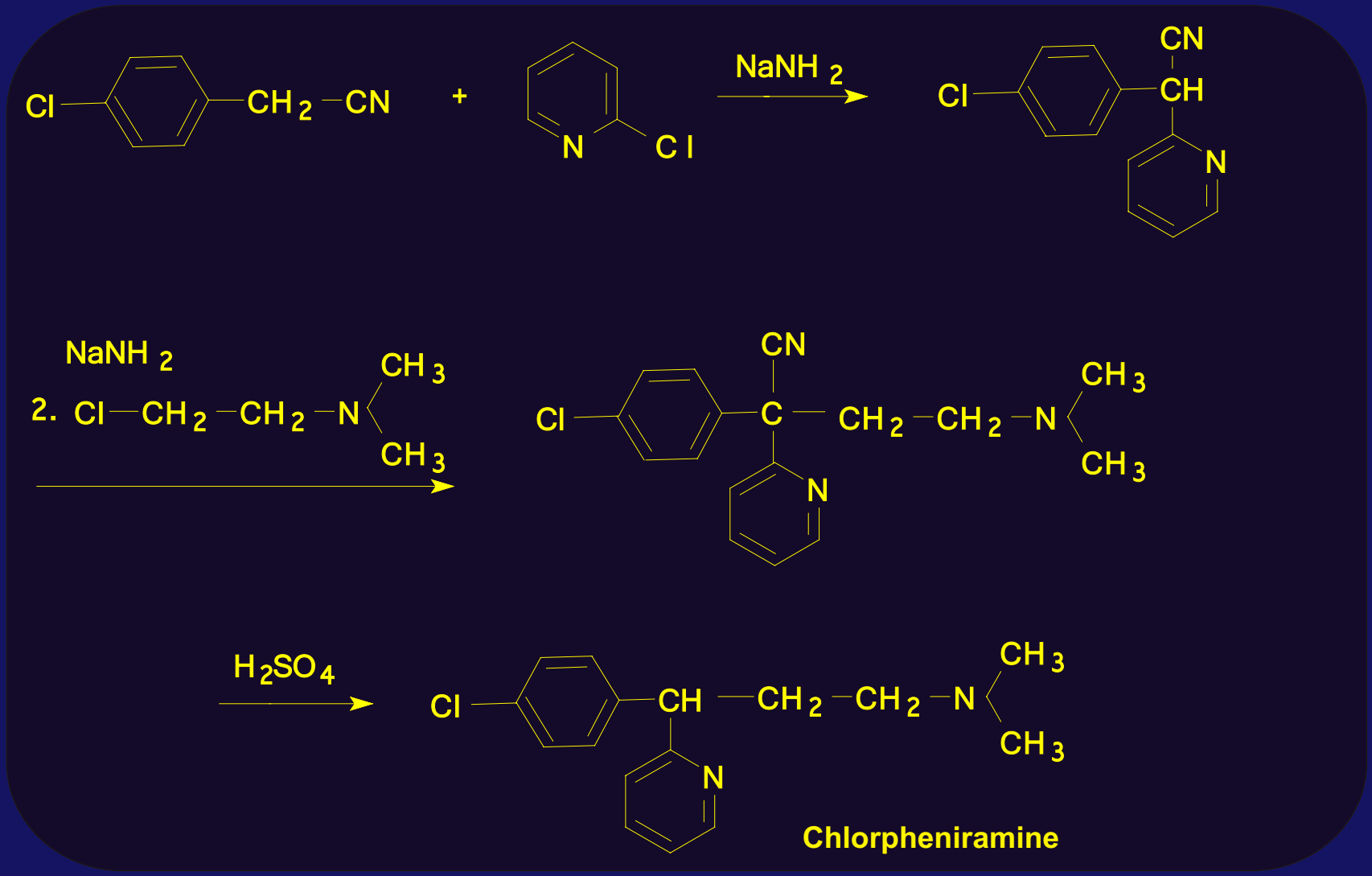
Derivative Type: Maleate
CAS Registry Number: 113-92-8
Trademarks: Allergisan (Pharmacia); Antagonate (Miles); Chlor-Trimeton (Schering); Chlor-Tripolon (Schering); Cloropiril; C-Meton (SS Pharm); Histadur (Cooper); Histaspan (USV); Lorphen (Geneva); Piriton (Allen & Hanburys); Pyridamal-100 (Bel-Mar); Teldrin (SK & F)
Molecular Formula: C16H19ClN2.C4H4O4
Molecular Weight: 390.87.
Percent Composition: C 61.46%, H 5.93%, Cl 9.07%, N 7.17%, O 16.37%
Properties: Crystals, mp 130-135°. uv max (water): 261 nm (□ 5760). Soly in mg/ml at 25°: ethanol 330; chloroform 240; water 160; methanol 130. Slightly sol in benzene, ether. pH of a 2% aq soln about 5. LD50 orally in mice: 162 mg/kg (Smith).
Melting point: mp 130-135°
Absorption maximum: uv max (water): 261 nm (□ 5760)
Toxicity data: LD50 orally in mice: 162 mg/kg (Smith)

Derivative Type: d-Form
CAS Registry Number: 25523-97-1
Additional Names: Dexchlorpheniramine; d-chlorpheniramine
Properties: Oily liquid. [□]D25 +49.8° (c = 1 in DMF).
Optical Rotation: [□]D25 +49.8° (c = 1 in DMF)

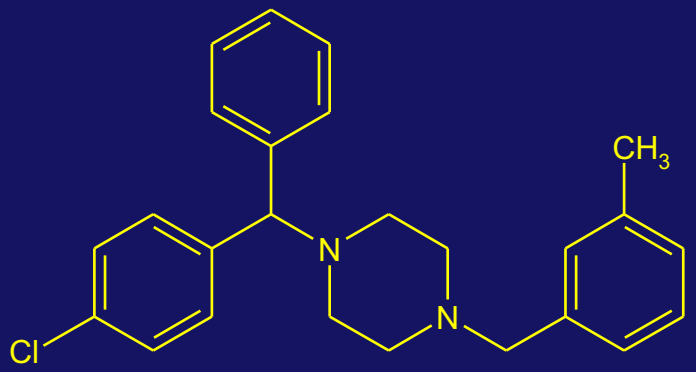
Derivative Type: d-Form maleate
CAS Registry Number: 2438-32-6
Trademarks: Fortamine; Isomerine; Phenamin (Nycomed); Phendextro; Polamin (Schering); Polaramine (Schering); Polaronil (Schering); Sensidyn (Leiras)
Properties: Crystals from ethyl acetate, mp 113-115°. [□]D25 +44.3° (c = 1 in dimethylformamide). pH of 1% soln 4-5.
Melting point: mp 113-115°
Optical Rotation: [□]D25 +44.3° (c = 1 in dimethylformamide)

Therap-Cat: Antihistaminic.
Therap-Cat-Vet: Antihistaminic.

H_1 ANTI-HISTAMINSKI PREPARATI - ALKIL-AMINI. PRIMER: SINTEZA **CHLORPHENIRAMINE**-a



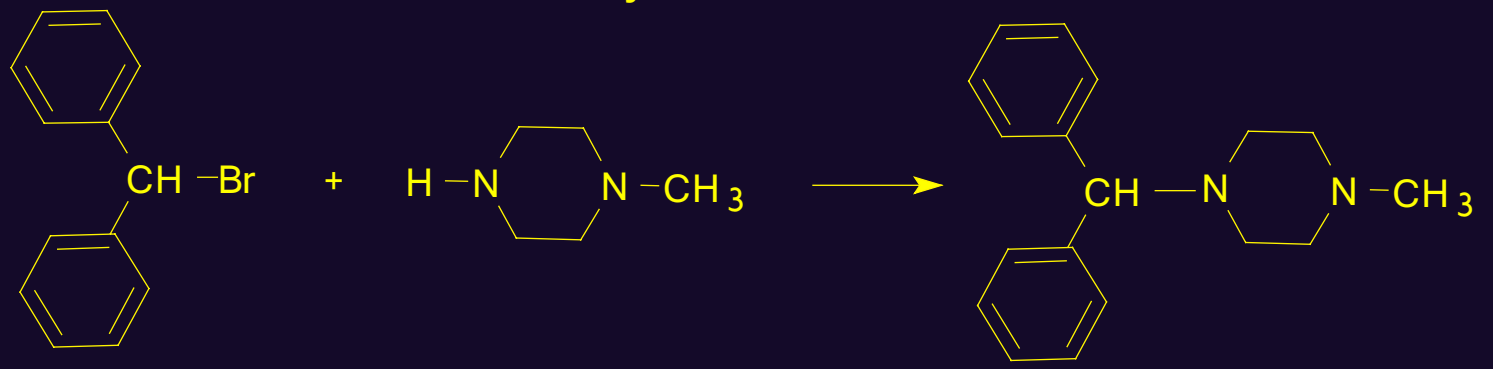
Monograph Number: 5800
Title: Meclizine
CAS Registry Number: 569-65-3
CAS Name: 1-[(4-Chlorophenyl)phenylmethyl]-4-[(3-methylphenyl)methyl]piperazine
Additional Names: 1-(p-chloro-□ -phenylbenzyl)-4-(m-methylbenzyl)piperazine; 1-(p-chlorobenzhydryl)-4-(m-methylbenzyl)piperazine; 1-(p-chlorobenzhydryl)-4-(m-methylbenzyl)diethylenediamine; meclozine; parachloramine
Molecular Formula: C25H27ClN2
Molecular Weight: 390.96.
Percent Composition: C 76.80%, H 6.96%, Cl 9.07%, N 7.17%
Literature References: Synthesis: Morren, BE 502889 (1951); GB 705979 (1954), US 2709169 (1955 to U.C.B.). Outline of reactions: Grivsky, Ind. Chim. Belge 17, 735 (1952). Clinical evaluation in vertigo: B. Cohen, J. M. B. Vianney de Jong, Arch. Neurol. 27, 129 (1972).
Properties: bp2 230°.
Boiling point: bp2 230°



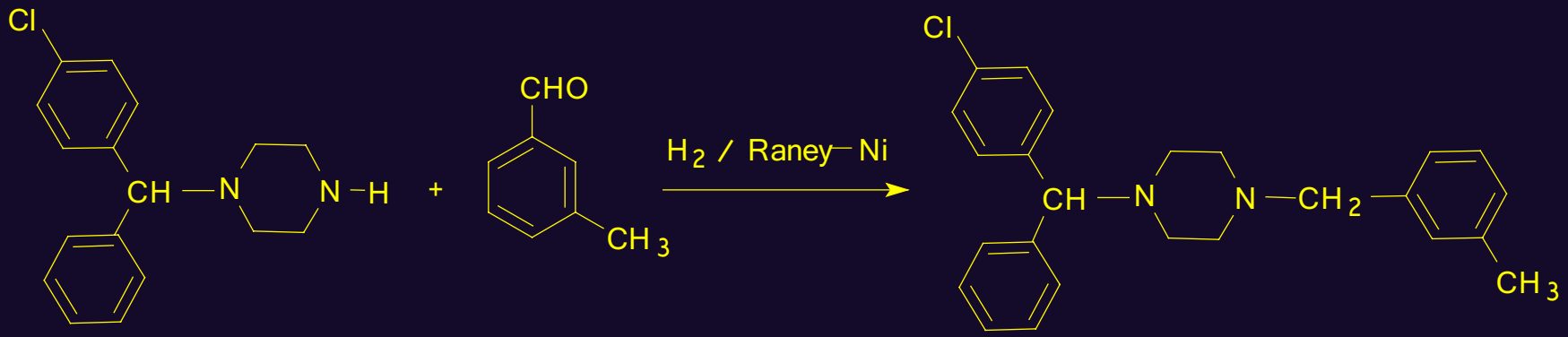
Derivative Type: Dihydrochloride monohydrate
CAS Registry Number: 31884-77-2
Manufacturers' Codes: UCB-5062
Trademarks: Ancolan (Boots); Antivert (Roerig); Bonamine (Pfizer); Bonine (Pfizer); Calmonal (Bristol-Myers Squibb); Peremesin (Bristol-Myers Squibb); Postafen (UCB); Sea-Legs (BDH)
Molecular Formula: C25H27ClN2.2HCl.H2O
Molecular Weight: 481.90.
Percent Composition: C 62.31%, H 6.48%, Cl 22.07%, N 5.81%, O 3.32%
Properties: Freely sol in chloroform, pyridine; slightly sol in dil acids, alc. Practically insol in water (0.1 gm/100 ml), ether.

H_1 ANTI-HISTAMINSKI PREPARATI - PIPERAZINI. PRIMERI: SINTEZA **CYCLIZINE**-a I **MECLIZINE**-a

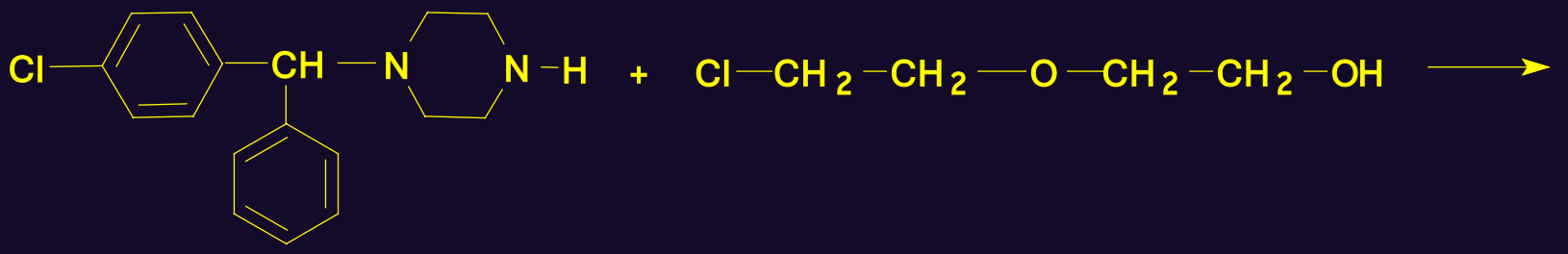
Cyclizine:

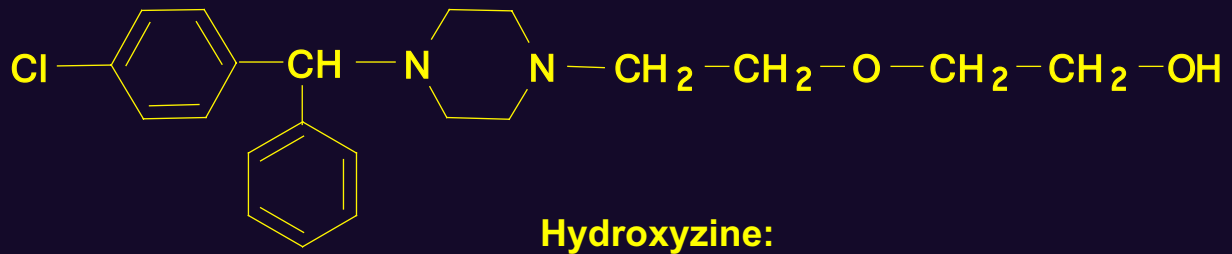


Meclizine:



H_1 ANTI-HISTAMINSKI PREPARATI - PIPERAZINI. PRIMERI: SINTEZA **HYDROXYZINE**-a





Hydroxyzine:

