THE MERCK INDEX

THIRTEENTH EDITION

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 1 of 65

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

Editorial Staff

Maryadele J. O'Neil, *Senior Editor*
Ann Smith, *Senior Associate Editor*
Patricia E. Heckelman, *Associate Editor*

John R. Obenchain Jr., *Editorial Assistant*
Jo Ann R. Gallipeau, *Technical Assistant*
Mary Ann D'Arecca, *Administrative Associate*

Susan Budavari, *Editor Emeritus*

Published by
Merck Research Laboratories
Division of

MERCK & CO., INC.
Whitehouse Station, NJ

2001

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 2 of 65

MERCK & CO., INC.
Whitehouse Station, NJ
USA

1st Edition—1889
2nd Edition—1896
3rd Edition—1907
4th Edition—1930
5th Edition—1940
6th Edition—1952
7th Edition—1960
8th Edition—1968
9th Edition—1976
10th Edition—1983
11th Edition—1989
12th Edition—1996

Library of Congress Catalog
Card Number 89-60001
ISBN Number 0911910-13-1

Copyright © 2001 by MERCK & CO., INC.
All rights reserved. Copyright under the Universal Copyright Convention
and the International Copyright Convention.
Copyright reserved under the Pan-American Copyright Convention.

Printed in the USA

FOREWORD

The Thirteenth edition of The Merck Index continues the tradition of publishing a concise, authoritative reference work designed primarily to serve the needs of chemists, biochemists, pharmacists and those in related professions. The information is assembled with today's need for quick reference in mind, but the commitment to excellence in scientific scholarship and to enhancing scientific communication remains paramount.

This edition contains a diverse collection of over 10,000 monographs. More than 4,000 monographs are devoted to a wide variety of drugs and pharmaceuticals, over 2,000 describe common organic chemicals and laboratory reagents, and another 2,000 cover naturally occurring substances and plants. An additional 1,000 monographs focus on the elements and on inorganic chemicals. Almost 1,000 pertain to compounds of agricultural significance, and several hundred describe endogenous substances and biological agents.

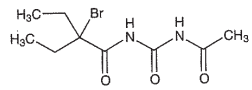
A number of changes have been made since the Twelfth Edition. The monograph section has been extensively revised and updated. In response to requests from our readership, the Chemical Abstracts Registry Numbers for title and derivative compounds have been embedded within the monographs. The derivative compound data presentation now mirrors the title compound such that registry numbers, molecular weights and literature references are included in addition to names and physical properties as in previous editions. Patent data has been reformatted using the two letter international country codes. The section on Organic Name Reactions has been updated and revised; further, the schema have been standardized. The Miscellaneous Table section has been redesigned and reordered to enhance access to the ancillary monograph information.

To facilitate the use of the information in the electronic age, The Merck Index will be expanding its electronic offerings from THE MERCK INDEX ONLINE[SM], and THE MERCK INDEX on CD-ROM to include a Web-accessible format. The latter two formats will be both text and structure searchable. Additionally, information that we are unable to maintain in print due to size restrictions will appear as part of the electronic versions.

Changes in size, scope and publishing mechanisms have been made with each edition to keep pace with the progress in science and information technologies in order to accommodate the diverse interests of an ever-broadening and sophisticated readership. In this environment, it is especially gratifying that so many still refer to The Merck Index on a daily basis. We hope that this edition, published by Merck & Co., Inc., as a service to the scientific community and the public, will prove to be a valuable resource to all.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 4 of 65

screening procedure in urine: H. H. Maurer, *J. Chromatog.* **530,** 307 (1990).

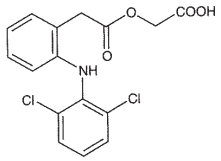


Crystals, slightly bitter taste, mp 108-109°. Slightly sol in water; freely sol in alcohol, ethyl acetate.

Caution: May be habit forming: **21 CFR,** 329.1.

THERAP CAT: Sedative, hypnotic.

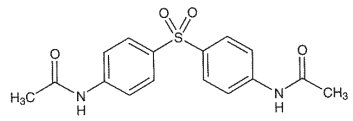
22. Aceclofenac. [89796-99-6] 2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid carboxymethyl ester; 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid; glycolic acid [*o*-(2,6-dichloroanilino)phenyl]acetate ester; PR-82/3; Airtal; Falcol; Gerbin; Preservex. $C_{16}H_{13}Cl_2NO_4$; mol wt 354.19. C 54.26%, H 3.70%, Cl 20.02%, N 3.95%, O 18.07%. Prepn: A. V. Casas, **ES 8404783**; *idem,* **US 4548952** (1984, 1985 both to Prodes). Gastrointestinal tolerance in rats in comparison with diclofenac, *q.v.*: V. Rimbau *et al., Farmaco Ed. Prat.* **43,** 19 (1988). Clinical trial in comparison with acetaminophen, *q.v.,* in episiotomal pain: A. Yscla, *Drugs Exp. Clin. Res.* **14,** 491 (1988). Clinical evaluation in rheumatoid arthritis: R. Ballesteros *et al., Clin. Trials J.* **27,** 12 (1990).



White crystals from cyclohexane, mp 149-150°. uv max (ethanol): 275 nm (log ε 4.14).

THERAP CAT: Anti-inflammatory; analgesic.

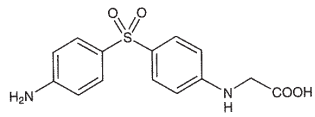
23. Acedapsone. [77-46-3] *N,N′*-(Sulfonyldi-4,1-phenylene)bisacetamide; 4′,4‴-sulfonylbis[acetanilide]; bis(4-acetamidophenyl)sulfone; 4,4′-diacetyldiaminodiphenyl sulfone; 4,4′-diacetylaminodiphenyl sulfone; *N,N′*-diacetyl-4,4′-diaminodiphenyl sulfone; DADDS; diacetyldapsone; sulfadiamine; 1399F; CI-556; Hansolar. $C_{16}H_{16}N_2O_4S$; mol wt 332.38. C 57.82%, H 4.85%, N 8.43%, O 19.25%, S 9.65%. Prepn: Fromm, Wittmann, *Ber.* **41,** 2270 (1908); Raiziss *et al., J. Am. Chem. Soc.* **61,** 2763 (1939); Elslager *et al., J. Med. Chem.* **12,** 357 (1969). Properties: Elslager, Worth, *Nature* **206,** 630 (1965). Clinical trial in leprosy: C. R. Boughton *et al., Med. J. Austral.* **1,** 1258 (1971); P. N. Neelan *et al., Indian J. Lepr.* **58,** 251 (1986).



Crystalline solid, mp 289-292°. uv max (methanol): 256, 284 nm (ε 25500, 36200). Soly in water: 0.003 mg/ml; in 40% benzyl benzoate-60% castor oil: 0.026 mg/ml.

THERAP CAT: Antibacterial (leprostatic).

24. Acediasulfone. [80-03-5] *N*-[4-[(4-Aminophenyl)-sulfonyl]phenyl]glycine; *N-p*-sulfanilylphenylglycine; *p*-amino-*p′*-(carboxymethylamino)diphenyl sulfone; 4-carboxymethylamino-4′-aminodiphenylsulfone; diaminodiphenylsulfone-*N*-acetic acid. $C_{14}H_{14}N_2O_4S$; mol wt 306.34. C 54.89%, H 4.61%, N 9.14%, O 20.89%, S 10.47%. Prepn: Jackson, *J. Am. Chem. Soc.* **70,** 680 (1948); **CH 254803** and **CH 278482** (1949, 1952, to Cilag Ltd.); Rawlins, **US 2589211** (1952 to Parke, Davis).



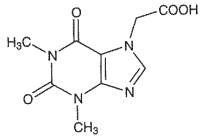
Crystals, mp 194°. Sol in methanol, dil sodium hydroxide, acetone.

Sodium salt. [127-60-6] Sulfon-Cilag. $C_{14}H_{13}N_2NaO_4S$; mol wt 328.32.

Morpholine salt. Bentrofene. $C_{18}H_{23}N_3O_5S$; mol wt 393.46. Prepn: Martin, Habicht, **US 2751382** (1956 to Cilag Ltd.). Glittering crystals, mp 133-135° (dec).

THERAP CAT: Antibacterial.

25. Acefylline. [652-37-9] 1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxopurine-7-acetic acid; carboxymethyltheophylline; 7-theophyllineacetic acid. $C_9H_{10}N_4O_4$; mol wt 238.20. C 45.38%, H 4.23%, N 23.52%, O 26.87%. Prepn: **DE 352980** (1922 to E. Merck); *Frdl.* **14,** 1320; S. M. Ride *et al., Pharmazie* **32,** 672 (1977). Prepn of salts: J. Baisse, *Bull. Soc. Chim. France* **1949,** 769; M. Milletti, F. Virgili, *Chimica (Milan)* **6,** 394 (1951), *C.A.* **46,** 8615h (1952). GC determn in urine: J. Zuidema, H. Hilbers, *J. Chromatog.* **182,** 445 (1980). HPLC determn in serum and pharmacokinetics: S. Sved *et al., Biopharm. Drug Dispos.* **2,** 177 (1981).



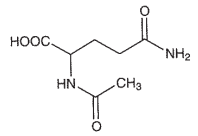
Crystals from water, mp 271°.

Sodium salt. [837-27-4] $C_9H_9N_4NaO_4$. Silky needles, mp >300°.

Compd with piperazine. Acefylline piperazine; acepifylline; Dynaphylline; Etaphylline; Etafillina. Undefined mixture of the 1:1 and 2:1 salts; contains 75-78% theophylline acetic acid and 22-25% anhydrous piperazine.

THERAP CAT: Bronchodilator.

26. Aceglutamide. [2490-97-3] N^2-Acetyl-L-glutamine; α-*N*-acetyl-L-glutamine; Acutil-S. $C_7H_{12}N_2O_4$; mol wt 188.18. C 44.68%, H 6.43%, N 14.89%, O 34.01%. Prepn: P. Karrer *et al., Helv. Chim. Acta* **9,** 301 (1926); **GB 792576** (1958 to Merck & Co.), *C.A.* **53,** 2109a (1959); I. J. Maschler, N. Lichtenstein, *Biochim. Biophys. Acta* **57,** 252 (1962). Stability study: G. Sekules, G. Guadagnini, *Farmaco Ed. Prat.* **21,** 22 (1966). NMR study: W. Voelter *et al., Z. Naturforsch. B* **26,** 213 (1971). Fermentation study: T. Nakanishi, *J. Ferment. Technol.* **56,** 573 (1978). Prepn of the aluminum complex: T. Kagawa *et al.,* **DE 2127176** corresp to **US 3787466** (1971, 1974 both to Kyowa). Physico-chemical properties: E. Hayakawa *et al., Yakugaku Zasshi* **97,** 731 (1977), *C.A.* **87,** 141198 (1977). Effect on exptl chronic gastric ulcer: H. Tanaka *et al., Oyo Yakuri* **7,** 1035 (1973), *C.A.* **81,** 33283v (1974). Cytoprotective effect: H. Tanaka, *Arzneimittel-Forsch.* **36,** 1485 (1986).



NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 5 of 65

Crystals from ethanol, mp 197°. $[\alpha]_D^{20}$ −12.5° (c = 2.9 in water).

Aluminum complex. [12607-92-0] Pentakis (N^2-acetyl-L-glutaminato)tetrahydroxytrialuminum; aceglutamide aluminum; KW-110; Glumal. $C_{35}H_{59}Al_3N_{10}O_{24}$; mol wt 1084.84. White powder, mp 221° (dec). Sol in water. Practically insol in methanol, ethanol, acetone. LD_{50} in male mice, rats (g/kg): 14.3, >14.5 orally; 5.0, 4.2 i.p.; 0.46, 0.40 i.v. (Kagawa).

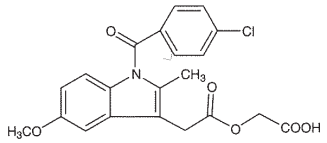
THERAP CAT: Free acid as nootropic; aluminum complex as antiulcerative.

27. Acemannan. Carrisyn. Long-chain, polydispersed, β-(1,4)-linked acetylated mannan obtained from the mucilage of *Aloe barbadensis,* Miller, *Liliaceae* (aloe vera). Isolation, purification, and characterization: B. H. McAnalley, **WO 87 00052**; *idem,* **US 4735935** (1987, 1988 both to Carrington Labs.). Structural study: S. Manna, B. H. McAnalley, *Carbohyd. Res.* **241,** 317 (1993). Immunostimulant effect *in vitro:* D. Womble, J. H. Helderman, *Int. J. Immunopharmacol.* **10,** 967 (1988). Inhibition of HIV-1 replication *in vitro*: J. B. Kahlon *et al., Mol. Biother.* **3,** 127 (1991). Veterinary trial in feline-leukemia virus infection: M. A. Sheets *et al., ibid.* 41; in canine and feline spontaneous tumors: C. Harris *et al., ibid.* 207. Toxicological evaluation: R. W. Fogleman *et al., Vet. Hum. Toxicol.* **34,** 201 (1992).

THERAP CAT: Antiviral; immunomodulator.

THERAP CAT (VET): Antiviral.

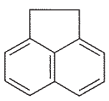
28. Acemetacin. [53164-05-9] 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid carboxymethyl ester; [[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetoxy]acetic acid; TV-1322; Acemix; Emflex; Rantudil; Solart. $C_{21}H_{18}ClNO_6$; mol wt 415.83. C 60.66%, H 4.36%, Cl 8.53%, N 3.37%, O 23.08%. Deriv of indomethacin, *q.v.* Prepn: K. H. Boltze *et al.,* **DE 2234651**; *eidem,* **US 3910952** (1972, 1975 both to Troponwerke). Series of articles on chemistry, analysis, pharmacodynamics, toxicology and clinical trials: *Arzneimittel-Forsch.* **30,** 1313-1468 (1980). Toxicity data: H. Jacobi, H.-D. Dell, *ibid.* 1398.



Very fine pale yellow crystals from petr ether, mp 150-153°. LD_{50} in male, female mice, male, female rats (mg/kg): 55.5, 18.42, 24.2, 30.1 orally; 34.1, 51.1, 38.1, 28.3 i.v. (Jacobi, Dell).

THERAP CAT: Anti-inflammatory.

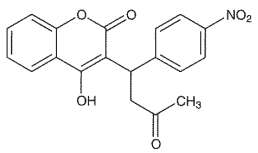
29. Acenaphthene. [83-32-9] 1,2-Dihydroacenaphthylene; *peri*-ethylenenaphthalene; 1,8-ethylenenaphthalene. $C_{12}H_{10}$; mol wt 154.21. C 93.46%, H 6.54%. Occurs in coal tar. Isoln: Ges. f. Teerverwertung, **DE 277110**; *Chem. Zentr.* **1914, II,** 597. In petroleum residues: Orloff *et al., C.A.* **31,** 2800[9] (1937). By passing ethylene and benzene or naphthalene though a red hot tube: Berthelot, *Bull. Soc. Chim.* [2] **7,** 274; **8,** 226, 245 (1867). By heating tetrahydroacenaphthene with sulfur to 180°: Braun *et al., Ber.* **55,** 1694 (1922). From acenaphthenone or acenaphthenequinone by high pressure hydrogenation in decalin with nickel at 180-240°: Braun, Bayer, *Ber.* **59,** 921, 923 (1926). From acenaphthenone oxime: Morgan, Stanley, *J. Soc. Chem. Ind. (London)* **44,** 494T (1925).



Orthorhombic bipyramidal needles from alcohol. d 1.189. mp 95°. bp 279°. uv spectrum: Seshan, *Proc. Indian Acad. Sci.* **A3,** 148 (1936). Factors influencing the uv spectrum: Jones, *J. Am. Chem. Soc.* **67,** 2127 (1945). Insol in water. One gram dissolves in 31 ml alcohol, 56 ml methanol, 25 ml propanol, 2.5 ml chloroform, 5 ml benzene or toluene. 3.2 g are sol in 100 ml glacial acetic acid. Forms water-sol, cryst complexes with desoxycholic acid, containing two molecules of the bile acid as a rule. The complexes crystallize when concentrated solns of the proper amount of the components in alcohol or dioxane are allowed to cool slowly.

USE: Dye intermediate; manuf plastics; insecticide; fungicide.

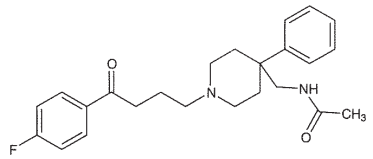
30. Acenocoumarol. [152-72-7] 4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2*H*-1-benzopyran-2-one; 3-(α-acetonyl-*p*-nitrobenzyl)-4-hydroxycoumarin; 3-(α-*p*-nitrophenyl-β-acetylethyl)-4-hydroxycoumarin; acenocoumarin; nicoumalone; G-23350; Mini-Sintrom; Sinthrome; Sintrom. $C_{19}H_{15}NO_6$; mol wt 353.32. C 64.59%, H 4.28%, N 3.96%, O 27.17%. Vitamin K antagonist; structurally similar to warfarin, *q.v.* Prepn: W. Stoll, F. Litvan, **US 2648682** (1953 to Geigy); I. C. Ivanov *et al., Arch. Pharm.* **323,** 521 (1990). Resolution and abs config of enantiomers: C. R. Wheeler, W. F. Trager, *J. Med. Chem.* **22,** 1122 (1979). Pharmacology and toxicity: M. Leroux, B. Jamain, *Thérapie* **11,** 85 (1956). GC-MS determn in plasma: F. Pommier *et al., J. Chromatog. B.* **654,** 35 (1994). Clinical trial: D. P. M. Brandjes *et al., N. Engl. J. Med.* **327,** 1485 (1992).



Crystals, mp 196-199°. Sparingly sol in water and most organic solvents. Forms water-sol salt with alkalies. LD_{50} orally in mice, rats: 1470, 1000 mg/kg (Leroux, Jamain).

THERAP CAT: Anticoagulant.

31. Aceperone. [807-31-8] *N*-[[1-[4-(4-Fluorophenyl)-4-oxobutyl]-4-phenyl-4-piperidinyl]methyl]acetamide; *N*-[[1-[3-(*p*-fluorobenzoyl)propyl]-4-phenyl-4-piperidyl]methyl]acetamide; 1-(*p*-fluorophenyl)-4-(4-phenyl-4-acetamidomethylpiperidino)-1-butanone; 1-[γ-(4-fluorobenzoyl)propyl]-4-acetamidomethyl-4-phenylpiperidine; *N*-[1-[3-(*p*-fluorobenzoyl)propyl]-4-phenylpiperidin-4-ylmethyl]acetamide; 4′-fluoro-4-(4-acetamidomethyl-4-phenylpiperido)butyrophenone; acetabutone; acetobuton; R-3248. $C_{24}H_{29}FN_2O_2$; mol wt 396.50. C 72.70%, H 7.37%, F 4.79%, N 7.07%, O 8.07%. Prepd by reacting γ-chloro-4-fluorobutyrophenone with 4-acetamidomethyl-4-phenylpiperidine: P. A. J. Janssen, **BE 606849** (1961), corresp to **US 3083205** (1961, 1963 both to Janssen). Crystal structure: N. Van Opdenbosch *et al., Acta Crystallogr.* **33B,** 171 (1977).



Crystals, mp 97-100°.

32. Acephate. [30560-19-1] Acetylphosphoramidothioic acid *O,S*-dimethyl ester; Ortho 12420; Orthene. $C_4H_{10}NO_3PS$; mol wt 183.17. C 26.23%, H 5.50%, N 7.65%, O 26.20%,

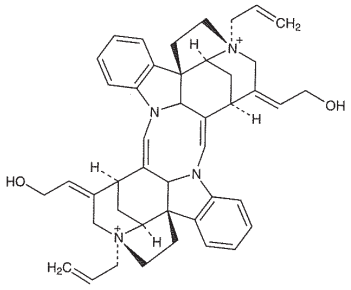
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 6 of 65

Crystals from acetone/hexane, mp 176-179°. $[\alpha]_D^{26}$ +47.5° (c = 0.3 in DMF). uv max (methanol): 242 nm (ε 15500).

17,21-Dipropionate. [66734-13-2] Sch-22219; Aclosone; Aclovate; Almeta; Delonal; Legederm; Modrasone; Perderm. $C_{28}H_{37}ClO_7$; mol wt 521.05. Crystals from acetone/methanol/isopropyl ether, mp 212-216°. $[\alpha]_D^{26}$ +42.6° (c = 0.3 in DMF). uv max (methanol): 242 nm (ε 15600).

THERAP CAT: Anti-inflammatory (topical).

220. Alcuronium. [23214-96-2] 4,4′-Didemethyl-4,4′-di-2-propenyltoxiferine I; *N,N′*-diallylnortoxiferinium; diallylbis(nortoxiferine); diallylnortoxiferine; diallyltoxiferine. $[C_{44}H_{50}N_4O_2]^{2+}$. Prepn of dichloride and diiodide: Boller *et al.*, **US 3080373** (1963 to Hoffmann-La Roche).



Dichloride. [15180-03-7] *N,N′*-Diallylnortoxiferinium dichloride; Ro-4-3816; Alloferin. $C_{44}H_{50}Cl_2N_4O_2$; mol wt 737.82. C 71.63%, H 6.83%, Cl 9.61%, N 7.59%, O 4.34%. Crystals from methanol or ethanol. Compd contains 5 moles of water of crystn after equilibration in air; $[\alpha]_D^{22}$ −348° (methanol); uv max (methanol): 292 nm (ε 43000).

Diiodide. $C_{44}H_{50}I_2N_4O_2$. Solid. uv max (methanol): 291 nm (ε 39900).

THERAP CAT: Neuromuscular blocking agent.

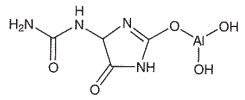
THERAP CAT (VET): Neuromuscular blocking agent.

221. Aldicarb. [116-06-3] 2-Methyl-2-(methylthio)-propanal *O*-[(methylamino)carbonyl]oxime; 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime; UC-21149; Temik. $C_7H_{14}N_2O_2S$; mol wt 190.27. C 44.19%, H 7.42%, N 14.72%, O 16.82%, S 16.85%. $CH_3SC(CH_3)_2CH{=}NOCONHCH_3$. Synthesis: Payne *et al., J. Agr. Food Chem.* **14,** 356 (1966). C^{14}-labeled synthesis: Bartley *et al., ibid.* 604. Metabolism: Bartley *et al., ibid.* **18,** 446 (1970). Mass spectrum: Benson, Damico, *J. Assoc. Offic. Anal. Chem.* **1968,** 347. Crystal and molecular structure: F. Takusagawa, R. A. Jacobson, *J. Agr. Food Chem.* **25,** 333 (1977). Toxicity study: Weiden *et al., J. Econ. Entomol.* **58,** 154 (1965). *Review:* Romine, *Anal. Methods Pestic. Plant Growth Regul.* **7,** 147-162 (1973).

Crystals from isopropyl ether, mp 99-100°. Soly at 25° (w/w) in water: 0.6%; acetone: 35%; benzene: 15%; xylene: 5%; methylene chloride: 30%. LD_{50} orally in female rats: ~1 mg/kg (Weiden).

USE: Insecticide, acaricide, nematocide.

222. Aldioxa. [5579-81-7] [(2,5-Dioxo-4-imidazolidinyl)ureato]dihydroxyaluminum; (allantoinato)dihydroxyaluminum; dihydroxy[(4,5-dihydro-2-hydroxy-5-oxo-1*H*-imidazol-4-yl)ureato]aluminum; aluminum dihydroxy allantoinate; RC-172; Alanetorin; Alusa; Arlanto; Ascomp; Chlokale; Isalon; Nische; Peptilate. $C_4H_7AlN_4O_5$; mol wt 218.10. C 22.03%, H 3.23%, Al 12.37%, N 25.69%, O 36.68%. Prepn: S. B. Mecca, **US 2761867** (1956 to Schuylkill Chem.). Pharmacology: R. Cahen, J. F. Clement, *Ann. Pharm. Franc.* **20,** 693 (1962); R Cahen, A. Pessonnier, *ibid.* 704. Toxicology: R. Cahen, A. Pessonnier, *ibid.* 623. Metabolism studies: K. Fukawa *et al., Oyo Yakuri* **11,** 421 (1976), *C.A.* **88,** 130701g (1978). HPLC determn in plasma: K. Hirota *et al., J. Chromatog.* **277,** 165 (1983). Clinical studies of combination therapy for peptic ulcer: M. Sakai *et al., Japan. Arch. Intern. Med.* **31,** 275 (1984); *idem et al., ibid.* **33,** 61 (1986); *idem et al., ibid.* **36,** 357 (1989). Review of cosmetic use and safety assessment: S. N. J. Pang, *J. Am. Coll. Toxicol.* **12,** 237-242 (1993).



White powder. mp 230°. Insol in polar and nonpolar solvents.

USE: Astringent and skin conditioning agent in cosmetics.

THERAP CAT: Antiulcerative.

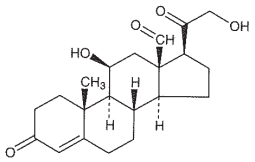
223. Aldol. [107-89-1] 3-Hydroxybutanal; 3-hydroxybutyraldehyde; acetaldol. $C_4H_8O_2$; mol wt 88.10. C 54.53%, H 9.15%, O 36.32%. $CH_3CH(OH)CH_2CHO$. Manuf by condensation of acetaldehyde in aq NaOH: Alhéritière, Gobron, **US 2713598** (1955 to Usines de Melle). Toxicity study: H. F. Smyth *et al., J. Ind. Hyg. Toxicol.* **31,** 60 (1949).

Colorless, thick liquid. d^{16} 1.109. bp_{20} 83°; dec about 85°. Miscible with water, alcohol, ether. LD_{50} orally in rats: 2.18 g/kg (Smyth).

USE: Manuf rubber vulcanizers, accelerators and age resisters; in perfumes; ore flotation.

THERAP CAT: Sedative; hypnotic.

224. Aldosterone. [52-39-1] (11β)-11,21-Dihydroxy-3,20-dioxopregn-4-en-18-al; 3,20-diketo-11β,18-oxido-4-pregnene-18,21-diol; Aldocorten. $C_{21}H_{28}O_5$; mol wt 360.44. C 69.98%, H 7.83%, O 22.19%. Adrenocortical steroid which exerts regulatory influence on metabolism of electrolytes and water. Isoln: Simpson *et al., Experientia* **9,** 333 (1953); *Helv. Chim. Acta* **37,** 1163 (1954); Mattox *et al., J. Am. Chem. Soc.* **75,** 4869 (1953); Harman *et al., ibid.* **76,** 5035 (1954). Solutions contain an equilibrium mixture of the aldehyde and the hemiacetal, the equilibrium favoring the latter. Structure: Tait *et al., Experientia* **10,** 132 (1954); *Helv. Chim. Acta* **37,** 1200 (1954). Crystal structure and molecular conformation: Duax, Hauptmann, *J. Am. Chem. Soc.* **94,** 5467 (1972). ^{13}C-NMR spectrum: P. Gerard, *Org. Magn. Resonance* **11,** 478 (1978). Total synthesis: Schmidlin *et al., Helv. Chim. Acta* **40,** 1438 (1957); Johnson *et al., J. Am. Chem. Soc.* **80,** 2585 (1958); **85,** 1409 (1963). Three-step synthesis from corticosterone: Barton, Beaton, *ibid.* **82,** 2640 (1960); **83,** 4083 (1961). Alternate synthesis: D. H. R. Barton *et al., J. Chem. Soc., Perkin Trans. I* **1975,** 2243; M. Miyano, *J. Org. Chem.* **46,** 1846 (1981). Biosynthesized in the zona glomerulosa and transported chiefly by albumin. In man, 400 μg secreted normally in one day. Secretion influenced by ACTH, growth hormone, plasma sodium and potassium, and the renin-angiotensin system. Causes reabsorption of Na^+, Cl^-, and HCO_3^- and diuresis of K^+. *Review:* L. F. Fieser, M. Fieser, *Steroids* (Reinhold, New York, 1959) pp 701-720.



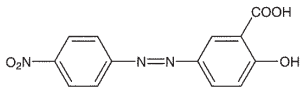
Hydrated crystals from dilute acetone, mp 108-112° (when anhydr mp 164°). $[\alpha]_D^{23}$ +152.2° (anhydr; c = 2 in acetone). $[\alpha]_D^{25}$ +161° (c = 0.1 in chloroform). uv max: 240 nm (log ε 4.20 for the monohydrate; ε_{mol} 15,000 for the anhydr).

21-Acetate. $C_{23}H_{30}O_6$. Synthesis: Wettstein *et al.;* Jeger, **US 3002972** and **US 3014029** (both 1958 to Ciba). Flat needles from acetone + ether, mp 198-199°. $[\alpha]_D^{24}$ +121.7° (c = 0.71 in chloroform).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 7 of 65

from golden orange to flat yellow (in water). pH 5.0-6.5 from yellow to purplish red.

250. Alizarine Yellow R. [2243-76-7] 2-Hydroxy-5-[(4-nitrophenyl)azo]benzoic acid; 5-(*p*-nitrophenylazo)salicylic acid; *p*-nitrobenzeneazosalicylic acid; Alizarine Yellow RW; C.I. Mordant Orange 1; C.I. 14030. $C_{13}H_9N_3O_5$; mol wt 287.23. C 54.36%, H 3.16%, N 14.63%, O 27.85%. Prepd by coupling diazotized *p*-nitroaniline with salicylic acid: Armento, **US 2746955** (1956 to General Aniline and Film); *Colour Index* **vol. 4** (3rd ed., 1971) p 4058.



Orange-brown needles from dil glacial acetic acid, dec 253-254°. Sol in water, alc; slightly sol in acetone, Cellosolve; practically insol in other org solvents.

Sodium salt. Mordant Yellow 3R. $C_{13}H_8N_3NaO_5$. Brownish yellow powder. Sol in water.

USE: Sodium salt used as indicator in 0.1% aq soln pH: yellow to red, range 10.2 to 12.0.

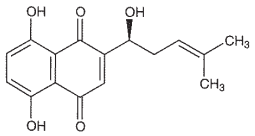
251. Alkanet. Alkanna; orcanette; dyer's alkanet; anchusa; orkanet. The root of *Alkanna tinctoria* Tausch, *Boraginaceae. Habit.* Asia Minor, Hungary, Greece, Mediterranean region. *Constit.* Alkannin (the coloring principle) and tannin. Extraction of roots: Betrabet, Chakravarti, *J. Indian Inst. Sci.* **16A,** 51 (1933); *C.A.* **28,** 1038 (1934); Majamdar, Chakravarti, *J. Indian Chem. Soc.* **17,** 272 (1940); *C.A.* **34,** 6262 (1940).

Alkannin paper. Anchusin paper; Boettger's paper. White paper impregnated with a 1% alc tincture of alkanet root and dried. A blue paper can be made from the red paper by treating the latter with a 1% Na_2CO_3 soln. This paper acts nearly like litmus paper. Alkalies = green or blue; acids = red. pH: 8.0 red; 10.0 blue.

USE: For coloring wines, cosmetics, confectionery. Alkannin paper as indicator.

THERAP CAT: Astringent.