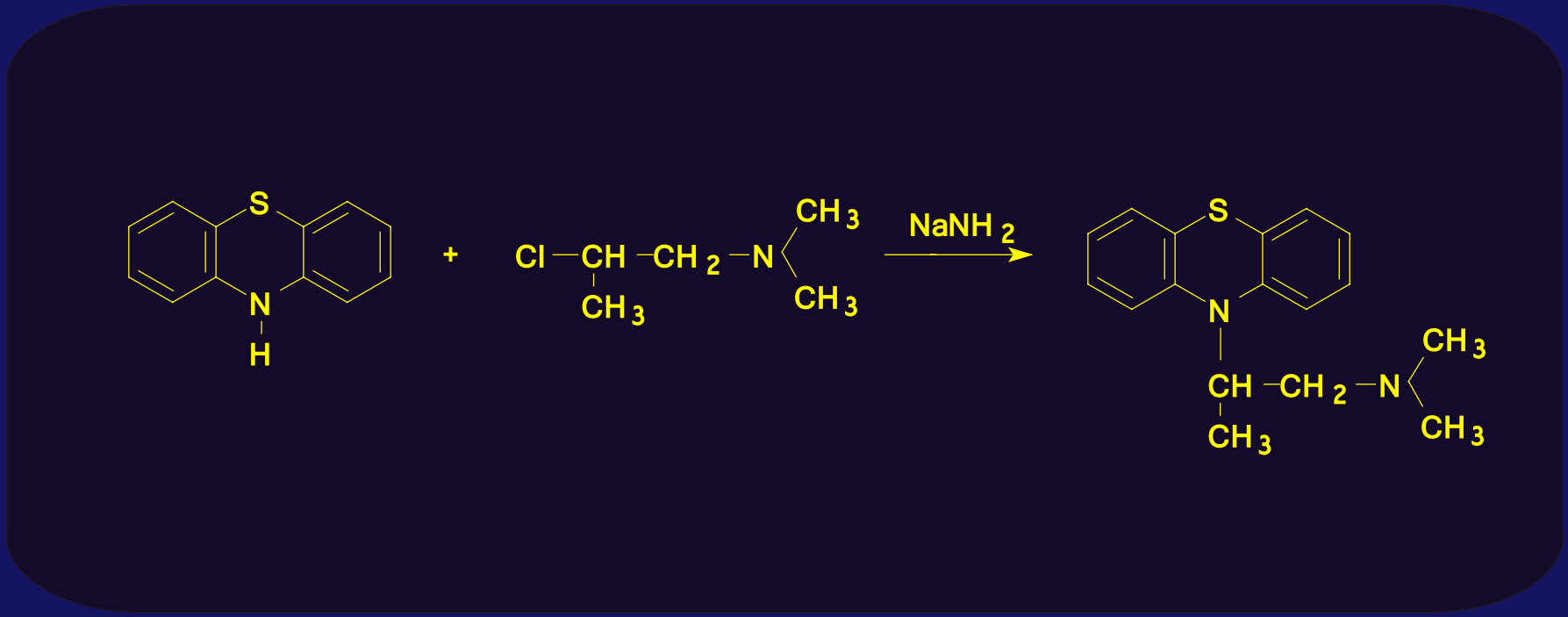
Monograph Number: 7878
Title: Promethazine
CAS Registry Number: 60-87-7
CAS Name: N,N,□ -Trimethyl-10H-phenothiazine-10-ethanamine
Additional Names: 10-(2-dimethylaminopropyl)phenothiazine; 10-(2-dimethylamino-2-methylethyl)phenothiazine; N-(2□ -dimethylamino-2□ -methyl)ethylphenothiazine; proazamine
Manufacturers' Codes: RP-3277
Molecular Formula: C17H20N2S
Molecular Weight: 284.43.
Percent Composition: C 71.79%, H 7.09%, N 9.85%, S 11.27%
Literature References: Prepn from 10-phenothiazinepropyl chloride and dimethylamine in presence of Cu: Charpentier, Compt. Rend. 225, 306 (1947); US 2530451 (1950 to Rhône-Poulenc); from Grignard complexes of dimethylaminopropyl halide and phenothiazine: Berg, Ashley, US 2607773 (1952 to Rhône-Poulenc). Structure and isomerism: Edge, Wragg, J. Pharm. Pharmacol. 5, 279 (1953). Metabolic studies: Huang et al., J. Pharm. Sci. 59, 772 (1970). Toxicity: Rajsner, Coll. Czech. Chem. Commun. 34, 1019 (1969). Comprehensive description: C. M. Shearer, S. M. Miller, Anal. Profiles Drug Subs. 5, 429-465 (1976).
Properties: Crystals, mp 60°. bp3 190-192°.
Melting point: mp 60°
Boiling point: bp3 190-192°

Derivative Type: Hydrochloride
CAS Registry Number: 58-33-3
Manufacturers' Codes: RP-3389
Trademarks: Atosil (Bayer); Dorme (A.V.P.); Duplamin (Bruschettini); Fellozine (Chromalloy); Fenazil (Sella); Genphen (Tutag); Hiberna (Yoshitomi); Lergigan (Kabi); Phencen (Central Pharm.); Phenergan (Wyeth); Prorex (Hyrex); Prothazine (RPR); Remsed (DuPont Pharma)
Molecular Formula: C17H20N2S.HCl
Molecular Weight: 320.89.
Percent Composition: C 63.63%, H 6.60%, N 8.73%, S 9.99%, Cl 11.05%
Properties: Crystals from ethylene dichloride, mp 230-232° (some dec). Turns blue on prolonged exposure to air and moisture. Lower mp reported in the literature are caused by admixture with isopromethazine, q.v. uv max (water): 249, 297 nm (□ 28770, 3400). pH of 10% aq soln 5.3. Freely sol in water. Sol in alcohol, chloroform. Practically insol in acetone, ether, ethyl acetate. LD50 i.v. in mice: 55.0 mg/kg (Rajsner).
Melting point: mp 230-232° (some dec)
Absorption maximum: uv max (water): 249, 297 nm (□ 28770, 3400)
Toxicity data: LD50 i.v. in mice: 55.0 mg/kg (Rajsner)

Derivative Type: Compd with 8-chlorotheophylline
CAS Registry Number: 17693-51-5
Additional Names: Promethazine teoclate
Trademarks: Avomine (RPR)
Molecular Formula: C17H20N2S.C7H7ClN4O2
Molecular Weight: 499.04.
Percent Composition: C 57.76%, H 5.45%, N 16.84%, S 6.43%, Cl 7.10%, O 6.41%

Therap-Cat: Antihistaminic.

H_1 ANTI-HISTAMINSKI PREPARATI - PHENOTHIAZINES. PRIMERI: SINTEZA **PROMETHAZINE**-a



H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: SINTEZA **CYPROHEPTADINE**-a

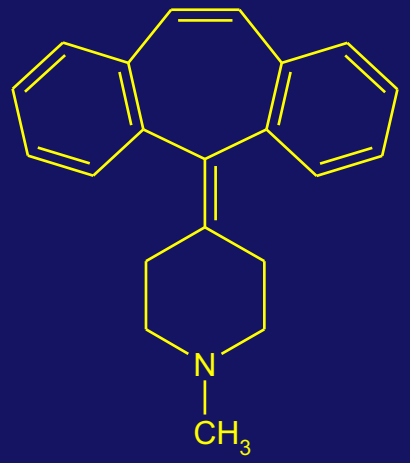
Monograph Number: 2802
Title: Cyproheptadine
CAS Registry Number: 129-03-3
CAS Name: 4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine
Additional Names: 1-methyl-4-(5H-dibenzo[a,d]cycloheptenylidene)piperidine; 5-(1-methylpiperidylidene-4)-5H-dibenzo[a,d]cycloheptene; 1-methyl-4-(5-dibenzo[a,e]cycloheptatrienylidene)piperidine
Trademarks: Periactinol (Merck & Co.)
Molecular Formula: C21H21N
Molecular Weight: 287.40.
Percent Composition: C 87.76%, H 7.36%, N 4.87%
Literature References: Prepn: Engelhardt, US 3014911 (1961 to Merck & Co.); Engelhardt et al., J. Med. Chem. 8, 829 (1965).
Metabolism: C. C. Porter et al., Drug Metab. Dispos. 3, 189 (1975).
Toxicity study: J. J. Loux et al., Arzneimittel-Forsch. 28, 1644 (1978).
Comprehensive description: H. Y. Aboul-Enein, A. A. Al-Badr, Anal. Profiles Drug Subs. 9, 155-179 (1980).
Properties: Crystals from dil ethanol, mp 112.3-113.3°.
Melting point: mp 112.3-113.3°

Derivative Type: Hydrochloride sesquihydrate
CAS Registry Number: 41354-29-4
Trademarks: Antegan (Frosst); Ifrasarl (Showa Shinyaku); Nuran (Frosst); Periactin (Merck & Co.); Vimicon (Frosst); Cipractin (Andromaco); Peritol (EGYT)
Molecular Formula: C21H22ClN.1½H2O
Molecular Weight: 332.88.
Percent Composition: C 75.77%, H 6.96%, Cl 10.65%, N 4.21%, O 2.40%
Properties: Crystals from abs ethanol + ether, dec 252.6-253.6°. uv max (0.1N H2SO4): 224, 285 nm (E1%1cm 1656, 355). 1.0 g is sol in 1.5 ml methanol, 16 ml chloroform, 35 ml alc, 275 ml H2O. Practically insol in ether. LD50 orally in mice: 74.2 mg/kg (Loux).

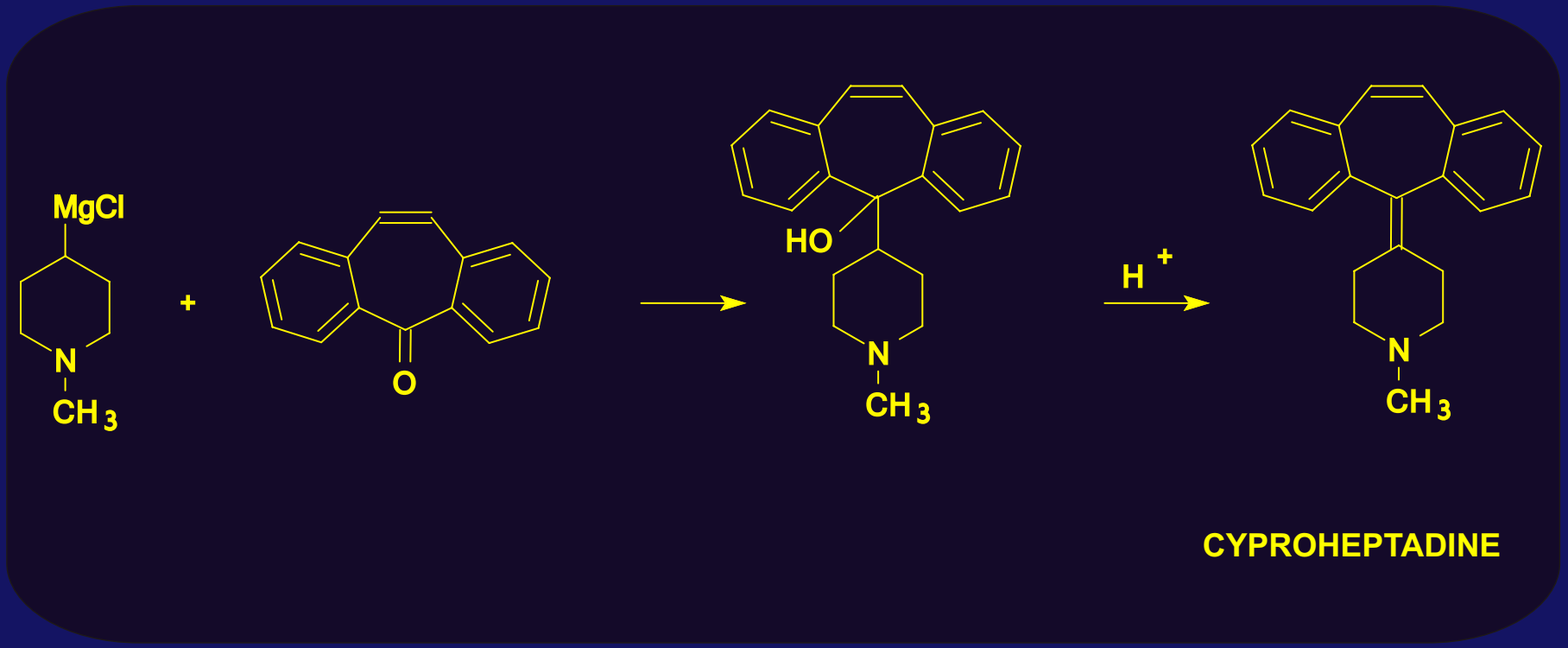
Absorption maximum: uv max (0.1N H2SO4): 224, 285 nm (E1%1cm 1656, 355)
Toxicity data: LD50 orally in mice: 74.2 mg/kg (Loux)

Derivative Type: Hydrochloride monohydrate
CAS Registry Number: 6032-06-0
Properties: Crystals, mp 214-216°. Soly in water: ~5 mg/ml.
Melting point: mp 214-216°

Therap-Cat: Antihistaminic



H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: SINTEZA **CYPROHEPTADINE**-a

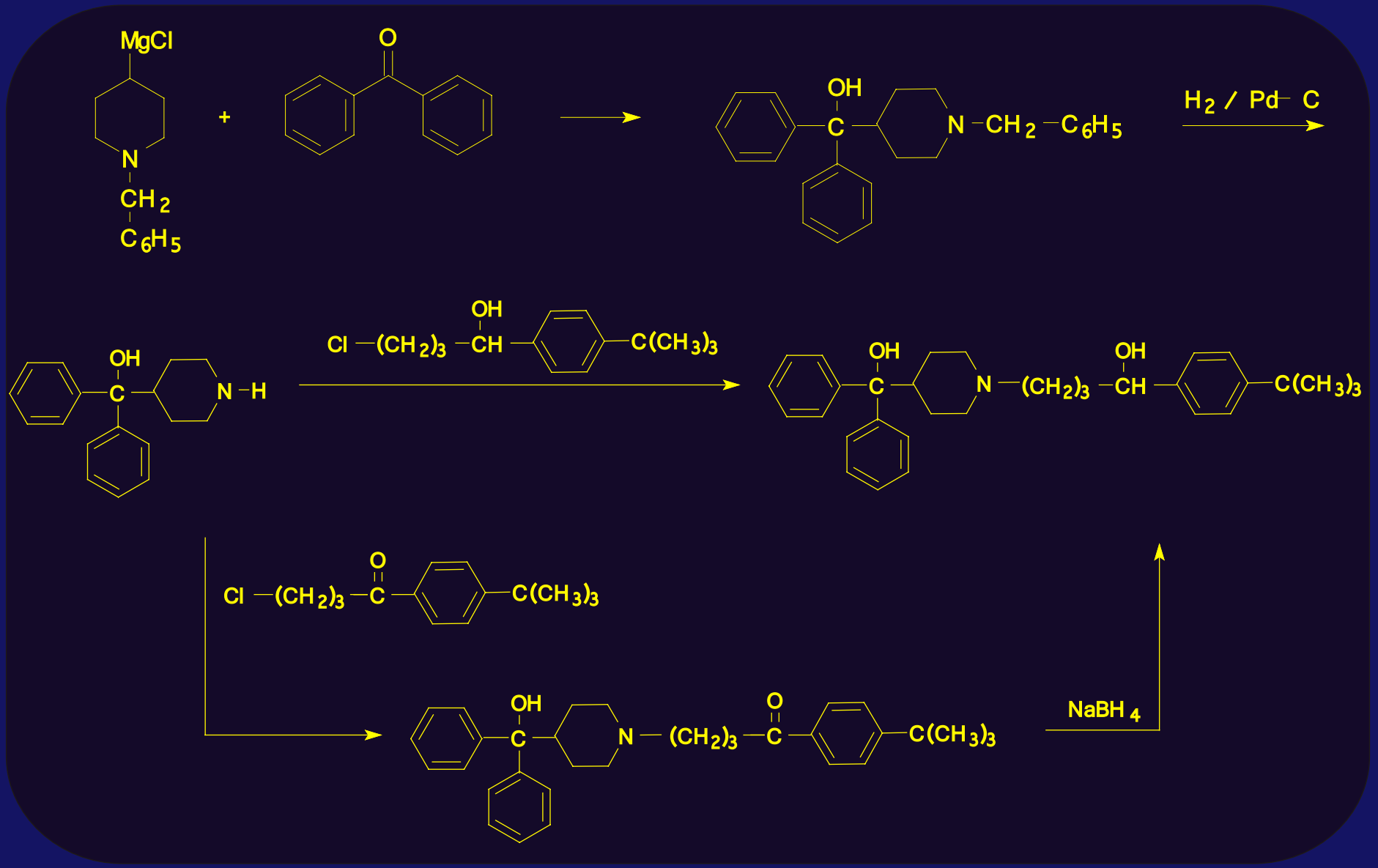


H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: SINTEZA **TERFENADINE**-a

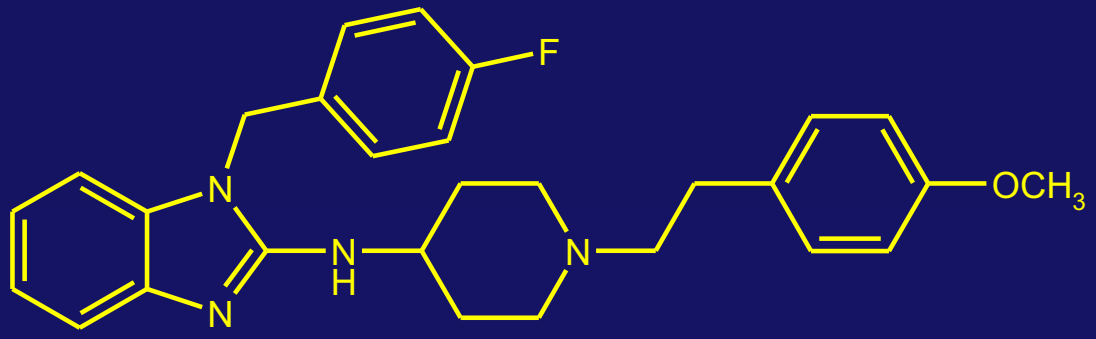
Monograph Number: 9239
Title: Terfenadine
CAS Registry Number: 50679-08-8
CAS Name: □ -[4-(1,1-Dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol
Additional Names: 1-(p-tert-butylphenyl)-4-[4□ -(□ -hydroxydiphenylmethyl)-1□ -piperidyl]butanol; □ -(p-tert-butylphenyl)-4-(□ -hydroxy-□ -phenylbenzyl)-1-piperidinebutanol
Manufacturers' Codes: MDL-9918
Trademarks: Allerplus (AstraZeneca); Cyater (Lederle); Seldane (Aventis); Teldane (Aventis); Teldanex (AstraZeneca); Terfex (Leiras); Ternadin (Cantabria); Triludan (Aventis)
Molecular Formula: C32H41NO2
Molecular Weight: 471.67.
Percent Composition: C 81.49%, H 8.76%, N 2.97%, O 6.78%
Literature References: Nonsedating-type histamine H1-receptor antagonist. Prepn: A. A. Carr, C. R. Kinsolving, DE 2303306; eidem, US 3878217 (1973, 1975 both to Richardson-Merrell); A. A. Carr, D. R. Meyer, Arzneimittel-Forsch. 32, 1157 (1982). Series of articles on chemistry, pharmacology, toxicology and clinical studies: ibid. 32, 1153-1218 (1982). Metabolism in human liver: M. Jurima-Romet et al., Drug Metab. Dispos. 22, 849 (1994). Comprehensive description: A. A. Badwan et al., Anal. Profiles Drug Subs. 19, 627-662 (1990). Review: H. C. Masheter, Clin. Rev. Allergy 11, 5-34 (1993).
Properties: Crystals from acetone, mp 146.5-148.5°; may exist in three polymorphic forms, mp 149-152°, 146-148°, 142-144°. Soly at 30° (g/100ml): water 0.001; ethanol 3.780; methanol 3.750; hexane 0.034; 0.1M HCl 0.012; 0.1M citric acid 0.110; 0.1M tartaric acid 0.045. uv max (methanol): 260 nm (A 660.4); (ethanol): 260 nm (A 671.4); (dichloromethane): 260 nm (A 762.2). LD50 orally in mice: >2000 mg/kg (Carr, Meyer).
Melting point: mp 146.5-148.5°; mp 149-152°, 146-148°, 142-144°

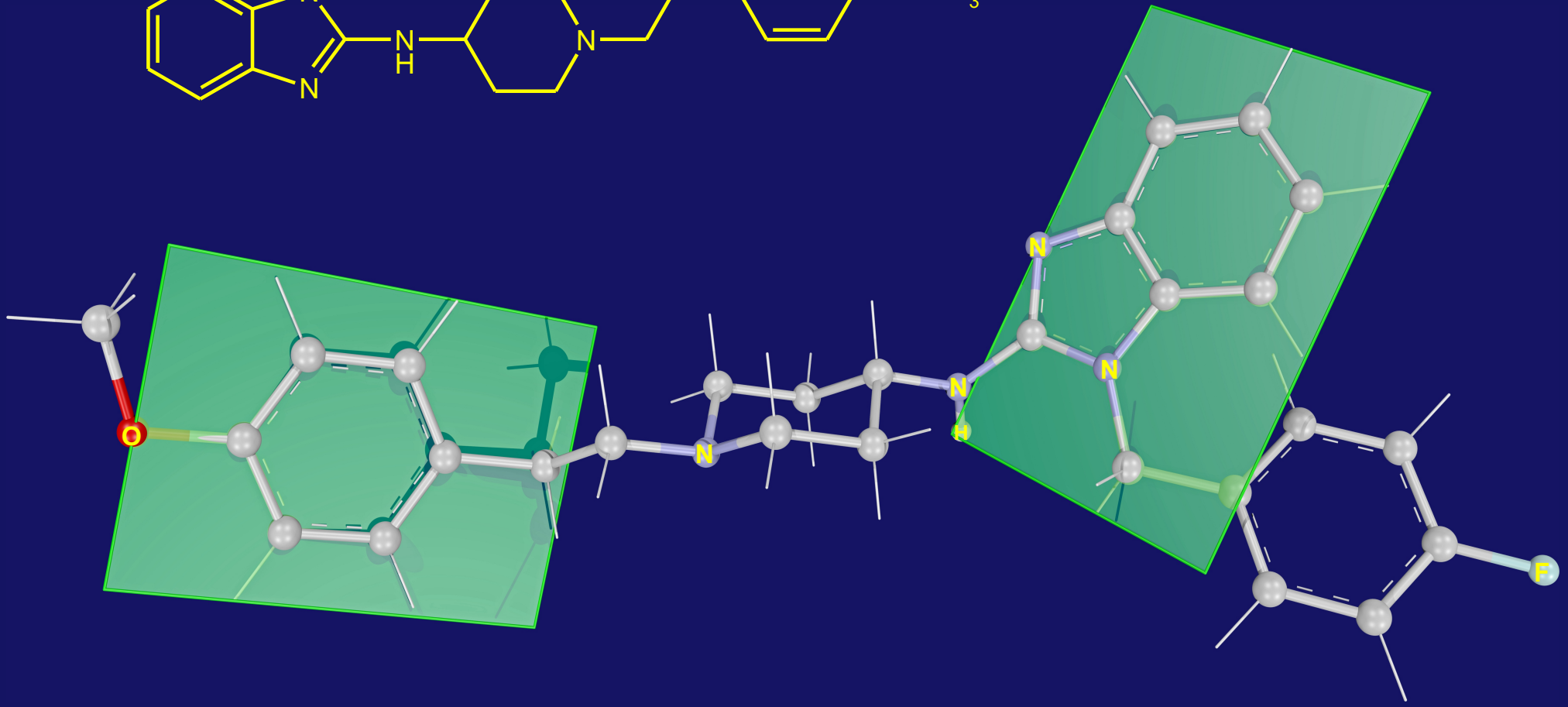
Absorption maximum: uv max (methanol): 260 nm (A 660.4); (ethanol): 260 nm (A 671.4); (dichloromethane): 260 nm (A 762.2)
Toxicity data: LD50 orally in mice: >2000 mg/kg (Carr, Meyer)
Therap-Cat: Antihistaminic.

H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: SINTEZA **TERFENADINE**-a

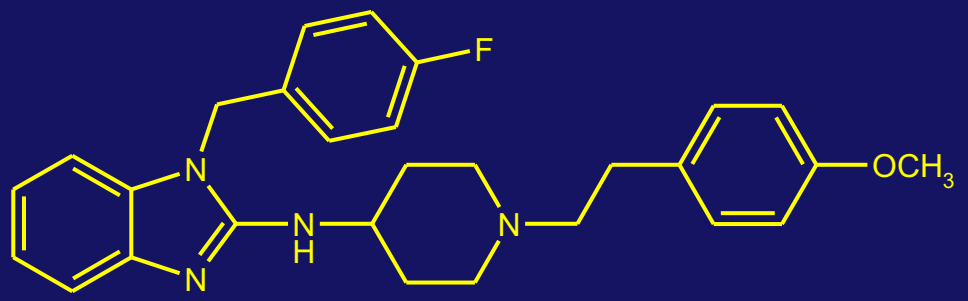


H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: ASTEMIZOLE

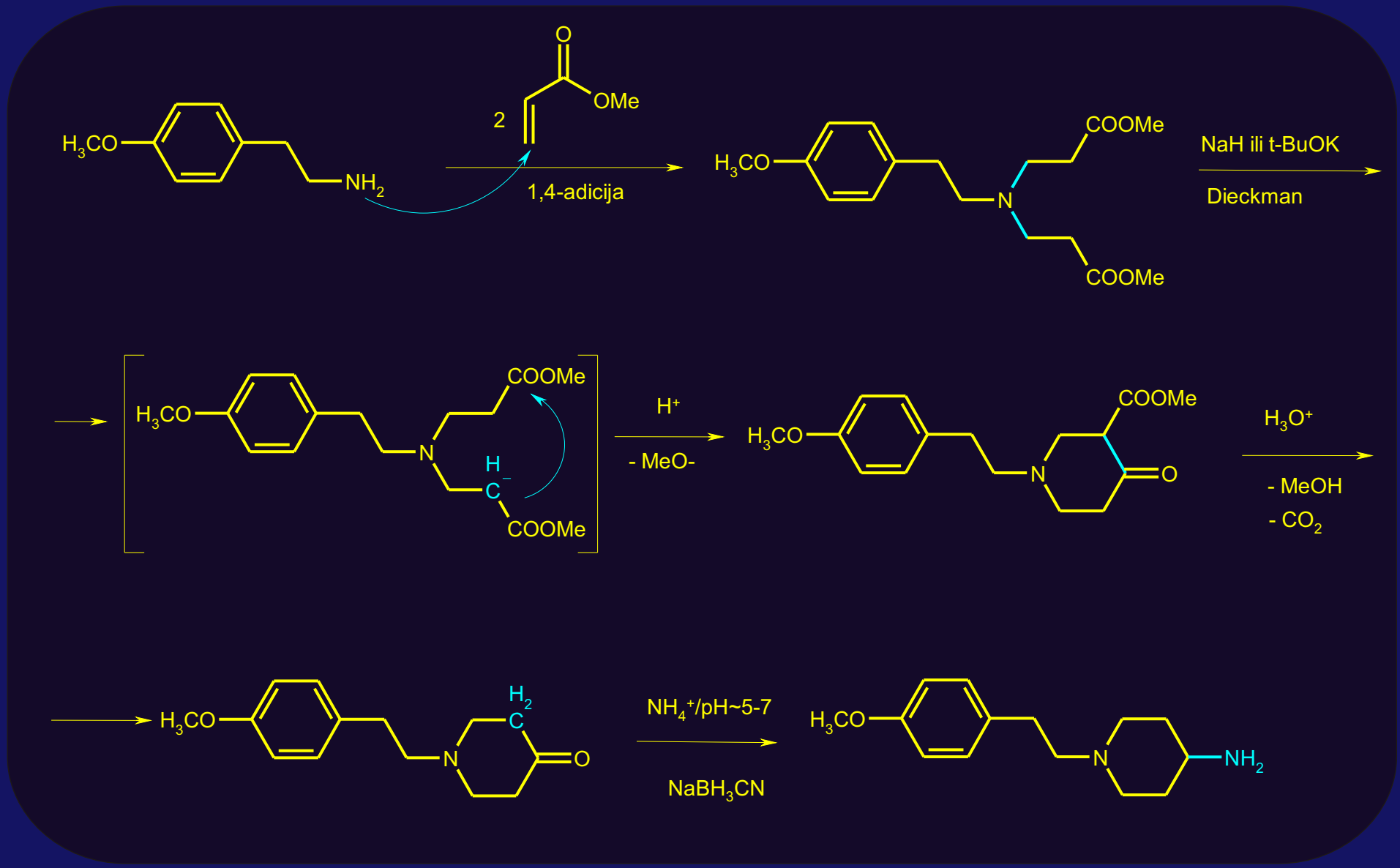




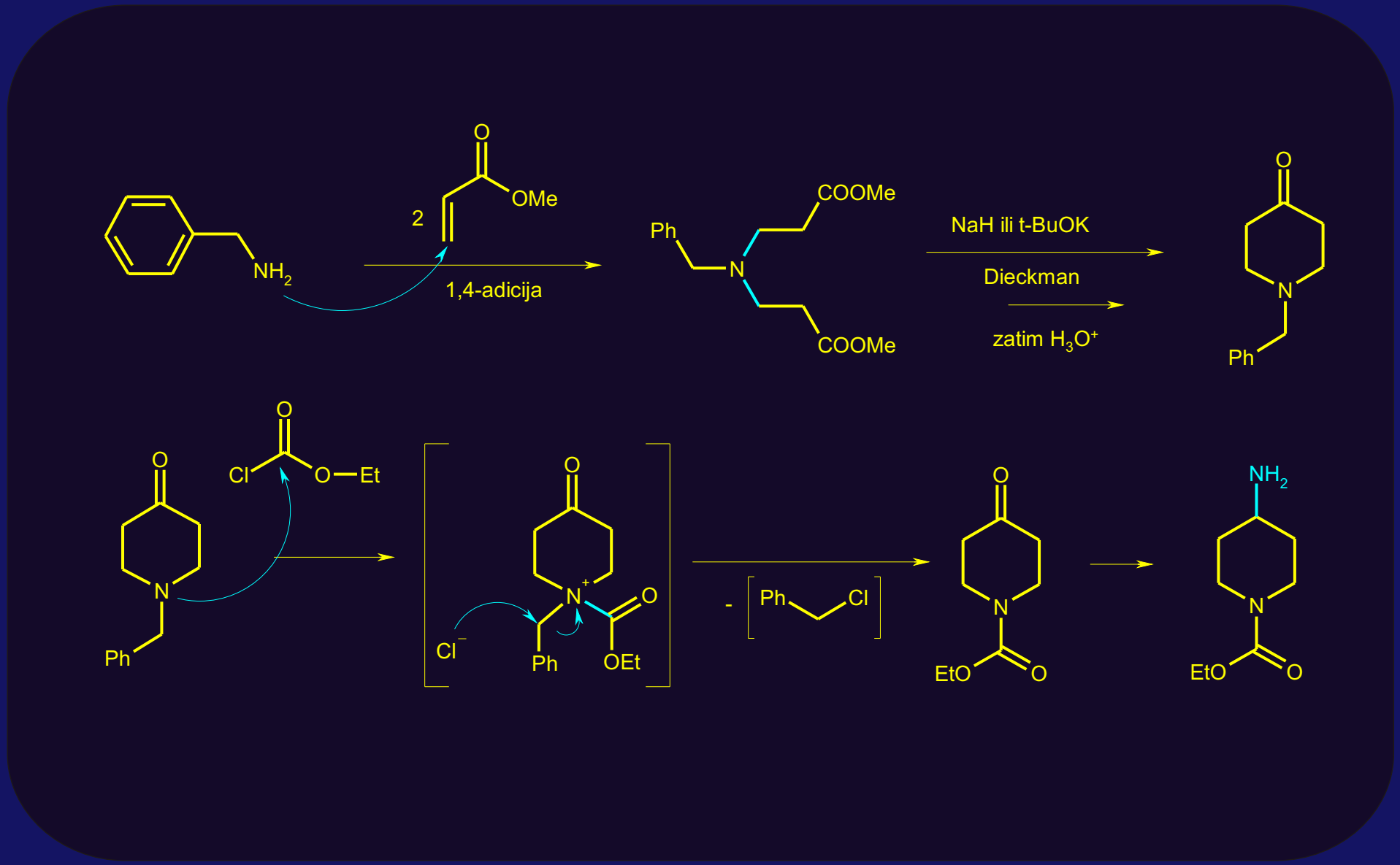
Monograph Number: 861
Title: Astemizole
CAS Registry Number: 68844-77-9
CAS Name: 1-[(4-Fluorophenyl)methyl]-*N*-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine
Additional Names: 1-(*p*-fluorobenzyl)-2-[[1-(*p*-methoxyphenethyl)-4-piperidyl]amino]benzimidazole
Manufacturers' Codes: R-43512
Trademarks: Astemisan (Zdravlje); Hismanal (Janssen); Histamen (Polipharma); Histaminos (Lesvi); Kelp (Omni); Laridal (Elfar-Drag); Metodik (Labinca); Novo-Nastizol A (Bago); Paralergin (Vita); Retolen (Byk Elmu); Waruzol (Farmanic)
Molecular Formula: C28H31FN4O
Molecular Weight: 458.57.
Percent Composition: C 73.34%, H 6.81%, F 4.14%, N 12.22%, O 3.49%
Literature References: Nonsedating-type histamine H1-receptor antagonist. Prepn: F. Janssens *et al.*, **EP 5318**; *eidem,* **US 4219559** (1979, 1980 both to Janssen). Pharmacology: J. Van Wauwe *et al., Arch. Int. Pharmacodyn. Ther.* **251,** 39 (1981); A. Wauquier, C. J. E. Niemegeers, *Eur. J. Pharmacol.* **72,** 245 (1981). *In vitro* and *in vivo* binding characteristics: P. M. Laduron *et al., Mol. Pharmacol.* **21,** 294 (1982). Effect on human psychomotor performance: T. Seppala, K. Savolainen, *Curr. Ther. Res.* **31,** 638 (1982). Clinical study in treatment of hay fever: J. Callier *et al., ibid.* **29,** 24 (1981). Mutagenicity study: P. Vanparys *et al., Arch. Toxicol.* **50,** 167 (1982). Review of pharmacology and clinical trials: D. M. Richards *et al., Drugs* **28,** 38-61 (1984). Comprehensive description: A. M. Al-Obaid, M. S. Mian, *Anal. Profiles Drug Subs.* **20,** 173-208 (1991).
Properties: Crystals from 2,2□-oxybispropane, mp 172.9°. Freely sol in organic solvents. Practically insol in water. uv max (ethanol): 219, 249, 286 nm (□ 27250.229, 6480.293, 8634.280); (0.1*N* HCl): 209, 277 nm (□ 57889.908, 18073.394).
Melting point: mp 172.9°
Absorption maximum: uv max (ethanol): 219, 249, 286 nm (□ 27250.229, 6480.293, 8634.280)
Therap-Cat: Antihistaminic.