252. Alkannin. [517-88-4] 5,8-Dihydroxy-2-[(1*S*)-1-hydroxy-4-methyl-3-pentenyl]-1,4-naphthalenedione; (−)-5,8-dihydroxy-2-(1-hydroxy-4-methyl-3-pentenyl)-1,4-naphthoquinone; anchusa acid; anchusin; alkanna red; alkanet extract; (1-hydroxy-3-isohexenyl)naphthazarine; 2-(1-hydroxy-4-methyl-3-pentenyl)-5,8-dihydroxy-1,4-naphthoquinone; C.I. Natural Red 20; C.I. 75530. $C_{16}H_{16}O_5$; mol wt 288.29. C 66.66%, H 5.59%, O 27.75%. Isoln from the root of *Alkanna tinctoria* Tausch, *Boraginaceae:* Brockmann, *Ann.* **521,** 1 (1936); Toribara, Underwood, *Anal. Chem.* **21,** 1352 (1949). Absolute configuration: Arakawa, Nakagaki, *Chem. & Ind. (London)* **1961,** 947. Toxicity study: L. Majlathova, *Nahrung* **15,** 505 (1971), *C.A.* **76,** 122513j (1972).



Brownish-red prisms with a metallic sheen from benzene, mp 149°. Can be sublimed in high vac at 140-150°. $[\alpha]_{Cd}^{20}$ −165° (benzene); −226° (chloroform). Also reported as −254 ± 7° (chloroform) (Toribara). Sol in organic solvents, sparingly sol in water. Buffered aq solns are red at pH 6.1; purple at pH 8.8; blue at pH 10.0. LD_{50} in male, female mice, rats (g/kg): 3.0 ± 1.0; 3.1 ± 0.1; >1.0 orally (Majlathova).

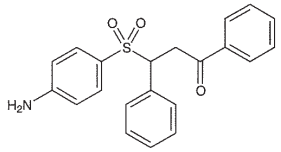
(+)-Form. Shikonin.

(±)-Form. Shikalkin.

USE: Red dye for cosmetics and food; spectrophotometric microdetermination of beryllium.

THERAP CAT: Astringent.

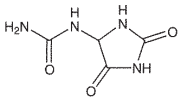
253. Alkofanone. [7527-94-8] 3-[(4-Aminophenyl)sulfonyl]-1,3-diphenyl-1-propanone; 3-phenyl-3-sulfanilylpropiophenone; *p*-aminophenyl(2-benzoyl-1-phenylethyl)sulfone; Nu-404; Ro-2-0404; Alfone. $C_{21}H_{19}NO_3S$; mol wt 365.45. C 69.02%, H 5.24%, N 3.83%, O 13.13%, S 8.77%. Prepn: Goldberg *et al., Jubilee Volume Emil Barell* (Basle, 1946) p 341; Goldberg, **US 2421836** (1947 to Hoffmann-La Roche).



Decomp 221-223°. Slightly soluble in acetone, dioxane. Practically insol in most of the common organic solvents.

THERAP CAT: Antidiarrheal.

254. Allantoin. [97-59-6] (2,5-Dioxo-4-imidazolidinyl)urea; 5-ureidohydantoin; glyoxyldiureide; cordianine. $C_4H_6N_4O_3$; mol wt 158.12. C 30.38%, H 3.82%, N 35.43%, O 30.36%. Product of purine metabolism. Prepd synthetically by the oxidation of uric acid with alkaline potassium permanganate: *Org. Syn.* **coll. vol. II,** 23 (1943). By heating urea with dichloroacetic acid: C. N. Zellner, J. R. Stevens, **US 2158098** (1939 to Merck & Co.) Acetyl derivs: Biltz, Loewe, *J. Prakt. Chem.* **141,** 291 (1934). Optically active forms have been obtained by extraction procedures.

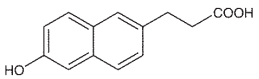


Racemic form. Monoclinic plates or prisms from water, mp 238°. One gram dissolves in 190 ml water, 500 ml alcohol; more sol in hot water and hot alcohol. Almost insol in ether. pH of satd water soln: 5.5.

THERAP CAT: Vulnerary.

THERAP CAT (VET): Vulnerary; debriding agent.

255. Allenolic Acid. [553-39-9] 6-Hydroxy-2-naphthalenepropanoic acid; 2-hydroxy-6-naphthalenepropionic acid; amphihydroxynaphthyl-β-propionic acid. $C_{13}H_{12}O_3$; mol wt 216.23. C 72.21%, H 5.59%, O 22.20%. Prepn from the corresponding methoxy compd: Jacques, Horeau, *Bull. Soc. Chim. France* **1948,** 714.



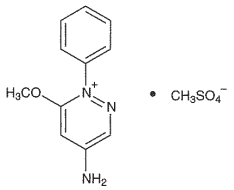
Crystals from aq methanol, mp 180-181°. Sol in alcohol, methanol, pyridine.

USE: In biochemical research, in the prepn of estrogenic compds.

256. Allethrins. Allyl cinerins. Synthetic analogs of the naturally occurring insecticides cinerins, jasmolins, and pyrethrins, *q.q.v. Review:* Barthel, *World Rev. Pest Contr.* **6,** 59 (1967); World Health Org., *Environ. Health Criteria* **87,** 1-75 (1989).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 8 of 65

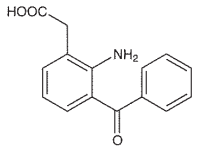
392. Amezinium Methyl Sulfate. [30578-37-1] 4-Amino-6-methoxy-1-phenylpyridazinium methyl sulfate; LU-1631; Regulton; Risumic; Supratonin. $C_{12}H_{15}N_3O_5S$; mol wt 313.33. C 46.00%, H 4.83%, N 13.41%, O 25.53%, S 10.23%. Sympathomimetic agent with vascular and cardiac activity. Prepn: F. Richenender, R. Kropp, **DE 1912941**; *eidem*, **US 3631038** (1970, 1971 both to BASF). Series of articles on synthesis, pharmacology, mechanism of action, metabolism, pharmacokinetics, bioavailability, clinical trials: *Arzneimittel-Forsch.* **31,** 1527-1671 (1981). Acute toxicity data: H. J. Teschendorf, *ibid.* 1580. HPLC determn in human plasma: D. Hotz, E. Brode, *J. Chromatog.* **277,** 217 (1983). Disposition and identification of major metabolites in rats: K. Nambu *et al., Arzneimittel-Forsch.* **38,** 909 (1988).



Crystals from water, mp 176° (dec). LD_{50} in mice, rats (mg/kg): 1630, 1410 orally; 40.4, 45.5 i.v. (Teschendorf).

THERAP CAT: Antihypotensive.

393. Amfenac. [51579-82-9] 2-Amino-3-benzoylbenzeneacetic acid; 2-amino-3-benzoylphenylacetic acid. $C_{15}H_{13}NO_3$; mol wt 255.27. C 70.58%, H 5.13%, N 5.49%, O 18.80%. Prepn: W. J. Welstead, H. W. Moran, **DE 2324768** *C.A.* **80,** 59708s (1974) and **US 4045576** (1973, 1977 both to A. H. Robbins). Synthesis and anti-inflammatory activity: W. J. Welstead *et al., J. Med. Chem.* **22,** 1074 (1979). Anti-inflammatory, analgesic, antipyretic activities: H. Fujimura *et al., Oyo Yakuri* **22,** 381 (1981), *C.A.* **97,** 49427m (1982). Platelet aggregation inhibition: *eidem, ibid.* 399, *C.A.* **97,** 49502g (1982). Effect on polymorphonuclear leukocytes: T. Matsumoto *et al., Pharmacol. Res. Commun.* **14,** 523 (1982). Toxicity data: L. F. Sancilio *et al.,* 170th Am. Chem. Soc. Meet. (Chicago, Aug. 1975), Abstracts of Papers, MEDI 17.

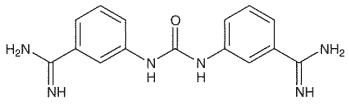


mp 121-123° (dec). LD_{50} in mice, rats (mg/kg): 615, 311 orally (Sancilio).

Sodium salt monohydrate. [61618-27-7] AHR-5850D; Fenazox. $C_{15}H_{12}NNaO_3.H_2O$; mol wt 295.27. Yellow solid from ethanol/isopropyl ether, mp 254-255.5°.

THERAP CAT: Anti-inflammatory.

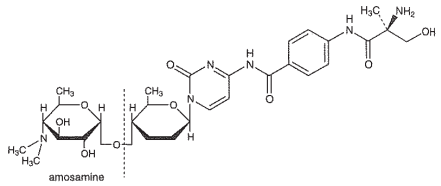
394. Amicarbalide. [3459-96-9] 3,3′-(Carbonyldiimino)bisbenzenecarboximidamide; *N,N′*-bis[3-(aminoiminomethyl)phenyl]benzenecarboximidamide; 3,3′-diamidinocarbanilide; *N,N′*-bis(*m*-amidinophenyl)urea; *N,N′*-di(*m*-amidinophenyl)-urea. $C_{15}H_{16}N_6O$; mol wt 296.33. C 60.80%, H 5.44%, N 28.36%, O 5.40%.



Diisethionate. [3671-72-5] M & B 5062A; Diampron. $C_{19}H_{28}N_6O_9S_2$; mol wt 548.60. Prepn: Ashley *et al., Nature* **185,** 461 (1960); Berg, **BE 585595** (1960 to May & Baker); *idem, J. Chem. Soc.* **1961,** 5097. Comparative efficacy: C. G. Stewart, *J. S. Afr. Vet. Assoc.* **54,** 47 (1983); and toxicity: E. Beveridge, *Res. Vet. Sci.* **10,** 534 (1969). Crystals, mp 209° (decomp 256°). Soly in water: ~100 g/100 ml. LD_{50} in mice, rats (mg/kg): 168, 186 s.c. (Beveridge).

THERAP CAT (VET): Babesiacide in cattle.

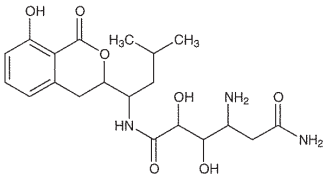
395. Amicetin. [17650-86-1] [2*R*-[2α(*S**),5β,6α]]-4-[(2-Amino-3-hydroxy-2-methyl-1-oxopropyl)amino]-*N*-[1-[5-[[4,-6-dideoxy-4-(dimethylamino)-α-D-glucopyranosyl]oxy]tetrahydro-6-methyl-2*H*-pyran-2-yl]-1,2-dihydro-2-oxo-4-pyrimidinyl]-benzamide. $C_{29}H_{42}N_6O_9$; mol wt 618.68. C 56.30%, H 6.84%, N 13.58%, O 23.27%. Antibiotic substance produced by *Streptomyces vinaceus-drappus* isolated from soil near Kalamazoo, Mich.: De Boer *et al., J. Am. Chem. Soc.* **75,** 499, 5864 (1953); McKormich, Hoehn, *Antibiot. & Chemother.* **3,** 718 (1953); De Boer, Hinman, **US 2909463**, **US 2909464** and **US 2909517** (all 1959 to Upjohn). Structure: Haskell, *J. Am. Chem. Soc.* **80,** 747 (1958); Stevens *et al., J. Org. Chem.* **27,** 2991 (1962). Structure of ***amosamine***: Stevens *et al., J. Am. Chem. Soc.* **85,** 1552 (1963). Configuration: Hanessian, Haskell, *Tetrahedron Letters* **1964,** 2451. Synthesis of amosamine: Stevens *et al., J. Org. Chem.* **31,** 2822 (1966).



Needles from cold water, mp 165-169°. Crystals from warm water, dec 243-244°. pKa = 10.4, 7.0. $[\alpha]_D^{25}$ +116.5° (c = 0.5 in 0.1*N* HCl). uv max in water: 305 nm ($E_{1cm}^{1\%}$ 465); in 0.1*N* HCl: 316 nm ($E_{1cm}^{1\%}$ 433); in 0.1*N* NaOH: 322 nm ($E_{1cm}^{1\%}$ 470). Soly in water at 25° = 2 mg/ml. Slightly sol in common organic solvents.

Dihydrochloride. $C_{29}H_{44}Cl_2N_6O_9$. Crystals from methanol + acetone, mp 190-192°. $[\alpha]_D^{24.5}$ +117° (c = 0.4 in alc).

396. Amicoumacin A. [78654-44-1] 3-Amino-2,3-dideoxy-*N*^{6}-[1-(3,4-dihydro-8-hydroxy-1-oxo-1*H*-2-benzopyran-3-yl)-3-methylbutyl]hexaramide. $C_{20}H_{29}N_3O_7$; mol wt 423.46. C 56.73%, H 6.90%, N 9.92%, O 26.45%. Major component of a complex of antibiotics produced by *Bacillus pumilus* BN-103. Also exhibits anti-inflammatory activity *in vivo*. Isoln and biol activity: **JP Kokai 83 18379** (1983 to Meiji Seika), *C.A.* **99,** 20906x (1983); J. Itoh *et al., J. Antibiot.* **34,** 611 (1981); *eidem, Agr. Biol. Chem.* **46,** 1255 (1982). Structure: *eidem, ibid.* 2659. Use as acaricide: **JP Kokai 83 216107** (1983 to Meiji Seika), *C.A.* **100,** 116494b (1984).

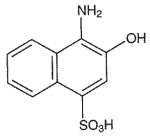


Hydrochloride. Colorless powder, mp 132-135° (dec). uv max (methanol): 208, 247, 315 nm (ε 27300, 6400, 4380). $[\alpha]_D^{23}$ −97.2° (c = 1.0 in methanol). LD_{50} orally in mice: 132 mg/kg (Itoh).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 9 of 65

USE: Polymerization inhibitor; prepn of 2-allyl-4-amino-1-naphthol hydrochloride (an antihemorrhagic cpd); prepn of 1,4-naphthoquinone.

453. 1-Amino-2-naphthol-4-sulfonic Acid. [116-63-2] 4-Amino-3-hydroxy-1-naphthalenesulfonic acid; 1,2,4-acid. $C_{10}H_9NO_4S$; mol wt 239.25. C 50.20%, H 3.79%, N 5.85%, O 26.75%, S 13.40%. Prepd by treatment of nitroso-β-naphthol with sodium bisulfite and sulfuric acid: L. F. Fieser, *Org. Syn.* **coll. vol. II,** 42 (1943); *cf. idem, J. Am. Chem. Soc.* **57,** 494 (1935).

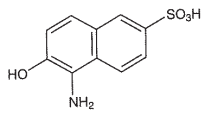


White or gray needles, usually contg 0.5 H_2O. May turn pink on exposure to light, especially when moist. Insol in water, alcohol, ether, benzene; sol in hot sodium bisulfite soln; sol in alkaline soln but such solns oxidize quickly on exposure to air yielding a brown substance which is sol in hot water giving a green soln. Controlled oxidation with HNO_3 yields ammonium 1,2-naphthoquinone-4-sulfonate, *see* Fieser, *loc. cit.*

Sodium salt. $C_{10}H_8NNaO_4S$. Needles, sol in hot water with blue fluorescence.

USE: Manuf of azo dyes, 1,2-naphthoquinone-4-sulfonic acid.

454. 1-Amino-2-naphthol-6-sulfonic Acid. [5639-34-9] 5-Amino-6-hydroxy-2-naphthalenesulfonic acid. $C_{10}H_9NO_4S$; mol wt 239.25. C 50.20%, H 3.79%, N 5.85%, O 26.75%, S 13.40%. Prepd by reduction of sodium 1-nitroso-2-naphthol-6-sulfonate with zinc and acetic acid: Fierz-David *et al., Helv. Chim. Acta* **29,** 1765 (1946).

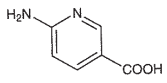


Needles or prisms. Slightly sol in boiling water, less sol in alc. Practically insol in ether.

Sodium salt hemipentahydrate. Eikonogen. $C_{10}H_8NNaO_4S.2½H_2O$; mol wt 306.27. Powder. Sol in water. Practically insol in alc, ether. Strong reducing action on silver salts.

USE: Free acid formerly used in manuf of azo dyes. Sodium salt used as photographic developer and for detection of potassium.

455. 6-Aminonicotinic Acid. [3167-49-5] 6-Amino-3-pyridinecarboxylic acid; 6-amino-3-carboxypyridine. $C_6H_6N_2O_2$; mol wt 138.12. C 52.18%, H 4.38%, N 20.28%, O 23.17%. Prepd by heating 6-chloronicotinic acid with ammonia: Marckwald, *Ber.* **26,** 2188 (1893); **27,** 1319 (1894); Räth, Prauge, *Ann.* **467,** 4 (1928); Johnson *et al., J. Biol. Chem.* **153,** 37 (1944).

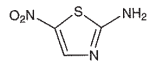


Dihydrate. Crystals from dil acetic acid. Dec above 300° yielding 2-aminopyridine and CO_2. Sparingly sol in most solvents.

Potassium salt. $C_6H_5KN_2O_2$. Crystals, freely sol in water, insol in alcohol.

Hydrochloride. $C_6H_6N_2O_2.HCl$. Needles, freely sol in water, slightly sol in alcohol.

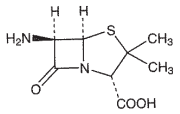
456. 2-Amino-5-nitrothiazole. [121-66-4] 5-Nitro-2-thiazolamine; Enheptin. $C_3H_3N_3O_2S$; mol wt 145.14. C 24.83%, H 2.08%, N 28.95%, O 22.05%, S 22.09%. Prepd by deacetylation of 2-acetamido-5-nitrothiazole: Hubbard; Steahly, **US 2573641**; **US 2573656**; **US 2573657** (all 1951 to Monsanto).



Greenish-yellow to orange-yellow fluffy powder, dec 202°. Slightly bitter taste. uv max (0.0005% in water): 386 nm (ε 0.540); min: 295 nm. Very sparingly soluble in water. (To make a water soln, a 15% stock soln in propylene glycol should first be prepd.) One gram dissolves in 150 g of 95% alcohol; in 250 g ether. Almost insol in chloroform. Sol in dilute mineral acids.

THERAP CAT (VET): Antihistomonad in turkeys. For trichomoniasis in pigeons.

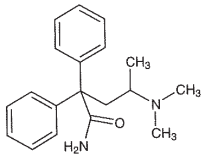
457. 6-Aminopenicillanic Acid. [551-16-6] (2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid; 6-APA; penicin; penin. $C_8H_{12}N_2O_3S$; mol wt 216.26. C 44.43%, H 5.59%, N 12.95%, O 22.19%, S 14.83%. Obtained from cultures of *Penicillium chrysogenum* in the absence of side chain precursors: F. R. Batchelor *et al., Nature* **183,** 257 (1959). Synthesis: J. C. Sheehan, K. R. Henery-Logan, *J Am. Chem. Soc.* **81,** 5838 (1959); **84,** 2983 (1962). Intermediate in the manuf of synthetic penicillins: J. C. Sheehan, **US 3159617** (1964 to Arthur D. Little). HPLC determn: J. Haginaka, J. Wakai, *Anal. Biochem.* **158,** 146 (1986). Review of prepn: F. M. Huber *et al.* in *Cephalosporins Penicillins: Chem. Biol.*, E. H. Flynn, Ed. (Academic, New York, 1972) pp 27-73. Review of chemistry: E. J. Vandamme, J. P. Voets, *Adv. Appl. Microbiol.* **17,** 311-369 (1974). General review: G. N. Rolinson, *J. Antimicrob. Chemother.* **22,** 5-14 (1988).



Crystals from water + HCl, dec 208-209°, also reported as 207-208° (dried) (Sheehan). $[\alpha]_D^{31}$ +273° (c = 1.2 in 0.1*N* HCl).

USE: In manuf of synthetic penicillins.

458. Aminopentamide. [60-46-8] α-[2-(Dimethylamino)propyl]-α-phenylbenzeneacetamide; 4-dimethylamino-2,2-diphenylvaleramide; α,α-diphenyl-γ-dimethylaminovaleramide; dimevamide; BL-139. $C_{19}H_{24}N_2O$; mol wt 296.41. C 76.99%, H 8.16%, N 9.45%, O 5.40%. Anticholinergic. Prepn similar to that of methadone, starts by condensing diphenylmethyl cyanide with chlorodimethylaminopropane: Walton, *et al., J. Chem. Soc.* **1949,** 648; Cheney *et al., J. Org. Chem.* **17,** 770 (1952); Specter, **US 2647926** (1953 to Bristol). Prepn of optical isomers: Wheatley *et al., J. Org. Chem.* **19,** 794 (1954). *See also* Moffett, Aspergren, *J. Am. Chem. Soc.* **79,** 4451 (1957). Toxicity study: Cazort, *J. Pharmacol. Exp. Ther.* **100,** 325 (1950).



***dl*-Form.** Long prisms from dilute alcohol, mp 183-184°. Practically insol in water.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 10 of 65

***d*-Form.** Crystals from petr ether, mp 136.5-137.5° (sintering). $[\alpha]_D^{23}$ +98.9° (methanol).

***l*-Form.** Crystals from petr ether, mp 136.5-137.5° (sintering). $[\alpha]_D^{23}$ −101.9° (methanol).

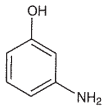
***dl*-Form hydrochloride.** $C_{19}H_{24}N_2O.HCl$. Slightly deliquescent leaflets from alcohol + ether, dec 190-191°. Bitter taste. Soluble in water, alcohol. A 1% aq soln has a pH of 6.8. LD_{50} in mice (mg/kg): 34.7 i.v.; 396 orally (Cazort).

***dl*-Form acid sulfate.** Centrine. $C_{19}H_{24}N_2O.H_2SO_4$; mol wt 394.49. Deliquescent crystals from isopropanol + ethyl acetate, mp 185-187°. The commercial medicinal grade, mp 178-181°. Bitter taste. uv max (1% H_2SO_4): 258.5 nm ($A_{1cm}^{1\%}$ 10.3); min: 249 nm. Freely sol in water, alc. Very slightly sol in chloroform. Practically insol in ether. pH of 2.5% aq soln 1.3-2.2.

THERAP CAT: Antispasmodic.

THERAP CAT (VET): Antispasmodic; antiemetic.

459. *m*-Aminophenol. [591-27-5] 3-Amino-1-hydroxybenzene; 3-hydroxyaniline. C_6H_7NO; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Manuf by reduction of *m*-nitrophenol: Freifelder, Robinson, **US 3079435** (1963 to Abbott). Toxicity study: Koelzer, Giesen, *Z. Naturforsch.* **6b,** 183 (1951).



Crystals, mp 122-123°. Sol in 40 parts cold water, freely in hot water, alcohol, ether, amyl alcohol; slightly in benzene, very slightly in petr ether. LD_{50} i.p. in mice: 4.5 mg/20g (Koelzer, Giesen).

USE: Dye intermediate, manuf *p*-aminosalicylic acid.

460. *o*-Aminophenol. [95-55-6] 2-Aminophenol; 2-amino-1-hydroxybenzene; 2-hydroxyaniline. C_6H_7NO; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Manuf by reduction of *o*-nitrophenol: Freifelder, Robinson, **US 3079435** (1963 to Abbott).

Crystals, rapidly becoming brown, mp 170-174°; sublimes. One gram dissolves in 50 ml cold water, 23 ml alcohol; freely soluble in ether, very slightly in benzene. *Keep tightly closed and protected from light.*

Hydrochloride. $C_6H_7NO.HCl$. Crystals readily becoming gray on exposure to light. Freely sol in water or alcohol.

USE: Manuf azo and sulfur dyes; dyeing furs and hair. Hydrochloride used in dyeing fur, hair, leather, etc.

461. *p*-Aminophenol. [123-30-8] *p*-Hydroxyaniline; 4-amino-1-hydroxybenzene; Azol; Rodinal; Unal; Ursol P. C_6H_7NO; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Usually prepd by the reduction of *p*-nitrophenol: *BIOS Final Report* **986;** Freifelder, Robinson, **US 3079435** (1963 to Abbott).

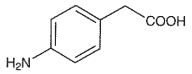
Orthorhombic plates from water. *Deteriorates under the influence of air and light.* mp 189.6-190.2°. The commercial product is usually pink, mp 186°. Can be sublimed at 0.3 mm and 110° without decompn. bp_{760} 284° (decompn); $bp_{8.0}$ 167°; $bp_{3.0}$ 150°; $bp_{0.3}$ 130.2°. Kb at 15° = 6.6×10^{-9}. Forms salts with acids and bases. Soly in water: 0.39% at 13°; 0.65% at 24°; 0.80% at 30°; 1.5% at 50°; 4.7% at 80°; 8.5% at 96°. Soly in ethyl methyl ketone: 9.3% at 58.5°; in abs ethanol: 4.5% at 0°. Practically insol in benzene, chloroform.

Hydrochloride. $C_6H_7NO.HCl$. Cryst powder; gradually becomes darker. Decomp about 306°. Very sol in water; sol in alc.

Caution: May cause skin sensitization, dermatitis. Inhalation can cause asthma, methemoglobin formation.

USE: Photographic developer; intermediate in the manufacture of sulfur and azo dyes; in dyeing furs and feathers.

462. *p*-Aminophenylacetic Acid. [1197-55-3] 4-Aminobenzeneacetic acid; *p*-amino-α-toluic acid. $C_8H_9NO_2$; mol wt 151.16. C 63.57%, H 6.00%, N 9.27%, O 21.17%. Prepd by the reduction of *p*-nitrophenylacetic acid with hydrogen sulfide in the presence of ammonia: G. R. Robertson, *Org. Syn.* **coll. vol. I,** 52 (2nd ed., 1941).



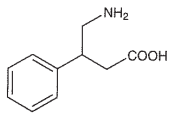
Plates, leaflets from water, mp 199-200° (dec). Moderately sol in hot water; sol in alcohol, in alkalies.

Hydrochloride. $C_8H_9NO_2.HCl$. Rods from HCl, freely sol in water, sol in alcohol (about 3% w/w).

Ethyl ester. $C_{10}H_{13}NO_2$. Platelets from water, mp 51°.

***N*-Benzoyl deriv.** Needles from alcohol, mp 205-206°.

463. 4-Amino-3-phenylbutyric Acid. [1078-21-3] β-(Aminomethyl)benzenepropanoic acid; β-(aminomethyl)hydrocinnamic acid; 4-amino-3-phenylbutanoic acid; β-phenyl-γ-aminobutyric acid; phenygam; PhGABA; Phenigam; Fenigam; Phenigama; Fenigama. $C_{10}H_{13}NO_2$; mol wt 179.22. C 67.02%, H 7.31%, N 7.82%, O 17.85%. Prepn starting with α,γ-diamino-β-phenylpropane: Jackson, Kenner, *J. Chem. Soc.* **1928,** 1657. Alternate prepn: Cologne, Pouchol, *Bull. Soc. Chim. France* **1962,** 598. Pharmacology: R. A. Khaunina, *Bull. Exp. Biol. Med.* **57,** 52 (1964). Structure-activity studies: *idem, Farmakol. Toksikol.* **31,** 202 (1968). Activity studies of the isomers: *eidem, Byull. Eksp. Biol. Med.* **72,** 49 (1971), *C.A.* **76,** 81208t (1972).



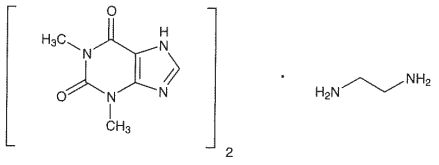
mp 250-253° (dec).

Hydrobromide. [103095-38-1] $C_{10}H_{13}NO_2.HBr$. Irregular platelets from benzene, mp 114°.

Hydrochloride. [3060-41-1] LD_{50} in mice, rats (mg/kg): 900, 700 i.p. (Khaunina, 1964).

THERAP CAT: Mood elevator, tranquilizer.

464. Aminophylline. [317-34-0] 3,7-Dihydro-1,3-dimethyl-1*H*-purine-2,6-dione compd with 1,2-ethanediamine (2:1); theophylline compd with ethylenediamine; theophylline ethylenediamine; theophyllamine; Afonilum; Aminodur; Cardophylin; Euphyllina; Pecram; Phyllocontin; Phyllotemp; Planphylline; Pulmovet; Tefamin. $C_{16}H_{24}N_{10}O_4$; mol wt 420.43. C 45.71%, H 5.75%, N 33.32%, O 15.22%. Prepn: Grüter, **US 919161** (1909 to Byk). Toxicity data: C. R. Thompson, M. R. Warren, *J. Lab. Clin. Med.* **31,** 1337 (1946). Comprehensive description: K. D. Thakker, L. T. Grady, *Anal. Profiles Drug Subs.* **11,** 1-44 (1982). Reviews of clinical experience: J. A. Stirt, S. F. Sullivan, *Anesth. Analg.* **60,** 587-602 (1981); A. G. Perry, *AACN Clin. Issues* **6,** 297-306 (1995).



Occurs as the dihydrate. White or slightly yellowish granules or powder. Slight ammoniacal odor. Bitter taste. Gradually absorbs carbon dioxide from the air and becomes incompletely sol due to liberation of theophylline. One gram dissolves in about 5 ml water, but the soln may become turbid on standing.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 11 of 65

roform, 200 ml ether, 31 ml carbon disulfide, 86 ml carbon tetrachloride, 125 ml toluene. Anthracene darkens in sunlight. According to Downs, **US 1303639** (1919), when solns of crude anthracene in coal tar naphtha are exposed to ultraviolet irradiation, the anthracene is precipitated as dianthracene (*para*-anthracene) which is reconverted to anthracene by sublimation. Forms molecular addn products with nitro compounds.

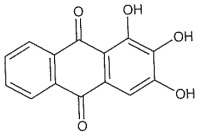
Picric acid complex. mp 139°.

***sym*-Trinitrobenzene complex.** mp 164°.

Trinitrotoluene complex. mp 162°.

USE: Important source of dyestuffs (manuf anthraquinone, alizarin dyes).

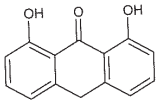
688. Anthragallol. [602-64-2] 1,2,3-Trihydroxy-9,10-anthracenedione; 1,2,3-trihydroxyanthraquinone; anthragallic acid; anthracene brown. $C_{14}H_8O_5$; mol wt 256.21. C 65.63%, H 3.15%, O 31.22%. From gallic acid and benzoic acid with sulfuric acid at 125° or from phthalic anhydride and pyrogallol with sulfuric acid at 160°: Seuberlich, *Ber.* **10,** 39 (1877). Other methods: Kubota, Perkin, *J. Chem. Soc.* **127,** 1889 (1925); Perkin, Story, *ibid.* **1929,** 1399; Cross, Perkin, *ibid.* **1930,** 292. Absorption spectrum: Meyer, Fischer, *Ber.* **46,** 85 (1913).



Brown crystals, mp 312-313°. Sublimes 290°. Slightly sol in water, chloroform; sol in alcohol, ether, glacial acetic acid. Its soln in concd H_2SO_4 is reddish-brown. Greenish-brown soln in ammonia water changes to blue on heating. Forms salts with Na, K, Ba, Tl, Pb, La, Ce, Nd, Co.

Trimethyl ether. $C_{17}H_{14}O_5$. Yellow needles from benzene + petr ether, mp 168°. Insol in water solns of alkalies.

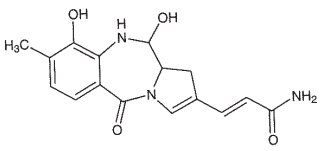
689. Anthralin. [1143-38-0] 1,8-Dihydroxy-9(10*H*)-anthracenone; 1,8-dihydroxyanthrone; dithranol; Anthraforte; Anthranol; Anthrascalp; Antraderm; Cignolin; Dithrocream; Drithocreme; Dritho-Scalp; Micanol; Psoradrate; Psoriderm. $C_{14}H_{10}O_3$; mol wt 226.23. C 74.33%, H 4.46%, O 21.22%. Prepn: Y. Hirosé, *Ber.* **45,** 2474 (1912); K. Zahn, H. Koch, *ibid.* **71B,** 172 (1938). Revised structure: H. M. Avdovich, G. A. Neville, *Can. J. Spectrosc.* **25,** 110 (1980); F. R. Ahmed, *Acta Crystallogr.* **B36,** 3184 (1980). Historical review: R. E. Ashton *et al., J. Am. Acad. Dermatol.* **9,** 173-192 (1983). Review of mechanism of action: L. Kemény *et al., Skin Pharmacol.* **3,** 1-20 (1990); of clinical pharmacology and efficacy in psoriasis: G. Mahrle, *Clin. Dermatol.* **15,** 723-737 (1997).