H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: ASTEMIZOLE

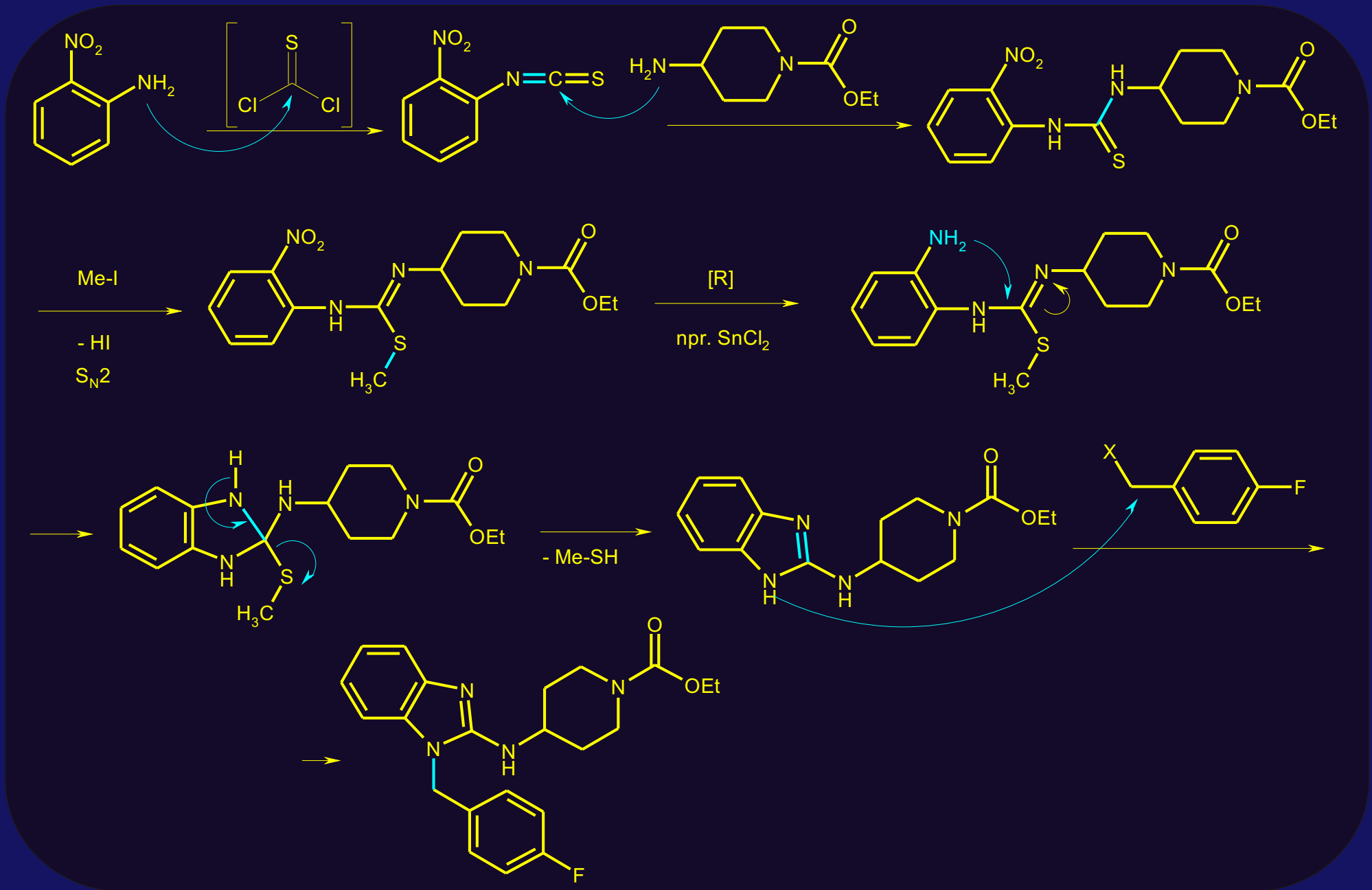


H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: ASTEMIZOLE -nastavak

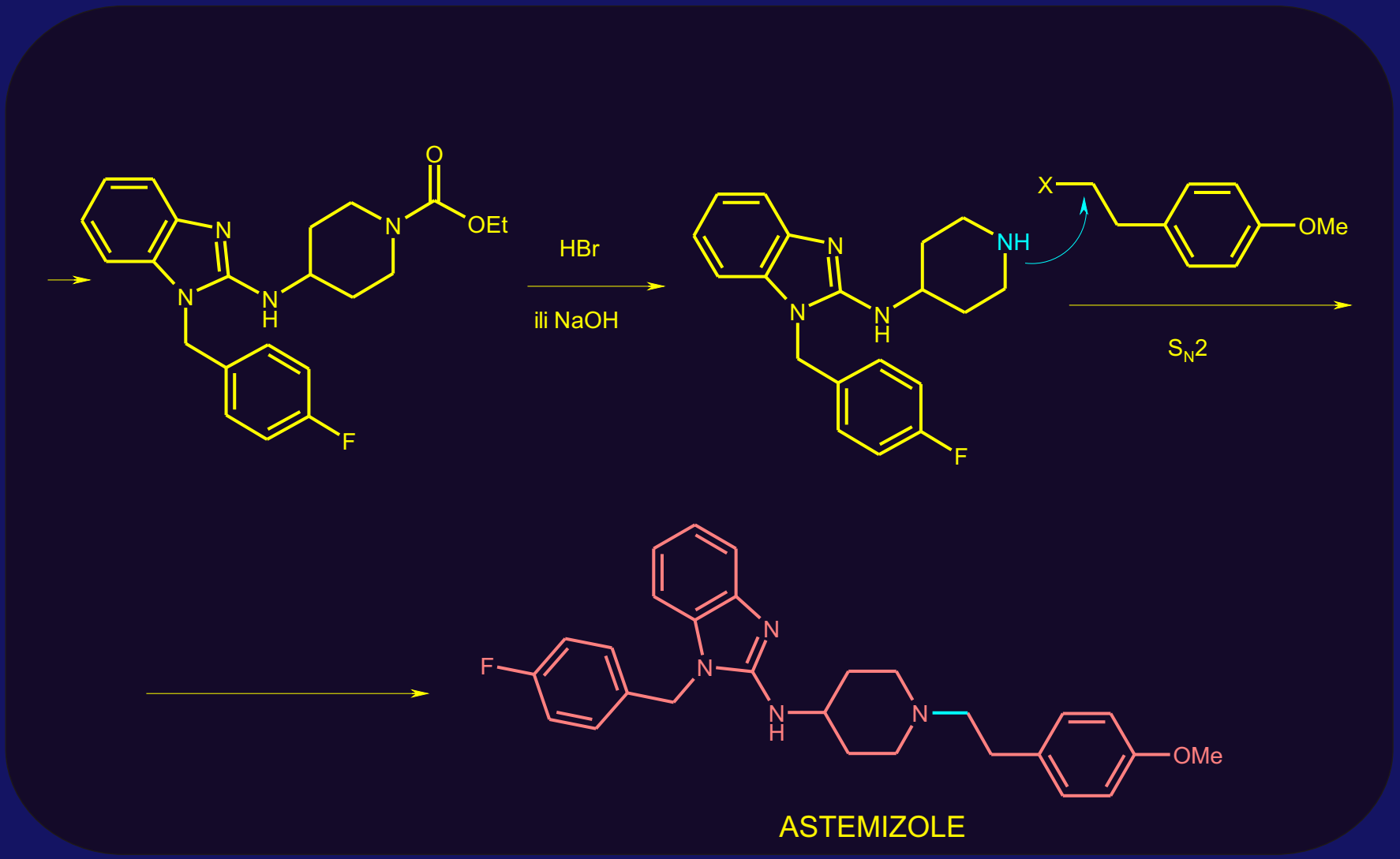


H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: ASTEMIZOLE -nastavak

DODATAK



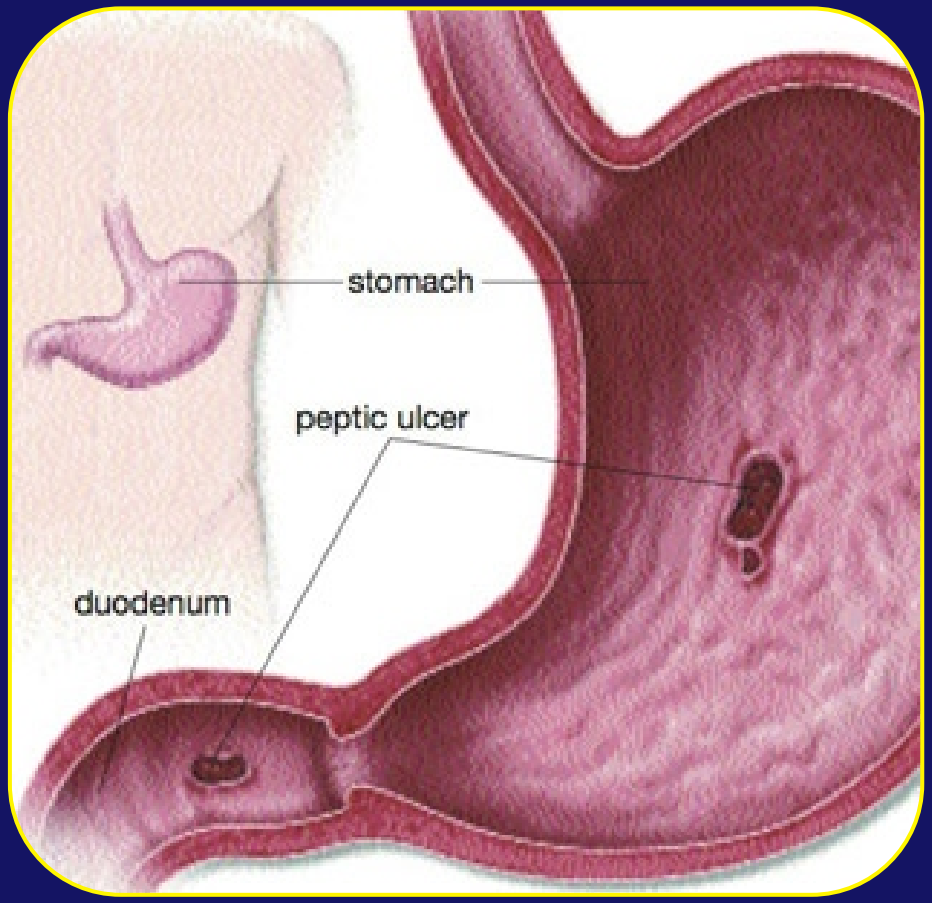
H_1 ANTI-HISTAMINSKI PREPARATI - PIPERIDINI. PRIMERI: ASTEMIZOLE -nastavak

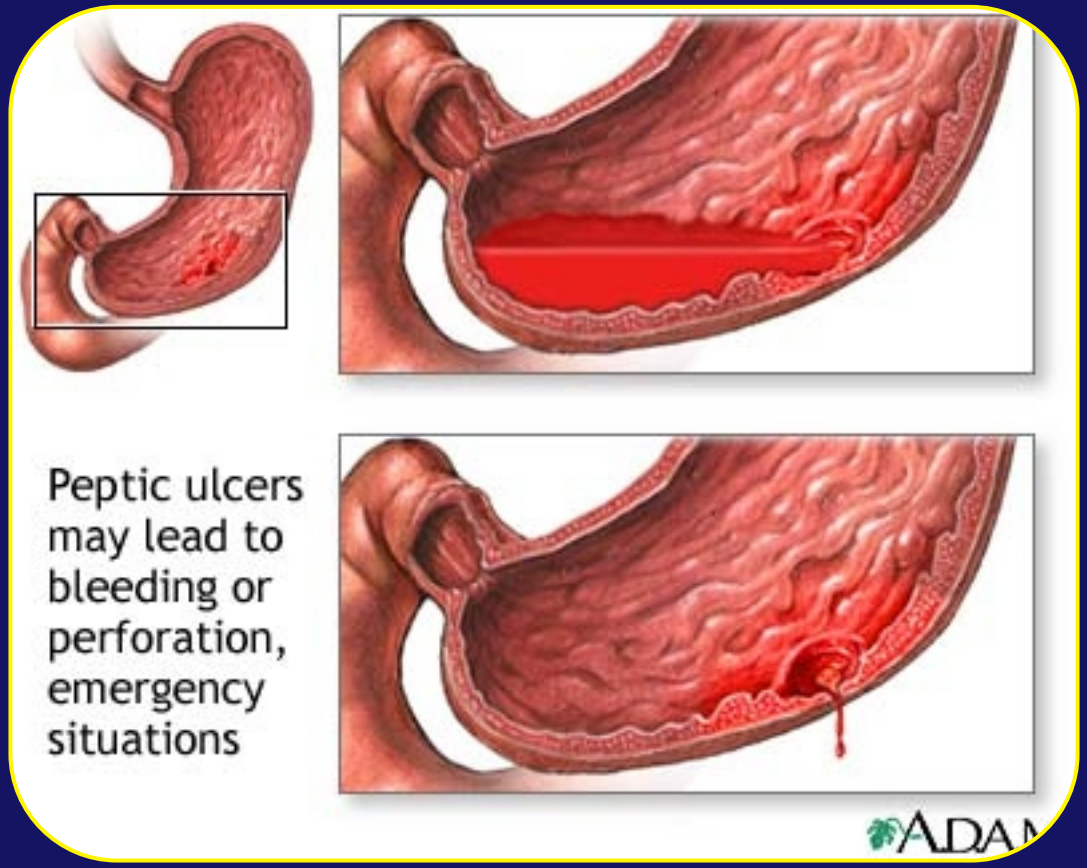


ANTAGONISTI H_2 RECEPTORA - IZGLED ČIRA U ŽELUCU

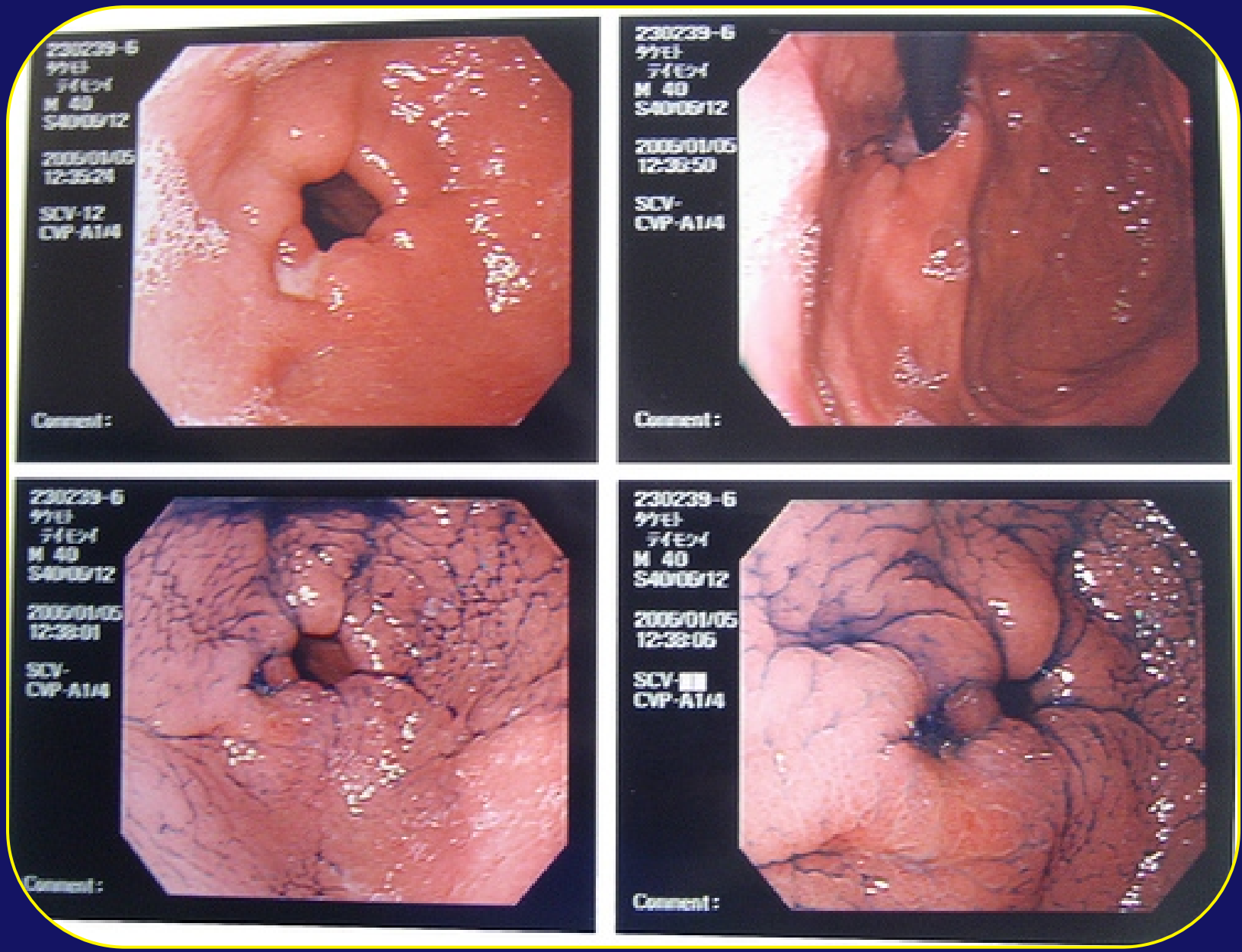
-ULOGA H_2 RECEPTORA JE U REGULACIJI LUČENJA ŽELUDAČNE KISELINE. MEĐUTIM PRETERANO LUČENJE ŽELUDAČNE KISELINE JE IZRAZITO ŠTETNO PO ZDRAVLJE I PREDSTAVLJA FAKTOR U NASTAJANJU MNOGIH OBOLJENJA, IZMEĐU OSTALOG ČIRA (GRIZLICE) U ŽELUCU I U TANKOM CREVU.

-TAKVA OBOLJENJA PREDSTAVLJAJU TEŽAK, HRONIČNI ZDRAVSTVENI PROBLEM, KOJI ČESTO ZAHTEVA HIRURŠKU INTERVENCIJU, A U ZNATNOM BROJU SLUČAJEVA IMA I FATALNI ISHOD. POSEBNO SU OPASNA KRVARENJA, DOK PUCANJE (PERFORACIJA) ČIRA ODN. ŽELUCA, VRLO ČESTO IMA SMRTNI ISHOD.



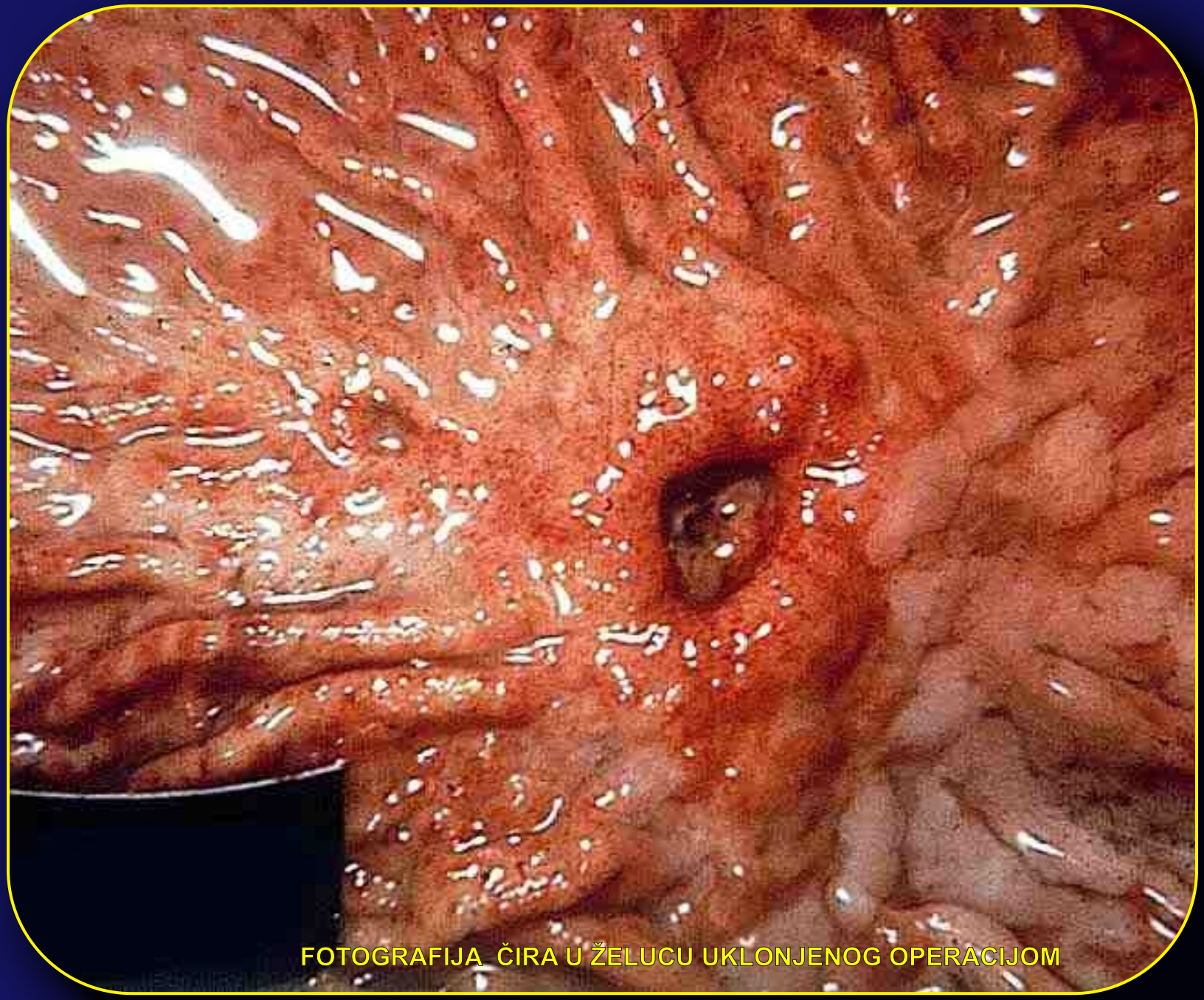


ANTAGONISTI H_2 RECEPTORA - IZGLED ČIRA U ŽELUCU



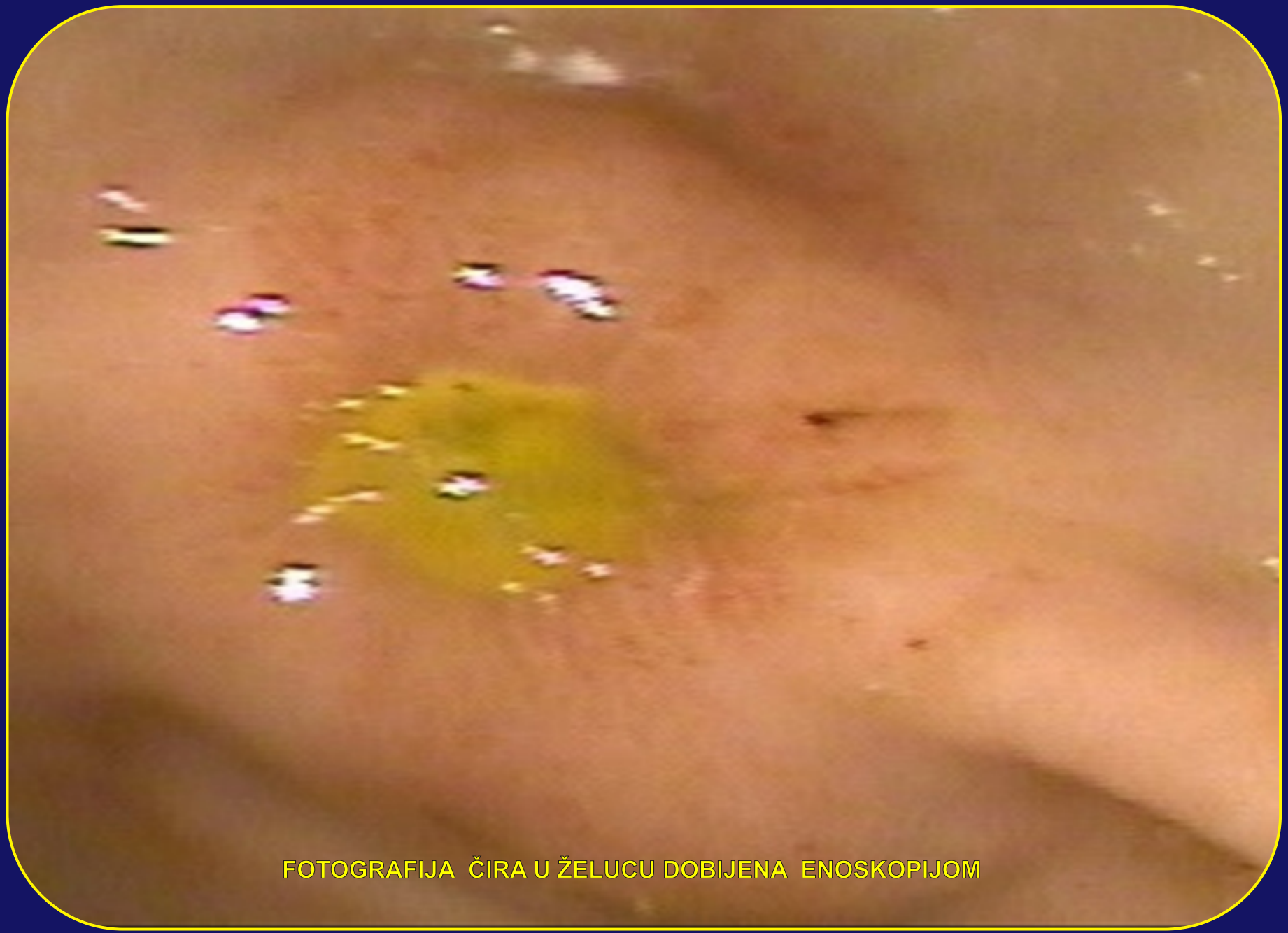
FOTOGRAFIJE ČIRA U ŽELUCU DOBIJENE ENOSKOPIJOM (SNIMANJE POMOĆU SONDE)

ANTAGONISTI H_2 RECEPTORA - IZGLED ČIRA U ŽELUCU



FOTOGRAFIJA_ČIRA U ŽELUCU UKLONJENOG OPERACIJOM

ANTAGONISTI H_2 RECEPTORA - IZGLED ČIRA U ŽELUCU



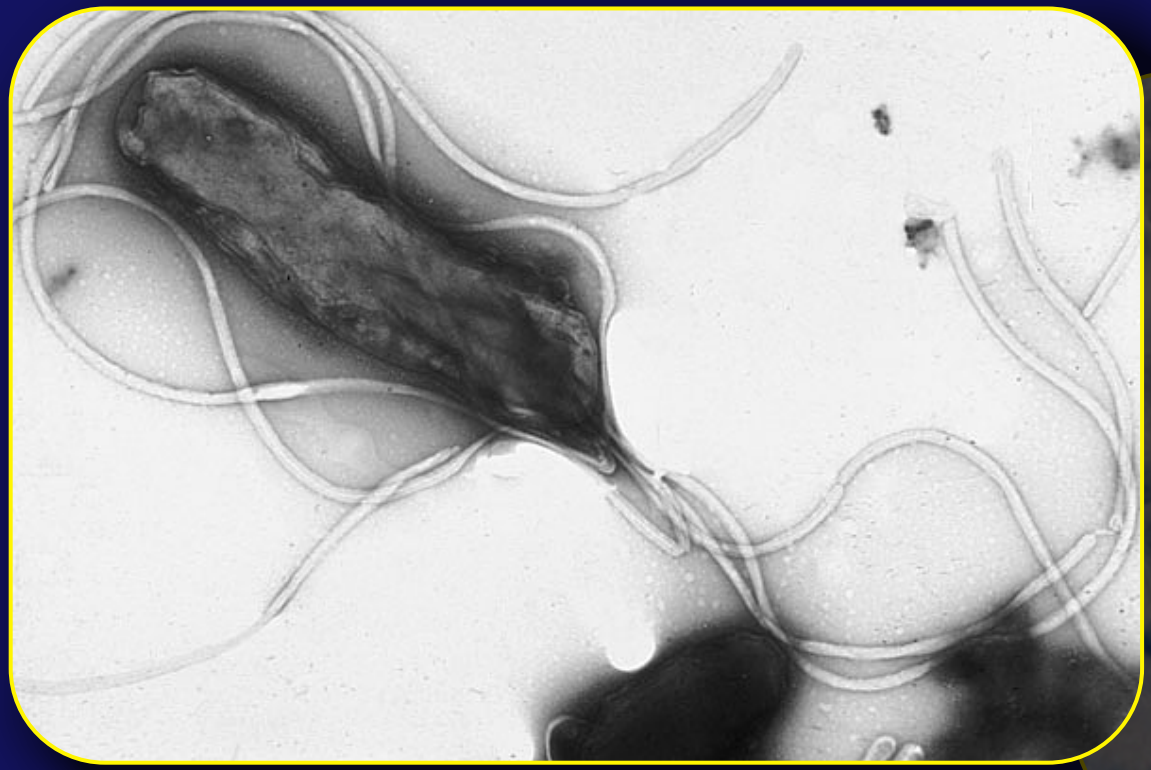
FOTOGRAFIJA ČIRA U ŽELUCU DOBIJENA ENOSKOPIJOM

ANTAGONISTI H_2 RECEPTORA - INFEKCIJA KAO GLAVNI UZROK NASTAJANJA VEĆINE ŽELUDAČNIH ČIREVA

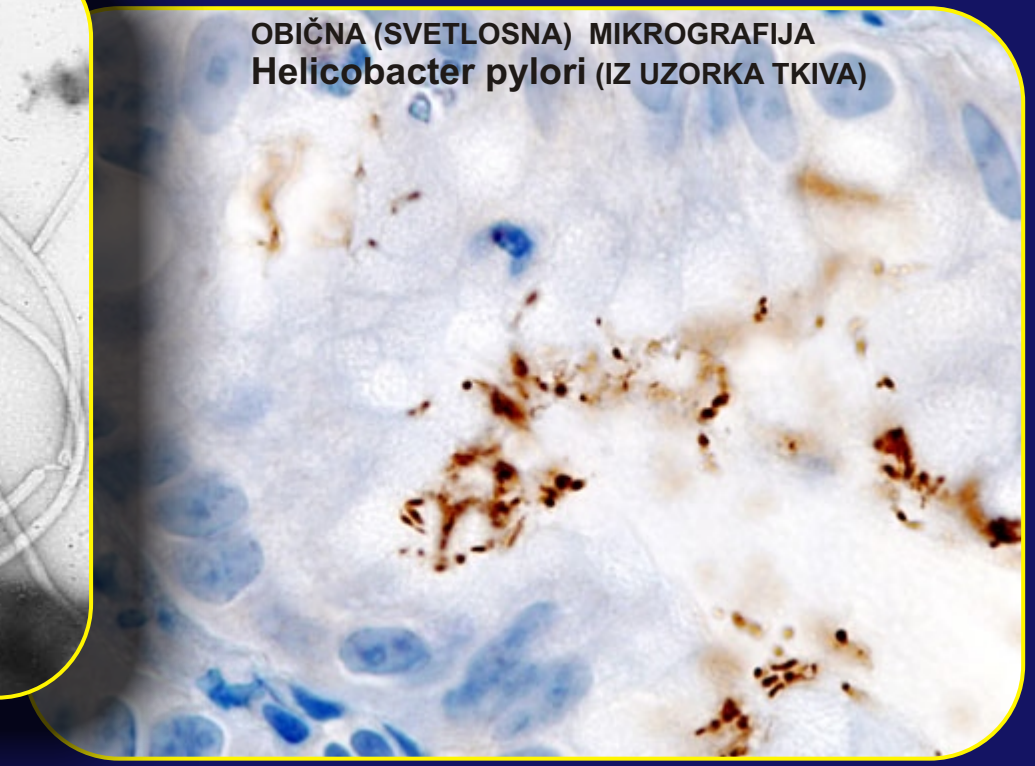
-POČETKOM 80-ih GODINA OTKRIVENA JE NOVA VRSTA BAKTERIJE, Helicobacter pylori, KOJA ŽIVI U ŽELUDAČNOM TKIVU. KASNIJE JE POKAZANO DA INFEKCIJA OVOM BAKTERIJOM PREDSTAVLJA OSNOVNI UZROK NASTAJANJA 80-90% ČIREVA U ŽELUCU I TANKOM CREVU.

-KONSEKVENTNO, UVEDEN JE NOV I IZUZETNO EFIKASAN NAČIN LEČENJA OVIH OBOLJENJA, KOMBINACIJOM ANTIBIOTIKA I I ANTAGONISTA H_2 RECEPTORA.

-POSEBNO SU EFIKASNE KOMBINACIJE TRI ANTIBIOTIKA (npr. AMOXICILLIN + CLARITHROMYCIN + METRONIDAZOLE) I NEKOG OD H_2 ANTAGONISTA, TOKOM 10-14 DANA.



TRANSMISIONA ELEKTRONSKA MIKROGRAFIJA Helicobacter pylori



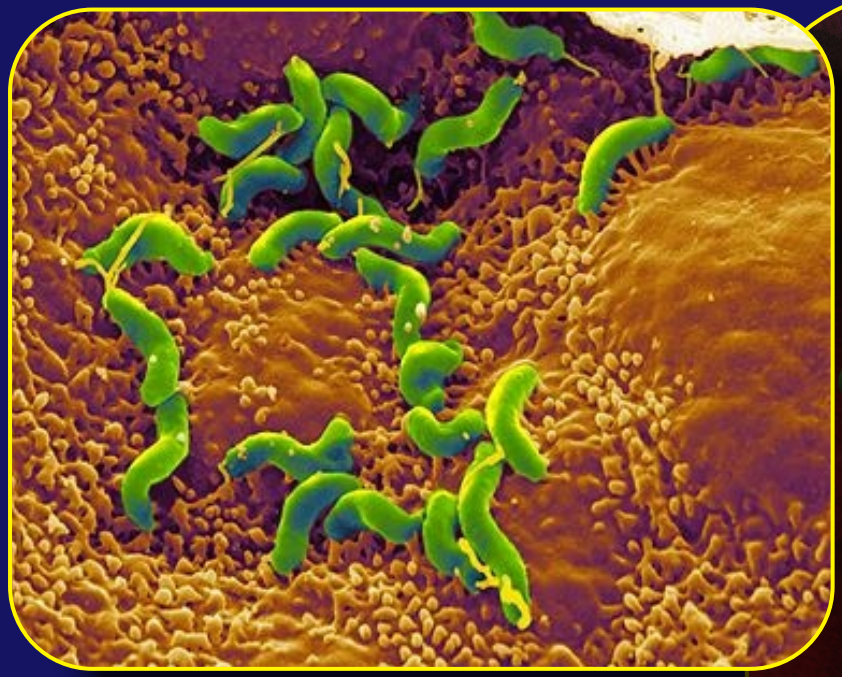
OBIČNA (SVETLOSNA) MIKROGRAFIJA
Helicobacter pylori (IZ UZORKA TKIVA)

- ZA OVO OTKRIĆE, AUTORI SU 2005. GODINE DOBILE NOBELOVU NAGRADU ZA MEDICINU

BARRY MARSHALL

ROBIN WARREN

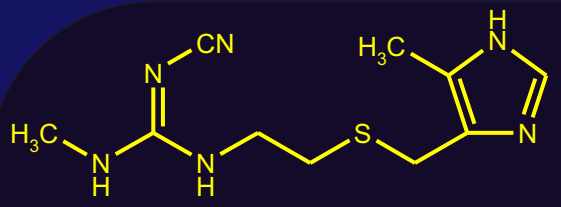
ANTAGONISTI H_2 RECEPTORA - INFEKCIJA KAO GLAVNI UZROK NASTAJANJA VEĆINE ŽELUDAČNIH ČIREVA



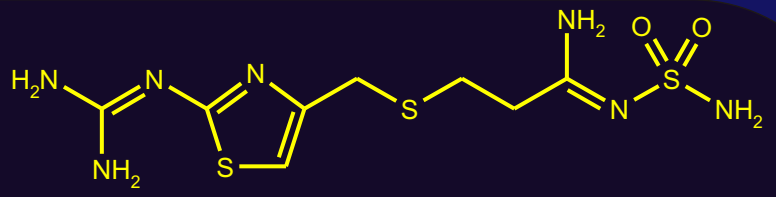
SKENIRAJUĆA ELEKTRONSKA MIKROGRAFIJA
Helicobacter pylori (VEŠTAČKO, DIGITALNO BOJENJE)