Lemon yellow leaflets or needles from ligroin, mp 176-181°. Practically insol in water. Sol in chloroform, acetone, benzene. Slightly sol in alcohol, ether, glacial acetic acid. Sol in dil NaOH with yellow color and green fluorescence, becoming orange-red on exposure to air.

THERAP CAT: Antipsoriatic.

690. Anthramycin. [4803-27-4] [11*R*-[2(*E*),11α,-11aβ]]-3-(5,10,11,11a-Tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-2-yl)-2-propenamide; 5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-1*H*-pyrrolo[2,1-*c*][1,4-]benzodiazepin-2-acrylamide. $C_{16}H_{17}N_3O_4$; mol wt 315.32. C 60.94%, H 5.43%, N 13.33%, O 20.30%. From *Streptomyces refuineus* var *thermotolerans,* NRRL 3143: Leimgruber *et al., J. Am. Chem. Soc.* **87,** 5791 (1965); Berger *et al.,* **US 3361742** (1968 to Hoffmann-La Roche). Also from *Streptomyces spadicogriseus:* N. Komatsu *et al., J. Antibiot.* **33,** 54 (1980). Structure: Leimgruber *et al., J. Am. Chem. Soc.* **87,** 5793 (1965). Synthesis: *eidem, ibid.* **90,** 5641 (1968); Batcho, Leimgruber, **US 3524849** (1970 to Hoffmann-La Roche). Activity studies: Horwitz, Grollman, *Antimicrob. Ag. Chemother.* **1968,** 21. Biosynthesis: L. H. Hurley *et al., J. Am. Chem. Soc.* **97,** 4372 (1975). *Review:* Kohn in *Antibiotics* **vol. 3,** J. W. Corcoran, F. E. Hahn, Eds. (Springer-Verlag, New York, 1975) pp 3-11.

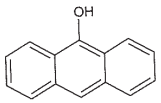


Yellow prisms from acetone + water, dec 188-194°. uv max (acetonitrile): 235, 333 nm (ε 18,200, 31,800). $[\alpha]_D^{25}$ +930° (DMF).

Methyl ether hydrate. $C_{17}H_{19}N_3O_4.H_2O$. Pale yellow needles from methanol + water, dec above 120°.

THERAP CAT: Antineoplastic.

691. Anthranol. [529-86-2] 9-Anthracenol; 9-anthrol; 9-hydroxyanthracene. $C_{14}H_{10}O$; mol wt 194.23. C 86.57%, H 5.19%, O 8.24%. Prepd by dissolving anthrone in 5 to 10% boiling NaOH soln, cooling to −5° and pouring in cooled 5% H_2SO_4: Meyer, *Ann.* **379,** 56 (1911). Also prepared from anthraquinone.



Needles from glacial acetic acid, plates from dil alcohol. Orthorhombic, mp 120° (if bath is heated to 110°). Sinters at 120°, mp 152° (if bath is cold at start). Absorption spectrum (of acetate): Barnett *et al., J. Chem. Soc.* **1928,** 885. Sol in most solvents with blue fluorescence. The solid is fairly stable when kept dry. In solution it changes quickly to anthrone. Recrystallizations of anthranol may lead to a less pure compound.

Acetate. $C_{16}H_{12}O_2$. Crystals from petr ether, mp 134°.

Benzoate. $C_{21}H_{14}O_2$. Crystals from pyridine + alcohol, mp 170-172°.

Methyl ether. $C_{15}H_{12}O$. Crystals from alcohol, mp 97-98°.

Ethyl ether. $C_{16}H_{14}O$. Crystals from methanol, mp 73°.

USE: In the manuf of dyes.

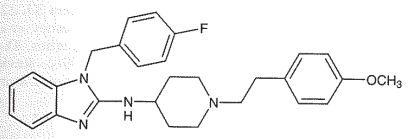
692. Anthraquinone. [84-65-1] 9,10-Anthracenedione; 9,10-anthraquinone; 9,10-dioxoanthracene; Flight Control. $C_{14}H_8O_2$; mol wt 208.21. C 80.76%, H 3.87%, O 15.37%. Prepn: A. Laurent, *Ann.* **34,** 287 (1840). Structural relationship with anthracene: C. Graebe, C. Liebermann, *Ber.* **2,** 332 (1869). Industrial prepn from phthalic anydride and benzene: Klipstein, *Ind. Eng. Chem.* **18,** 1327 (1926). From anthracene with vanadium pentoxide, sodium chlorate, glacial acetic and sulfuric acids: *Org. Syn.* **coll. vol. II,** 554 (1943). Convenient lab procedure: L. F. Fieser, *Organic Experiments* (Heath & Co., Boston, 1964) pp 195-200. Review of chemistry: M. Phillips, *Chem. Rev.* **6,** 157 (1929); of manufacture and uses: A. J. Cofrancesco in *Kirk-Othmer Encyclopedia of Chemical Technology,* **Vol. 2** (Wiley-Interscience, New York, 4th ed., 1992) pp 801-814. Development as bird repellent: R. M. Poché, *Proc. 18th Vertebr. Pest Conf.* **1998,** 338. Field trial to control Canadian geese: P. Devers *et al. ibid.* 345.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 12 of 65

Needles from acetone/light petroleum, mp 182-183°. uv max: (CS_2) 503 nm; (methanol) 472 nm; (hexane) 466-467 nm; (chloroform) 485 nm (Cooper *et al.*). Also reported as shiny purple platelets with gold luster from pyridine, mp 216° (some decompn). Readily sol in pyridine, from which it can be cryst by the addn of water (Kuhn, Sörensen).

Diacetate. $C_{44}H_{56}O_6$. Stout, blue-black needles, mp 203-205° (vac).

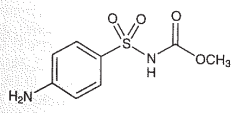
861. Astemizole. [68844-77-9] 1-[(4-Fluorophenyl)methyl]-*N*-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine; 1-(*p*-fluorobenzyl)-2-[[1-(*p*-methoxyphenethyl)-4-piperidyl]amino]benzimidazole; R-43512; Astemisan; Hismanal; Histamen; Histaminos; Kelp; Laridal; Metodik; Novo-Nastizol A; Paralergin; Retolen; Waruzol. $C_{28}H_{31}FN_4O$; mol wt 458.57. C 73.34%, H 6.81%, F 4.14%, N 12.22%, O 3.49%. Nonsedating-type histamine H_1-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).



Crystals from 2,2′-oxybispropane, mp 172.9°. Freely sol in organic solvents. Practically insol in water. uv max (ethanol): 219, 249, 286 nm (ε 27250.229, 6480.293, 8634.280); (0.1*N* HCl): 209, 277 nm (ε 57889.908, 18073.394).

THERAP CAT: Antihistaminic.

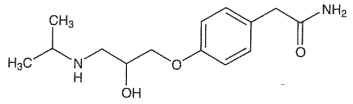
862. Asulam. [3337-71-1] [(4-Aminophenyl)sulfonyl]-carbamic acid methyl ester; N^1-methoxycarbonylsulfanilamide; sulfanilylcarbamic acid methyl ester; methyl *p*-aminobenzenesulfonylcarbamate; M & B 9057; Asulox. $C_8H_{10}N_2O_4S$; mol wt 230.24. C 41.73%, H 4.38%, N 12.17%, O 27.80%, S 13.93%. Carbamate herbicide; folic acid biosynthesis inhibitor. Prepn: **BE 622214** (1963 to May & Baker). Description of herbicidal properties: H. J. Cottrell, B. J. Heywood, *Nature* **207,** 655 (1965). Persistence in soil: A. E. Smith, A. Walker, *Pestic. Sci.* **8,** 449 (1977). Mode of action: P. Veerasekaran *et al.*, *Pestic. Sci.* **12,** 325, 330 (1981). Field study on sugarcane and torpedograss: M. A. Hossain *et al.*, *J. Weed Sci. Tech.* **43,** 10 (1998); in bracken control: R. J. Pakeman *et al.*, *J. Environ. Management* **53,** 255 (1998). Review of properties and analytical methods: C. H. Brockelsby, D. F. Muggleton, *Anal. Methods Pestic. Plant Growth Regul.* **7,** 497 (1973); A. Guardigli *et al.*, *ibid.* **13,** 197 (1984).



White crystals, mp 143-144° (dec). Soly: water 0.5%, hydrocarbons <2%, chlorinated hydrocarbons <2%, acetone 34%, methanol 28%. pKa 4.82. LD_{50} in rats, mice, dogs, rabbits (mg/kg): >5000, >5000, >5000, >2000 orally; in rats (mg/kg): >1200 dermally (Brockelsby).

USE: Herbicide.

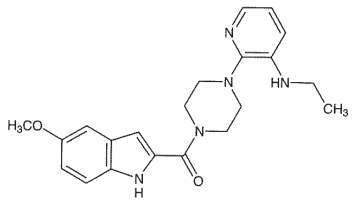
863. Atenolol. [29122-68-7] 4-[2-Hydroxy-3-[(1-methylethyl)amino]propoxy]benzeneacetamide; 2-[*p*-[2-hydroxy-3-(isopropylamino)propoxy]phenyl]acetamide; 1-*p*-carbamoylmethylphenoxy-3-isopropylamino-2-propanol; ICI-66082; Atehexal; Ateno basan; Atenol; Cuxanorm; Ibinolo; Myocord; Prenormine; Seles Beta; Tenoblock; Tenormin; Uniloc. $C_{14}H_{22}N_2O_3$; mol wt 266.34. C 63.13%, H 8.33%, N 10.52%, O 18.02%. Cardioselective β-adrenergic blocker. Prepn: Barrett *et al.*, **DE 2007751**; *eidem*, **US 3663607** and **US 3836671** (1970, 1972, 1974 all to I.C.I.). Pharmacology and clinical studies: Giudicelli *et al.*, *Compt. Rend. Soc. Biol.* **167,** 232 (1973); Hansson *et al.*, *Acta Med. Scand.* **194,** 549 (1973); Amery *et al.*, *N. Engl. J. Med.* **290,** 284 (1974). Clinical trial in treatment of alcohol withdrawal syndrome: M. L. Kraus *et al.*, *ibid.* **313,** 905 (1985). HPLC determn of enantiomers in plasma and urine: S. K. Chin *et al.*, *J. Chromatog.* **489,** 438 (1989). Comprehensive description: V. Caplar *et al.*, *Anal. Profiles Drug Subs.* **13,** 1-25 (1984). *Review:* J. D. Fitzgerald in *Pharmacological and Biochemical Properties of Drug Substances* **vol. 2,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1979) pp 98-147; E. Marmo, *Drugs Exp. Clin. Res.* **6,** 639-663 (1980). Symposium on clinical studies: *Drugs* **25,** Suppl. 2, 1-346 (1983).



Crystals from ethyl acetate, mp 146-148°. Also reported as mp 150-152° (Caplar). Freely sol in methanol; sol in acetic acid, DMSO; sparingly sol in 96% ethanol; slightly sol in water, isopropanol; very slightly sol in acetone, dioxane. Practically insol in acetonitrile, ethylacetate, chloroform. pKa 9.6. Partition coefficient (*n*-octanol/phosphate buffer): 0.008 (pH 7.0); 0.052 (pH 8.0). Dipole moment: 5.71 ±0.20 D at 20° in propionic acid. uv max (methanol): 225, 275, 283 nm. LD_{50} in mice, rats (mg/kg): 2000, 3000 orally; 98.7, 59.24 i.v. (Fitzgerald).

THERAP CAT: Antihypertensive, antianginal, antiarrhythmic (class II).

864. Atevirdine. [136816-75-6] 1-[3-(Ethylamino)-2-pyridinyl]-4-[(5-methoxy-1*H*-indol-2-yl)carbonyl]piperazine; *N*-ethyl-2-[4-(5-methoxy-1*H*-indol-2-ylcarbonyl)-1-piperazinyl]-3-pyridinamine; 1-[5-methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine; U-87201. $C_{21}H_{25}N_5O_2$; mol wt 379.45. C 66.47%, H 6.64%, N 18.46%, O 8.43%. Bisheteroarylpiperazine (BHAP) reverse transcriptase inhibitor. Prepn: D. L. Romero *et al.*, **WO 91 09849** (1991 to Upjohn); and structure-activity studies: *idem et al.*, *J. Med. Chem.* **37,** 999 (1994). Mechanism of action study: I. W. Althaus *et al.*, *J. Biol. Chem.* **268,** 6119 (1993). Clinical pharmacokinetics: A. M. M. Been-Tiktak *et al.*, *Antimicrob. Ag. Chemother.* **39,** 602 (1995). Clinical evaluation of combination with zidovudine, *q.v.*, in AIDS: R. C. Reichman *et al.*, *J. Infect. Dis.* **171,** 297 (1995).



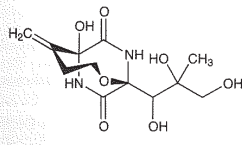
mp 153-154°.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 13 of 65

Crystals from dil ethanol, mp 193-195° (slight decompn). pKa (20°): 8.35. pKa_2 (0.1*M*): 0°, 8.7; 20°, 8.35; 37°, 8.2. $\Delta pKa/°C$ −0.018. Saturated aq soln is 1.1*M* at 0°. Slightly sol in water. Forms a water-soluble sodium salt.

USE: Biological buffer and chelating agent.

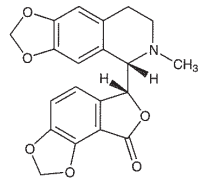
1206. Bicozamycin. [38129-37-2] Bicyclomycin; aizumycin; 8,10-diaza-6-hydroxy-5-methylene-1-(2-methyl-1,2,3-trihydroxypropyl)-2-oxabicyclo[4.2.2]decan-7,9-dione; antibiotic 5879; WS-4545 antibiotic; Bacteron; Bacfeed. $C_{12}H_{18}N_2O_7$; mol wt 302.28. C 47.68%, H 6.00%, N 9.27%, O 37.05%. Cyclic peptide antibiotic substance. Prepn by fermentation of *Streptomyces sapporensis:* T. Miyoshi *et al.,* **DE 2150593**; H. Imanaka *et al.,* **US 3923790** (1972, 1975 both to Fujisawa). Isoln and characterization: T. Miyoshi *et al., J. Antibiot.* **25,** 569 (1972). Isoln from *S. aizunensis* and identity with antibiotic 5879: S. Miyamura *et al., ibid.* **26,** 479 (1973). Bicyclomycin has a unique chemical structure which bears no relation to any group of known antibiotics. Structural elucidation: T. Kamiya *et al., ibid.* **25,** 576 (1972). Crystal and molecular structure: Y. Tokuma *et al., Bull. Chem. Soc. Japan* **47,** 18 (1974). *In vitro* and *in vivo* activity studies: M. Nishida *et al., J. Antibiot.* **25,** 582 (1972). Metabolism: *eidem, ibid.* 594. Mechanism of action: N. Tanaka *et al., ibid.* **29,** 155 (1976); N. Tanaka in *Antibiotics* **vol. 5**(pt. 1), E. Hahn, Ed. (Springer, New York, 1979) p 18. Synthetic approaches: L. V. Dunkerton, R. M. Ahmed, *Tetrahedron Letters* **21,** 1803 (1980); R. M. Williams, *ibid.* **22,** 2341 (1981); S. Nakatsuka *et al., ibid.* 4973; J. H. Hoare, P. Yates, *Chem. Commun.* **1981,** 1126. Total synthesis of (±)-bicyclomycin: S. Nakatsuka *et al., Tetrahedron Letters* **24,** 5627 (1983); of (+)-bicyclomycin: R. M. Williams *et al., J. Am. Chem. Soc.* **106,** 5749 (1984); *eidem, ibid.* **107,** 3253 (1985). Review of synthetic, mechanistic and biological studies: R. M. Williams, C. A. Durham, *Chem. Rev.* **88,** 511-540 (1988).



Monoclinic crystals from ethanol, mp 188-191° (dec); rhombic crystals from methanol + acetone, mp 187-189° (dec) (Imanaka), also reported as mp 166-170° (Nakatsuka *et al.*). $[\alpha]_D^{23}$ +63.5° (methanol). Weakly basic substance. Soly in water: 192 mg/ml. Sol in methanol; sparingly sol in ethanol. Slightly sol in acetone. Practically insol in chloroform, ethyl acetate, benzene, *n*-hexane. Unstable in alkaline soln. LD_{50} in mice: >4 g/kg (Williams, Durham).

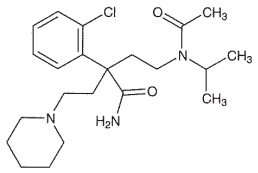
THERAP CAT (VET): Antibacterial; feed additive (livestock).

1207. Bicuculline. [485-49-4] (6*R*)-6-[(5*S*)-5,6,7,8-Tetrahydro-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]furo[3,4-*e*]-1,3-benzodioxol-8(6*H*)-one. $C_{20}H_{17}NO_6$; mol wt 367.35. C 65.39%, H 4.66%, N 3.81%, O 26.13%. Alkaloid naturally occurring in the *d*-form; found in *Dicentra cucullaria* (L.) Bernh., *Adlumia fungosa* (Ait.) Greene, *Fumariaceae,* and several *Corydalis* species: Manske, *Can. J. Res.* **7,** 265 (1932); **8,** 210, 407 (1933); **9,** 436 (1933); Edwards, Handa, *Can. J. Chem.* **39,** 1801 (1961). Synthesis of *dl*-form: Groenewoud, Robinson, *J. Chem. Soc.* **1936,** 199. Resolution of isomers: Haworth *et al., Nature* **165,** 529 (1950). Stereoisomer of adlumidine, *q.v.,* and of capnoidine: Manske, *J. Am. Chem. Soc.* **72,** 3207 (1950). Preliminary stereochemical studies: Safe, Moir, *Can. J. Chem.* **42,** 160 (1964). Revised stereochemistry: Blaha *et al., Coll. Czech. Chem. Commun.* **29,** 2328 (1964); Snatzke *et al., Tetrahedron* **25,** 5059 (1969). Crystal and molecular structure: Gorinsky, Moss, *J. Cryst. Mol. Struct.* **3,** 299 (1973). Shows GABA *(q.v.)* antagonist activity: Curtis *et al., Nature* **226,** 1222 (1970).



Elongated plates from chloroform-methanol, mp 215°; also reported as mp 177°, solidifies and remelts 193-195°: Manske, *Can. J. Res.* **21B,** 13 (1943). uv max (acidified ethanol): 225, 296, 324 nm (ε 36700, 6390, 5870). $[\alpha]_D^{25}$ +130.5° ($CHCl_3$). pKa 4.84. Sol in benzene, chloroform, ethyl acetate. Sparingly sol in alc and ether.

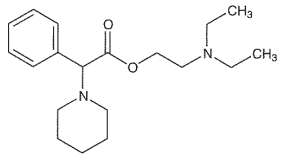
1208. Bidisomide. [116078-65-0] α-[2-[Acetyl(1-methylethyl)amino]ethyl]-α-(2-chlorophenyl)-1-piperidinebutanamide; (±)-α-(*o*-chlorophenyl)-α-[2-(*N*-isopropylacetamido)ethyl]-1-piperidinebutyramide; SC-40230. $C_{22}H_{34}ClN_3O_2$; mol wt 407.99. C 64.77%, H 8.40%, Cl 8.69%, N 10.30%, O 7.84%. Sodium channel blocker. Prepn: B. N. Desai *et al.,* **EP 170901**; *eidem,* **US 4639524** (1986, 1987 both to Searle); *eidem, J. Med. Chem.* **31,** 2158 (1988). Cardiovascular pharmacology: L. G. Frederick *et al., Cardiovasc. Res.* **23,** 897 (1989). Electrophysiologic study: S. M. Garthwaite *et al., Drug Dev. Res.* **27,** 329 (1992). Bioavailability and tolerability in humans: R. L. Page *et al., Clin. Pharmacol. Ther.* **51,** 371 (1992). Clinical pharmacokinetics: C. S. Cook *et al., Pharm. Res.* **10,** 1675 (1993).



Crystals from ethyl acetate, mp 140-141°.

THERAP CAT: Antiarrhythmic (class I).

1209. Bietamiverine. [479-81-2] α-Phenyl-1-piperidineacetic acid 2-(diethylamino)ethyl ester; β-diethylaminoethyl phenylpiperidinoacetate; β-diethylaminoethyl α-(1-piperidyl)-phenylacetate. $C_{19}H_{30}N_2O_2$; mol wt 318.45. C 71.66%, H 9.50%, N 8.80%, O 10.05%. Prepd by reacting piperidine with phenylchloroacetic acid ethyl ester in chloroform: Reetz, **DE 859892** (1952 to Nordmark-Werke); from β-diethylaminoethyl phenylbromoacetate and piperidine in chloroform: Blicke *et al., J. Am. Chem. Soc.* **76,** 3161 (1954); from ethyl α-(1-piperidyl)phenylacetate and β-diethylaminoethyl chloride: Moffett, Hart, *J. Am. Pharm. Assoc. Sci. Ed.* **42,** 717 (1953). Clinical tests: Ciravegna *et al., Clin. Ter.* **57,** 227 (1971).



Liquid, d_4^{25} 1.0184. bp_1 65°. n_D^{25} 1.5070.

Hydrochloride. [1477-10-7] Novosparol. $C_{19}H_{30}N_2O_2.HCl$; mol wt 354.92. Crystals from methyl isobutyl ketone, mp 187-189°.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 14 of 65

Colorless liquid; also reported to be pale yellow. Long prisms when solid. mp 8.77°. bp 125.75°. d^{25} 2.8030. *Smokes in air. Attacks skin. Very reactive.*

Caution: Corrosive and irritating to skin, eyes, mucous membranes, respiratory tract.

USE: Solvent for fluorides.

1381. Bromisovalum. [496-67-3] *N*-(Aminocarbonyl)-2-bromo-3-methylbutanamide; (α-bromoisovaleryl)urea; 2-monobromoisovalerylurea; α-bromo-β-dimethylpropanoylurea; bromvaletone; B.V.U.; Bromural; Bromisoval; Uvaleral; Bromuvan; Somnurol; Brovalurea; Dormigene; Isobromyl; Alluval; Pivadorm. $C_6H_{11}BrN_2O_2$; mol wt 223.07. C 32.31%, H 4.97%, Br 35.82%, N 12.56%, O 14.34%. $(CH_3)_2CHCHBrCONHCONH_2$. Prepn from urea and α-bromoisovaleryl bromide: **US 914518** (1909). Toxicity: R. I. Mrongovius *et al., Clin. Exp. Pharmacol. Physiol.* **3,** 443 (1976).

Practically tasteless needles, mp 147-149°. Sublimes. Slightly sol in cold water, but freely sol in hot water. Readily sol in alcohol, ether and in alkaline solns. LD_{50} in male mice (mmoles/kg): 3.25 i.p. (Mrongovius).

Caution: May be habit forming: **21 CFR,** 329.1.

THERAP CAT: Sedative, hypnotic.

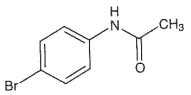
1382. *N*-Bromoacetamide. [79-15-2] Acetobromamide. C_2H_4BrNO; mol wt 137.96. C 17.41%, H 2.92%, Br 57.92%, N 10.15%, O 11.60%. $CH_3CONHBr$. Prepd by treating a cooled (0-5°) soln of acetamide dissolved in bromine with ice cold aq 50% KOH, allowing to stand for 2-3 hr at 0-5°, treating with NaCl, and extracting with chloroform: Oliveto, Gerold, *Org Syn.* **31,** 17 (1951).

Needles from chloroform + hexane, mp 102-105°. Sol in warm water, freely sol in cold ether. Unstable to light and heat.

Monohydrate. Rectangular plates from hydr ether, mp 70-80°. Freely sol in cold water, alcohol, ether, less freely in chloroform.

USE: Brominating agent; in oxidation of primary and secondary alcohols.

1383. *p*-Bromoacetanilide. [103-88-8] *N*-(4-Bromophenyl)acetamide; 4′-bromoacetanilide; monobromoacetanilide; bromoanilide; Antisepsin; Asepsin; Bromoantifebrin. C_8H_8BrNO; mol wt 214.06. C 44.89%, H 3.77%, Br 37.33%, N 6.54%, O 7.47%. Prepd by bromination of acetanilide: Remmers, *Ber.* **7,** 346 (1874); Merker, Vona, *J. Chem. Ed.* **26,** 613 (1949); Knowles, Alt, **US 3012035** (1959 to Monsanto).



Crystals, from 95% alc, mp 168° (with previous softening). d 1.72. Practically insol in cold water. Sparingly sol in hot water; sol in benzene, chloroform, ethyl acetate; moderately sol in alcohol.

THERAP CAT: Analgesic, antipyretic.

1384. Bromoacetic Acid. [79-08-3] $C_2H_3BrO_2$; mol wt 138.95. C 17.29%, H 2.18%, Br 57.51%, O 23.03%. $BrCH_2COOH$. Prepn by bromination of acetic acid: Perkin, Duppa, *Ann.* **108,** 106 (1858); from chloroacetic acid and HBr: Lake, Asadorian; Asadorian, Burk, **US 2553518**; **US 3130222** (1951, 1964, both to Dow); from glycolic acid and HBr: Johnston, **US 2876255** (1959 to Ethyl Corp.).

Hygroscopic crystals, mp 50°. bp 208°. d 1.93. Very sol in water, alcohol. *Protect from air and moisture.*

Caution: Irritant and corrosive to skin, mucous membranes.

1385. Bromoacetone. [598-31-2] 1-Bromo-2-propanone. C_3H_5BrO; mol wt 136.98. C 26.31%, H 3.68%, Br 58.33%, O 11.68%. CH_3COCH_2Br. Prepn by bromination of acetone: Emmerling, Wagner, *Ann.* **204,** 29 (1880); Catch *et al., J. Chem. Soc.* **1948,** 272; Ross **US 2452154** (1948 to Colgate-Palmolive-Peet); by bromination acetone enol acetate: Magerlein, **US 2752341** (1956 to Upjohn).

Liquid, mp −36.5°. bp 137°, bp_{50} 63.5-64°. d^{23} 1.634. n_D^{15} 1.4697. Turns violet rapidly even in absence of air. Sparingly sol in water; sol in alcohol, acetone. *Keep tightly closed and protected from light.*

Caution: Violent lacrimator.

USE: Chemical war gas.

1386. ω-Bromoacetophenone. [70-11-1] 2-Bromo-1-phenylethanone; phenacyl bromide. C_8H_7BrO; mol wt 199.05. C 48.27%, H 3.54%, Br 40.14%, O 8.04%. $C_6H_5COCH_2Br$. Prepn from acetophenone and bromine: Rother, Reid, *J. Am. Chem. Soc.* **41,** 77 (1919); Cowper, Davidson, *Org. Syn.* **19,** 24 (1939); Shevchuk, Dombrovskii, *Zh. Obshch. Khim.* **33**(4), 1135 (1963).

Crystals, mp 50°. d 1.65. bp_{20} 133-135°. Irritating vapors. *Lacrimator!* Practically insol in water. Freely sol in alcohol, benzene, chloroform, ether.

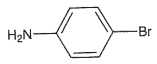
Caution: Highly irritating to skin, eyes, mucous membranes.

1387. *p*-Bromoacetophenone. [99-90-1] 1-(4-Bromophenyl)ethanone; methyl *p*-bromophenyl ketone. C_8H_7BrO; mol wt 199.05. C 48.27%, H 3.54%, Br 40.14%, O 8.04%. $BrC_6H_4COCH_3$. Prepd from bromobenzene and acetic anhydride in CS_2 in the presence of anhydr $AlCl_3$: Adams, Noller, *Org. Syn.* **5,** 17 (1925).

Leaflets from alc. mp 54°. bp_{736} 255.5°; bp_{15} 130°; bp_7 117°. Easily volatile with steam. Sol in alcohol, ether, glacial acetic acid, benzene, petr ether, carbon disulfide.

Oxime. C_8H_8BrNO. Needles from dil alc, mp 128.5°.

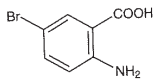
1388. *p*-Bromoaniline. [106-40-1] 4-Bromobenzeneamine; 4-bromoaniline. C_6H_6BrN; mol wt 172.03. C 41.89%, H 3.52%, Br 46.45%, N 8.14%. Prepd by steam distilling sodium hydroxide and *p*-bromoacetanilide: Scott, *J. Chem. Soc.* **123,** 3199 (1923); by direct bromination of aniline: Kosolapoff, *J. Am. Chem. Soc.* **75,** 3596 (1953).



Rhombic crystals from dil alc; mp 66-66.5°. $d_4^{99.6}$ 1.4970 (liq). Very sol in alcohol and ether. Insol in cold water. pKb (25°): 10.28 also reported as 9.98.

USE: In prepn of azo dyes; condensed with formaldehyde in prepn of dihydroquinazolines.

1389. 5-Bromoanthranilic Acid. [5794-88-7] 2-Amino-5-bromobenzoic acid; 5-bromo-2-aminobenzoic acid. $C_7H_6BrNO_2$; mol wt 216.03. C 38.92%, H 2.80%, Br 36.99%, N 6.48%, O 14.81%. Prepd by bromination of anthranilic acid: Wheeler, *J. Am. Chem. Soc.* **31,** 565 (1909); Wheeler, Oates, *ibid.* **32,** 771 (1910).



Crystals, mp 218-219°. Very slightly sol in water, moderately sol in alcohol, ether, chloroform, benzene, acetic acid, freely sol in acetone.

USE: Determination of cobalt, copper, nickel, and zinc.

1390. Bromobenzene. [108-86-1] Monobromobenzene; phenyl bromide. C_6H_5Br; mol wt 157.01. C 45.90%, H 3.21%, Br 50.89%. Prepd industrially by the action of bromide on benzene in the presence of iron powder: Gattermann-Wieland, *Praxis des organischen Chemikers* (de Gruyter, Berlin, 40th ed., 1961) p 95; alternate procedure using pyridine as halogen carrier: A. I. Vogel, *Practical Organic Chemistry* (Longmans, London, 3rd ed., 1959) p 535.

Mobile liquid. Aromatic odor. d_4^0 1.5220; d_4^{10} 1.5083; d_4^{15} 1.5017; d_4^{20} 1.4952; d_4^{30} 1.4815; d_4^{71} 1.426. mp −30.6°. bp_{760} 156.2°; bp_{400} 132.3°; bp_{200} 110.1°; bp_{40} 68.6°; bp_{20} 53.8°; bp_{10} 40.0°; bp_5 27.8°; $bp_{1.0}$ +2.9°. n_D^{15} 1.5625; n_D^{20} 1.5602. Flash pt

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 15 of 65

1591. Butyraldehyde. [123-72-8] Butanal. C_4H_8O; mol wt 72.11. C 66.62%, H 11.18%, O 22.19%. $CH_3CH_2CH_2CHO$. Prepn from butyryl chloride: Brown, Tsukamoto, *J. Am. Chem. Soc.* **83,** 2016 (1961); by reduction of corresponding nitrile: Gaiffe, Pallaud, *Compt. Rend.* **254,** 496 (1962); by alkali aluminum hydride reduction of methyl butyrate: Zakharkin *et al., Tetrahedron Letters* **1963,** 208; by oxidation of butanol: Harrison, *Proc. Chem. Soc.* **1964,** 110. Usually manuf by catalytic dehydrogenation of butanol, catalytic hydrogenation of crotonaldehyde, or by the oxo process from propene, *e.g., see:* Dunbar, Arnold, *J. Org. Chem.* **10,** 501 (1945); Horn, *Ind. Eng. Chem.* **51,** 655 (1959); W. L. Faith *et al., Industrial Chemicals* (John Wiley, New York, 3rd ed., 1965) pp 183, 304-305. Toxicity study: Smyth *et al., Arch. Ind. Hyg. Occup. Med.* **4,** 119 (1951). *Review:* P. D. Sherman in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 4** (Wiley-Interscience, New York, 3rd ed., 1978) pp 376-386.