Helicobacter pylori U ŽELUCU
(UMETNIČKA PREDSTAVA)

ANTAGONISTI H_2 RECEPTORA - STRUKTURE

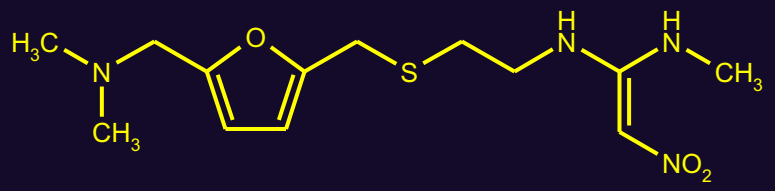


Cimetidine (Tagamet)

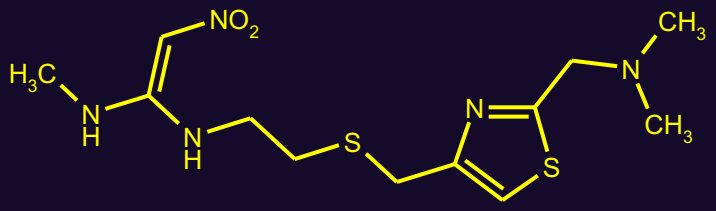


Famotidine

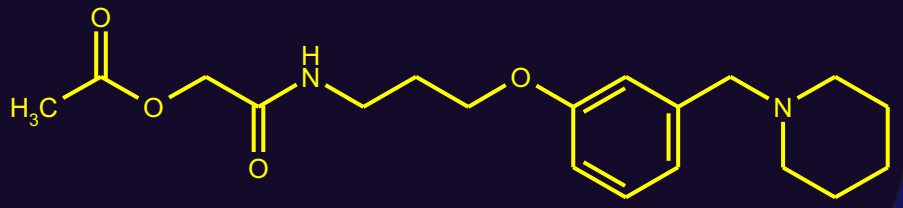
Lafutidine



Ranitidine

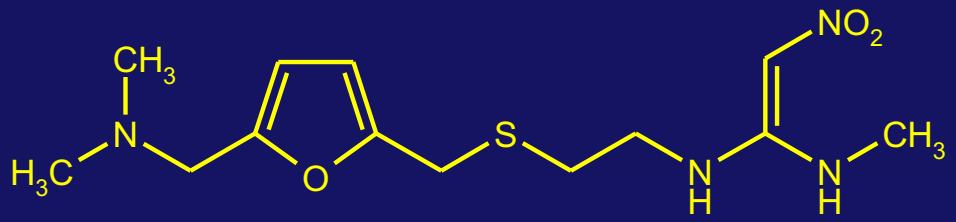


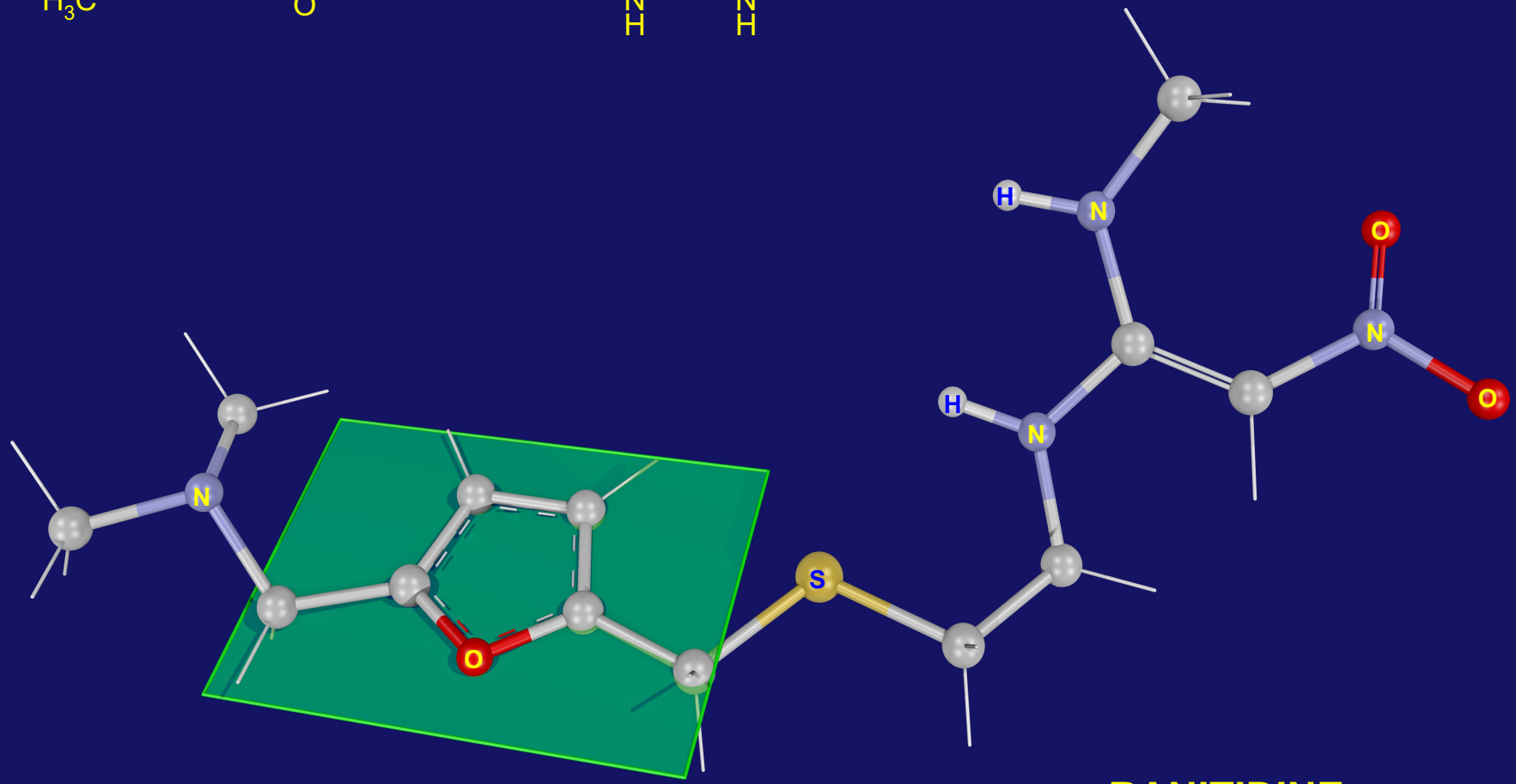
Nizatidine



Roxatidine Acetate

ANTAGONISTI H_2 RECEPTORA - RANITIDINE





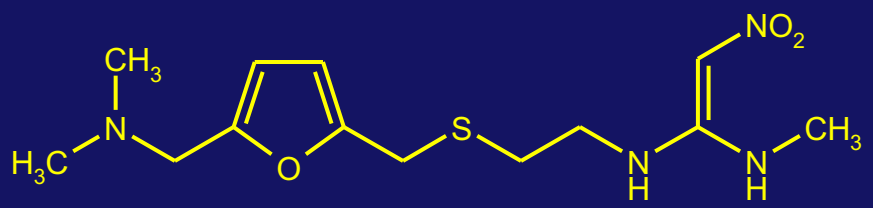
RANITIDINE

Monograph Number: 8198
Title: Ranitidine
CAS Registry Number: 66357-35-5
CAS Name: N-[2-[[[-5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N -methyl-2-nitro-1,1-ethenediamine
Molecular Formula: C13H22N4O3S
Molecular Weight: 314.41.
Percent Composition: C 49.66%, H 7.05%, N 17.82%, O 15.27%, S 10.20%
Literature References: Histamine H2-receptor antagonist which inhibits gastric acid secretion. Prepn: B. J. Price et al., FR 2384765; eidem, US 4128658 (both 1978 to Allen & Hanburys). HPLC determn in plasma: P. F. Carey, L. E. Martin, J. Liq. Chromatog. 1979, 1291. Pharmacological studies: J. Bradshaw et al., Brit. J. Pharmacol. 66, 464 (1979); M. J. Daly et al., Gut 21, 408 (1980). Efficacy in treatment of duodenal ulcers: A. Berstad et al., Scand. J. Gastroenterol. 15, 637 (1980); R. P. Walt et al., Gut 22, 49 (1981). Review of pharmacology and therapeutic use: R. N. Brogden et al., Drugs 24, 267-303 (1982). Comprehensive description: M. Hohnjec et al., Anal. Profiles Drug Subs. 15, 533-561 (1986).
Properties: Solid, mp 69-70°.
Melting point: mp 69-70°

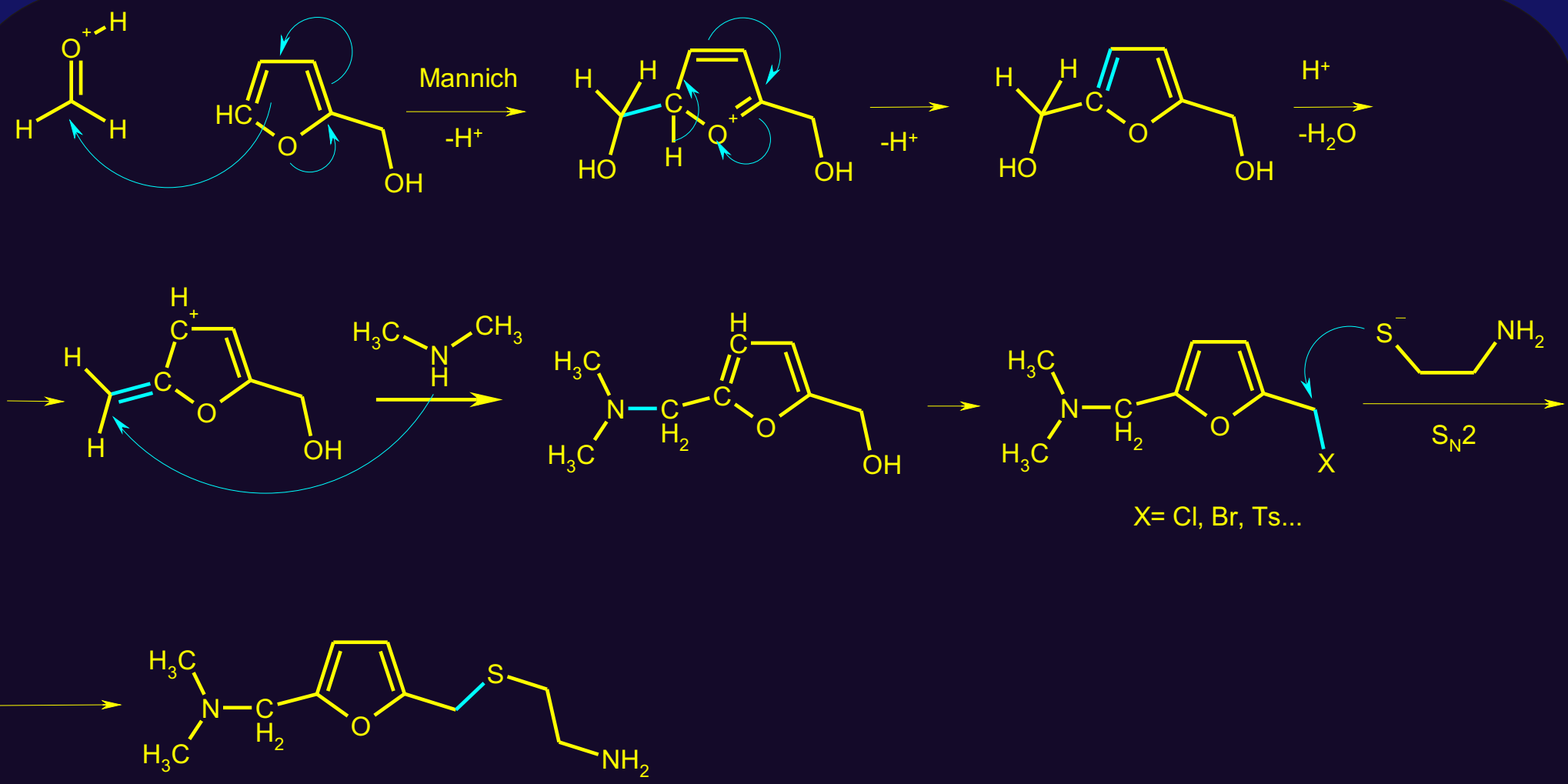
Derivative Type: Hydrochloride
CAS Registry Number: 66357-59-3
Manufacturers' Codes: AH-19065
Trademarks: Azantac (Glaxo Wellcome); Melfax (Apotex); Noctone (Gea); Raniben (Firma); Ranidil (Menarini); Raniplex (Fournier); Sostril (Cascan); Taural (Roemmers); Terposen (Vir); Trigger (Polifarma); Ulcex (Guidotti); Ultidine (Glaxo); Zantac (Glaxo Wellcome); Zantic (Glaxo Wellcome)
Molecular Formula: C13H22N4O3S.HCl
Molecular Weight: 350.87.
Percent Composition: C 44.50%, H 6.61%, N 15.97%, O 13.68%, S 9.14%, Cl 10.10%
Properties: Off-white solid, mp 133-134°. Freely sol in acetic acid and water, sol in methanol, sparingly sol in ethanol. Practically insol in chloroform.
Melting point: mp 133-134°

Derivative Type: Bismuth citrate
CAS Registry Number: 128345-62-0
Additional Names: Ranitidine bismutrex
Manufacturers' Codes: GR-122311X
Trademarks: Pylorid (Glaxo Wellcome); Tritec (Glaxo Wellcome)
Molecular Formula: C13H22N4O3S.C6H5BiO7
Molecular Weight: 712.49.
Percent Composition: C 32.03%, H 3.82%, N 7.86%, O 22.46%, S 4.50%, Bi 29.33%
Literature References: Pharmacology and activity vs Helicobacter sp: R. Stables et al., Aliment. Pharmacol. Ther. 7, 237 (1993).

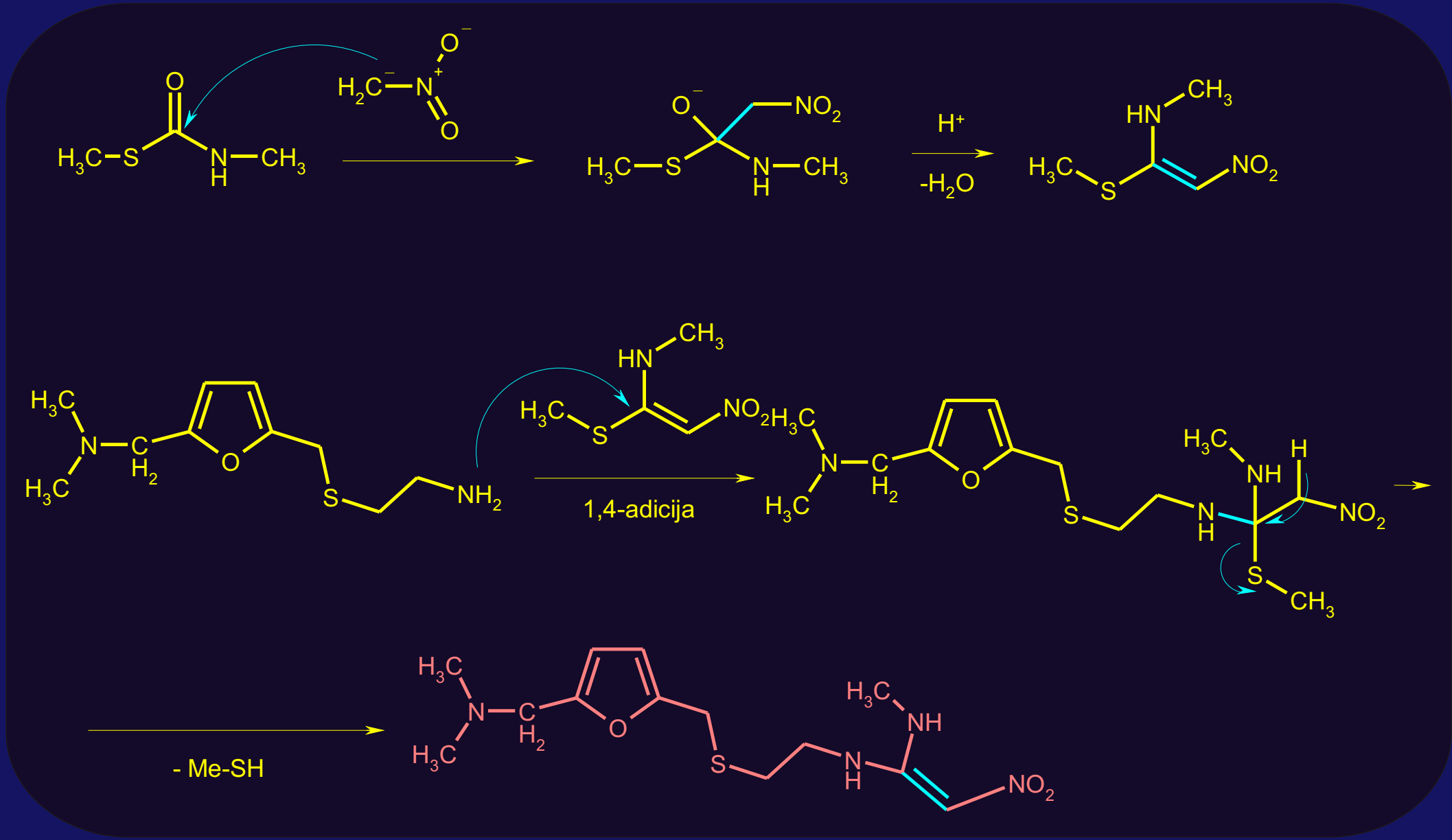
Therap-Cat: Antiulcerative.



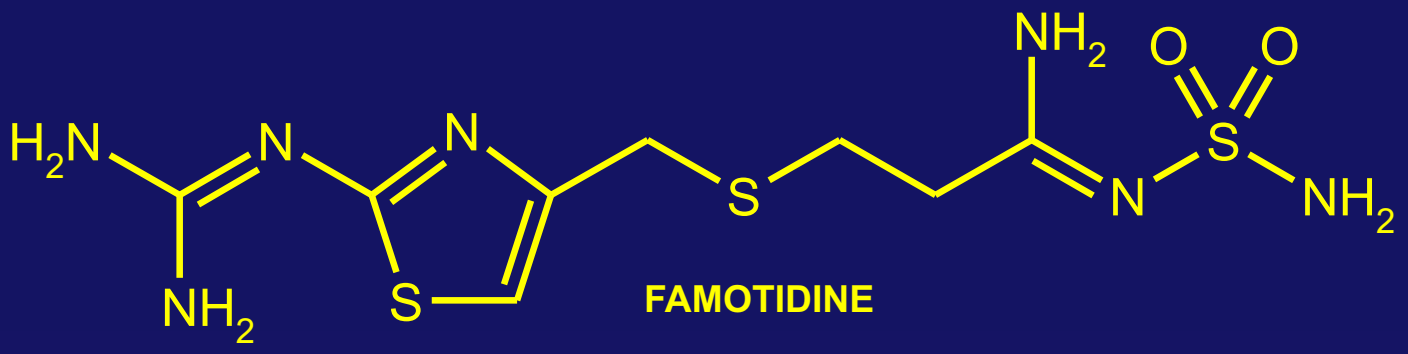
ANTAGONISTI H_2 RECEPTORA - SINTEZA RANITIDINE-a



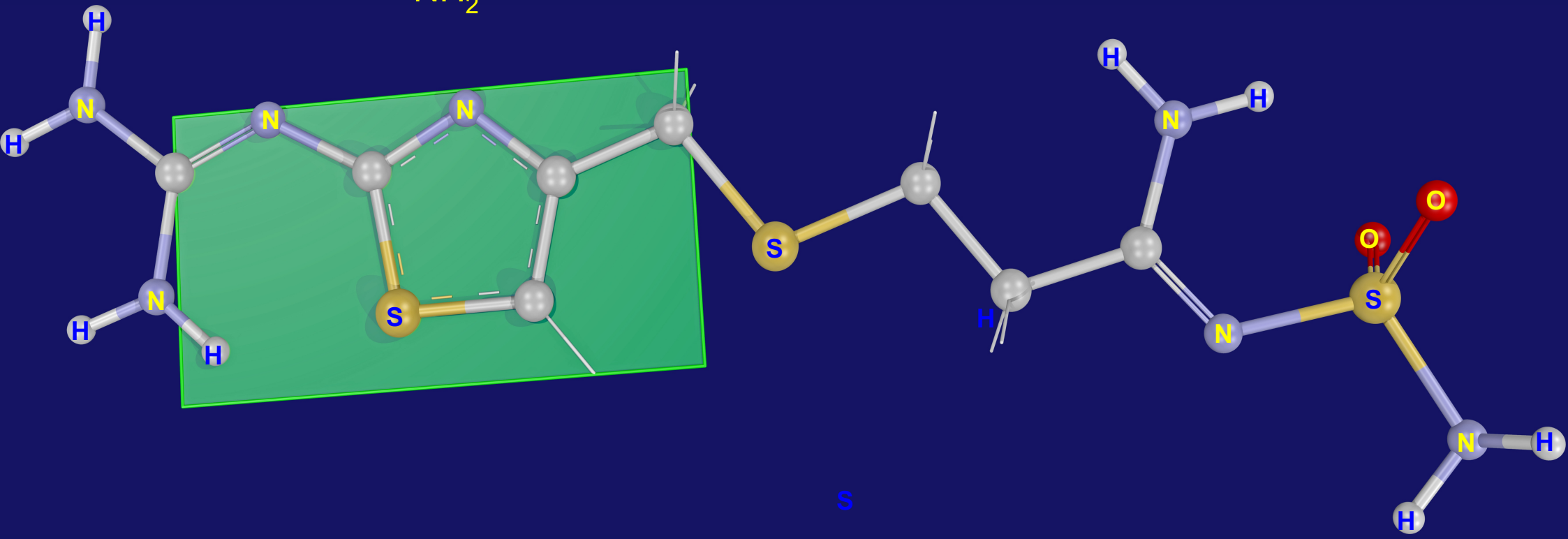
ANTAGONISTI H_2 RECEPTORA - SINTEZA RANITIDINE-a -nastavak



ANTAGONISTI H_2 RECEPTORA - FAMOTIDIN



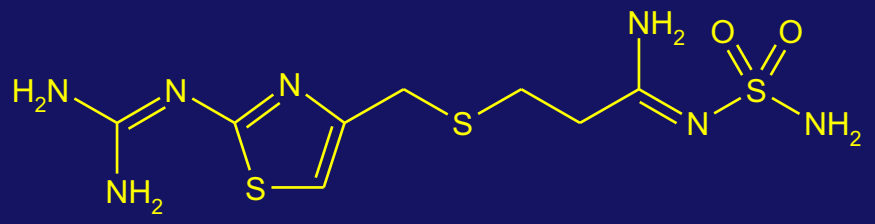
FAMOTIDINE



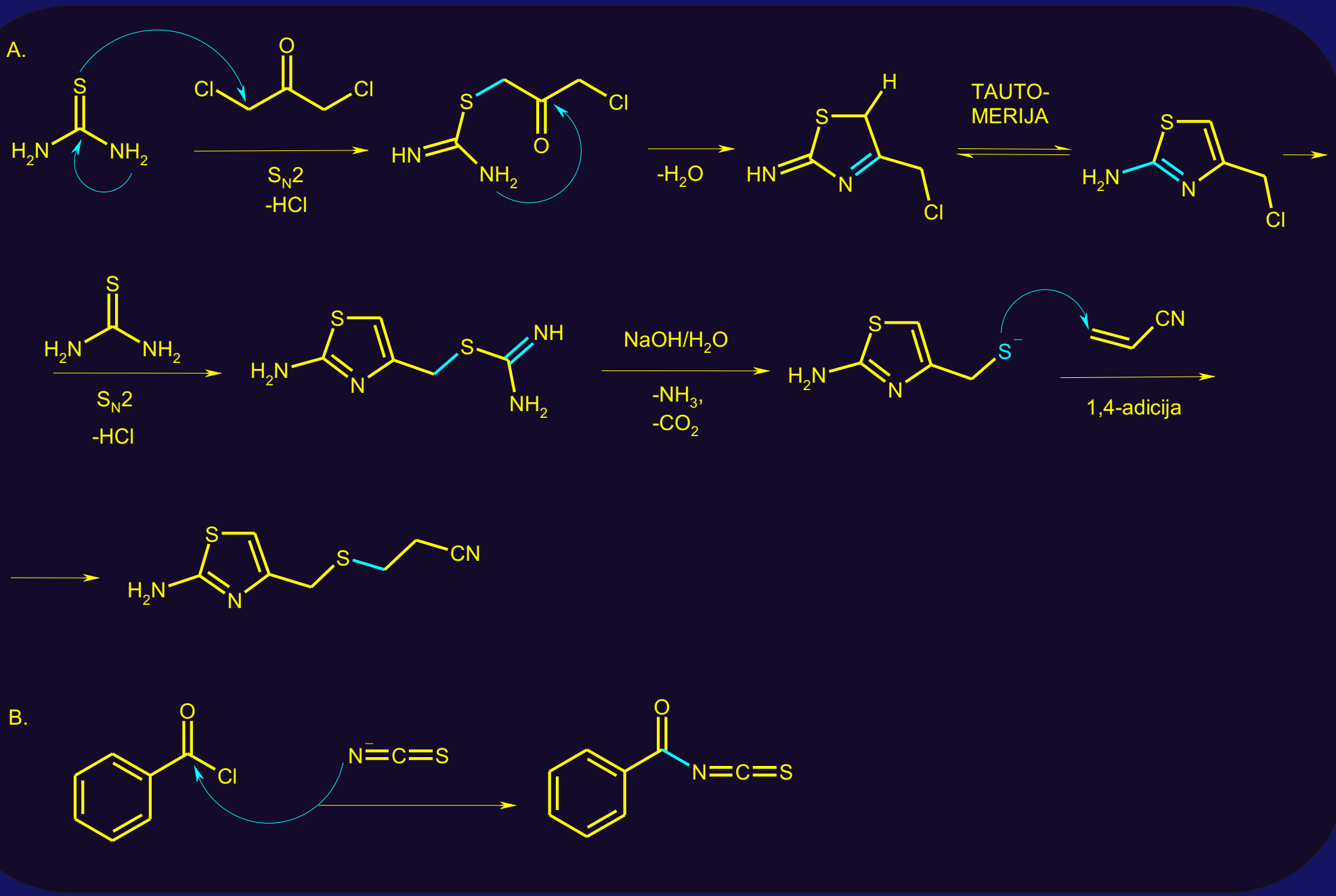
S

ANTAGONISTI H_2 RECEPTORA - FAMOTIDIN

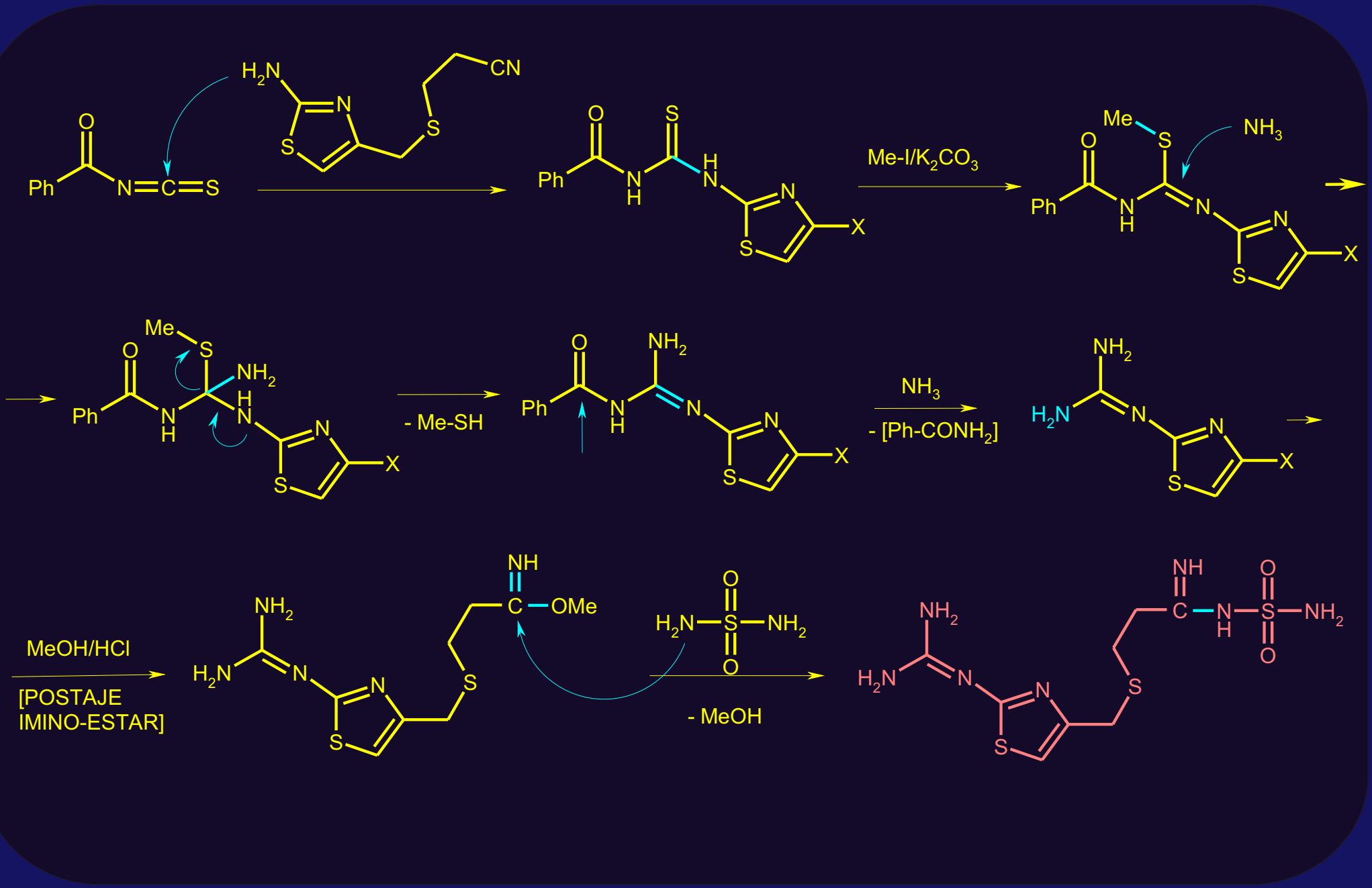
Monograph Number: 3961
Title: Famotidine
CAS Registry Number: 76824-35-6
CAS Name: 3-[[[2-[(Aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-(aminosulfonyl)propanimidamide
Additional Names: [1-amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propylidene]sulfamide; N-sulfamoyl-3-[(2-guanidinothiazol-4-yl)methylthio]propionamide
Manufacturers' Codes: YM-11170; MK-208
Trademarks: Amfamox (AMRAD); Dispromil (Liberman); Famodil (Sigma-Tau); Famodine (Farmasa); Famosan (Alkaloid); Famoxal (Silanes); Fanosin (Abello); Fibonel (Pharma Investi); Ganor (Thomae); Gaster (Yamanouchi); Gastridin (Merck & Co.); Gastropen (CEPA); Ifada (Wassermann); Lecedil (Zdravlje); Motiax (Neopharmed); Muclox (Sigma Tau); Nulcerin (Andromaco); Pepcid (Merck & Co.); Pepcidina (Merck & Co.); Pepcidine (Merck & Co.); Pepdine (Merck & Co.); Pepdul (Merck & Co.); Peptan (Vianex); Ulcetrax (Salvat); Ulfamid (Krka); Ulfinol (Roemmers)
Molecular Formula: C8H15N7O2S3
Molecular Weight: 337.45.
Percent Composition: C 28.47%, H 4.48%, N 29.06%, O 9.48%, S 28.51%
Literature References: Histamine H2-receptor antagonist. Prepn, NMR and mass spectral data: H. Yasufumi et al., BE 882071; eidem, US 4283408; JP Kokai 81 55383, C.A. 95, 203930n (1980, 1981, 1981 all to Yamanouchi). Inhibition of gastric acid and pepsin secretion in rats: M. Takeda et al., Arzneimittel-Forsch. 32, 734 (1982); in man: M. Miwa et al., J. Clin. Pharmacol. Ther. Toxicol. 22, 214 (1984). Effect on disposition of antipyrine in liver: Ch. Staiger et al., Arzneimittel-Forsch. 34, 1041 (1984). Chromatographic determn in plasma and urine: W. C. Vincek et al., J. Chromatog. 338, 438 (1985). Pharmacokinetics: T. Takabatke et al., Eur. J. Clin. Pharmacol. 28, 327 (1985). Clinical trial in Zollinger-Ellison syndrome: J. M. Howard et al., Gastroenterology 88, 1026 (1985).
Symposia on pharmacology and clinical efficacy: Am. J. Med. 81, Suppl. 4B, 1-64 (1986); Scand. J. Gastroenterol. 22, Suppl. 134, 1-62 (1987).
Properties: mp 163-164°. Soly at 20° (%, w/v): 80 in DMF; 50 in acetic acid; 0.3 in methanol; 0.1 in water; <0.01 in ethanol, ethyl acetate, chloroform. LD50 i.v. in mice: 244.4 mg/kg (Yasufumi).
Melting point: mp 163-164°
Toxicity data: LD50 i.v. in mice: 244.4 mg/kg (Yasufumi)
Therap-Cat: Antiulcerative.