Flammable liquid. bp 74.8°. mp −99°. Closed-cup flash pt −6.67°C (20°F). d_4^{20} 0.8016. n_D^{20} 1.379. Soly in water at 25°, 7.1 (wt-%): Smith, Bonner, *Ind. Eng. Chem.* **43,** 1169 (1951). Miscible with ethanol, ether, ethyl acetate, acetone, toluene, many other organic solvents and oils. Single-dose LD_{50} orally in rats: 5.89 g/kg (Smyth).

Caution: May act as irritant, narcotic.

USE: Chiefly in the manuf of rubber accelerators, synthetic resins, solvents, plasticizers.

1592. *n*-Butyramide. [541-35-5] Butanamide. C_4H_9NO; mol wt 87.12. C 55.15%, H 10.41%, N 16.08%, O 18.36%. $CH_3CH_2CH_2CONH_2$. Prepn by a modified Willgerodt reaction: Jelinek, **US 2572809**; **US 2572810** (both 1951 to GAF); from butyryl chloride: Philbrook, *J. Org. Chem.* **19,** 623 (1954); from butyraldoxime: Huber, **US 2721199** (1955 to du Pont); from butyric acid: Rahman, *Rec. Trav. Chim.* **79,** 188 (1960); from butyronitrile: Gilbert, Rumanowski, **US 3062883** (1962 to Allied Chem.).

Crystals, mp 115-116°. bp 216°. Sol in water, alcohol; slightly sol in ether.

1593. Butyric Acid. [107-92-6] Butanoic acid; *n*-butyric acid; ethylacetic acid. $C_4H_8O_2$; mol wt 88.10. C 54.53%, H 9.15%, O 36.32%. $CH_3CH_2CH_2COOH$. Discovered by Lieben and Rossi in 1869. Present in butter as an ester to the extent of 4-5%. Obtained by suitable fermentation of carbohydrates; prepn from *n*-propanol + CO at 200 atm in the presence of $Ni(CO)_4$ and NiI_2: Reppe *et al., Ann.* **582,** 83 (1953); lab prepn from ethylmalonic acid: Gattermann-Wieland, *Praxis des Organischen Chemikers* (de Gruyter, Berlin, 40th ed., 1961) p 221. Toxicity study: Smyth *et al., Arch. Ind. Hyg. Occup. Med.* **10,** 61 (1954).

Oily liq; unpleasant, rancid odor. d_4^{20} 0.959. bp 163.5°. mp −7.9°. n_D^{20} 1.3991. Flash pt, closed cup: 170°F (77°C). Neutralization value 636.79. Miscible with water, alcohol, ether. The calcium salt of this acid is less soluble in hot than in cold water (difference from isobutyric acid). LD_{50} orally in rats: 8.79 g/kg (Smyth).

Magnesium salt. Magnesium butyrate. $C_8H_{14}MgO_4$. Deliquesc leaflets. Sol in water. *Keep well closed.*

USE: Manuf of esters, some of which serve as bases of artificial flavoring ingredients of certain liqueurs, soda-water syrups, candies; also for varnishes; as decalcifier of hides.

1594. Butyric Anhydride. [106-31-0] Butanoic acid anhydride; butyryl oxide. $C_8H_{14}O_3$; mol wt 158.19. C 60.74%, H 8.92%, O 30.34%. $CH_3CH_2CH_2COOCOCH_2CH_2CH_3$. Prepn from butyric acid: Williams, Krynitsky, *Org. Syn.* **coll. vol. III,** 165 (1955); Kuwajima, Mukaiyama, *J. Org. Chem.* **29,** 1385 (1964). Manuf by catalytic hydrogenation of crotonic acid: Smith, Hunter, **US 2492403** (1949 to Celanese); by catalytic carbonylation of the corresponding acid ester: Reppe, Friederich, **US 2730546** (1956 to BASF).

Liq, bp 199.4-201.4°. mp −75°. d_4^{20} 0.9668. n_D^{20} 1.4070. Flash pt, open cup: 190°F (88°C). Sol in water and in alc with decompn; sol in ether.

1595. Butyroin. [496-77-5] 5-Hydroxy-4-octanone; 5-octanol-4-one. $C_8H_{16}O_2$; mol wt 144.21. C 66.63%, H 11.18%, O 22.19%. $CH_3(CH_2)_2CH(OH)CO(CH_2)_2CH_3$. Prepd by the reaction between an ether soln of ethyl butyrate and sodium or potassium: Bouveault, Locquin, *Bull. Soc. Chim.* [3] **35,** 629 (1906); Corson *et al., J. Am. Chem. Soc.* **52,** 3988 (1930); Scheibler, Emden, *Ann.* **434,** 265 (1923); Snell, McElvain, *Org. Syn.* **coll. vol. II,** 114 (1943).

Liquid. d_4^0 0.9367; $d_4^{16.7}$ 0.91075. bp_{760} 180-190°; bp_{155} 150-154°; bp_{20} 95°; bp_{10} 85°. $n_D^{16.7}$ 1.43455. Reduces Fehling's soln.

Oxime. $C_8H_{17}NO_2$. Viscous liquid, bp_{10} 143°.

1596. Butyrolactone. [96-48-0] Dihydro-2(3*H*)-furanone; γ-butyrolactone; 1,2-butanolide; 1,4-butanolide; γ-hydroxybutyric acid lactone; 3-hydroxybutyric acid lactone; 4-hydroxybutanoic acid lactone. $C_4H_6O_2$; mol wt 86.09. C 55.81%, H 7.02%, O 37.17%. Prepd from acetylene and formaldehyde: Reppe, *Chem. Ing. Technik* **1950,** 365; *Chem. Eng.* **58,** no. 6, 176 (1951); also prepd from ethylene chlorohydrin, glutaric acid, ν-hydroxybutyric acid solns, tetrahydrofuran, or vinylacetic acid: F. C. Whitmore, *Organic Chemistry* (Van Nostrand, New York, 2nd ed., 1951). Alternate synthesis: Y. Ogata *et al., J. Org. Chem.* **45,** 1320 (1980). Physical properties: McKinley, Copes *J. Am. Chem. Soc.* **72,** 5331 (1950). Toxicity: H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30,** 470 (1969).



Oily liquid. d_0^0 1.1441; d_0^{15} 1.1286. mp −43.53°. bp_{760} 204°. bp_{12} 89°. n_D^{25} 1.4348. Flash pt, open cup: 209°F (98°C). Volatile with steam. Misc with water. Sol in methanol, ethanol, acetone, ether, benzene. Hydrolyzed by hot alkaline solns. LD_{50} orally in rats: 17.2 ml/kg (Smyth).

USE: Intermediate in the synthesis of polyvinylpyrrolidone, DL-methionine, piperidine, phenylbutyric acid, thiobutyric acids. Solvent for polyacrylonitrile, cellulose acetate, methyl methacrylate polymers, polystyrene. Constituent of paint removers, textile aids, drilling oils.

1597. Butyronitrile. [109-74-0] Butanenitrile; propyl cyanide; butyric acid nitrile. C_4H_7N; mol wt 69.10. C 69.53%, H 10.21%, N 20.27%. $CH_3CH_2CH_2CN$. Prepd from 1-butanol by controlled cyanation with NH_3 at 300° in the presence of Ni—Al_2O_3 catalysts: Popov, Shuikin, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1958,** 713-718, *C.A.* **52,** 19924 (1958). Toxicity: H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **23,** 95 (1962).

Liquid. d_4^0 0.8091; d_4^{15} 0.7954; d_4^{30} 0.7817. mp −112°. bp_{760} 117.5°; bp_{400} 96.8°; bp_{200} 76.7°; bp_{100} 59.0°; bp_{60} 47.3°; bp_{40} 38.4°; bp_{20} 25.7°; bp_{10} 13.4°; bp_5 +2.1°; $bp_{1.0}$ −20.0°. n_D^{20} 1.38385. Flash pt, open cup: 85°F (29°C). Viscosity ($\eta \times 10^5$) at 15° = 624; at 30° = 515. Dipole moment 3.5. Sparingly sol in water. Misc with alcohol, ether, dimethylformamide. LD_{50} orally in rats: 0.14 g/kg (Smyth).

Caution: Potential symptoms of overexposure are irritation of eyes, skin, respiratory system; headache, dizziness, weakness, giddiness, confusion, convulsions; dyspnea; abdominal pain, nausea, vomiting. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 44.

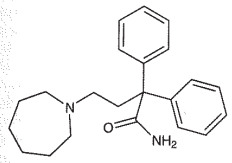
1598. *n*-Butyryl Chloride. [141-75-3] Butanoyl chloride; butyryl chloride. C_4H_7ClO; mol wt 106.55. C 45.09%, H 6.62%, Cl 33.27%, O 15.02%. $CH_3CH_2CH_2COCl$. Prepn from butyric acid: Helferich, Schaefer, *Org. Syn.* **coll. vol. I,** 147 (1941).

Liquid, bp 101-102°. mp −89°. $d_4^{20.6}$ 1.0263. n_D^{20} 1.412. Dissolves slowly with decompn in water, alcohol. Miscible with ether.

1599. Buzepide. [3691-21-2] Hexahydro-α,α-diphenyl-1*H*-azepine-1-butanamide; 2,2-diphenyl-4-hexamethyleneiminobutyramide; R-658. $C_{22}H_{28}N_2O$; mol wt 336.47. C 78.53%, H 8.39%, N 8.33%, O 4.76%. Anticholinergic. Prepn: Janssen *et al., J. Med. Pharm. Chem.* **1,** 187 (1959); of methiodide as well as free base: Janssen, de Jongh, **US 2881165** (1959 to N.V. Nederlandsche Combinatie Chem. Ind.). Clinical trial in irrita-

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 16 of 65

ble bowel syndrome: J. Ph. Barbier *et al., Ann. Gastroenterol. Hepatol.* **25,** 123 (1989).



Crystals from isopropanol, mp 141.5-143.5°.

Methiodide. [15351-05-0] Metazepium iodide; 1-(3-carbamoyl-3,3-diphenylpropyl)hexahydro-1-methylazepinium iodide; *N*-(3,3-diphenyl-3-carbamoylpropyl)-*N*-methylperhydroazepinium iodide; diphexamide methiodide. $C_{22}H_{28}N_2O.CH_3I$. Crystals, dec 212-213°.

Mixture with haloperidol. Vésadol.

THERAP CAT: Antispasmodic.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 17 of 65

Ethanedisulfonate. [125-86-0] $(C_{18}H_{27}NO_2)_2.C_2H_6O_6S_2$; mol wt 769.03. Crystals from acetone, mp 115-116°. More sol in water than the hydrochloride. Sol in alc, pharmaceutical syrups. Mixture with phenylpropanolamine hydrochloride, ***Tuss-Ornade***.

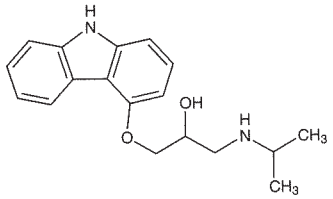
Hydrochloride. [125-85-9] $C_{18}H_{27}NO_2.HCl$; mol wt 325.88. Crystals, mp 145-146°. Sol in alc; slightly sol in water. LD_{50} i.p. in rats: 209 mg/kg (Kraatz).

THERAP CAT: Antitussive.

1784. Caraway. Dried ripe fruit of *Carum carvi* L., *Umbelliferae. Habit.* Europe, Central and Western Asia; cultivated in England, Russia, U.S. *Constit.* 3.5-7% volatile and fatty oils; resin, sugar, tannin, mucilage.

USE: As a spice in baking. Pharmaceutic aid (flavor).

1785. Carazolol. [57775-29-8] 1-(9*H*-Carbazol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol; BM-51052; Conducton; Suacron. $C_{18}H_{22}N_2O_2$; mol wt 298.38. C 72.46%, H 7.43%, N 9.39%, O 10.72%. β-Adrenergic blocker. Prepn: H. Leinert *et al.*, **DE 2240599** (1974 to Boehringer, Mann.), *C.A.* **80,** 133455a (1974). Comparative study of cardiac action: W. Bartsch *et al., Arzneimittel-Forsch.* **27,** 1022 (1977). Initial clinico-pharmacological study: E. Chorianopoulos *et al., Herz/Kreislauf* **9,** 965 (1977), *C.A.* **88,** 164460t (1978). Receptor binding studies: G. Kaiser *et al., Arch. Pharmacol.* **305,** 41 (1978); R. B. Innis *et al., Life Sci.* **24,** 2255 (1979). Use in treatment of stress syndrome in pigs: G. Ballarini, F. Guizzardi, *Tierärztl. Umschau* **36,** 171 (1981).

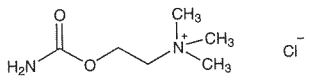


Hydrochloride. $C_{18}H_{23}ClN_2O_2$. Crystals, mp 234-235°.

THERAP CAT: Antihypertensive, antianginal, antiarrhythmic.

THERAP CAT (VET): Treatment of stress in pigs.

1786. Carbachol. [51-83-2] 2-[(Aminocarbonyl)oxy]-*N,N,N*-trimethylethanaminium chloride; (2-hydroxyethyl)trimethyl ammonium chloride carbamate; choline chloride carbamate; carbamylcholine chloride; carbocholine; Doryl; Isopto Carbachol; Jestryl; Miostat. $C_6H_{15}ClN_2O_2$; mol wt 182.65. C 39.46%, H 8.28%, Cl 19.41%, N 15.34%, O 17.52%. Parasympathomimetic. Prepn: O. Dalmer, C. Diehl, **DE 539329** (1930 to E. Merck); *eidem,* **US 1894162** (1933); Kreitmair, *Arch. Exp. Path. Pharmakol.* **164,** 346 (1932); R. D. Haworth *et al., J. Chem. Soc.* **1947,** 176. Toxicity: Molitor, *J. Pharmacol. Exp. Ther.* **58,** 337 (1936). Evaluation in bronchoprovocation test for asthma: G. Rosati *et al., Eur. J. Respir. Dis.* **64,** Suppl. 128, 417 (1983). Clinical effect on post-surgical intraocular pressure: R. S. Ruiz *et al., Am. J. Ophthalmol.* **107,** 7 (1989).

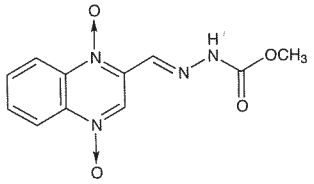


Prismatic crystals from alcohol-ether, mp 207° (Haworth); also reported as mp 204-205° (Kreitmair). Hygroscopic. Odorless or slight amine-like odor. One gram dissolves in 1 ml water, 50 ml alcohol. Practically insol in chloroform, ether. LD_{50} in mice (mg/kg): 15 orally, 0.3 i.v. (Molitor).

THERAP CAT: Cholinergic; miotic.

THERAP CAT (VET): Cholinergic; miotic.

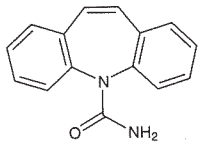
1787. Carbadox. [6804-07-5] (2-Quinoxalinylmethylene)hydrazinecarboxylic acid methyl ester *N,N'*-dioxide; 3-(2-quinoxalinylmethylene)carbazic acid methyl ester *N,N'*-dioxide; methyl 3-(2-quinoxalinylmethylene)carbazate N^1,N^4-dioxide; 2-formylquinoxaline-1,4-dioxide carbomethoxyhydrazone; GS-6244; Fortigro; Mecadox. $C_{11}H_{10}N_4O_4$; mol wt 262.22. C 50.38%, H 3.84%, N 21.37%, O 24.41%. Prepn: Johnston, **BE 669353**; *idem,* **US 3371090**; **US 3433871** (1964, 1968, 1969, all to Pfizer). Animal studies: Thrasher *et al., J. Anim. Sci.* **26,** 911 (1967); Kornegay *et al., ibid.* **27,** 1134 (1968).



Minute yellow crystals, mp 239.5-240°. uv max (water): 236, 251, 303, 366, 373 nm (ε 11000, 10900, 36400, 16100, 16200). Practically insol in water.

THERAP CAT (VET): Antimicrobial.

1788. Carbamazepine. [298-46-4] 5*H*-Dibenz[*b,f*]azepine-5-carboxamide; 5-carbamoyl-5*H*-dibenz[*b,f*]azepine; G-32883; Biston; Calepsin; Carbatrol; Epitol; Finlepsin; Sirtal; Stazepine; Tegretol; Telesmin; Timonil. $C_{15}H_{12}N_2O$; mol wt 236.27. C 76.25%, H 5.12%, N 11.86%, O 6.77%. Prepn: W. Schindler, **US 2948718** (1960 to Geigy). Toxicity: E. G. Stenger, F. C. Roulet, *Med. Exp.* **11,** 191 (1964). Review of GLC methods, pharmacokinetics and metabolism: S. Pynnönen, *Ther. Drug Monit.* **1,** 409-431 (1979). Comprehensive description: H. Y. Aboul-Enein, A. A. Al-Badr, *Anal. Profiles Drug Subs.* **9,** 87-106 (1980). Review of clinical use in pediatric seizures: J. T. Gilman, *DICP Ann. Pharmacother.* **25,** 1109-1112 (1991); in trigeminal neuralgia: A. Sidebottom, S. Maxwell, *J. Clin. Pharm. Ther.* **20,** 31-35 (1995).



Crystals from abs ethanol + benzene, mp 190-193°. Sol in alcohol, acetone, propylene glycol. Practically insol in water. LD_{50} orally in mice, rats: 3750, 4025 mg/kg (Stenger, Roulet).

THERAP CAT: Anticonvulsant. In treatment of pain associated with trigeminal neuralgia.

1789. Carbamide Peroxide. [124-43-6] Urea compd with hydrogen peroxide (1:1); urea hydrogen peroxide; Debrox; Exterol; Gly-Oxide; Hyperol; Ortizon (obsolete). $CH_6N_2O_3$; mol wt 94.07. C 12.77%, H 6.43%, N 29.78%, O 51.02%. $CO(NH_2)_2.H_2O_2$. Prepn: **GB 1555** (1911 to Bayer); M. Strauss, *Chem. Zentr.* **11,** 820 (1913). Use for prepn of H_2O_2: J. Milbauer, *Chem. Ztg.* **35,** 871 (1911), *C.A.* **5,** 3391 (1911). Clinical trial in aphthous stomatitis: M. F. Miller, N. W. Chilton, *Pharmacol. Ther. Dentist.* **5,** 55 (1980); as cerumenolytic: S. Fahmy, M. Whitefield, *Brit. J. Clin. Pract.* **36,** 197 (1982); as dental bleach: V. B. Haywood *et al., J. Am. Dent. Assoc.* **125,** 1219 (1994).

White crystals or cryst powder. Dec in air into urea, oxygen, and water. Sol in 2.5 parts water; partly dec by alcohol and ether into H_2O_2 and urea.

USE: For extemporaneous prepn of H_2O_2.

THERAP CAT: Antiseptic; cerumenolytic; dental bleach.

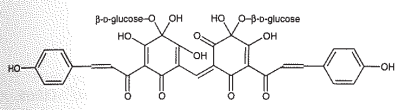
1790. Carbamyl Chloride. [463-72-9] Carbamic chloride; chloroformamide. CH_2ClNO; mol wt 79.49. C 15.11%, H 2.54%, Cl 44.60%, N 17.62%, O 20.13%. H_2NCOCl. Prepd by passing HCl gas over heated cyanuric acid: Gattermann, Rossolymo, *Ber.* **23,** 1190 (1890); Gattermann, *Ber.* **32,** 1117

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 18 of 65

from ethanol, mp 278°. LD_{50} in male mice, rats (mg/kg): 810, 1380 orally; 54.5, 158 i.v.; 380, 400 i.p. (Lang).

THERAP CAT: Antihypertensive, antianginal, antiarrhythmic, antiglaucoma.

1882. Carthamin. [36338-96-2] 6-β-D-Glucopyranosyl-2-[[3-β-D-glucopyranosyl-2,3,4-trihydroxy-5-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl]-6-oxo-1,4-cyclohexadien-1-yl]methylene]-5,6-dihydroxy-4-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl]-4-cyclohexene-1,3-dione; carthamic acid; safflor carmine; safflor red; C.I. Natural Red 26; C.I. 75140. $C_{43}H_{42}O_{22}$; mol wt 910.78. C 56.71%, H 4.65%, O 38.65%. Coloring principle from *Carthamus tinctorius* L., *Compositae* (safflower): Kametaka, Perkin, *J. Chem. Soc.* **97,** 1415 (1910). Extraction: Wada, **JP 55 8943** (1955). Structure: Kuroda, *J. Chem. Soc.* **1930,** 752, 765. Revised structure: H. Obara, J. Onodera, *Chem. Letters* **1979,** 201. Biogenesis: Shimokoriyama, Hattori, *Arch. Biochem. Biophys.* **54,** 93 (1955). *See also: Colour Index* **vol. 4** (3rd ed., 1971) p 4625.



Dark red, granular powder with green luster. Slightly sol in water; sol in dil alkali carbonates, alcohol. Practically insol in ether. Solns rapidly dec.

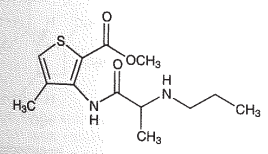
USE: As dye.

1883. Carthamus. Safflower; African saffron; thistle saffron; American saffron; false saffron; bastard saffron; Dyer's saffron. Florets of *Carthamus tinctorius* L. *Compositae. Habit.* Levant; Orient; cultivated extensively in Europe and America. *Constit.* Carthamin, safflor yellow.

USE: In dyeing; surrogate for Spanish saffron; coloring butter, liqueurs, confectionery, cosmetics.

THERAP CAT: Dietary supplement.

1884. Carticaine. [23964-58-1] 4-Methyl-3-[[1-oxo-2-(propylamino)propyl]amino]-2-thiophenecarboxylic acid methyl ester; 3-propylamino-α-propionylamino-2-carbomethoxy-4-methylthiophene; methyl 4-methyl-3-(2-propylaminopropionamido)thiophene-2-carboxylate; articaine. $C_{13}H_{20}N_2O_3S$; mol wt 284.38. C 54.91%, H 7.09%, N 9.85%, O 16.88%, S 11.28%. Prepn: H. Ruschig *et al.,* **ZA 68 04265**; *eidem,* **US 3855243** (1969, 1974 both to Farbwerke Hoechst). Pharmacological studies: R. Muschaweck, R. Rippel, *Prakt. Anaesth.* **9,** 135 (1974); H. Hofer *et al., ibid.* 157; A. Den Hertog, *Eur. J. Pharmacol.* **26,** 175 (1974). Toxicity studies: C. Baeder *et al., Prakt. Anaesth.* **9,** 147 (1974). Mechanism of action: U. Borchard, H. Drouin, *Eur. J. Pharmacol.* **62,** 73 (1980). *Review:* H. Schneider, *Schweiz. Monatsschr. Zahnheilkd.* **86,** 1188-1194 (1976).

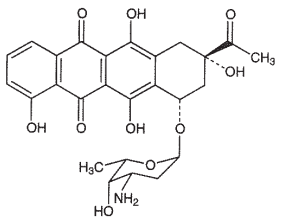


$bp_{0.3}$ 162-167°.

Hydrochloride. [23964-57-0] HOE-045; HOE-40045; Ultracain. $C_{13}H_{20}N_2O_3S.HCl$; mol wt 320.84. White, fine crystals, mp 177-178°. LD_{50} i.v. in mice: 37 mg/kg (Muschaweck, Rippel).

THERAP CAT: Anesthetic (local).

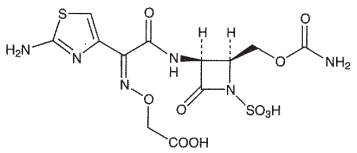
1885. Carubicin. [50935-04-1] (8*S-cis*)-Acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-1,6,8,11-tetrahydroxy-5,12-naphthacenedione; (1*S*,3*S*)-3-acetyl-1,2,3,4,6,11-hexahydro-3,5,10,12-tetrahydroxy-6,11-dioxo-1-naphthacenyl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside; 4-*O*-demethyldaunorubicin; carminomycin; carminomycin I; karminomycin. $C_{26}H_{27}NO_{10}$; mol wt 513.49. C 60.81%, H 5.30%, N 2.73%, O 31.16%. Anthracycline antitumor antibiotic, related to daunorubicin and doxorubicin, *q.q.v.* Isoln from *Actinomadura carminata:* G. F. Gauze *et al., Antibiotiki* **18,** 675 (1973); M. G. Brazhnikova *et al., ibid.* 678. Antitumor activity: V. A. Shorin *et al., ibid.* 681. Physicochemical characteristics, structure: M. G. Brazhnikova *et al., J. Antibiot.* **27,** 254 (1974). Pharmacokinetics, pharmacodynamics, toxicity study: L. E. Goldberg *et al., Antibiotiki* **19,** 57 (1974). Production: M. G. Brazhnikova *et al.,* **SU 508076** (1976 to Inst. Antibiot. Res., USSR), *C.A.* **86,** 15215 (1977). Stereochemistry: *eidem, J. Antibiot.* **29,** 469 (1976). Synthesis from daunomycinone: G. Cassinelli *et al., ibid.* **31,** 178 (1978). Molecular pharmacology: V. H. DuVernay *et al., Cancer Res.* **40,** 387 (1980). Analysis in human serum: S. E. Fandrich, K. A. Pittman, *J. Chromatog.* **223,** 155 (1981). Early clinical studies: L.H. Baker *et al., Cancer Treat. Rep.* **63,** 899 (1979). Embryotoxicity and teratogenicity study: I. Damjanov, A. Celluzzi, *Res. Commun. Chem. Pathol. Pharmacol.* **28,** 497 (1980).



Hydrochloride. [52794-97-5] NSC-180024. $C_{26}H_{27}NO_{10}.HCl$; mol wt 549.96. Crystals from ethanol/benzene. $[\alpha]_D^{20}$ +289°. uv max (ethanol): 236, 255, 462, 478, 492 ($E_{1cm}^{1\%}$ 300), 510, 525 nm. pKa_1 8.00; pKa_2 10.16. Sol in water, methanol. Practically insol in other organic solvents. LD_{50} in mice (mg/kg): 7.3 orally; 1.3 i.v.; 3.7 s.c. (Goldberg).

THERAP CAT: Antineoplastic.

1886. Carumonam. [87638-04-8] [[(*Z*)-[2-[[(2*S*,3*S*)-2-[[(Aminocarbonyl)oxy]methyl]-4-oxo-1-sulfo-3-azetidinyl]amino]-1-(2-amino-4-thiazolyl)-2-oxoethylidene]amino]oxy]acetic acid; *(Z)*-[[[(2-amino-4-thiazolyl)[[(2*S*,3*S*)-2-(hydroxymethyl)-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]methylene]amino]oxy]acetic acid carbamate (ester); (3*S*,4*S*)-*cis*-3-[2-(2-amino-4-thiazolyl)-2-*(Z)*-carboxymethoxyiminoacetamido]-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic acid. $C_{12}H_{14}N_6O_{10}S_2$; mol wt 466.41. C 30.90%, H 3.03%, N 18.02%, O 34.30%, S 13.75%. Synthetic monocyclic β-lactam (monobactam) antibiotic. Prepn: S. Kishimoto *et al.,* **EP 93376**; T. Matsuo *et al.,* **US 4572801** (1983, 1986 both to Takeda); M. Sendai *et al., J. Antibiot.* **38,** 346 (1985). Alternate synthesis: P. S. Manchard *et al., J. Org. Chem.* **53,** 5507 (1988). Comparative *in vitro* antimicrobial activity: R. J. Fass, V. L. Helsel, *Antimicrob. Ag. Chemother.* **28,** 834 (1985); B. R. Smith *et al., ibid.* **29,** 346 (1986); I. M. Hoepelman *et al., Chemotherapy (Basel)* **33,** 103 (1987). β-Lactamase stability: R. L. Then, *ibid.* **30,** 398 (1984). Pharmacokinetics in humans: E. Weidekamm *et al., Antimicrob. Ag. Chemother.* **26,** 898 (1984); C. A. M. McNulty *et al., ibid.* **28,** 425 (1985).

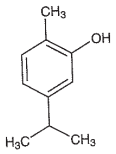


Colorless powder. $[\alpha]_D^{26}$ −45° (c = 1 in DMSO).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 19 of 65

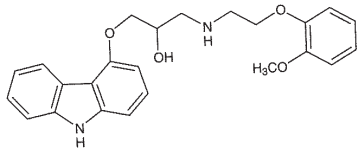
Disodium salt. [86832-68-0] AMA-1080; Ro-17-2301; Amasulin; Mobactam. $C_{12}H_{12}N_6Na_2O_{10}S_2$; mol wt 510.37.
THERAP CAT: Antibacterial.

1887. Carvacrol. [499-75-2] 2-Methyl-5-(1-methylethyl)phenol; 2-*p*-cymenol; 2-hydroxy-*p*-cymene; isopropyl-*o*-cresol; isothymol. $C_{10}H_{14}O$; mol wt 150.22. C 79.95%, H 9.39%, O 10.65%. Found in oil of origanum, thyme, marjoram, summer savory: E. Guenther, *The Essential Oils* **vol. 2** (Van Nostrand, New York, 1949) p 503; Carpenter, Easter, *J. Org. Chem.* **20,** 401 (1955). Prepn by chlorination of α-pinene with *tert*-butyl hypochlorite: Ritter, Ginsburg, *J. Am. Chem. Soc.* **72,** 2381 (1950); from 2-bromo-*p*-cymol: Strubell, Baumgartel, *Arch. Pharm.* **291,** 66 (1958). Toxicity data: Kochmann, *Arch. Exp. Pathol. Pharmakol.* **161,** 196 (1931).



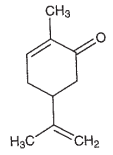
Liquid; thymol odor. d_4^{20} 0.976; d_{25}^{25} 0.9751. bp_{760} 237-238°; bp_{18} 118-122°; bp_3 93°. mp ~ 0°. n_D^{20} 1.52295. uv max (95% ethanol): 277.5 nm (log ε 3.262). Volatile with steam. Practically insol in water. Freely soluble in alc or ether. LD orally in rabbits: 100 mg/kg (Kochmann).
USE: As disinfectant; in organic syntheses.
THERAP CAT: Has been used as anti-infective; anthelmintic (Nematodes).

1888. Carvedilol. [72956-09-3] 1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol; BM-14190; DQ-2466; Coreg; Dilatrend; Dimitone; Eucardic; Kredex; Querto. $C_{24}H_{26}N_2O_4$; mol wt 406.47. C 70.92%, H 6.45%, N 6.89%, O 15.74%. Nonselective β-adrenergic blocker with α_1-blocking activity. Prepn: F. Wiedemann *et al.,* **DE 2815926**; *eidem,* **US 4503067** (1979, 1985 both to Boehringer Mannheim). General pharmacological profile: M. Hirohashi *et al., Arzneimittel-Forsch.* **40,** 735 (1990). HPLC determn in biological fluids: K. Reiff, *J. Chromatog.* **413,** 355 (1987). Series of articles on clinical pharmacology and efficacy in hypertension: *J. Cardiovasc. Pharmacol.* **19,** Suppl. 1, S1-S146 (1992). Clinical trial in chronic heart failure: M. Packer *et al., N. Engl. J. Med.* **334,** 1349 (1996). *Review:* W. H. Frishman, *ibid.* **339,** 1759-1765 (1998).



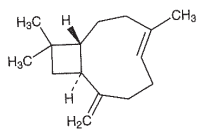
Colorless crystals from ethyl acetate, mp 114-115°. Freely sol in DMSO; sol in methylene chloride, methanol; sparingly sol in ethanol, isopropanol; slightly sol in ethyl ether. Practically insol in water.
THERAP CAT: Antihypertensive; in treatment of congestive heart failure.

1889. Carvone. [99-49-0] 2-Methyl-5-(1-methylethenyl)-2-cyclohexene-1-one; *p*-mentha-6,8-dien-2-one; 1-methyl-4-isopropenyl-Δ^6-cyclohexen-2-one; carvol. $C_{10}H_{14}O$; mol wt 150.22. C 79.95%, H 9.39%, O 10.65%. *d*-Carvone is found in caraway seed and dill seed oils: Schweizer, *J. Prakt. Chem.* **24,** 257 (1841); Gladstone, *J. Chem. Soc.* **25,** 1 (1872). Isoln of *d*-carvone from mandarin peel oil *(Citrus reticulata* Blanco, *Rutaceae):* Kugler, Kováts, *Helv. Chim. Acta* **46,** 1480 (1963). *l*-Carvone is found in spearmint and kuromoji oils: Kwaenick, *Ber.* **24,** 82 (1891). *dl*-Carvone is found in gingergrass oil: Walbaum, Hüthig, *J. Prakt. Chem.* **71,** 459 (1905). Prepn from α-pinene: Booth, Klein, **US 2796428** (1957 to Glidden). Structure: Wagner, *Ber.* **27,** 2270 (1894); Tiemann, Semmler, *ibid.* **28,** 2147 (1895). Synthesis of *l*-carvone: Royals, Horne, *J. Am. Chem. Soc.* **73,** 5856 (1951); Shono *et al., Chem. Letters* **1975,** 4330. Synthesis of *dl*-carvone: Suga, *Bull. Chem. Soc. Japan* **31,** 569 (1958); I. Fleming, I. Patterson, *Synthesis* **1979,** 736. Toxicity study: P. M. Jenner *et al., Food Cosmet. Toxicol.* **2,** 327 (1964). *Review:* J. L. Simonsen, *The Terpenes* **vol. I** (University Press, Cambridge, 2nd ed., 1947) pp 394-408; B. Singaram, J. Verghese, *Perfum. Flavor.* **2,** 47 (1977).

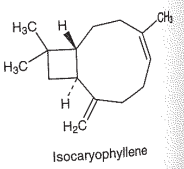


***d*-Form.** Liquid, bp_{755} 230°; $bp_{5\text{-}6}$ 91°. d_4^{20} 0.965. n_D^{20} 1.4989. $[\alpha]_D^{20}$ +61.2°.
***l*-Form.** Liquid, bp_{763} 230-231°. d_{15}^{15} 0.9652. n_D^{20} 1.4988. $[\alpha]_D^{20}$ −62.46°.
***dl*-Form.** Liquid, bp 230-231°. d_{15}^{15} 0.9645. n_D^{20} 1.5003. Practically insol in water. Misc with alc. LD_{50} orally in rats: 1640 mg/kg (Jenner).
USE: As oil of caraway; also for flavoring liqueurs; in perfumery and soaps.
THERAP CAT: Carminative.

1890. Caryophyllene. [87-44-5] [1*R*-(1*R**,4*E*,9*S**)]-4,11,11-Trimethyl-8-methylenebicyclo[7.2.0]undec-4-ene; β-caryophyllene; *trans*-caryophyllene. $C_{15}H_{24}$; mol wt 204.35. C 88.16%, H 11.84%. Sesquiterpenoid occurring in many essential oils and especially in clove oil, the oils from stems and flowers of *Syzygium aromaticum* (L.) Merrill & Perry (*Jambrosa caryophyllus* Niedenzu; *Eugenia caryophyllata* Thunb.), *Myrtaceae.* Occurs in nature as a mixture with isocaryophyllene and α-caryophyllene (humulene, *q.v.*). Isolation of mixture: Schreiner, Kremers, *Pharm. Arch.* **2,** 273, 293 (1899). Existence of isomers: Deussen, *Ann.* **356,** 1 (1907). Structure: Aebi *et al., J. Chem. Soc.* **1953,** 3124; Ramage, Whitehead, *ibid.* **1954,** 4336. Abs config: Barton, Nickon, *ibid.* 4665. Total synthesis of racemic *trans/cis*-forms: Corey *et al., J. Am. Chem. Soc.* **86,** 485 (1964). Rearrangement to isocaryophyllene: Rachlin, DE **2044018** (1971 to I.F.F.), *C.A.* **75,** 49364j (1971). *Reviews:* Simonsen, *The Terpenes* **vol. III** (University Press, Cambridge, 1952) pp 39-71; Barton, de Mayo, *Quart. Rev. (London)* **11,** 197 (1957); Halsall, *ibid.* **16,** 101 (1962).



Caryophyllene

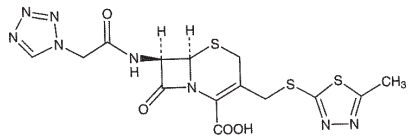


Isocaryophyllene

Liquid. Has a terpene odor about midway between odor of cloves and turpentine. bp_{14} 129-130°; $bp_{9.7}$ 118-119°. $[\alpha]_D^{25}$ −5.2°. n_D^{17} 1.5009; n_D^{15} 1.5030. d_4^{17} 0.9052.
Dihydrochloride. $C_{15}H_{24}.2HCl$. mp 69-70°.
Nitrosochloride. $C_{15}H_{24}.ClNO$. Crystals, dec 159°. $[\alpha]_D^{17}$ −98.07°.
Isocaryophyllene. [118-65-0] γ-Caryophyllene; *cis*-caryophyllene. Liquid. bp_{19} 130°; $bp_{14.5}$ 125-125.5°. $[\alpha]_D^{19}$ −26.17°. n_D^{19} 1.4966. d^{19} 0.8995. When treated with hydrogen chloride gives β-caryophyllene dihydrochloride.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 20 of 65

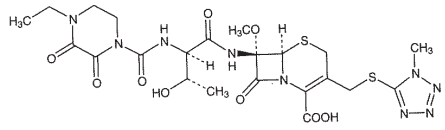
in aq acetone, aq dioxane, aq ethanol; slightly sol in methanol. Practically insol in chloroform, benzene, ether.



Sodium salt. [27164-46-1] Sodium CEZ; SKF-41558; Acef; Ancef; Atirin; Biazolina; Bor-Cefazol; Cefacidal; Cefamedin; Cefamezin; Cefazil; Cefazina; Elzogram; Firmacef; Gramaxin; Kefzol; Lampocef; Liviclina; Totacef; Zolicef. $C_{14}H_{13}N_8NaO_4S_3$; mol wt 476.50. White to yellowish-white, odorless crystalline powder with a bitter, salty taste. Crystallizes in α, β, and γ-forms (Kariyone). Easily sol in water, slightly sol in methanol, ethanol. Practically insol in benzene, acetone, chloroform. LD_{50} in mice, rats (mg/kg): 3.9, 3.18 i.v.; 6.2, 7.4 i.p. (Birkhead).

THERAP CAT: Antibacterial.

1930. Cefbuperazone. [76610-84-9] (6*R*,7*S*)-7-[[(2*R*,-3*S*)-2-[[(4-Ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]-3-hydroxy-1-oxobutyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; (6*R*,7*S*)-7-[(2*R*,3*S*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-3-hydroxybutyramido]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid; 7β-[D-α-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-β-(*S*)-hydroxybutanamido]-7α-methoxy-3-[5-(1-methyl-1,2,3,4-tetrazolyl)thiomethyl]-Δ^3-cephem-4-carboxylic acid. $C_{22}H_{29}N_9O_9S_2$; mol wt 627.66. C 42.10%, H 4.66%, N 20.08%, O 22.94%, S 10.22%. Broad spectrum injectable cephamycin. Prepn: I. Saikawa *et al.*, **BE 879217**; *eidem*, **US 4263292** (1980, 1981 both to Toyama). Distribution of ^{14}C-cefbuperazone in mice: *eidem, Japan. J. Antibiot.* **35,** 2159 (1982), *C.A.* **98,** 11062w (1982). *In vitro* and *in vivo* antibacterial activity: M. Tai *et al., Antimicrob. Ag. Chemother.* **22,** 728 (1982). General pharmacology: A. Takai *et al., Japan. J. Antibiot.* **35,** 2139 (1982), *C.A.* **98,** 65142r (1982). Absorption, distribution, excretion: I. Saikawa *et al., ibid.* 2163, *C.A.* **98,** 100691t (1982). Series of articles on cefbuperazone: *Chemotherapy (Tokyo)* **30,** Suppl. 3 (1982) 986 pp. Stability and degradation studies: S. Takano *et al., Yakugaku Zasshi* **103,** 62 (1983).

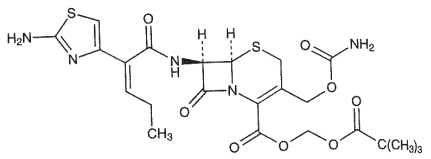


Solid, mp 118-120° (dec).

Sodium salt. [76648-01-6] T-1982; Keiperazon; Tomiporan. $C_{22}H_{28}N_9NaO_9S_2$; mol wt 649.64.

THERAP CAT: Antibacterial.

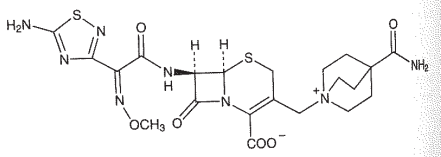
1931. Cefcapene Pivoxil. [105889-45-0] (6*R*,7*R*)-3-[[(Aminocarbonyl)oxy]methyl]-7-[[(2*Z*)-2-(2-amino-4-thiazolyl)-1-oxo-2-pentenyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (2,2-dimethyl-1-oxopropoxy)methyl ester; (6*R*,7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-pentenoylamino]-3-(carbamoyloxymethyl)-3-cephem-4-carboxylic acid pivaloyloxymethyl ester; S-1108; Flumax. $C_{23}H_{29}N_5O_8S_2$; mol wt 567.64. C 48.67%, H 5.15%, N 12.34%, O 22.55%, S 11.30%. Orally absorbed cephalosporin; ester prodrug of the active free acid metabolite, cefcapene. Prepn: Y. Hamashima *et al.*, **BE 904517**; *idem et al.*, **US 4731361** (1986, 1988 both to Shionogi); K. Ishikura *et al., J. Antibiot.* **47,** 466 (1994). *In vitro* activity and stability of the free acid: H. C. Neu *et al., Antimicrob. Ag. Chemother.* **36,** 1336 (1992). Metabolism: K. Totsuka *et al., ibid.* 757. Safety and pharmacokinetics: M. Nakashima *et al., ibid.* 762.



Free acid. [135889-00-8] S-1006. $C_{17}H_{19}N_5O_6S_2$; mol wt 453.50.

THERAP CAT: Antibacterial.

1932. Cefclidin. [105239-91-6] 4-(Aminocarbonyl)-1-[[(6*R*,7*R*)-7-[[(2*Z*)-(5-amino-1,2,4-thiadiazol-3-yl)(methoxyimino)acetyl]amino] - 2 - carboxy - 8 - oxo - 5 - thia - 1 - azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]-1-azoniabicyclo[2.2.2]octane inner salt; (6*R*,7*R*)-3-[(4-carbamoyl-1-quinuclidinio)methyl]-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-(*Z*)-2-methoxyiminoacetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-1-ene-2-carboxylate; (+)-1-[[(6*R*,7*R*)-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-4-carbamoylquinuclidinium hydroxide inner salt 7^2-(*Z*)-(*O*-methyloxime); 7β-[(*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-(4-carbamoyl-1-quinuclidinio)methyl-3-cephem-4-carboxylate; E-1040. $C_{21}H_{26}N_8O_6S_2$; mol wt 550.62. C 45.81%, H 4.76%, N 20.35%, O 17.43%, S 11.65%. Broad spectrum fourth generation cephalosporin antibiotic. Prepn: H. Yamauchi *et al.*, **EP 188255**; *eidem*, **US 4748171** (1986, 1988 both to Eisai). Structure activity study: I. Sugiyama *et al., J. Antibiot.* **45,** 103 (1992). Comparative *in vitro* antibacterial spectrum and β-lactamase resistance: N.-A. Watanabe *et al., Antimicrob. Agents Chemother.* **32,** 693 (1988). *In vivo* antipseudomonal activity: T. Toyosawa *et al., Chemotherapy (Tokyo)* **42,** 1242 (1994). Clinical pharmacokinetics: M. Nakashima *et al., J. Clin. Pharmacol.* **29,** 144 (1989). Toxicity study: K. Ogura *et al., Chemotherapy (Tokyo)* **40,** Suppl. 4, 95 (1992).



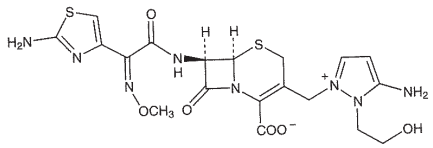
LD_{50} in male, female mice, rats (mg/kg): >10000, >10000, 2236, 2147 i.v.; >10000 both species orally; >10000 both species s.c.; >5000 both species i.m. (Ogura).

THERAP CAT: Antibacterial.

1933. Cefdinir. [91832-40-5] (6*R*,7*R*)-7-[[(2*Z*)-(2-Amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; *syn*-7-[2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid; FK-482; BMY-28488; Omnicef. $C_{14}H_{13}N_5O_5S_2$; mol wt 395.42. C 42.53%, H 3.31%, N 17.71%, O 20.23%, S 16.22%. Cephalosporin antibiotic structurally similar to cefixime, *q.v.* Prepn: T. Takaya *et al.*, **BE 897864**; *eidem*, **US 4559334** (1984, 1985 both to Fujisawa); Y. Inamoto *et al., J. Antibiot.* **41,** 828 (1988). Antibacterial spectrum *in vitro* and *in vivo:* Y. Mine *et al., ibid.* 1873, 1888. Pharmacokinetics in animals: H. Sakamoto *et al., ibid.* 1896. Series of articles on antibacterial activity, pharmacology and clinical efficacy: *Chemotherapy (Tokyo)* **37,** Suppl. 2, 1-1111 (1989).

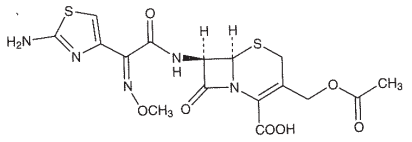
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 21 of 65

aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate; (−)-5-amino-2-[[(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-(2-hydroxyethyl)pyrazolium hydroxide inner salt 7²-(*Z*)-(*O*-methyloxime). $C_{19}H_{22}N_8O_6S_2$; mol wt 522.57. C 43.67%, H 4.24%, N 21.44%, O 18.37%, S 12.27%. Fourth generation cephalosporin antibiotic. Prepn: K. Sakane *et al.*, **EP 307804**; *eidem*, **US 4952578** (1989, 1990 both to Fujisawa); H. Ohki *et al.*, *J. Antibiot.* **46,** 359 (1993). *In vitro* activity and β-lactamase stability: H. C. Neu *et al.*, *Antimicrob. Ag. Chemother.* **37,** 566 (1993). Clinical pharmacokinetics: R. Wise *et al.*, *ibid.* **38,** 2369 (1994). Series of articles on activity, clinical pharmacology and therapeutic efficacy: *Chemotherapy (Tokyo)* **42,** Suppl. 3, 1-464 (1994).



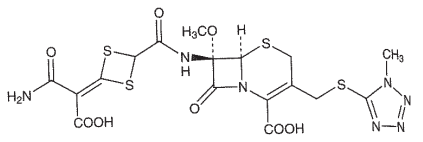
Sulfate. [122841-12-7] FK-037; Wincef. $C_{19}H_{22}N_8O_6S_2.H_2SO_4$; mol wt 620.64.
THERAP CAT: Antibacterial.

1946. Cefotaxime. [63527-52-6] (6*R*,7*R*)-3-[(Acetyloxy)methyl]-7-[[(2*Z*)-(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; (6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 7²-(*Z*)-(*O*-methyloxime) acetate; 7-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]cephalosporanic acid. $C_{16}H_{17}N_5O_7S_2$; mol wt 455.47. C 42.19%, H 3.76%, N 15.38%, O 24.59%, S 14.08%. Broad spectrum third generation cephalosporin antibiotic. The name cefotaxime applies to the isomer having a *syn*-methoxyimino group. Prepn (unspecified stereochemistry): M. Ochiai *et al.*, **DE 2556736**; *eidem*, **US 4098888** (1976, 1978 both to Takeda); *syn*-isomer: R. Heymes, A. Lutz, **DE 2702501**; *eidem*, **US 4152432** (1977, 1979 both to Roussel-UCLAF). Antibacterial activity: R. Wise, *Antimicrob. Ag. Chemother.* **14,** 807 (1978); H. W. Van handuyt, M. Pyckavet, *ibid.* **16,** 109 (1979). Human pharmacology: R. Lüthy *et al.*, *ibid.* 127. Symposia: *Drug Therapy* **Suppl.,** 1-108 (Jan. 1981); *Rev. Infect. Dis.* **4,** Suppl., S281-S488 (1982); *Diagn. Microbiol. Infect. Dis.* **2**(3), Suppl., 1S-92S (1984); *Infection* **13,** Suppl. 1, S1-S162 (1985). Comprehensive description: F. J. Muhtadi, M. M. A. Hassan, *Anal. Profiles Drug Subs.* **11,** 139-168 (1982). Series of articles on clinical efficacy: *J. Antimicrob. Chemother.* **26,** Suppl. A, 1-83 (1990).



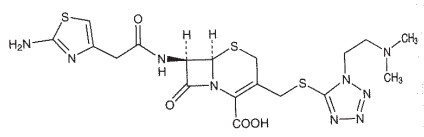
Sodium salt (*syn*-isomer). [64485-93-4] HR-756; RU-24756; Cefotax; Chemcef; Claforan; Pretor; Tolycar. $C_{16}H_{16}N_5NaO_7S_2$; mol wt 477.45. $[\alpha]_D^{20}$ +55±2° (c = 0.8 in water).
THERAP CAT: Antibacterial.

1947. Cefotetan. [69712-56-7] (6*R*,7*S*)-7-[[[4-(2-Amino-1-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; (6*R*,7*S*)-7-[4-(carbamoylcarboxymethylene)-1,3-dithietane-2-carboxamido]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. $C_{17}H_{17}N_7O_8S_4$; mol wt 575.62. C 35.47%, H 2.98%, N 17.03%, O 22.24%, S 22.28%. Broad-spectrum injectable semi-synthetic antibiotic derived from cephamycin C, *q.v.* Prepn: M. Iwanami *et al.*, **DE 2824559**; *eidem*, **US 4263432** (1979, 1981 both to Yamanouchi); *eidem*, *Chem. Pharm. Bull.* **28,** 2629 (1980). *In vitro* comparison of antibacterial activity: B. Chattopadhyay, J. C. Teli, *J. Antimicrob. Chemother.* **10,** 151 (1982). Toxicity study: K. Imamura *et al.*, *Chemotherapy (Tokyo)* **30,** Suppl. 1, 212 (1982). Series of articles on pharmacology, clinical studies, toxicology: *ibid.* 1-947; *J. Antimicrob. Chemother.* **11,** Suppl. A, 1-236 (1983). Review of antibacterial activity, pharmacokinetics, therapeutic use: A. Ward, D. M. Richards, *Drugs* **30,** 382-426 (1985).



Disodium salt. [74356-00-6] ICI-156834; YM-09330; Apatef; Cefotan; Ceftenon; Cepan; Darvilen. $C_{17}H_{15}N_7Na_2O_8S_4$; mol wt 619.59. LD_{50} in male mice, rats (g/kg): 6.35, 8.48 i.v.; 8.12, 8.37 i.p.; >10 orally and s.c. both species (Imamura).
THERAP CAT: Antibacterial.

1948. Cefotiam. [61622-34-2] (6*R*,7*R*)-7-[[(2-Amino-4-thiazolyl)acetyl]amino]-3-[[[1-[2-(dimethylamino)ethyl]-1*H*-tetrazol-5-yl]-thio]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid; 7β-[2-(aminothiazol-4-yl)-acetamido]-3-[[[1-(2-dimethylaminoethyl)-1*H*-tetrazol-5-yl]-thio]methyl]ceph-3-em-4-carboxylic acid; SCE-963. $C_{18}H_{23}N_9O_4S_3$; mol wt 525.64. C 41.13%, H 4.41%, N 23.98%, O 12.17%, S 18.30%. Semi-synthetic cephalosporin antibiotic. Prepn: S. Terao *et al.*, **DE 2458695**; M. Numata *et al.*, **US 4080498** (1975, 1978 both to Takeda); *eidem*, *J. Antibiot.* **31,** 1262 (1978). Prepn of the crystalline dihydrochloride: K. Naito *et al.*, **DE 2738711**; *eidem*, **US 4146710** (1978, 1979 both to Takeda). Pharmacodynamics: K. Tsuchiya *et al.*, *ibid.*, 1272. Antibacterial spectrum: *eidem*, *Antimicrob. Ag. Chemother.* **14,** 557 (1978). Clinical trial in respiratory infections: H. M. Beumer *et al.*, *Int. J. Clin. Pharmacol. Ther. Toxicol.* **23,** 105 (1985).



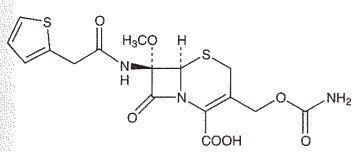
Dihydrochloride. [66309-69-1] Abbott 48999; CGP-14221/E; Halospor; Pansporin; Pansporine; Spizef; Sporidyn. $C_{18}H_{23}N_9O_4S_3.2HCl$; mol wt 598.56. White to light yellow crystals. Sol in methanol. Slightly sol in ethanol.

1-(Cyclohexyloxycarbonyloxy)ethyl ester dihydrochloride. [95789-30-3] Cefotiam hexetil hydrochloride; SCE-2174; Pansporin T; Taketiam; Texodil. $C_{27}H_{37}N_9O_7S_3.2HCl$; mol wt 768.77. Prepn: T. Nishimura *et al.*, **EP 128029**; *eidem*, **US 5120841** (1984, 1992 both to Takeda); *eidem et al.*, *J. Antibiot.* **40,** 81 (1987). Acute toxicity: S. Chiba *et al.*, *Oyo Yakuri* **35,** 179 (1988), *C.A.* **109,** 31615c (1988). Clinical trial: H. Maier *et al. Arzneimittel-Forsch.* **42,** 980 (1992). Colorless powder. Soly in water at pH 4.5: >1 mg/ml. LD_{50} in male, female mice, male, female rats (mg/kg): 1290, 1150, 1470, 1620 i.p.; >2000 s.c.; >5000 orally (Chiba).
THERAP CAT: Antibacterial.

1949. Cefoxitin. [35607-66-0] (6*R*,7*S*)-3-[[(Aminocarbonyl)oxy]methyl]-7-methoxy-8-oxo-7-[(2-thienylacetyl)-amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 22 of 65

3-(hydroxymethyl)-7-methoxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate (ester); 3-carbamoyloxymethyl-7α-methoxy-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylic acid. $C_{16}H_{17}N_3O_7S_2$; mol wt 427.46. C 44.96%, H 4.01%, N 9.83%, O 26.20%, S 15.00%. Semi-synthetic antibiotic derived from cephamycin C, *q.v.*, possessing high resistance to β-lactamase inactivation. Synthesis: B. G. Christensen *et al.*, **DE 2129675**; **DE 2203653**; *eidem*, **US 4297488** (1971, 1972, 1981 all to Merck & Co.); Karady *et al., J. Am. Chem. Soc.* **94,** 1410 (1972); Ratcliffe, Christensen, *Tetrahedron Letters* **1973,** 4653. Biological evaluation: Wallick, Hendlin, *Antimicrob. Ag. Chemother.* **5,** 25 (1974); Miller *et al., ibid.* 33; Onishi *et al., ibid.* 38; Hamilton, Miller *et al., J. Antibiot.* **27,** 42 (1974). Mode of action: Onishi *et al., Ann. N.Y. Acad. Sci.* **235,** 406 (1974). Toxicity: S. Takayama *et al., Chemotherapy (Tokyo)* **26,** Suppl. 1, 150 (1978). Comprehensive reviews: *J. Antimicrob. Chemother.* **4,** Suppl. B, 1-256 (1978); R. N. Brogden *et al., Drugs* **17,** 1-37 (1979); E. O. Stapley, K. R. Brown, in *Pharmacological and Biochemical Properties of Drug Substances* **vol. 3,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1981) pp 262-290. Comprehensive description: G. S. Brenner, *Anal. Profiles Drug Subs.* **11,** 169-195 (1982). Symposium on therapeutic use in anaerobic and aerobic infectons: *Hospital Practice* **25,** Suppl. 4, 1-56 (1990).

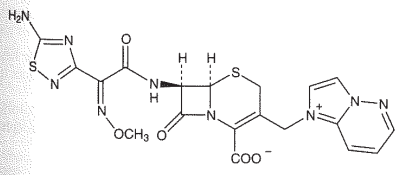


Crystals, mp 149-150° (dec). pKa 2.2. Very sol in acetone; sol in aq $NaHCO_3$; very slightly sol in water. Practically insol in ether and chloroform.

Sodium salt. [33564-30-6] MK-306; Betacef; Farmoxin; Mefoxin; Mefoxitin; Merxin; Cenomycin. $C_{16}H_{16}N_3NaO_7S_2$; mol wt 449.44. White crystals with characteristic odor. $[\alpha]^{25}_{589nm}$ +210° (c = 1 in methanol). Very sol in water; sol in methanol; sparingly sol in ethanol and acetone. Insol in aromatic and aliphatic hydrocarbons. LD_{50} in mice, rats, dogs (g/kg): 5.10, 8.98, >10.0 i.v. (Takayama).

THERAP CAT: Antibacterial.

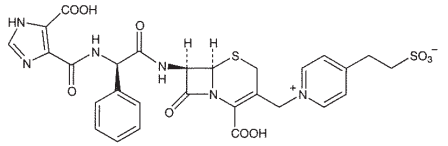
1950. Cefozopran. [113359-04-9] 1-[[(6*R*,7*R*)-7-[[(2*Z*)-(5-Amino-1,2,4-thiadiazol-3-yl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]imidazo[1,2-b]pyridazinium inner salt; 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-methoxyiminoacetamido]-3-[(imidazo[1,2-*b*]pyridazinium-1-yl)methyl]-3-cephem-4-carboxylate. $C_{19}H_{17}N_9O_5S_2$; mol wt 515.53. C 44.27%, H 3.32%, N 24.45%, O 15.52%, S 12.44%. Prepn: A. Miyake *et al.*, **WO 8605183**; *eidem*, **US 4864022** (1986, 1989 both to Takeda); A. Miyake *et al., J. Antibiot.* **45,** 709 (1992). Antibacterial spectrum: T. Iwahi *et al., Antimicrob. Ag. Chemother.* **36,** 1358 (1992). *In vivo* activity: Y. Iizawa *et al., ibid.* **37,** 100 (1993). Pharmacokinetics: W. Paulfeuerborn *et al., ibid.* 1835. HPLC determn in serum and urine: K. Borner, E. Borner, *J. Chromatog.* **615,** 174 (1993).



Hydrochloride. SCE-2787; Firstcin. $C_{19}H_{17}N_9O_5S_2.HCl$; mol wt 551.99.

THERAP CAT: Antibacterial.

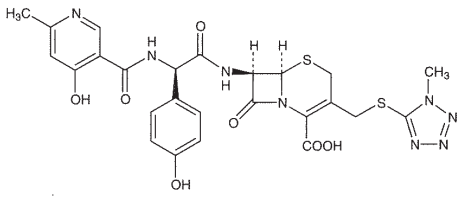
1951. Cefpimizole. [84880-03-5] 1-[[(6*R*,7*R*)-2-Carboxy-7-[[(2*R*)-[[(5-carboxy-1H-imidazol-4-yl)carbonyl]-amino]phenylacetyl]amino]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]-4-(2-sulfoethyl)pyridinium inner salt; 1-[(6*R*,7*R*)-2-carboxy-7-[(*R*)-2-(5-carboxy-4-imidazolyl-carboxamido)-2-phenylacetamido]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-ylmethyl]pyridino-4-ethylsulfonate; 7-β-[D-(−)-α-(4-carboxyimidazole-5-carboxamido)phenylacetamido]-3-(4-β-sulfoethylpyridinium)methyl-3-cephem-4-carboxylic acid; U-63196; AC-1370. $C_{28}H_{26}N_6O_{10}S_2$; mol wt 670.68. C 50.14%, H 3.91%, N 12.53%, O 23.85%, S 9.56%. Third generation injectable cephalosporin antibiotic. Prepn: N. Yasuda *et al.*, **DE 2826546**; *eidem*, **US 4217450** (1979, 1980 both to Ajinomoto); N. Yasuda *et al., J. Antibiot.* **36,** 242 (1983). *In vitro* antibacterial activity and β-lactamase stability: H. C. Neu, P. Labthavikul, *Antimicrob. Ag. Chemother.* **24,** 375 (1983). Potentiating effect on phagocyte functions: H. Ohnishi *et al., ibid.* **23,** 874 (1983). Toxicity study: S. Hashimoto *et al., Toxicol. Letters* **23,** 135 (1984). Therapeutic efficacy in mice: Y. Obana *et al., J. Antimicrob. Chemother.* **16,** 727 (1985). HPLC determn in human plasma and urine: D. B. Lakings, J. M. Wozniak, *J. Chromatog.* **308,** 261 (1984). Pharmacokinetics in humans: D. B. Lakings *et al., Antimicrob. Ag. Chemother.* **29,** 271 (1986). Efficacy and tolerance in gonorrhea in men: E. T. Sandberg *et al., ibid.* 849.



Monosodium salt. [85287-61-2] U-63196E; Ajicef; Renilan. $C_{28}H_{25}N_6NaO_{10}S_2$; mol wt 692.66. $[\alpha]_D^{20}$ −28.2° (c = 0.5 in water). uv max (water): 257 nm (ε 22400). Sol in water. LD_{50} in male, female mice, male, female rats (g/kg): 2.7, 2.9, 4.2, 3.5 i.v.; 8.2, 6.8, 12.2, 11.5 s.c.; all >15.0 orally (Hashimoto).

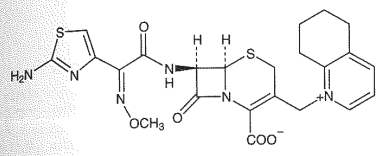
THERAP CAT: Antibacterial.