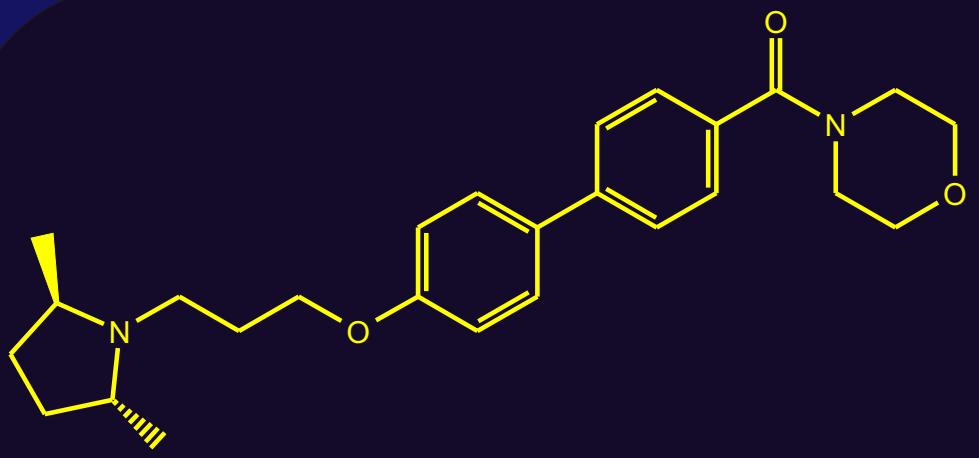
ANTAGONISTI H_2 RECEPTORA - SINTEZA FAMOTIDINE-a



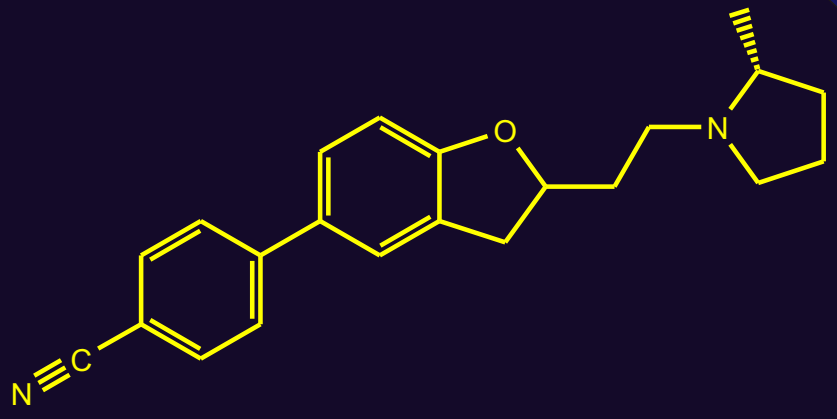
ANTAGONISTI H_2 RECEPTORA - SINTEZA FAMOTIDINE-a - nastavak



ANTAGONISTI H_3 RECEPTORA - STRUKTURE



CAS 372513-99-0



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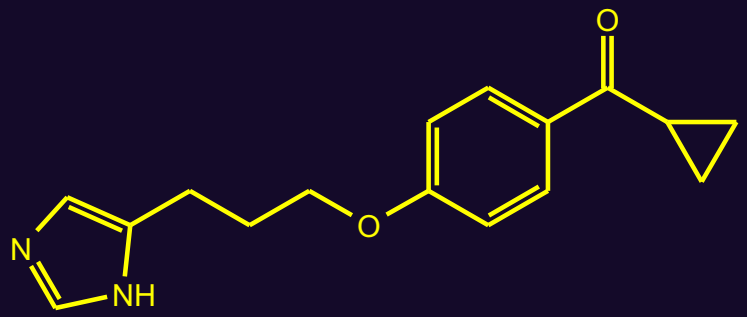


CAS 184025-18-1

Ciproxifan; FUB 359

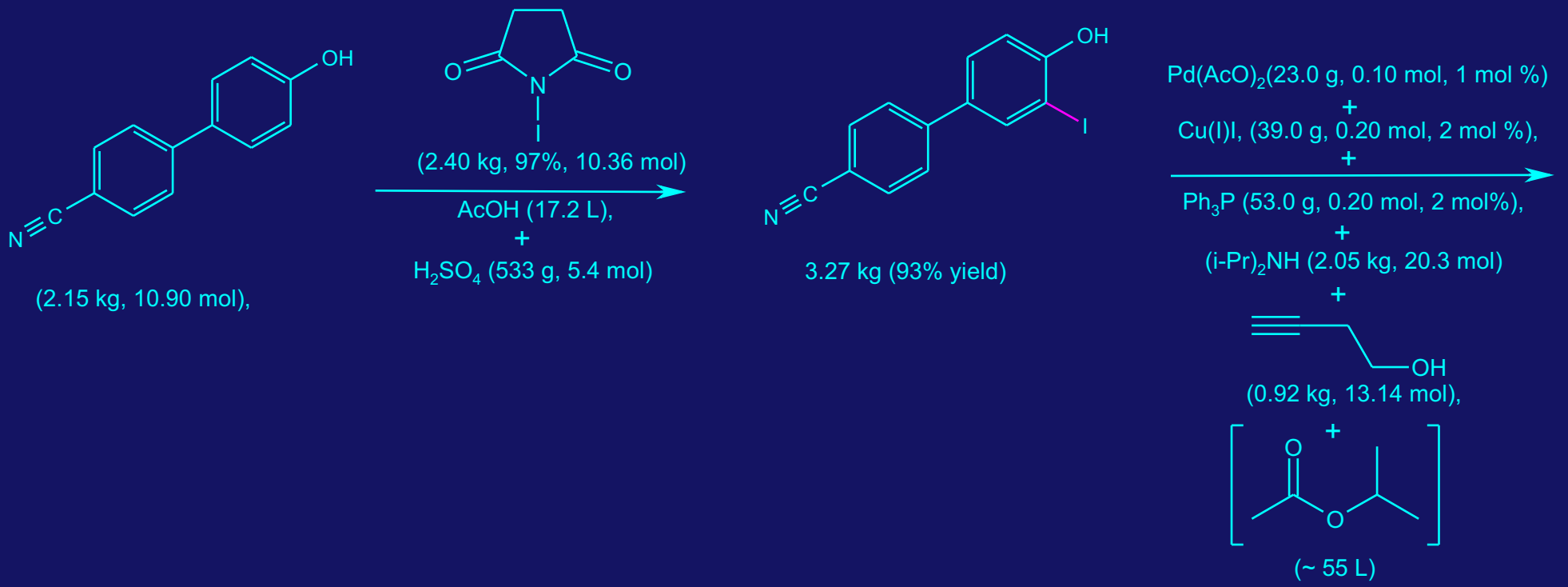
CAS 145231-45-4

Clobenpropit; VUF 9153

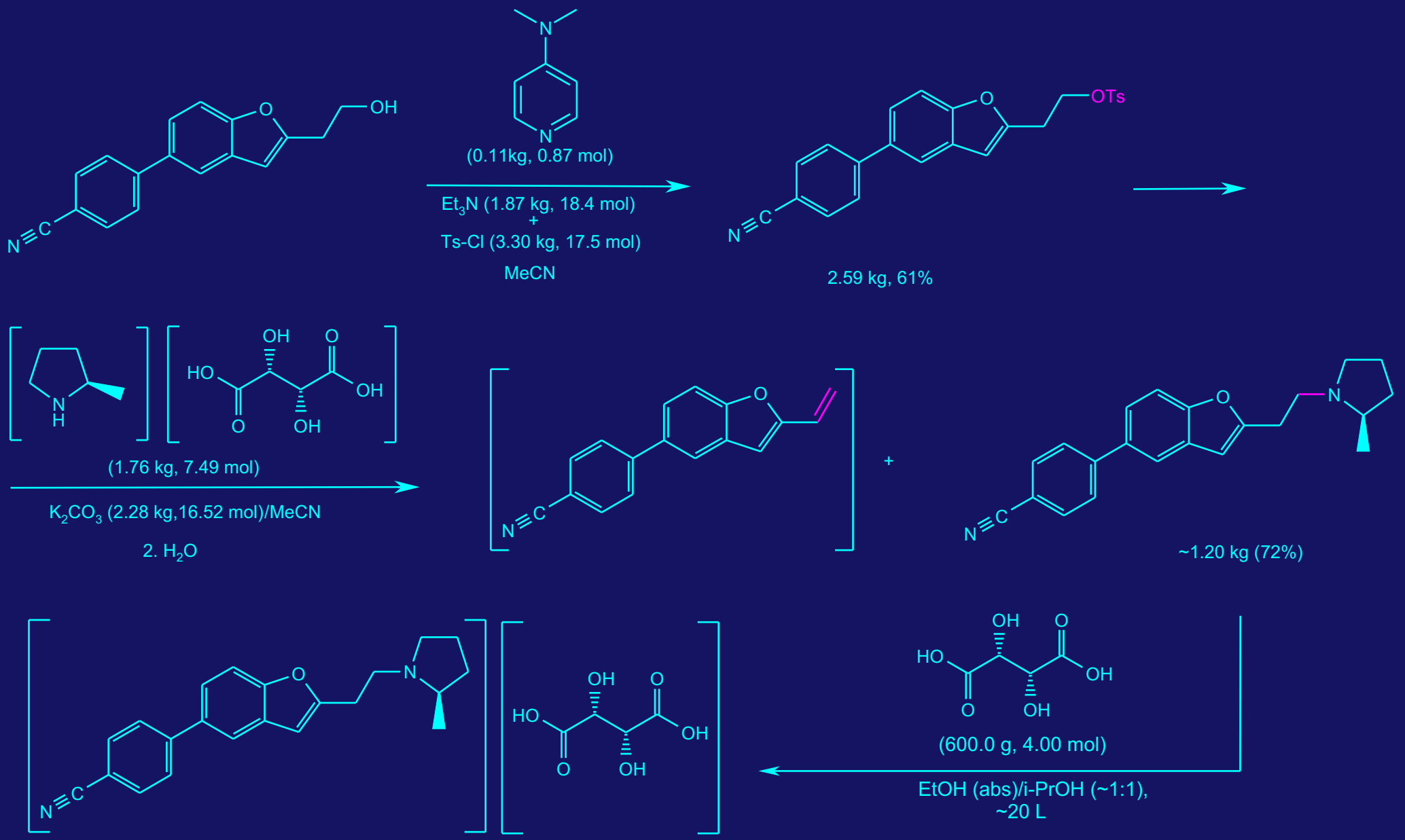
Organic Process Research & Development 2005, 9, 45-50

A Facile and Scaleable Synthesis of ABT-239, A Benzofuranoid H3 Antagonist

Yu-Ming Pu,* Timothy Grieme, Ashok Gupta, Daniel Plata, Ashok V. Bhatia, Marlon Cowart,† and Yi-Yin Ku



Organic Process Research & Development 2005, 9, 45-50 -nastavak

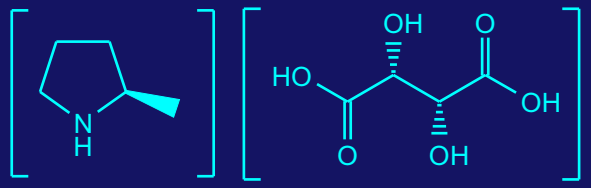


TARTARATNA SO, **ABT-239** 1.70 kg (70%, 99.5% by HPLC; ee = 98.0% by chiral HPLC

Organic Process Research & Development 2005, 9, 45-50 -nastavak

(rac)

- (5.00 kg, 58.8 mol)

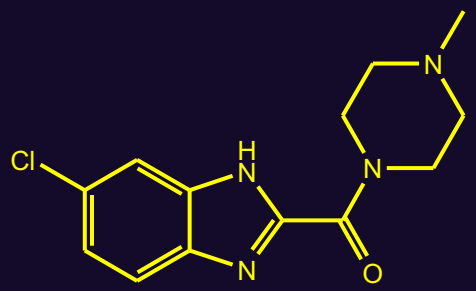


3.90 kg (ee) 97.0%, PRINOS= 55%

(R)-2-METIL-PIROLIDIN L-TARTARAT

ANTAGONISTI H_4 RECEPTORA - STRUKTURE

CAS 459168-41-3
JNJ 7777120



CAS 73903-17-0
VUF 6002

J. Med. Chem. **2003,** *46,* 3957-3960

DODATK

The First Potent and SelectiveNon-Imidazole Human Histamine H4 Receptor Antagonists

Jill A. Jablonowski,* Cheryl A. Grice, Wenying Chai, Curt A. Dvorak, Jennifer D. Venable, Annette K. Kwok, Kiev S. Ly, Jianmei Wei, Sherry M. Baker, Pragnya J. Desai, Wen Jiang, Sandy J. Wilson, Robin L. Thurmond, Lars Karlsson, James P. Edwards, Timothy W. Lovenberg, and Nicholas I. Carruthers

Abstract: Following the discovery of the human histamine H4 receptor, a high throughput screen of our corporate compound collection identified compound **6** as a potential lead. Investigation of the SAR resulted in the discovery of novel compounds **10e** and **10l**, which are the first potent and selective histamine H4 receptor antagonists to be described.

Introduction. Histamine1 has been shown to play a critical role in several diverse physiological processes.2-4 It is a key component in the inflammatory response via activation of the histamine H1 receptor,5 gastric acid secretion via the histamine H2 receptor,6 and mediation of neurotransmitter release in the central nervous system via the histamine H3 receptor.7 Recently a fourth histamine receptor, the histamine H4 receptor, 8-13 was identified. The histamine H4 receptor is a 390 amino acid, seventransmembrane G-protein-coupled receptor. It is expressed mainly on eosinophils and mast cells and has been shown to be involved in chemotaxis of both cell types.9,10,13-15 The receptor has also been implicated in the release of IL-16 from CD8+ T cells.16 These data indicate that the histamine H4 receptor may play a role in the inflammatory response. The existence of a fourth histamine receptor was postulated by Raible and co-workers as a result of experiments in which histamine produced an increase in cytosolic calcium in eosinophils.15,17 This calcium influx was not blocked by the known H1 or H2 antagonists, pyrilamine or cimetidine, respectively. Interestingly, the known H3 antagonist thioperamide (**1**) blocked the calcium influx. However, the potent H3 agonist (R)- R-methylhistamine (**2**) only weakly activated a calcium response in eosinophils. Thus, it was concluded that the increase in cytosolic calcium in eosinophils was the action of a novel receptor. The recent cloning of the histamine H4 receptor and subsequent experiments8-13 confirmed the pharmacology described by Raible et al.15,17 Among the histamine receptors, the H4 receptor exhibits the highest degree of homology to the H3 receptor at 40%. Many of the imidazole-based ligands that exhibit binding affinity for the H4 receptor also show significant affinity for the H3 receptor as shown in Chart 1.8 A high affinity non-imidazole H3 antagonist, 4-(3-piperdin-1-ylpropoxy)benzonitrile (**5**) 18 is devoid of activity at the H4 receptor, demonstrating that specificity between the two receptors could be achieved. Following the discovery of the H4 receptor, we set out to identify potent, selective, non-imidazole histamine H4 ligands. We began with a high throughput screen of our corporate compound collection, which produced several lead compounds including indolylpiperazine **6**.19 Based on these leads, a medicinal chemistry program was initiated to evaluate the structure-activity relationships (SAR) for indole **6**. The SAR for this series and the biological evaluation of selected analogues will be discussed.

J. Med. Chem. 2005, 48, 8289-8298

DODATK

Preparation and Biological Evaluation of Indole, Benzimidazole, and Thienopyrrole Piperazine Carboxamides: Potent Human Histamine H_4 Antagonists

Jennifer D. Venable,* Hui Cai, Wenying Chai, Curt A. Dvorak, Cheryl A. Grice, Jill A. Jablonowski, Chandra R. Shah, Annette K. Kwok, Kiev S. Ly, Barbara Pio, Jianmei Wei, Pragnya J. Desai, Wen Jiang, Steven Nguyen, Ping Ling, Sandy J. Wilson, Paul J. Dunford, Robin L. Thurmond, Timothy W. Lovenberg, Lars Karlsson, Nicholas I. Carruthers, and James P. Edwards

Three series of H_4 receptor ligands, derived from indoly-2-yl-(4-methyl-piperazin-1-yl)-methanones, have been synthesized and their structure-activity relationships evaluated for activity at the H_4 receptor in competitive binding and functional assays. In all cases, substitution of small lipophilic groups in the 4 and 5-positions led to increased activity in a [^{3}H]histamine radiolabeled ligand competitive binding assay. In vitro metabolism and initial pharmacokinetic studies were performed on selected compounds leading to the identification of indole 8 and benzimidazole 40 as potent H_4 antagonists with the potential for further development. In addition, both 8 and 40 demonstrated efficacy in in vitro mast cell and eosinophil chemotaxis assays.

Introduction Until recently, the pharmacological effects of the endogenous chemical mediator histamine were attributed to its interaction with three known G-protein coupled receptors H_1, H_2 and H_3. The human histamine H_1 receptor is expressed widely throughout the body and is involved in numerous functions including smooth muscle and endothelial cell contraction causing increases in vascular permeability.[2,3] These effects account for the role of the H_1 receptor in allergic and inflammatory responses and consequently for the application of H_1 receptor antagonists for the treatment of allergies. Although the H_2 receptor also participates in vasodilation, due to its expression in vascular smooth muscle, the major physiological role of this receptor is in the gastrointestinal tract where histamine stimulates acid secretion.[4] Antagonists of this receptor are widely used for treatment of ulcerative conditions. The histamine H_3 receptor behaves as a presynaptic autoreceptor on histamine neurons and as a heteroreceptor on nonhistamine neurons controlling the release of histamine and other neurotransmitters in the central nervous system. [5,6] While the therapeutic importance has not been clinically defined, it has been implicated in various conditions involving deficits in arousal, vigilance, and cognition. The fourth human histamine receptor was disclosed in 2000 as a 390 amino acid GPCR with a 37- 43% sequence homology to the human H_3 receptor.[7-12] This high degree of similarity is reflected by the affinity of well-known H_3 ligands thioperamide (**1**) and (*R*)-Rmethylhistamine (**2**) (Figure 1) for the H_4 receptor.[13] While the H_3 receptor is found in the peripheral and central nervous systems, the H_4 receptor is primarily expressed in eosinophils, mast cells, dendritic cells, and other leukocytes, implying that the H_4 receptor may play a key role in inflammation and regulation of the immune system.[2,9,14,15] The H_4 receptor is known to mediate chemotaxis of eosinophils and mast cells[14-16,35,36] and is also implicated in histamine-induced release of interleukin-16 from CD-8+ T cells.[2] Additionally, a selective H_4 receptor antagonist demonstrated antiinflammatory activity in a mouse peritonitis model.[16]