1952. Cefpiramide. [70797-11-4] (6*R*,7*R*)-7-[[(2*R*)-[[(4-Hydroxy-6-methyl-3-pyridinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; 7-[(*R*)-2-(4-hydroxy-6-methylnicotinamido)-2-(*p*-hydroxyphenyl)acetamido]-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; D-7-[(4-hydroxy-6-methylnicotinamido)-4-hydroxyphenylacetamido]-3-(1-methyltetrazol-5-yl)thiomethylcephem-4-carboxylic acid. $C_{25}H_{24}N_8O_7S_2$; mol wt 612.65. C 49.01%, H 3.95%, N 18.29%, O 18.28%, S 10.47%. Broad spectrum semi-synthetic cephalosporin antibiotic. Prepn: H. Yamada *et al.*, **BE 833063**; *eidem*, **US 4156724**; **US 4160087** (1975, 1979, 1979 all to Sumitomo); *eidem*, **JP Kokai 79 119497** (1979 to Sumitomo), *C.A.* **92,** 11042j (1980); I. Isaka *et al.*, **JP Kokai 79 30197** (1979 to Yamanouchi), *C.A.* **91,** 57037a (1979); **JP Kokai 84 65094** (1984 to Sumitomo), *C.A.* **101,** 110641w (1984). Prepn, NMR data, antibacterial activity: H. Yamada *et al., J. Antibiot.* **36,** 522, 543 (1983). Pharmacokinetics: H.



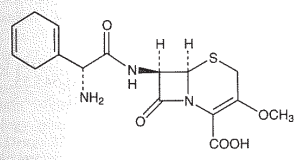
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 23 of 65

yl]-5,6,7,8-tetrahydroquinolinium inner salt; HOE-111. $C_{23}H_{24}N_6O_5S_2$; mol wt 528.61. C 52.26%, H 4.58%, N 15.90%, O 15.13%, S 12.13%. Broad-spectrum fourth generation injectable aminothiazolyl cephalosporin. Prepn: **BE 893163**; R. Lattrell *et al.*, **US 5071979** (1982, 1991 both to Hoechst); R. F. Brown *et al., J. Med. Chem.* **33,** 2114 (1990). Antibacterial spectrum and pharmacokinetics in animals: M. Limbert *et al., Antimicrob. Ag. Chemother.* **35,** 14 (1991). *In vitro* activity against bovine bacterial isolates: A. Böttner *et al., J. Vet. Med. B.* **42,** 377 (1995). Efficacy in the treatment of mastitis in dairy cows: N. Y. Shpigel *et al., J. Dairy Sci.* **80,** 318 (1997).



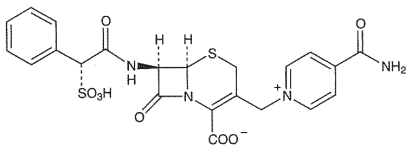
Sulfate. [118443-89-3] HR-111V; Cobactan. $C_{23}H_{24}N_6O_5S_2.H_2SO_4$; mol wt 626.69.
THERAP CAT (VET): Antibacterial.

1957. Cefroxadine. [51762-05-1] (6*R*,7*R*)-7-[[(2*R*)-Amino-1,4-cyclohexadien-1-ylacetyl]amino]-3-methoxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; 7-[D-2-amino-2-(1,4-cyclohexadienyl)acetamide]-3-methoxy-3-cephem-4-carboxylic acid; CGP-9000; Oraspor. $C_{16}H_{19}N_3O_5S$; mol wt 365.41. C 52.59%, H 5.24%, N 11.50%, O 21.89%, S 8.78%. Orally active cephalosporin deriv. Prepn: R. Scartazzini, H. Bickel, **DE 2331133**; *eidem,* **US 4073902** (1974, 1978 both to Ciba-Geigy). Antibiotic activity: O. Zak *et al., J. Antibiot.* **29,** 653 (1976). *In vivo* and *in vitro* microbiological evaluation: K. Yasuda *et al., Antimicrob. Ag. Chemother.* **18,** 105 (1980). Pharmacokinetics: T. Bergan, *Chemotherapy* **26,** 225 (1980). Series of articles on activity, toxicity, reproduction studies: *Chemotherapy (Tokyo)* **28,** Suppl 3, 1-335 (1980).



Internal salt, mp 170° (dec.). $[\alpha]_D^{20}$ +87° (c = 1.093 in 0.1*N* HCl). uv max (0.1*N* HCl): 267 nm (ε 6100). LD_{50} in mice (mg/kg): >6000 orally; 7090 i.p. (Scartazzini, Bickel, 1978).
THERAP CAT: Antibacterial.

1958. Cefsulodin. [62587-73-9] 4-(Aminocarbonyl)-1-[[(6*R*,7*R*)-2-carboxy-8-oxo-7-[[(2*R*)-phenylsulfoacetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium inner salt; 7-(α-sulphophenylacetamido)-3-(4′-carbamoylpyridinium)methyl-3-cephem-4-carboxylic acid. $C_{22}H_{20}N_4O_8S_2$; mol wt 532.55. C 49.62%, H 3.79%, N 10.52%, O 24.03%, S 12.04%. Third generation cephalosporin antibiotic. Prepn: S. Morimoto *et al.,* **DE 2234280**; *eidem,* **US 4065619** (1973, 1977 both to Takeda). Prepn and separation of isomers: H. Nomura *et al., J. Med. Chem.* **17,** 1312 (1974). *In vitro* and *in vivo* antibacterial activity: K. Tsuchiya *et al., Antimicrob. Ag. Chemother.* **13,** 137 (1978). Absorption, distribution, excretion in mice, rats, dogs: *eidem, J. Antibiot.* **31,** 593 (1978). Activity and susceptibility to β-lactamases: A. King *et al., Antimicrob. Ag. Chemother.* **17,** 165 (1980). *In vitro* comparison with other antibacterials: H. Grimm, *Arzneimittel-Forsch.* **30,** 1478 (1980). Clinical pharmacology: J. Fuellhaas *et al., Curr. Chemother., Proc. 10th Int. Congr. Chemother.* (Washington, D.C., 1978) **2,** 848-851. Review of activity: H. C. Neu, B. E. Scully, *Rev. Infec. Dis.* **6,** Suppl. 3, S667-S677 (1984). *Review:* A. Bryskier, *Lyon Pharm.* **34,** 343-355 (1983); D. B. Wright, *Drug Intell. Clin. Pharm.* **20,** 845-849 (1986).

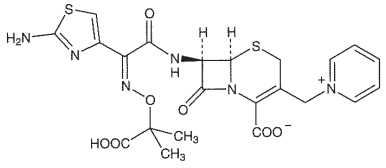


Sodium salt. [52152-93-9] Sulcephalosporin; Abbott 46811; CGP-7174/E; SCE-129; Cefomonil; Monaspor; Pseudomonil; Pseudocef; Pyocefal; Takesulin; Tilmapor; Ulfaret. $C_{22}H_{19}N_4NaO_8S_2$; mol wt 554.53. Colorless needles from ethanol/water, mp 175° (dec). LD_{50} in mice (mg/kg): >4000 i.p.; >15000 orally (Bryskier).

***d*-Form sodium salt.** $[\alpha]_D^{23}$ +16.5° (c = 1.08 in water). uv max (water): 263 nm (ε 14600).

***l*-Form sodium salt.** $[\alpha]_D^{23}$ −16.8° (c = 1.01 in water).
THERAP CAT: Antibacterial.

1959. Ceftazidime. [72558-82-8] 1-[[(6*R*,7*R*)-7-[[(2*Z*)-(2-Amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium inner salt; 1-[[(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium hydroxide inner salt 7^2-(*Z*)-[*O*-(1-carboxy-1-methylethyl)oxime]; GR-20263. $C_{22}H_{22}N_6O_7S_2$; mol wt 546.58. C 48.34%, H 4.06%, N 15.38%, O 20.49%, S 11.73%. Third generation cephalosporin antibiotic. Prepn: C. H. O'Callaghan *et al.,* **DE 2921316**; *eidem,* **US 4258041** (1979, 1981 both to Glaxo). Prepn of crystalline pentahydrate: A. Brodie, L. A. Wetherill, **DE 3037102**; *eidem,* **US 4329453** (1981, 1982 both to Glaxo). Chemical and antibacterial properties: *eidem, Antimicrob. Ag. Chemother.* **17,** 876 (1980). Activity vs. *Pseudomonas* and *Enterobacteriaceae:* L. Verbist, J. Verhaegen, *ibid.* 807. *In vitro* comparison with other β-lactams: R. Wise *et al., ibid.* 884; L. Verbist, *ibid.* **19,** 407 (1981). Symposium on clinical studies: *J. Antimicrob. Chemother.* **12,** Suppl. A, 1-414 (1983). Review of antibacterial activity, pharmacokinetics and therapeutic use: D. M. Richards, R. N. Brogden, *Drugs* **29,** 105-161 (1985). Comprehensive description: M. A. Abounassif *et al., Anal. Profiles Drug Subs.* **19,** 95-121 (1990).

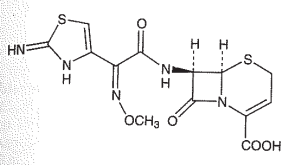


Pentahydrate. [78439-06-2] Fortam; Fortaz; Fortum; Fortumset; Glazidim; Kefadim; Kefamin; Kefazim; Modacin; Panzid; Spectrum; Starcef; Tazicef; Tazidime. $C_{22}H_{22}N_6O_7S_2.5H_2O$; mol wt 636.66. Crystalline solid. uv max (pH 6): 257 nm ($E^{1\%}_{1cm}$ 348).
THERAP CAT: Antibacterial.

1960. Cefteram. [82547-58-8] (6*R*,7*R*)-7-[[(2*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[(5-methyl-2*H*-tetrazol-2-yl)methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid; (+)-(6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-[(5-methyl-2*H*-tetrazol-2-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; 7-[2-(2-aminothiazol-4-yl)-2-*syn*-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazolyl)-methyl]-Δ^3-cephem-4-carboxylic acid; (+)-(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-[(5-methyl-2*H*-

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 24 of 65

Arzneimittel-Forsch. **30,** 1662-1687 (1980). Toxicity and reproduction studies: K. Fukuhara *et al., ibid.* 1669. Phase I clinical study: N. Nakashima *et al., J. Clin. Pharmacol.* **21,** 388 (1981). *Reviews: J. Antimicrob. Chemother.* **10,** Suppl. C, 1-355 (1982); D. M. Richards, R. C. Heel, *Drugs* **29,** 281-329 (1985).

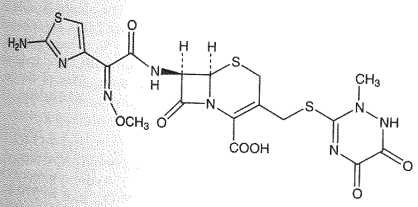


Crystals, mp 227° (dec).

Sodium salt. [68401-82-1] FK-749; FR-13479; SKF-88373; Cefizox; Ceftix; Ceftizon; Epocelin; Eposerin. $C_{13}H_{12}N_5NaO_5S_2$; mol wt 405.39. LD_{50} in mice, rats (mg/kg): ~6000 i.v. (Fukuhara).

THERAP CAT: Antibacterial.

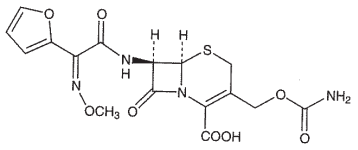
1965. Ceftriaxone. [73384-59-5] (6*R*,7*R*)-7-[[(2*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)-thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; (6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-*as*-triazin-3-yl)thio]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 7^2-(*Z*)-(*O*-methyloxime); cefatriaxone. $C_{18}H_{18}N_8O_7S_3$; mol wt 554.59. C 38.98%, H 3.27%, N 20.21%, O 20.19%, S 17.35%. Parenteral third generation cephalosporin antibiotic. Prepn: M. Montavon, R. Reiner, **GB 2022090**; *eidem,* **US 4327210** (1979, 1982 both to Hoffmann-La Roche); R. Reiner *et al., J. Antibiot.* **33,** 783 (1980). *In vitro* and *in vivo* studies: P. Angehrn *et al., Antimicrob. Ag. Chemother.* **18,** 913 (1980). Pharmacokinetics: M. Seddon *et al., ibid.* 240. Determn in plasma, urine, bile: K. H. Trautmann, P. Haefelfinger, *J. High Resolut. Chromatogr. Chromatogr. Commun.* **4,** 54 (1981), *C.A.* **94,** 202437 (1981). Mechanism of action study: R. B. Wright *et al., J. Antibiot.* **34,** 590 (1981). Kinetics in humans: K. Stoekel *et al., Clin. Pharmacol. Ther.* **29,** 650 (1981). Toxicity data: K. Teelman *et al.,* "Experimentelle Toxikologie von Ceftriaxon", in *Ceftriaxon ein neues parenterales Cephalosporin,* Proc. Hahnenklee Symp., 1981, R. Grieshalber, Ed. (Editiones Roche, Basel, 1982) pp 91-111. Review of antibacterial activity, toxicology, pharmacology and clinical studies: D. M. Richards *et al., Drugs* **27,** 469 (1984); T. R. Beam, *Pharmacotherapy* **5,** 237-253 (1985).



Disodium salt hemiheptahydrate. [104376-79-6] Ro-13-9904/001; Rocefin; Rocephin(e). $C_{18}H_{16}N_8Na_2O_7S_3.3½H_2O$; mol wt 661.60. White cryst powder, mp >155° (dec). $[\alpha]_D^{25}$ −165° (c = 1 in water) (calc for water-free substance). uv max (water): 242, 272 nm (ε 32300, 29530). pKa: ~3 (COOH), 3.2 (NH_3^+), 4.1 (enolic OH). Soly in water at 25°: ~40 g/100 ml. LD_{50} in male, female, mice, rats (mg/kg): 3000, 2800, 2175, 2175 i.v.; >10000 all species orally; >5000 all species s.c. (Teelman).

THERAP CAT: Antibacterial.

1966. Cefuroxime. [55268-75-2] (6*R*,7*R*)-3-[[(Aminocarbonyl)oxy]methyl]-7-[[(2*Z*)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; (6*R*,7*R*)-3-carbamoyloxymethyl-7-[2-(2-furyl)-2-(methoxyimino)acetamido]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid; (6*R*,7*R*)-3-carbamoyloxymethyl-7-[2-(2-furyl)-2-(methoxyimino)acetamido]ceph-3-em-4-carboxylic acid. $C_{16}H_{16}N_4O_8S$; mol wt 424.39. C 45.28%, H 3.80%, N 13.20%, O 30.16%, S 7.56%. Prepn: M. C. Cook *et al.,* **DE 2439880**; *eidem,* **US 3974153** (1973, 1976 both to Glaxo). Prepn of the 1-acetoxyethyl ester: M. Gregson, B. Sykes, **DE 2706413**; *eidem,* **US 4267320** (1977, 1981 both to Glaxo). *In vitro* studies: C. H. O'Callaghan *et al., Antimicrob. Ag. Chemother.* **9,** 511 (1976); R. N. Jones *et al., ibid.* **12,** 47 (1977). *In vitro* antibacterial activity, human pharmacokinetics: C. H. O'Callaghan *et al., J. Antibiot.* **29,** 29 (1976). Pharmacology: H. Freiesleben *et al., Proc. 10th Int. Congr. Chemother.,* Zürich, 1977 (Am. Soc. for Microbiol., Washington, 1978) **II,** pp 873-874. Pharmacokinetics: P. E. Gower, *ibid.* 877-878; J. Kosmidis *et al., ibid.* 875-876. Clinical studies: P. F. Wood *et al., ibid.* 1042-1044; R. Norrby *et al., J. Antimicrob. Chemother.* **3,** 355 (1977). Review of antibacterial activity, pharmacology and therapeutic efficacy: R. N. Brogden *et al., Drugs* **17,** 233-266 (1979). Comprehensive description: T. J. Wozniak, J. R. Hicks, *Anal. Profiles Drug Subs.* **20,** 209-236 (1991).



White crystalline solid. $[\alpha]_D^{20}$ +63.7° (c = 1.0 in 0.2*M* pH 7 phosphate buffer). uv max (pH 6 phosphate buffer): 274 nm (ε 17600).

Sodium salt. [56238-63-2] Anaptivan; Biociclin; Biofurex; Bioxima; Cefamar; Cefoprim; Cefumax; Cefurex; Cefurin; Curocef; Curoxim; Duxima; Gibicef; Ipacef; Kefurox; Kesint; Lampsporin; Medoxim; Novocef; Spectrazole; Ultroxim; Zinacef. $C_{16}H_{15}N_4NaO_8S$; mol wt 446.37. White solid. $[\alpha]_D^{20}$ +60° (c = 0.91 in water). uv max (water): 274 nm (ε 17400). Freely sol in water and buffered solutions; sol in methanol; very slightly sol in ethyl acetate, diethyl ether, octanol, benzene and chloroform. Soly in water: 500 mg/2.5 ml. pKa (water): 2.5; (DMF): 5.1. Solns are stable at room temp for 13 hrs; <10% decompn in 48 hrs at 25° (O'Callaghan, *J. Antibiot.*).

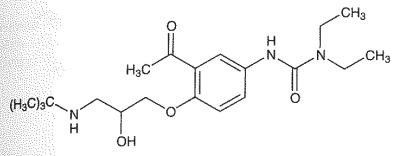
1-Acetoxyethyl ester. Cefuroxime axetil; CCI-15641; Ceftin; Cefurax; Cepazine; Elobact; Oraxim; Zinat; Zinnat. $C_{20}H_{22}N_4O_{10}S$; mol wt 510.48.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

1967. Cefuzonam. [82219-78-1] (6*R*,7*R*)-7-[[(2*Z*)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[(1,2,3-thiadiazol-5-ylthio)methyl]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid; (−)-(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[(1,2,3-thiadiazol-5-ylthio)-methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 7^2-(*Z*)-(*O*-methyloxime); 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid; CL-118523. $C_{16}H_{15}N_7O_5S_4$; mol wt 513.60. C 37.42%, H 2.94%, N 19.09%, O 15.58%, S 24.97%. Semi-synthetic third generation cephalosporin. Prepn and bactericidal activity: W. V. Curran, A. S. Ross, **FR 2488258**; *eidem,* **US 4399132** (1982, 1983 both to Am. Cyanamid); *eidem, J. Antibiot.* **36,** 179 (1983). Improved prepn of sodium salt: K. Naito *et al.,* **EP 145395** (1985 to Takeda). *In vitro* antibacterial spectrum: M. Hikada *et al., J. Antimicrob. Chemother.* **18,** 585 (1986). Toxicity study: S. Takita, *Chemotherapy (Tokyo)* **34,** Suppl. 3, 96 (1986). Conference proceedings: *Recent Adv. Chemother., Antimicrobial Sect. 2., Proc. 14th Int. Congr. Chemother., Kyoto 1985,* J. Ishigami, Ed.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 25 of 65

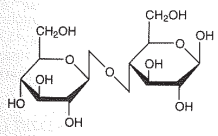


Crystals, mp 110-112°.

Hydrochloride. [57470-78-7] Celectol; Corliprol; Selecor; Selectol. $C_{20}H_{33}N_3O_4$.HCl; mol wt 415.96. White, odorless crystals, mp 197-200° (dec). Soly at ~25°C (g/100 ml): water 15.1, methanol 18.2, ethanol 1.61, chloroform 0.42. uv max (water): 231, 324 nm ($E_{1\%}$ 652, 57); (0.01*N* HCl): 231, 324 nm ($E_{1\%}$ 660, 60); (0.01*N* NaOH): 231, 324 nm ($E_{1\%}$ 640, 60); (methanol): 232, 329 nm ($E_{1\%}$ 775, 58). LD_{50} in male mice, rats (mg/kg): 56.2, 68.3 i.v.; 1834, 3826 orally (Wendtlandt, Pittner).

THERAP CAT: Antihypertensive, antianginal.

1973. Cellobiose. [528-50-7] 4-*O*-β-D-Glucopyranosyl-D-glucose; β-cellobiose; cellose; 4-(β-D-glucosido)-D-glucose. $C_{12}H_{22}O_{11}$; mol wt 342.30. C 42.11%, H 6.48%, O 51.41%. Unit of cellulose and lichenin. Does not occur free in nature, or as glucoside. Prepn from cotton: Braun, *Org. Syn.* **coll. vol. II,** 122, 124 (1943). Prepn from cell-free enzymatic hydrolyzate of cellulose: Whistler, Smart, *J. Am. Chem. Soc.* **75,** 1916 (1953). Structure: Haworth, Hirst, *J. Chem. Soc.* **119,** 193 (1923); Charlton *et al., ibid.* **1926,** 89; Zemplén, *Ber.* **59,** 1254 (1926); Haworth *et al., J. Chem. Soc.* **1927,** 2809; Peterson, Spencer, *J. Am. Chem. Soc.* **49,** 2822 (1927); Helferich *et al., Ber.* **63,** 992 (1930); Hess, Dziengel, *ibid.* **68,** 1594 (1935); Hassid, Ballou in *The Carbohydrates,* W. Pigman, Ed. (Academic Press, New York, 1957) p 490. Synthesis: Haskins *et al., J. Am. Chem. Soc.* **64,** 1289 (1942). *Review:* Pazur in *The Carbohydrates* **vol. 2A,** W. Pigman *et al.,* Eds. (Academic Press, New York, 2nd ed., 1970) pp 109-110; R. G. Edwards, *Dev. Food Carbohyd.* **2,** 229-273 (1980).



Minute crystals from dil alcohol which retain 0.25 to 0.50 mol water after drying in vacuo. Indifferent taste. Dec 225°. Shows mutarotation. $[\alpha]_D^{20}$ +14.2° → +34.6° (15 hrs, c = 8). One gram dissolves in 8 ml water, in 1.5 ml boiling water. Almost insol in abs alc and ether. Reduces Fehling's soln. Hydrolysis with acid or emulsin yields 2 mols β-D-glucose. Not fermented by brewers' yeast, maltase, or invertase.

Octaacetyl-aldehydro-cellobiose. $C_{28}H_{38}O_{19}$; mol wt 678.59. mp 105-110°. $[\alpha]_D^{20}$ +17.7° (c = 3 in chloroform).

Octaacetyl-α-cellobiose. $C_{28}H_{38}O_{19}$; mol wt 678.59. mp 229°. $[\alpha]_D^{20}$ +41° (c = 6 in chloroform).

Octaacetyl-β-cellobiose. mp 202°. $[\alpha]_D^{20}$ −14.7° (c = 5 in chloroform).

1974. Cellocidin. [543-21-5] 2-Butynediamide; acetylenedicarboxamide; acetylenedicarboxylic acid diamide; aquamycin; lenamycin. $C_4H_4N_2O_2$; mol wt 112.09. C 42.86%, H 3.60%, N 24.99%, O 28.55%. $H_2NOC{\equiv}CCONH_2$. Antibiotic substance with antibacterial activity. Produced by *Streptomyces chibaensis* from soil collected at Chiba City, Japan: Suzuki *et al., J. Antibiot.* **11,** 81 (1958). Synthesis from dimethyl acetylenedicarboxylate and concd ammonium hydroxide at −10°: Saggiomo, *J. Org. Chem.* **22,** 1171 (1957); Suzuki, Okuma, *J. Antibiot.* **11,** 84 (1958). Identity with lenamycin: Y. Sekizawa, *Meiji Seika Kenkyu Nempo* **1960,** 42, *C.A.* **56,** 14609a (1962). Biosynthesis: E. R. H. Jones, *J. Chem. Soc. Perkin Trans. I* **1973,** 148.

Crystals from dil methanol, dec. 216-218°. uv max (0.1*N* NaOH): 299 nm ($E_{1cm}^{1\%}$ 290). Sparingly sol in water, methanol, ethanol, acetone, chloroform, glacial acetic acid. Relatively stable in neutral or acid solns, showing no loss of activity at pH 2 to 7 when heated for 10 min at 100°. Unstable in alkaline soln evolving ammonia. LD_{50} i.v. in mice: 11 mg/kg (Suzuki).

1975. Cellophane. Francephane. Transparent, flexible cellulose sheeting made from viscose. The word "cellophane" is not a trademark in the U.S.

1976. Celluloid®. [8050-88-2] Pyralin; Zylonite. Prepd from nitrocellulose and camphor.

Colorless, amorphous mass. *Flammable.* Prone to spontaneous decompn which is retarded or prevented by the addition of urea, ZnO, $MgCO_3$, diphenylamine, etc. It is rendered less flammable by addition of ammonium phosphate. Softens in boiling water; sol in acetone.

USE: Plastic material for manuf of toilet articles, toys, photographic films; substitute for amber, ivory, ebonite, tortoise shell; also in surgery for bandages and in dentistry as substitute for rubber.

1977. Cellulose. [9004-34-6] $(C_6H_{10}O_5)_n$. Polysaccharide with the glucose units linked as in cellobiose. Chief constituent of the fiber of plants; cotton is the purest natural form, contg about 90%. Rayon is regenerated cellulose. Books: C. Dorée, *The Methods of Cellulose Chemistry* (Chapman & Hall, London, 1947); T. Lieser, *Kurzes Lehrbuch der Cellulosechemie* (Gebrüder Borntraeger, Berlin, 1953); S. D. Antonovskii, *Chemistry of Wood and Cellulose* (Vsesoyuz. Zaochnyi Lesotekh Instit., Leningrad, 1954); E. Ott *et al., Cellulose and Cellulose Derivatives,* **vols. 1-3** (Interscience, New York, 1954, 1955). *Reviews:* Several authors in *Encyclopedia of Polymer Science and Technology* **vol. 3,** N. M. Bikales, Ed. (Interscience, New York, 1965) pp 131-539; Shafizadeh, *Pure Appl. Chem.* **35,** 195-208 (1973); A. F. Turbak *et al.* in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 5** (Wiley-Interscience, New York, 3rd ed., 1979) pp 70-89. Comprehensive review on constitution, conformation, size of molecule, fine structure and superstructure: H. Krässig, *Papier (Darmstadt)* **33,** 9-20 (1979). Review of toxicity studies: R. L. Anderson *et al., Cancer Letters* **63,** 83-92 (1992).

White substance. Practically insol in water or other usual solvents. Dissolved by concd soln of zinc chloride, by ammoniacal copper hydroxide soln; also by caustic alkali with carbon disulfide.

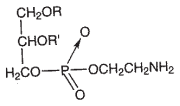
Microcrystalline form. Avicel. Prepn and manuf of crystallite cellulosic aggregates: Battista, *Ind. Eng. Chem.* **42,** 502 (1950); Battista, Smith, **US 2978446** (1961 to Am. Viscose); **US 3141875** (1964 to FMC). Non-fibrous powder. Particle shape: rigid rods. *Refractive index:* 1.55. Bulk density: 18-19 lb/cubic foot. Practically insol, but dispersible in water; practically insol in and resistant to dil acid; practically insol and inert in organic acids. Partially sol with swelling in dil alkali.

Caution: Potential symptoms of overexposure are irritation of eyes, skin, mucous membranes. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 56.

USE: Fibrous form is the basic material for the textile and paper industries. Nitrated it yields nitrocellulose used for manuf of explosives, collodion, lacquers. Basic material also for cellulose acetate, cellulose xanthate. Also used in chromatography and as ion exchange material especially in the form of derivatives such as ***DEAE-cellulose*** (diethylaminoethyl cellulose) and ECTEOLA-cellulose, *q.v.* Microcrystalline forms of cellulose are used as combination binder-disintegrants in tableting, as separatory medium in thin-layer and column chromatography. Colloidal cellulose particles aid in stabilization and emulsification of liquid and foam systems. May be used as pure cellulose raw-material. Incorporation of cellulose crystallite aggregates in foods to reduce caloric content: Battista, **US 3023104** (1962 to American Viscose); also used in food industry as stabilizer, thickener, texturizer.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 26 of 65

1987. Cephalins. Kephalins; phosphatidylethanolamine. Group of phospholipids found in all living organisms. Significant constituent of nervous tissue and brain substance. Cephalins consist of glycerophosphoric acid in which the two free hydroxyls are esterified with long-chain fatty acid residues, and ethanolamine forms an ester linkage with the phosphate group. α-Isomers are derivatives of α-glycerophosphoric acid, *q.v.*; β-isomers are derivatives of β-glycerophosphoric acid, *q.v.* Natural products occur in the α-form, while the β-form is now recognized to be an artifact. Prepn from commercial "soybean lecithin": Scholfield, Dutton, *Biochem. Prepn.* **5,** 5 (1957); **US 2801255** (1957 to USDA). Diagnostic use: C. R. Ratliff *et al., Am. J. Gastroenterol.* **55,** 589 (1971). Reviews on natural and synthetic cephalins: E. Baer in *Progress in the Chemistry of Fats and Other Lipids* **vol. 6,** (MacMillan, New York, 1963) pp 39-44; Van Deenen, de Haas in *Advances in Lipid Research* **vol. 2** (Academic Press, New York, 1964) pp 183-189; Verkade, *Bull. Soc. Chim. France* **1963,** 1993.



R and R' can be, but are not necessarily, identical fatty acids.

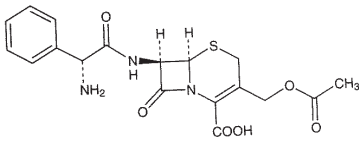
α - Cephalin

Yellowish amorphous substances; characteristic odor and taste. Practically insol in water, acetone. Freely sol in chloroform, ether; slightly sol in ethanol.

USE: Clinical reagent (liver function test).

THERAP CAT: Hemostatic (local).

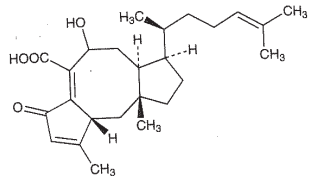
1988. Cephaloglycin. [3577-01-3] (6*R*,7*R*)-3-[(Acetyloxy)methyl]-7-[[(2*R*)-aminophenylacetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; 7-(2-amino-2-phenylacetamido)-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid acetate (ester); 7-(D-2-amino-2-phenylacetamido)-3-acetoxymethyl-Δ^3-cephem-4-carboxylic acid; 7-(D-α-aminophenylacetamido) cephalosporanic acid; Kefglycin. $C_{18}H_{19}N_3O_6S$; mol wt 405.43. C 53.33%, H 4.72%, N 10.36%, O 23.68%, S 7.91%. Semi-synthetic cephalosporin antibiotic. Prepn: **BE 635137**; F. W. Wall *et al.*, **US 3422103** (1964, 1969 both to Glaxo); **GB 1017624** (1966 to Merck & Co.); Spencer *et al., J. Med. Chem.* **9,** 746 (1966); of D- and DL-forms: **GB 985747** (1965 to Lilly); Kurita *et al., J. Antibiot.* **19A,** 243 (1966). Metabolism and pharmacokinetics in man: J. Haginaka *et al., J. Antibiot.* **33,** 236 (1980).



Dihydrate. [22202-75-1] Kafocin. Crystalline powder, mp 223-250° (dec). uv max (2% DMF): 258 nm ($E^{1\%}_{1cm}$ 166). Isoelectric point and pH of maximum stability: 4.5.

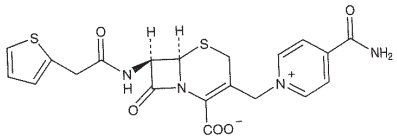
THERAP CAT: Antibacterial.

1989. Cephalonic Acid. [18456-04-7] 8-Hydroxy-5-oxoophiobola-3,6,19-trien-25-oic acid; ophiobolin D. $C_{25}H_{36}O_4$; mol wt 400.55. C 74.96%, H 9.06%, O 15.98%. Minor antibiotic metabolite produced by *Cephalosporium caerulens.* Exhibits weak activity against *Staphylococcus aureus.* Isolation, structure elucidation and physical data: Itai *et al., Tetrahedron Letters* **1967,** 4111; Nozoe *et al., ibid.* 4113. Crystal structure: Itai *et al., Acta Cryst.* **25B,** 872 (1969). Synthetic studies on related compounds: P. C. Dutta, T. K. Das, *Syn. Commun.* **6,** 253 (1976); W. G. Dauben, D. S. Hart, *J. Org. Chem.* **42,** 922 (1977); R. K. Boeckman *et al., ibid.* 3630.



Solid, mp 139°. $[\alpha]_D$ +76.2° (c = 0.54 in chloroform). uv max: 259 nm (ε 11700).

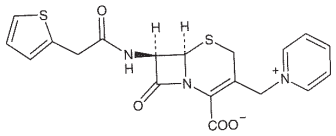
1990. Cephalonium. [5575-21-3] 4-(Aminocarbonyl)-1-[[(6*R*,7*R*)-2-carboxy-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium inner salt; cefalonium; 2-thienylmethyl isonicotinamide cephalosporin C_A; Cepravin Dry Cow. $C_{20}H_{18}N_4O_5S_2$; mol wt 458.52. C 52.39%, H 3.96%, N 12.22%, O 17.45%, S 13.99%. Cephalosporin antibiotic. Prepn: E. H. Flynn, **GB 1067644** (1967 to Lilly); and antibacterial activity: J. L. Spencer *et al., Antimicrob. Agents Chemother.* **1966,** 573. Determn in milk samples: J. E. Hillerton *et al., J. Dairy Sci.* **82,** 704 (1999). Prophylactic use in dry udder infections: R. Curtis *et al., Vet. Rec.* **100,** 557 (1977); in mastitis: J. H. Williamson *et al., N. Z. Vet. J.* **43,** 228 (1995); in combination with a teat sealer: M. W. Woolford *et al., ibid.* **46,** 12 (1998).



Crystals from hot water, mp 147-150° (dec). uv max: 233, 262 nm (ε 16650, 13550). pKa: 3.3.

THERAP CAT (VET): Prophylactic use in mastitis and dry udder therapy.

1991. Cephaloridine. [50-59-9] 1-[[(6*R*,7*R*)-2-Carboxy-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]pyridinium inner salt; 1-[(7′-β-[2-(2-thienyl)acetamido]-8′-oxo-1′-aza-5′-thiabicyclo[4.2.0]oct-2′-en-3′-yl)methyl]pyridinium-2′-carboxylate; *N*-[7-[(2-thienyl)-acetamido]ceph-3-em-3-ylmethyl]pyridinium-4-carboxylate; *N*-[7-(2′-thienylacetamidoceph-3-ylmethyl)]pyridinium-2-carboxylate; cefaloridin; Ceflorin; Cepaloridin; Cer; Faredina; Ceporan; Ceporin; Cilifor; Intrasporin; Keflodin; Keflordin (obsolete); Lloncefal; Sefacin; Cepalorin; Deflorin; Kefspor; Loridine; Ampligram; Floridin. $C_{19}H_{17}N_3O_4S_2$; mol wt 415.49. C 54.93%, H 4.12%, N 10.11%, O 15.40%, S 15.43%. Semi-synthetic cephalosporin antibiotic. Prepn: **FR 1384197** (1965 to Glaxo), *C.A.* **63,** 11591c (1965); E. H. Flynn, **US 3449338** (1969 to Lilly). Toxicity studies: Atkinson *et al., Toxicol. Appl. Pharmacol.* **8,** 398 (1966).



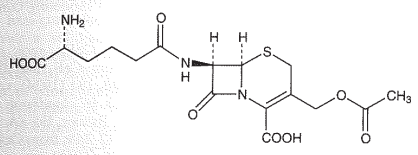
Crystals. Soluble in water. Aq solns are slightly acid (pH 4.5-5); $[\alpha]_D$ +47.7° (c = 1.25 in water). uv max: 239, 252 nm (ε 15160, 13950). pKa 3.2. Aq solns (20% w/v) are stable for four weeks at 4° in the dark. Exposure to sunlight causes discoloration. LD_{50} mice, rats (g/kg): >15, 2.5-4 orally; in monkeys (g/kg): >0.2 i.m. (Atkinson).

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 27 of 65

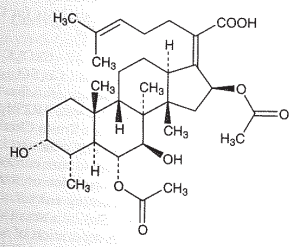
1992. Cephalosporin C. [61-24-5] (6*R*,7*R*)-3-[(Acetyloxy)methyl]-7-[[(5*R*)-5-amino-5-carboxy-1-oxopentyl]-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; 7-(D-5-amino-5-carboxyvaleramido)-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid acetate. $C_{16}H_{21}N_3O_8S$; mol wt 415.42. C 46.26%, H 5.10%, N 10.12%, O 30.81%, S 7.72%. Antibiotic substance produced along with penicillin N by a *Cephalosporium* sp. cultivated from sea water near a sewage outlet on the coast of Sardinia: G. Brotzu, *Lav. Ist. Igiene Cagliari* (1948); Newton, Abraham, *Nature* **175,** 548 (1955); *eidem, Biochem. J.* **62,** 651 (1956); *eidem,* **DE 1014711** (1957 to Natl. Res. Dev. Corp.); **GB 810196** (1959); Kelly *et al.,* **US 3082155** (1963 to Natl. Res. Dev. Corp.); Demain, **US 3116216**; **US 3116217** (both 1963 to Merck & Co.). Biosynthesis: Demain, Newkirk, *Appl. Microbiol.* **10,** 321 (1962). Has the same side chain as penicillin N, but the nucleus is different and is named 7-aminocephalosporanic acid: Jago, Heatley, *Brit. J. Pharmacol.* **16,** 170 (1961). Structure: Abraham, Newton, *Biochem. J.* **79,** 377 (1961); Hodgkin, Maslen, *ibid.* 393. In ***cephalosporin*** C_A the acetoxy group is replaced by a pyridinium group: Hale *et al., ibid.* 403. Transformation to ***cephalosporin*** C_C for which greater activity is claimed: Abraham *et al.,* **US 3049541** (1962 to Natl. Res. Dev. Corp.). Total synthesis: Woodward *et al., J. Am. Chem. Soc.* **88,** 852 (1966). Review of cephalosporin C and related compounds: Abraham, *Quart. Rev. Chem. Soc.* **21,** 231 (1967); Abraham, Loder, in *Cephalosporins and Penicillins,* E. H. Flynn, Ed. (Academic Press, New York, 1972) pp 1-26.



Sodium salt, dihydrate. $C_{16}H_{20}N_3NaO_8S.2H_2O$. Monoclinic crystals from dil alc. $[\alpha]_D^{20}$ +103° (H_2O). uv max: 260 nm ($E_{1cm}^{1\%}$ 200). pKa values: <2.6, 3.1, 9.8. Sol in water. Practically insol in ethanol, ether. Aq solns are stable at pH 2.5 to 8. Low toxicity. Shows *in vitro* activity against penicillin-resistant staphylococci.

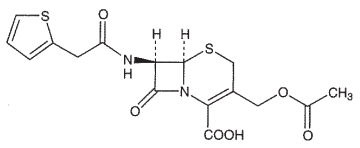
THERAP CAT: Antibacterial.

1993. Cephalosporin P_1. [28393-42-2] (3α,4α,6α,7β,8α,9β,13α,14β,16β,17*Z*)-6,16-Bis(acetyloxy)-3,7-dihydroxy-29-nordammara-17(20),24-dien-21-oic acid. $C_{33}H_{50}O_8$; mol wt 574.74. C 68.96%, H 8.77%, O 22.27%. Antibiotic substance produced by a *Cephalosporium* sp. cultivated from the sea near Sardinia. Crude cephalosporin P contains at least 5 components: P_1, P_2, P_3, P_4, P_5, the major active substance being cephalosporin P_1. Isoln: Burton, Abraham, *Biochem. J.* **50,** 168 (1951). Structure: Baird *et al., Proc. Chem. Soc.* **1961,** 257; Halsall *et al., ibid.* **1963,** 16; Melera, *Experientia* **19,** 565 (1963); Halsall *et al., Chem. Commun.* **1966,** 685.



Orthorhombic crystals from 50% aq ethanol, $C_{33}H_{50}O_8.H_2O.\frac{1}{2}C_2H_5OH$. mp 147°. $[\alpha]_D^{20}$ +28° (c = 2.7 in chloroform). uv max: 211 nm (ε 9140). Readily sol in chloroform and ethanol; sparingly sol in hexane and water.

1994. Cephalothin. [153-61-7] (6*R*,7*R*)-3-[(Acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; 3-(hydroxymethyl)-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid acetate; 7-(2-thienylacetamido)cephalosporanic acid; 7-(thiophene-2-acetamido)cephalosporanic acid. $C_{16}H_{16}N_2O_6S_2$; mol wt 396.44. C 48.48%, H 4.07%, N 7.07%, O 24.21%, S 16.18%. Semi-synthetic cephalosporin antibiotic. Prepn: Chauvette *et al., J. Am. Chem. Soc.* **84,** 3401 (1962); E. H. Flynn, **US 3218318** (1965 to Lilly); **FR 1384197** (1965 to Glaxo), *C.A.* **63,** 11591c (1965). Bacteriology and pharmacology: Lee, Anderson, *Antimicrob. Ag. Chemother.* **1962,** 695; Walters *et al., ibid.* 706; Naumann, *Arzneimittel-Forsch.* **16,** 1099 (1966). Acute toxicity: M. Kuramoto *et al., Japan. J. Antibiot.* **27,** 746 (1974), *C.A.* **83,** 71972t (1975). Comprehensive description: R. J. Simmons, *Anal. Profiles Drug Subs.* **1,** 319-341 (1972).



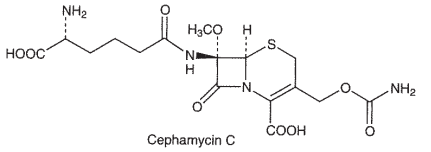
mp 160-160.5°. $[\alpha]_D^{20}$ +50° (c = 1.03 in acetonitrile), *see* R. B. Woodward *et al., J. Am. Chem. Soc.* **88,** 852 (1966).

Sodium salt. [58-71-9] Averon-1; Cefalotin; Cemastin; Cephation; Ceporacin; Cepovenin; Chephalotin; Coaxin; Keflin; Lospoven; Synclotin; Toricelocin. $C_{16}H_{15}N_2NaO_6S_2$; mol wt 418.42. mp 204-205°. $[\alpha]_D$ +135° (c = 1.0 in water). uv max: 236, 260 nm (ε 12950, 9350). LD_{50} in mice, rats (mg/kg): >20000, >10000 orally; 5670, 7716 i.p. (Kuramoto).

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

1995. Cephamycins. A family of β-lactam antibiotics produced by various *Streptomyces* species. Detection and production: Stapley *et al., Antimicrob. Ag. Chemother.* **2,** 122 (1972). Chemical characterization: Miller *et al., ibid.* 132. Cephamycins A, B, and C have been isolated, the latter being identical to a *Streptomyces clavuligerus* metabolite: Nagarajan *et al., J. Am. Chem. Soc.* **93,** 2308 (1971). Structures: Albers-Schoenberg *et al., Tetrahedron Letters* **1972,** 2911. Antibacterial activity studies: Miller *et al., Antimicrob. Ag. Chemother.* **2,** 281, 287 (1972); Daoust *et al., ibid.* **3,** 254 (1973). Review of syntheses: T. Hiraoka *et al., Heterocycles* **8,** 719 (1977).

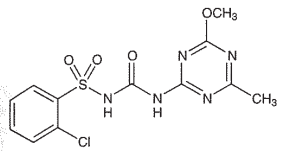


Cephamycin C

1996. Cephapirin Sodium. [24356-60-3] (6*R*,7*R*)-3-[(Acetyloxy)methyl]-8-oxo-7-[[(4-pyridinylthio)acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monosodium salt; 3-(hydroxymethyl)-8-oxo-7-[2-(4-pyridylthio)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid acetate monosodium salt; 7-[α-(4-pyridylthio)acetamido]-cephalosporanic acid sodium salt; sodium 7-(pyrid-4-ylthioacetamido)cephalosporanate; BL-P-1322; Ambrocef; Brisfirina; Bristocef; Cefadyl; Cefa-Lak; Piricef; ToDay. $C_{17}H_{16}N_3NaO_6S_2$; mol wt 445.45. C 45.84%, H 3.62%, N 9.43%, Na 5.16%, O 21.55%, S 14.40%. A cephalosporin C antibiotic effective

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 28 of 65

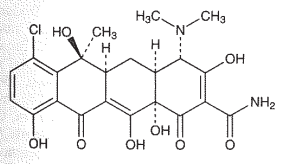
sulfonamide; DPX-4189; Glean; Telar. $C_{12}H_{12}ClN_3O_4S$; mol wt 357.78. C 40.29%, H 3.38%, Cl 9.91%, N 19.57%, O 17.89%, S 8.96%. Selective pre- and post-emergence herbicide. Prepn: G. Levitt, **DE 2715786**; *idem,* **US 4127405** (1977, 1978 both to du Pont). Activity: G. Levitt *et al., J. Agr. Food Chem.* **29,** 416 (1981). Mode of action: T. B. Ray, *Pestic. Biochem. Physiol.* **17,** 10 (1982).



Crystals from ether, mp 174-178°. Soly in water: 125 ppm. Moderately sol in methylene chloride; less sol in acetone, acetonitrile. Low soly in hydrocarbon solvents. LD_{50} in male, female rats (mg/kg): 5545, 6293 orally (Levitt).

USE: Herbicide.

2211. Chlortetracycline. [57-62-5] [4*S*-(4α,4aα,5aα,6β,12aα)]-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide; 7-chlorotetracycline; Acronize; Aureocina; Aureomycin; Biomitsin; Centraureo; Chrysomykine; Orospray. $C_{22}H_{23}ClN_2O_8$; mol wt 478.89. C 55.18%, H 4.84%, Cl 7.40%, N 5.85%, O 26.73%. Antibiotic substance isolated from the substrate of *Streptomyces aureofaciens:* Duggan, *Ann. N.Y. Acad. Sci.* **51,** 177 (1948); **US 2482055** (1949 to Am. Cyanamid); Broschard *et al., Science* **109,** 199 (1949). Structure: Stephens *et al., J. Am. Chem. Soc.* **74,** 4976 (1952); **76,** 3568 (1954). Crystal structure: Donohue *et al., ibid.* **85,** 851 (1963). Absolute configuration: Dobrynin *et al., Tetrahedron Letters* **1962,** 901. Purification: Winterbottom *et al.,* **US 2899422** (1959 to Am. Cyanamid). Improved process: Miller *et al.;* Goodman, **US 2987449**; **US 3050446** (1961, 1962 to Am. Cyanamid). Toxicity: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* **18,** 185 (1971). Comprehensive description: G. Schwartzman *et al., Anal. Profiles Drug Subs.* **8,** 101-137 (1979).



Golden-yellow crystals, mp 168-169°. $[\alpha]_D^{23}$ −275.0° (methanol). uv max (0.1*N* HCl): 230, 262.5, 367.5 nm; (0.1*N* NaOH): 255, 285, 345 nm. Soly in water: 0.5-0.6 mg/ml. Very sol in aq solns above pH 8.5. Freely sol in the Cellosolves, dioxane, and Carbitol. Slightly sol in methanol, ethanol, butanol, acetone, ethyl acetate, benzene. Practically insol in ether, petr ether.

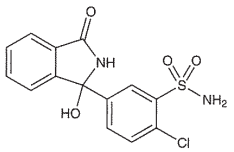
Crystal salt. White powder. Insol in water. Marketed as suspension preserved with methyl and propyl *p*-hydroxybenzoate; stable and fully active for at least one year at room temps.

Hydrochloride. [64-72-2] Aureociclina; Isphamycin. $C_{22}H_{23}ClN_2O_8.HCl$; mol wt 515.35. Bitter, yellow rhomboid crystals. Dec above 210°. $[\alpha]_D^{23}$ −240°. Soly at about 28° (mg/ml): water 8.6; methanol 17.4; ethanol 1.7: Weiss *et al., Antibiot. Chemother.* **7,** 374 (1957). Sol in solns of alkali hydroxides and carbonates. Practically insol in acetone, ether, chloroform, dioxane. pH of satd aq soln 2.8-2.9. LD_{50} orally in rats: 10300 mg/kg (Goldenthal).

THERAP CAT: Antibacterial; antiamebic.

THERAP CAT (VET): Antimicrobial.

2212. Chlorthalidone. [77-36-1] 2-Chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1*H*-isoindol-1-yl)benzenesulfonamide; 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzenesulfonamide; 3-hydroxy-3-(4-chloro-3-sulfamylphenyl)phthalimidine; 2-chloro-5-(3-hydroxy-1-oxoisoindolin-3-yl)benzenesulfonamide; 1-oxo-3-(3-sulfamyl-4-chlorophenyl)-3-hydroxyisoindoline; 3-(4′-chloro-3′-sulfamoylphenyl)-3-hydroxyphthalimidine; 1-keto-3-(3′-sulfamyl-4′-chlorophenyl)-3-hydroxyisoindoline; chlorphthalidolone; phthalamudine; phthalamodine; G-33182; Higroton; Hydro-long; Hygroton; Thalitone. $C_{14}H_{11}ClN_2O_4S$; mol wt 338.77. C 49.64%, H 3.27%, Cl 10.47%, N 8.27%, O 18.89%, S 9.47%. Prepn: Graf *et al., Helv. Chim. Acta* **42,** 1085 (1959); **US 3055904** (1962 to Geigy). Activity and side effects: Holtmeier *et al., Med. Welt* **1967,** 1384; Zsoter *et al., J. Pharmacol. Exp. Ther.* **180,** 723 (1972). Metabolism: Beisenherz *et al., Arch. Int. Pharmacodyn. Ther.* **161,** 76 (1966). Comprehensive description: J. M. Singer *et al., Anal. Profiles Drug Subs.* **14,** 1-36 (1985).

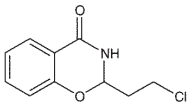


Crystals from 50% acetic acid, dec 224-226°. mp range may extend from 218 to 264° on slow heating. Can form a monohydrate. uv max (methanol): <220 nm. Soly in water: 12 mg/100 ml (20°); 27 mg/100 ml (37°); in 0.1*N* Na_2CO_3: 577 mg/100 ml (20°); 990 mg/100 ml (37°). More sol in aq solns of NaOH. Soluble in warm ethanol; slightly sol in ether.

THERAP CAT: Diuretic; antihypertensive.

THERAP CAT (VET): Diuretic.

2213. Chlorthenoxazin(e). [132-89-8] 2-(2-Chloroethyl)-2,3-dihydro-4*H*-1,3-benzoxazin-4-one; 2-(β-chloroethyl)-2,3-dihydro-4-oxo-(benzo-1,3-oxazine); 4-oxo-2-(β-chloroethyl)-2,3-dihydrobenzo-1,3-oxazine; 2-(β-chloroethyl)-2,3-dihydro-4-keto-(benzo-1,3-oxazine); AP-67; Valtorin; Piroxina; Ossazone; Reumagrip; Ossipirina; Apirazin; Valmorin. $C_{10}H_{10}ClNO_2$; mol wt 211.65. C 56.75%, H 4.76%, Cl 16.75%, N 6.62%, O 15.12%. Prepn: Ohnacker, **US 2943087** (1960 to Thomae).

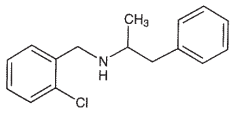


Crystals from ethanol, mp 146-147° (dec). Sol in chloroform. uv max (chloroform): 297.5 nm. Ingredient of ***Trigatan***, ***Fiobrol***.

THERAP CAT: Antipyretic; analgesic.

2214. Chlorzoxazone. [95-25-0] 5-Chloro-2(3*H*)-benzoxazolone; 5-chloro-2-benzoxazolol; 5-chloro-2-hydroxybenzoxazole; 2-hydroxy-5-chlorobenzoxazole; 5-chlorbenzoxazolin-2-one; 5-chlorobenzoxazolidone; Paraflex; Biomioran; Solaxin. $C_7H_4ClNO_2$; mol wt 169.57. C 49.58%, H 2.38%, Cl 20.91%, N 8.26%, O 18.87%. Prepn from 2-amino-5-chlorobenzoxazole: Marsh, **US 2895877** (1959 to McNeil Labs.). LC determn in plasma: I. L. Honigsberg *et al., J. Pharm. Sci.* **68,** 253 (1979). Fluorometric determn in tablets and biological fluids: J. T. Stewart, C. W. Chan, *ibid.* 910. Clinical studies: R. Herman, *Curr. Ther. Res.* **9,** 537 (1967); J. J. Scheiner, *ibid.* **19,** 51 (1976). Metabolism study: R. Twele, G. Spiteller, *Arzneimittel-Forsch.* **32,** 759 (1982). Toxicity: G. Hofrichter *et al., Arzneimittel-Forsch.* **17,** 242 (1967). Review of clinical studies: J. K. Elenbaas, *Am. J. Hosp. Pharm.* **37,** 1313 (1980). Com-

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 29 of 65

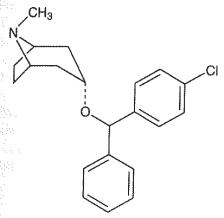


$bp_{0.1}$ 132-134°.

Hydrochloride. [5843-53-8] Ba-7205; SD-271-12; Dinintel; Rexigen. $C_{16}H_{18}ClN.HCl$; mol wt 296.24. Crystals, mp 182-183° (isopropanol). $[\alpha]_D^{20}$ +26.3° (water). Sol in water, ethanol. Slightly sol in methanol, chloroform. LD_{50} i.p. in mice: 103 mg/kg (Boissier *et al.*).

THERAP CAT: Anorexic.

2386. Clobenztropine. [5627-46-3] 3-[(4-Chlorophenyl)-phenylmethoxy]-8-methyl-8-azabicyclo[3.2.1]octane; 3-[(*p*-chloro-α-phenylbenzyl)oxy]tropane; tropine 4-chlorobenzhydryl ether; Teprin. $C_{21}H_{24}ClNO$; mol wt 341.88. C 73.78%, H 7.08%, Cl 10.37%, N 4.10%, O 4.68%. Prepn: Fromer, **US 2799680** (1957); Nield, Bosch, **US 2782200** (1957 to Schenley Labs.).



Hydrochloride. $C_{21}H_{24}ClNO.HCl$. Crystals from isopropanol, mp 215-217°. Sol in water, ethanol. Practically insol in acetone, benzene, ether.

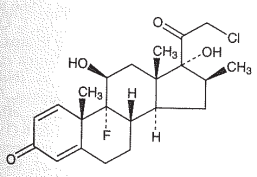
Hydrobromide. $C_{21}H_{24}ClNO.HBr$. mp 197-200°. Sol in hot water, hot ethanol. Practically insol in acetone, benzene, ether.

Methobromide. $C_{21}H_{24}ClNO.CH_3Br$. mp 245-248°. Sol in hot water, in ethanol. Practically insol in acetone, benzene, ether.

Methochloride. $C_{21}H_{24}ClNO.CH_3Cl$. mp 261-263°. Sol in water, ethanol. Practically insol in acetone, benzene, ether.

THERAP CAT: Antihistaminic.

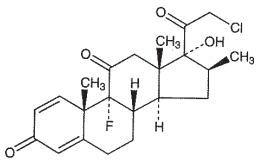
2387. Clobetasol. [25122-41-2] (11β,16β)-21-Chloro-9-fluoro-11,17-dihydroxy-16-methylpregna-1,4-diene-3,20-dione. $C_{22}H_{28}ClFO_4$; mol wt 410.91. C 64.31%, H 6.87%, Cl 8.63%, F 4.62%, O 15.57%. Prepn: Elks *et al.*, **DE 1902340**; *eidem*, **US 3721687** (1969, 1973 both to Glaxo).



17-Propionate. [25122-46-7] GR-2/925; Clobesol; Dermoval; Dermovate; Dermoxin; Dermoxinale; Temovate. $C_{25}H_{32}ClFO_5$; mol wt 466.98. Crystals, mp 195.5-197°. $[\alpha]_D$ +103.8° (c = 1.04 in dioxane). uv max (ethanol): 237 nm (ε 15000).

THERAP CAT: Glucocorticoid; anti-inflammatory.

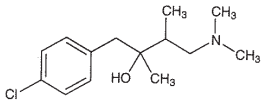
2388. Clobetasone. [54063-32-0] (16β)-21-Chloro-9-fluoro-17-hydroxy-16-methylpregna-1,4-diene-3,11,20-trione; 21-chloro-11-dehydrobetamethasone. $C_{22}H_{26}ClFO_4$; mol wt 408.90. C 64.62%, H 6.41%, Cl 8.67%, F 4.65%, O 15.65%. Prepn: Elks *et al.*, **DE 1902340**; *eidem*, **US 3721687** (1969, 1973, both to Glaxo). Activity: Munro, Wilson, *Brit. Med. J.* **3,** 626 (1975). Radioimmunoassay: W. A. Webb, R. V. Brooks, *Acta Endocrinol. Suppl.* **212,** 203 (1977). Toxicology: J. Tamura *et al., J. Toxicol. Sci.* **5,** 45, 177 (1980). Comparative clinical studies: A. Lassus, *Curr. Med. Res. Opin.* **6,** 165 (1979); T. Fredriksson, K. Nordin, *ibid.* 322. Clinical evaluation of ophthalmic form: D. Lloyd-Jones *et al., Brit. J. Ophthalmol.* **65,** 641 (1981); L. A. Eilon, S. R. Walker, *ibid.* 644; K. R. Wilhelmus *et al., ibid.* 699.



17-Butyrate. [25122-57-0] GR-2/1214; Emovate; Eumovate; Molivate (obsolete). $C_{26}H_{32}ClFO_5$; mol wt 478.99. Crystals from methanol, mp 90-100°.

THERAP CAT: Glucocorticoid; anti-inflammatory.

2389. Clobutinol. [14860-49-2] 4-Chloro-α-[2-(dimethylamino)-1-methylethyl]-α-methylbenzeneethanol; *p*-chloro-α-[2-(dimethylamino)-1-methylethyl]-α-methylphenethyl alcohol; 2-(*p*-chlorobenzyl)-3-dimethylaminomethyl-2-butanol; 1-*p*-chlorophenyl-2,3-dimethyl-4-dimethylamino-2-butanol. $C_{14}H_{22}ClNO$; mol wt 255.79. C 65.74%, H 8.67%, Cl 13.86%, N 5.48%, O 6.25%. Prepn: **GB 898010**; Berg, **US 3121087** (1962, 1964 both to Thomae). Pharmacology: Engelhorn, *Arzneimittel-Forsch.* **10,** 785 (1960). Metabolism: Beisenherz *et al., ibid.* **19,** 79 (1969).

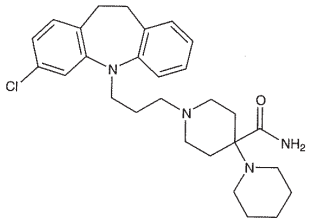


bp_{12} 179-180°.

Hydrochloride. [1215-83-4] KAT-256; Biotertussin; Silomat. $C_{14}H_{22}ClNO.HCl$; mol wt 292.25. Minute crystals, mp 169-170°. Slightly bitter, acidic taste. Numbs the tongue. Sol in water. LD_{50} in mice (mg/kg): 600 orally; 130 i.p. (Engelhorn).

THERAP CAT: Antitussive.

2390. Clocapramine. [47739-98-0] 1′-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyl][1,4′-bipiperidine]-4′-carboxamide; 3-chloro-5-[3-(4-piperidino-4-carbamoylpiperidino)propyl]-10,11-dihydro-5*H*-dibenz[*b,f*]azepine; 3-chlorocarpipramine; clocarpramine; CCP. $C_{28}H_{37}ClN_4O$; mol wt 481.08. C 69.91%, H 7.75%, Cl 7.37%, N 11.65%, O 3.33%. Prepn: Nakanishi, Tashiro, **DE 1905765** corresp to **US 3668210** (1969, 1972, both to Yoshitomi); M. Nakanishi *et al., J. Med. Chem.* **13,** 644 (1970). Pharmacology and toxicity: M. Nakanishi *et al., Arzneimittel-Forsch.* **21,** 391 (1971). Effect on metabolism of serotonin and catecholamines: M. Nakanishi, M. Setoguchi, *ibid.* **23,** 806 (1973). Metabolism: M. Nakanishi *et al., J. Pharm. Soc. Japan* **91,** 1042 (1971). HPLC determn in plasma: K. Hikida *et al., Anal. Sci.* **6,** 367 (1990). *Review: Japan. Med. Gaz.* **10**(7), 5 (1973).

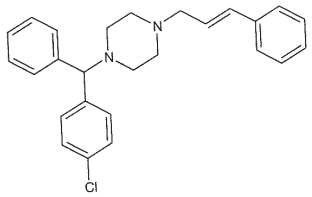


NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 30 of 65

Dihydrochloride monohydrate. [60789-62-0] Y-4153; Clofekton. $C_{28}H_{37}ClN_4O.2HCl.H_2O$; mol wt 572.02. White, bitter tasting, crystalline powder, mp 267°. Soly in water: <3.5 g/100 ml. Freely sol in glacial acetic acid. Practically insol in ether, acetone. LD_{50} in mice, rats (mg/kg): 160, 125 i.p.; 2550, 6800 orally (Nakanishi).

THERAP CAT: Antipsychotic.

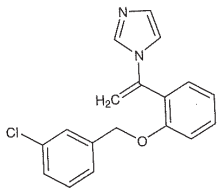
2391. Clocinizine. [298-55-5] 1-[(4-Chlorophenyl)phenylmethyl]-4-(3-phenyl-2-propenyl)piperazine; 1-(*p*-chloro-α-phenylbenzyl)-4-cinnamylpiperazine; 1-cinnamyl-4-(4-chlorobenzhydryl)piperazine; cliocinizine. $C_{26}H_{27}ClN_2$; mol wt 402.97. C 77.50%, H 6.75%, Cl 8.80%, N 6.95%. Prepn: **GB 809760** (1959 to Janssen). HPLC determn in cough-cold preparations: G. Cavazzutti *et al., J. Liq. Chromatog.* **18,** 227 (1995).



Hydrochloride. Crystals, mp 200-201°.

THERAP CAT: Antihistaminic.

2392. Cloconazole. [77175-51-0] 1-[1-[2-[(3-Chlorophenyl)methoxy]phenyl]ethenyl]-1*H*-imidazole; 1-[1-[2-[(3-chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole; croconazole. $C_{18}H_{15}ClN_2O$; mol wt 310.78. C 69.57%, H 4.87%, Cl 11.41%, N 9.01%, O 5.15%. Antimycotic vinylimidazole. Prepn and antifungal properties: M. Ogata *et al.,* **BE 883665**; *eidem,* **US 4328348** (1980, 1982 both to Shionogi); *eidem, J. Med. Chem.* **26,** 768 (1983). Pharmacology: K. Yamamoto *et al., Oyo Yakuri* **27,** 533 (1984), *C.A.* **101,** 16881c (1984). Series of articles on metabolism in rats and rabbits: K. Mizojiri *et al., Iyakuhin Kenkyu* **16,** 177-206 (1985), *C.A.* **103,** 47788y; 47789z; 47790t (1985). Mechanism of action study: T. Hiratani, H. Yamaguchi, *Chemotherapy (Tokyo)* **33,** 579 (1985).

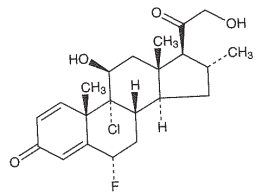


mp 72-73°. Sol in ethyl acetate.

Monohydrochloride. [77174-66-4] 710674-S; Pilzcin. $C_{18}H_{15}ClN_2O.HCl$; mol wt 347.25. Crystals from ethyl acetate + acetonitrile, mp 148.5-150°. LD_{50} in rats (mg/kg): 7000 s.c.; 2500 orally (Ogata, 1983).

THERAP CAT: Antifungal (topical).

2393. Clocortolone. [4828-27-7] (6α,11β,16α)-9-Chloro-6-fluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione; 9-chloro-6α-fluoro-16α-methyl-1,4-pregnadiene-11β,21-diol-3,20-dione. $C_{22}H_{28}ClFO_4$; mol wt 410.91. C 64.31%, H 6.87%, Cl 8.63%, F 4.62%, O 15.57%. Prepn: **NL 6412708** (1965); Kaspar, Philippson, **DE 2011559** corresp to **US 3729495** (1971, 1973) (all to Schering AG). Clinical trials: Wortmann, *Wien. Med. Wochenschr.* **122,** 701 (1972); Baumann, *Praxis* **61,** 536 (1972).



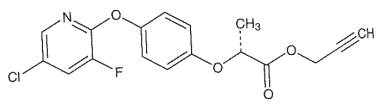
Crystals from methanol-methylene chloride, mp 254° (dec).

21-Acetate. [4258-85-9] SH-818. $C_{24}H_{30}ClFO_5$; mol wt 452.95. Crystals from methanol-methylene chloride, mp 252° (dec).

21-Pivalate. [34097-16-0] CL-68; SH-863; Cloderm; Purantix. $C_{27}H_{36}ClFO_5$; mol wt 495.03.

THERAP CAT: Glucocorticoid.

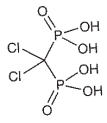
2394. Clodinafop-Propargyl. [105512-06-9] (2*R*)-2-[4-[(5-Chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]propanoic acid 2-propynyl ester; 2-propynyl (*R*)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propionate; CGA-184927; Topik. $C_{17}H_{13}ClFNO_4$; mol wt 349.75. C 58.38%, H 3.75%, Cl 10.14%, F 5.43%, N 4.00%, O 18.30%. Pyridyloxyphenoxy herbicide for use in cereal crops. Prepn: R. Schurter, **EP 248968**; R. Schurter, H. Rempfler, **US 4713109** (both 1987 to Ciba-Geigy). Description: J. Amrein *et al., Proc. Brighton Crop Prot. Conf. - Weeds* **1989,** 71-76. Review of field trials with the crop safener, cloquintocet, *q.v.*: D. W. Cornes, *ibid.* 729-734; R. D. Welsh, *Proc. 47th N. Z. Plant Prot. Conf.* **1994,** 22-26.



Odorless, crystalline solid, mp 59.3°. $[\alpha]_D^{20}$ +45.4° (c = 2 in acetone). Vapor pressure (20°): 5.3×10^{-6} Pa. Soly in water (20°): 2.5 ppm. Sol in most organic solvents. LD_{50} in rats (mg/kg): 1829 orally; >2000 dermally. LC_{50} in rats (4 hr): >2325 mg/m³ by inhalation (Amrein).

USE: Herbicide.

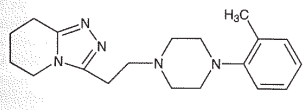
2395. Clodronic Acid. [10596-23-3] (Dichloromethylene)bisphosphonic acid; (dichloromethylene)diphosphonic acid; dichloromethanediphosphonic acid; Cl_2MDP; DMDP. $CH_4Cl_2O_6P_2$; mol wt 244.89. C 4.90%, H 1.65%, Cl 28.95%, O 39.20%, P 25.30%. Bisphosponate antiresorptive agent. Prepn and use as detergent additive: **BE 672205** (1966 to Procter and Gamble), *C.A.* **67,** 4040u (1967). Prepn: O. T. Quimby *et al., J. Org. Chem.* **32,** 4111 (1967). Effect on hydroxyapatite (durapatite, *q.v.*) crystal aggregation: N. M. Hansen *et al., Biochim. Biophys. Acta* **451,** 549 (1976); S. Bisaz *et al., ibid.* 560. HPLC determn in urine: V. Virtanen, L. H. J. Lajunen, *J. Chromatog.* **617,** 291 (1993). Symposium on therapeutic efficacy in neoplastic bone disease: *Bone* **8,** Suppl. 1, S1-S86 (1987). Review of pharmacology and clinical efficacy in resorptive bone disease: G. L. Plosker, K. L. Goa, *Drugs* **47,** 945-982 (1994). Clinical reduction of new metastases in breast cancer: I. J. Diel *et al., N. Engl. J. Med.* **339,** 357 (1998).



mp 249-251°.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 31 of 65

2846. Dapiprazole. [72822-12-9] 5,6,7,8-Tetrahydro-3-[2-[4-(2-methylphenyl)-1-piperazinyl]ethyl]-1,2,4-triazolo[4,3-*a*]pyridine; 5,6,7,8-tetrahydro-3-[2-(4-*o*-tolyl-1-piperazinyl)-ethyl]-*s*-triazolo[4,3-*a*]pyridine. $C_{19}H_{27}N_5$; mol wt 325.45. C 70.12%, H 8.36%, N 21.52%. α-Adrenergic blocker. Prepn: B. Silvestrini, L. Baiocchi, **DE 2915318**; *eidem*, **US 4252721** (1979, 1981 both to Angelini Francesco). Series of articles on general pharmacology: *Arzneimittel-Forsch.* **32,** 674-681 (1982); and toxicity: B. Silvestrini *et al., ibid.* 668. Ocular pharmacokinetics in rabbits: P. Valeri *et al., Pharmacol. Res. Commun.* **18,** 1093 (1986). Topical effects in human eye: A. Reibaldi *et al., Acta Ther.* **10,** 381 (1984); C. Malpassi *et al., ibid* **12,** 55 (1986). Clinical trial in reversal of mydriasis: R. W. Allinson *et al., Ann. Ophthalmol.* **22,** 131 (1990).

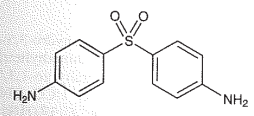


mp 158-160°.

Monohydrochloride. [72822-13-0] AF-2139; Glamidolo; Reversil; Rev-Eyes. $C_{19}H_{27}N_5.HCl$; mol wt 361.92. Crystals from absolute ethanol, mp 206-207°. LD_{50} in mice (mg/kg): 260 i.p. (Silvestrini).

THERAP CAT: Antiglaucoma; miotic.

2847. Dapsone. [80-08-0] 4,4′-Sulfonylbisbenzeneamine; 4,4′-sulfonyldianiline; bis(4-aminophenyl)sulfone; 4,4′-diaminodiphenyl sulfone; DDS; diaphenylsulfone; DADPS; 1358F; Avlosulfon; Croysulfone; Diphenasone; Disulone; Dumitone; Eporal; Novophone; Sulfona-Mae; Sulphadione; Udolac. $C_{12}H_{12}N_2O_2S$; mol wt 248.31. C 58.05%, H 4.87%, N 11.28%, O 12.89%, S 12.91%. Prepn: **FR 829926** (1938 to I. G. Farbenind.), *C.A.* **33,** 1761 (1939); Buckles, *J. Chem. Ed.* **31,** 36 (1954); Ferry *et al., Org. Syn.* **coll. vol. III,** 239 (1955). Antibacterial action and metabolism: J. Francis, A. Spinks, *Brit. J. Pharmacol.* **5,** 565 (1950). Mechanism of toxic action: Wu, DuBois, *Arch. Int. Pharmacodyn. Ther.* **183,** 36 (1970). Comprehensive description: C. E. Orzech *et al., Anal. Profiles Drug Subs.* **5,** 87-114 (1976). Review of pharmacology and therapeutic use: J. Uetrecht, *Clin. Dermatol.* **7,** 111-120 (1989).



Crystals from 95% ethanol. mp 175-176° (also a higher melting form, mp 180.5°). pKb 13.0. Soluble in alcohol, methanol, acetone, dil hydrochloric acid. Practically insol in water.

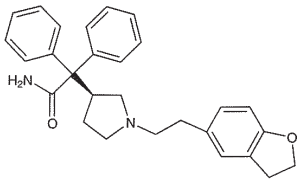
USE: Hardening agent in the curing of epoxy resins.

THERAP CAT: Antibacterial (leprostatic); in treatment of dermatitis herpetiformis.

THERAP CAT (VET): Antibacterial; coccidostat.

2848. Darifenacin. [133099-04-4] (3S)-1-[2-(2,3-Dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-3-pyrrolidineacetamide; 3-(S)-(−)-(1-carbamoyl-1,1-diphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]pyrrolidine; (S)-2-[1-[2-(2,3,-dihydrobenzfuran-5yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide; UK-88525. $C_{28}H_{30}N_2O_2$; mol wt 426.55. C 78.84%, H 7.09%, N 6.57%, O 7.50%. Selective muscarinic M_3-receptor antagonist. Prepn: P. E. Cross, A. R. MacKenzie, **EP 388054**; *eidem*, **US 5096890** (1990, 1992 both to Pfizer). HPLC/MS determn in plasma: B. Kaye *et al., Anal. Chem.* **68,** 1658 (1996). Binding profile for receptor subtypes: C. M. Smith, R. W. Wallis, *J. Recept. Signal Transduct. Res.* **17,** 177 (1997); and pharmacology: R. M. Wallis, C. M. Napier, *Life Sci.* **64,** 395 (1999). Pharmacokinetics and metabolism: K. C. Beaumont *et al., Xenobiotica* **28,** 63 (1998).

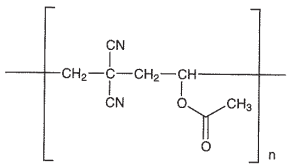
Foam or colorless glass. $[\alpha]_D^{25}$ −20.6° (c = 1.0 in methylene chloride).



Hydrobromide. [133099-07-7] $C_{28}H_{31}N_2O_2Br$. mp 229°. $[\alpha]_D^{25}$ −30.3° (c = 1.0 in methylene chloride).

THERAP CAT: Antispasmodic.

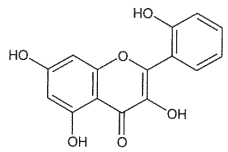
2849. Darvan®. [9003-24-1] Vinylidene cyanide-vinyl acetate copolymer; Darlan; Travis. ***Methylenemalononitrile copolymer with vinyl acetate*** contg about equal parts of each component. Polymerization of vinylidene cyanide with vinyl acetate: Gilbert *et al., J. Am. Chem. Soc.* **78,** 1669 (1956); Gilbert, Miller, **US 2615866** and Sayre, **US 2975158** (1952, 1961, both to B. F. Goodrich). *Review:* R. W. Moncrieff, *Man-Made Fibres* (John Wiley, New York, 4th ed., 1963) pp 488-494. Approximate structure:



A wool-like fiber, sp gr 1.18. Softens at about 175°. Flammability similar to cotton and viscose. Insol in acetone, methylene chloride. Good resistance to sunlight, clothes-moth and carpet-beetle attack, and mildew; moderate resistance to 10% H_2SO_4 at 100° for hrs, and to 0.5% caustic soda at 43° for 7 days. Shrinks about 1% when immersed in boiling water for 3 minutes. Difficult to dye. Relatively resistant to pilling.

USE: Knitted garments, pile coats, and in blends for tropical suitings and men's shirtings.

2850. Datiscetin. [480-15-9] 3,5,7-Trihydroxy-2-(2-hydroxyphenyl)-4*H*-1-benzopyran-4-one; 2′,3,5,7-tetrahydroxyflavone; 2′-hydroxycrysidenolon 1493. $C_{15}H_{10}O_6$; mol wt 286.24. C 62.94%, H 3.52%, O 33.54%. Cleavage product of datiscin: Stenhouse, *Ann.* **98,** 166 (1856). From roots of *Datisca cannabina* L., *Datiscaceae:* Marchlewski, *Biochem. Z.* **3,** 286 (1907). Structure: Leskiewicz, Marchlewski, *Ber.* **47,** 1599 (1914). Synthesis: Kalf, Robinson, *J. Chem. Soc.* **127,** 1968 (1925); Simpson, Wally, *ibid.* **1955,** 166.



Pale yellow needles from alc, mp 271°. uv max (96% alc): 264.0, 375.0 nm (log ε 4.265, 4.005). Sol in alcohol, ether, other organic solvents; practically insol in water. Sol in alkaline solns with yellow color.

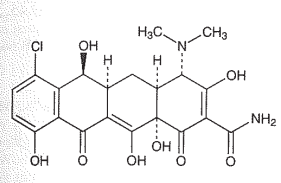
2851. Daucol. [887-08-1] Octahydro-6,8a-dimethyl-3-(1-methylethyl)-1*H*-3a,6-epoxyazulen-7-ol; 2,3,4,5,6,7a,8,8a-octahydro-3-isopropyl-6,8a-dimethyl-1*H*-3a,6-epoxyazulen-7-ol. $C_{15}H_{26}O_2$; mol wt 238.36. C 75.58%, H 10.99%, O 13.42%. From oil of carrot seeds, *Daucus carota* L., *Umbelliferae:* Richter, *Arch. Pharm.* **247,** 391 (1909). Structure: Sykora *et al., Coll. Czech. Chem. Commun.* **26,** 788 (1961); Zalkow *et al., J.*

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 32 of 65

White, slightly hygroscopic powder, dec 162-167°. Freely sol in water, alc. Sparingly sol in acetone. Insol in ether. Aq solns are neutral, stable, and may be sterilized by heat.

THERAP CAT: Cholinergic (ophthalmic).

2905. Demeclocycline. [127-33-3] [4*S*-(4α,4aα,5aα,-6β,12aα)]-7-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-2-naphthacenecarboxamide; 7-chloro-6-demethyltetracycline; demethylchlortetracycline (obsolete); RP-10192; Bioterciclin; Declomycin; Deganol; Ledermycin; Periciclina. $C_{21}H_{21}ClN_2O_8$; mol wt 464.86. C 54.26%, H 4.55%, Cl 7.63%, N 6.03%, O 27.53%. Antibiotic related to tetracycline produced by *Streptomyces aureofaciens.* Prepn: McCormick *et al., J. Am. Chem. Soc.* **79,** 4561 (1957); **US 2878289** (1959 to Am. Cyanamid). Improved fermentation processes: Szumski, **US 3012946**; Goodman, Matrishin, **US 3019172**; Goodman, **US 3050446** (1961, 1962, 1962 all to Am. Cyanamid); **FR 1344645** (1963 to Merck & Co.); Neidleman, **US 3154476** (1964 to Olin Mathieson). Abs config: Dobrynin *et al., Tetrahedron Letters* **1962,** 901. Toxicity data: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* **18,** 185 (1971).



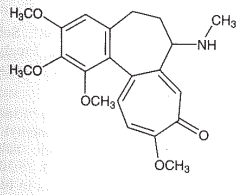
Sesquihydrate. mp 174-178° (dec). $[\alpha]_D^{25}$ −258° (c = 0.5 in 0.1*N* H_2SO_4). Solubilities: Marsh, Weiss, *J. Assoc. Offic. Anal. Chem.* **50,** 457 (1967).

Hydrochloride. [64-73-3] Clortetrin; Demetraciclina; Detravis; Meciclin; Mexocine. LD_{50} orally in rats: 2372 mg/kg (Goldenthal).

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

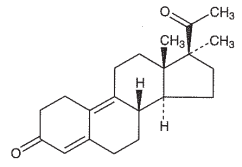
2906. Demecolcine. [477-30-5] 6,7-Dihydro-1,2,3,10-tetramethoxy-7-(methylamino)benzo[*a*]heptalen-9(5*H*)-one; *N*-deacetyl-*N*-methylcolchicine; *N*-methyl-*N*-desacetylcolchicine; colchamine; Santavy's substance F; Colcemid; Omaine. $C_{21}H_{25}NO_5$; mol wt 371.43. C 67.91%, H 6.78%, N 3.77%, O 21.54%. Isoln from *Colchicum autumnale* L., *Liliaceae:* Santavy, *Pharm. Acta Helv.* **25,** 248 (1950); Santavy, Reichstein, *Helv. Chim. Acta* **33,** 1606 (1950); Schlittler, Uffer, **DE 936268** (1955 to Ciba), *C.A.* **53,** 1396 (1959). Structure: Santavy *et al., Helv. Chim. Acta* **36,** 1319 (1953). Synthesis: Uffer *et al., ibid.* **37,** 18 (1954); H. G. Capraro, A. Brossi, *ibid.* **62,** 965 (1979).



Pale yellow prisms from ethyl acetate + ether, mp 186°. $[\alpha]_D^{20}$ −129.0° (c = 1 in chloroform). uv max (alc): 245, 355 nm (log ε 4.55, 4.24). Basic reaction. Soluble in acidified water, in alcohol, ether, chloroform, benzene.

THERAP CAT: Antineoplastic.

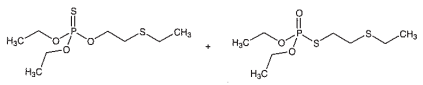
2907. Demegestone. [10116-22-0] 17-Methyl-19-norpregna-4,9-diene-3,20-dione; 17α-methyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione; 17α-methyl-Δ^9-19-norprogesterone; R-2453; Lutionex. $C_{21}H_{28}O_2$; mol wt 312.44. C 80.73%, H 9.03%, O 10.24%. Prepn: **NL 6517141** corresp to Vignau *et al.,* and Joly *et al.,* **US 3453267** and **US 3547959** (1966, 1969, 1970, all to Roussel-UCLAF); Velluz *et al., Tetrahedron,* **Suppl 8,** part II, 495 (1966); Joly *et al., Bull. Soc. Chim. France* **1973,** 2694.



Crystals from ether, mp 106°. $[\alpha]_D$ −275° (c = 0.5 in ethanol). uv max (ethanol): 214, 302 nm (ε 6350, 21000).

THERAP CAT: Progestogen.

2908. Demeton. [8065-48-3] Phosphorothioic acid *O,O*-diethyl *O*-[2-(ethylthio)ethyl] ester mixture with *O,O*-diethyl *S*-[2-(ethylthio)ethyl]phosphorothioate; mercaptophos; Bayer 8169; E-1059; Systox. $C_8H_{19}O_3PS_2$; mol wt 258.34. C 37.19%, H 7.41%, O 18.58%, P 11.99%, S 24.82%. Cholinesterase inhibitor. Isomeric mixture consisting of demeton-O and demeton-S (*O,O*-diethyl *O*(and *S*)-ethylmercaptoethyl thiophosphates). Another name for demeton-S is ***Isosystox***. Prepn: Schrader, **US 2571989** and **US 2597534** (1951, 1952 both to Bayer); Gardner, Heath, *Anal. Chem.* **25,** 1849 (1953). Toxicity study: T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14,** 515 (1969).

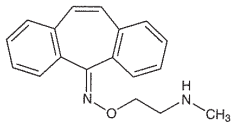


Oily liq. Faint odor. bp_2 134°. Virtually insol in water. Sol in ethanol, propylene glycol, toluene and similar hydrocarbons. Absorbed by plants, rendering the foliage and plant fluids toxic to insects. LD_{50} in female, male rats (mg/kg): 2.5, 6.2 orally; 8.2, 14 dermally (Gaines).

Caution: Potential symptoms of overexposure are miosis, aching eyes, rhinorrhea and headache; chest tightening, wheezing, laryngeal spasms, salivation and cyanosis; anorexia, nausea, vomiting, abdominal cramps and diarrhea; local sweating; muscle fasciculation, weakness and paralysis; giddiness, confusion and ataxia; convulsions, coma; low blood pressure; cardiac irregularities; irritation of eyes and skin. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 90.

USE: Insecticide.

2909. Demexiptiline. [24701-51-7] 5*H*-Dibenzo[*a,d*]cyclohepten-5-one *O*-[2-(methylamino)ethyl]oxime. $C_{18}H_{18}N_2O$; mol wt 278.35. C 77.67%, H 6.52%, N 10.06%, O 5.75%. Prepn: S. Schütz *et al.,* **DE 1247302**; *eidem,* **US 3963778** (1967, 1976 both to Bayer). Synthesis and pharmacological properties: G. Aichinger *et al., Arzneimittel-Forsch.* **19,** 838 (1969); S. Rossi *et al., Farmaco Ed. Sci.* **24,** 685 (1969).



Colorless oil.

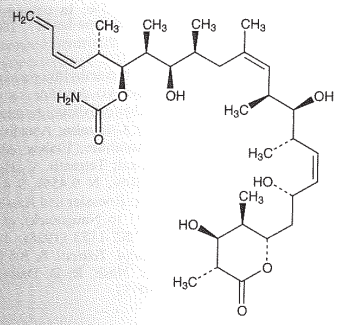
Hydrochloride. [18059-99-9] LM-2909; Deparon. $C_{18}H_{18}N_2O.HCl$; mol wt 314.82. Crystals from isopropanol, mp 232-233°. LD_{50} in rats (mg/kg): 330 orally, 25 i.v. (Rossi).

THERAP CAT: Antidepressant.

2910. Denatonium Benzoate. [3734-33-6] *N*-[2-[(2,6-Dimethylphenyl)amino]-2-oxoethyl]-*N,N*-diethylbenzenemeth-

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 33 of 65

3390. Discodermolide. [127943-53-7] (3*R*,4*S*,5*R*,6*S*)-6-[(2*S*,3*Z*,5*S*,6*S*,7*S*,8*Z*,11*S*,12*R*,13*S*,14*S*,15*S*,16*Z*)-14-[(Aminocarbonyl)oxy]-2,6,12-trihydroxy-5,7,9,11,13,15-hexamethyl-3,8,16,18-nonadecatetraenyl]tetrahydro-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one; YM-19020. $C_{33}H_{53}NO_8$; mol wt 591.77. C 66.98%, H 9.03%, N 2.37%, O 21.63%. Polyhydroxylated lactone isolated from the marine sponge, *Discodermia dissoluta*. Naturally occurring (+)-form stabilizes microtubles and inhibits cell proliferation with the same mechanism as paclitaxel, *q.v.* Isoln and structure determn: S. P. Gunasekera *et al., J. Org. Chem.* **55,** 4912 (1990); correction: *ibid.* **56,** 1346 (1991). Total synthesis: A. B. Smith, III *et al., Org. Letters* **1,** 1823 (1999); stereocontrolled: I. Paterson, G. J. Florence, *Tetrahedron Letters* **41,** 6935 (2000). Mechanism of action: D. T. Hung *et al., Chem. Biol.* **3,** 287 (1996); E. ter Haar *et al., Biochemistry* **35,** 243 (1996). Activity in comparison with paclitaxel in cancer cells: R. Balachandran *et al., Anti-Cancer Drugs* **9,** 67 (1998); L. A. Martello *et al., Clin. Cancer Res.* **6,** 1978 (2000).



Monoclinic white crystals, mp 115-116°. uv max (methanol): 210, 226 235 nm (ε 35400, 19500, 12500). $[\alpha]_D^{25}$ +7.2° (c = 0.72 in methanol).

USE: Reagent for mitotic studies.

3391. Disilane. [1590-87-0] Disilicoethane; disilicon hexahydride; silicoethane; disilicane. H_6Si_2; mol wt 62.22. H 9.72%, Si 90.28%. Si_2H_6. Obtained by separation of mixed silanes prepd from magnesium silicide and hydrochloric acid: Moissan, Smiles, *Compt. Rend.* **134,** 569, 1549 (1902); Stock, Somiesky, *Ber.* **49,** 111 (1916); **54B,** 524 (1921); **56B,** 247 (1923); Culbertson, **US 2551571** (1951 to Union Carbide); prepd by conversion of silane to higher silanes in an ozonizer type electric discharge: Spanier, MacDiarmid, *Inorg. Chem.* **1,** 432 (1962).

Gas; repulsive odor. d_4^{-25} 0.686. mp −132.5°. bp −14.5°. Dec 300°. Ignites spontaneously in air. Slowly dec in water. Explodes on contact with sulfur hexafluoride; reacts vigorously with carbon tetrachloride and chloroform. Sol in carbon disulfide, ethyl alcohol, benzene, and ethyl silicate. Potassium hydroxide liberates hydrogen.

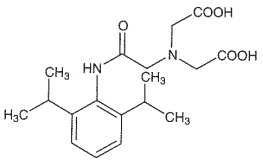
Caution: A powerful irritant.

3392. Disodium Phenyl Phosphate. [3279-54-7] $C_6H_5Na_2O_4P$; mol wt 218.05. C 33.05%, H 2.31%, Na 21.09%, O 29.35%, P 14.20%. $C_6H_5PO_4Na_2$.

White, cryst powder. Freely sol in water, sparingly in alcohol; insol in acetone or ether.

USE: Reagent in the testing of milk for proper pasteurization and for the presence of unpasteurized milk.

3393. Disofenin. [65717-97-7] *N*-[2-[[2,6-Bis(1-methylethyl)phenyl]amino]2 - oxoethyl] - *N* - (carboxymethyl)glycine; [[[(2,6-diisopropylphenyl)carbamoyl]methyl]imino]diacetic acid; (2,6-diisopropylacetanilido)iminodiacetic acid; *N*-(carboxymethyl)-*N*-[2-(2,6-diisopropylphenyl)amino]-2-oxoethylglycine; DISIDA. $C_{18}H_{26}N_2O_5$; mol wt 350.41. C 61.70%, H 7.48%, N 7.99%, O 22.83%. Iminodiacetic acid analog. Prepn of acid and ^{99m}Tc-complex: M. de Schrijver, **DE 2723605**; *idem,* **US 4316883** (1977, 1982 both to Solco Basel). High yield synthesis of acid: M. P. Best *et al., Aust. J. Chem.* **35,** 2371 (1982). Biodistribution: G. Subramanian *et al., Nuklearmedizin, Suppl.* **16,** 136 (1978). Chromatographic determn of radiochemical purity: A. M. Zimmer *et al., Eur. J. Nucl. Med.* **7,** 88 (1982). Chemical and biological properties: B. Zmbova *et al., Appl. Radiat. Isot.* **38,** 35 (1987). Pharmacokinetics: I. A. Fraser *et al., Eur. J. Nucl. Med.* **14,** 431 (1988); J. E. Love *et al., ibid.* 436. Clinical evaluation as hepatobiliary imaging agent: R. C. Stadalnik *et al., Radiology* **140,** 797 (1981).

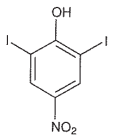


White crystals, mp 196-198° (Zmbova). Also reported as crystals from water, mp 191-192.5° (Best); and as mp 166-175° (de Schrijver). Insol in water.

^{99m}Tc complex. ^{99m}Tc diisopropyl IDA; ^{99m}Tc-DISIDA; Hepatolite. Distribution coefficient (ethylene dichloride/water): 0.0086.

THERAP CAT: ^{99m}Tc-complex as diagnostic aid (radioactive imaging agent).

3394. Disophenol. [305-85-1] 2,6-Diiodo-4-nitrophenol; DNP; Ancylol. $C_6H_3I_2NO_3$; mol wt 390.90. C 18.44%, H 0.77%, I 64.93%, N 3.58%, O 12.28%. Prepd by iodination of *p*-nitrophenol with iodine—potassium iodide soln in aq ammonia: Datta, Prosad, *J. Am. Chem. Soc.* **39,** 446 (1917). As an anthelmintic: Thorson *et al.,* **US 3081224** (1963 to Am. Cyanamid). Toxicity studies: J. A. Kaiser, *Toxicol. Appl. Pharmacol.* **6,** 232 (1964); Fowler, *Brit. Vet. J.* **127,** 304 (1971). Comparative field trial in sheep: C. A. Hall *et al., Res. Vet. Sci.* **31,** 104 (1981).



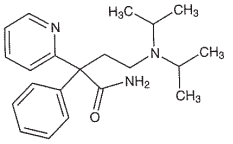
Light yellow, feathery crystals from glacial acetic acid, mp 157°. Freely sol in alcohol, very sparingly sol in water. LD_{50} in rats, mice (mg/kg): 170, 212 orally; 105, 88 i.v.; 105, 107 i.p.; 122, 110 s.c. (Kaiser).

THERAP CAT (VET): Anthelmintic (hookworm).

3395. Disopyramide. [3737-09-5] α-[2-[Bis(1-methylethyl)amino]ethyl]-α-phenyl-2-pyridineacetamide; α-[2-(diisopropylamino)ethyl]-α-phenyl-2-pyridineacetamide; 4-(diisopropylamino)-2-phenyl-2-(2-pyridyl)butyramide; H-3292; SC-7031; Dicorantil; Isorythm; Lispine; Ritmodan; Rythmodan. $C_{21}H_{29}N_3O$; mol wt 339.47. C 74.30%, H 8.61%, N 12.38%, O 4.71%. Prepn: Cusic, Sause, **BE 617730** *C.A.* **58,** 12522e (1963) and **US 3225054** (1962 and 1965, both to Searle). Synthesis and biological activity: Adelstein, *J. Med. Chem.* **16,** 309 (1973). Pharmacology: *J. Am. Med. Assoc.* **213,** 697 (1970); Mathur, *Am. Heart J.* **84,** 764 (1972); B. Befeler, R. Lazzara, *Heart Lung* **9,** 475 (1980). Conformation-activity study: J. L. Czeisler, R. M. El-Rashidy, *J. Pharm. Sci.* **74,** 750 (1985). Toxicity: P. C. Ruenitz, C. M. Mokler, *J. Med. Chem.* **22,** 1142 (1979). *Reviews:* R. R. Dean *et al.,* in *Pharmacological and*

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 34 of 65

Biochemical Properties of Drug Substances **vol. 2,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1979) pp 165-185; E. H. Taylor, A. A. Pappas, *Ann. Clin. Lab. Sci.* **16,** 289-295 (1986).

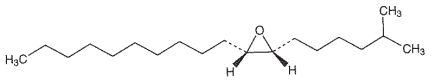


Crystals from hexane, mp 94.5-95.0°. pKa 10.2; also reported as 10.45. LD_{50} i.p. in mice: 517 μmol/kg (Ruenitz, Mokler).

Phosphate. [22059-60-5] SC-13957; Dirythmin SA; Diso-Duriles; Norpace; Rythmodul. $C_{21}H_{29}N_3O.H_3PO_4$; mol wt 437.47.

THERAP CAT: Antiarrhythmic (class IA).

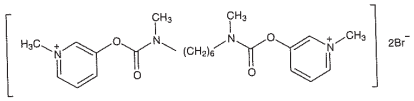
3396. Disparlure. [29804-22-6] (*cis*-form); [54910-51-9] (2*S*-*cis*-form). (2*S*-*cis*)-2-Decyl-3-(5-methylhexyl)oxirane; *cis*-7,8-epoxy-2-methyloctadecane; ENT-34886; Disrupt. $C_{19}H_{38}O$; mol wt 282.50. C 80.78%, H 13.56%, O 5.66%. Potent sex pheromone of the gypsy moth *Lymantria dispar* (formerly *Porthetria dispar).* Isoln and characterization: B. A. Bierl *et al., Science* **170,** 87 (1970); *eidem, J. Econ. Entomol.* **65,** 659 (1972). Synthesis: S. Iwaki *et al., J. Am. Chem. Soc.* **96,** 7842 (1974); D. G. Farnum *et al., Tetrahedron Letters* **1977,** 4009; K. Mori *et al., Tetrahedron* **35,** 833 (1979); B. E. Rossiter *et al., J. Am. Chem. Soc.* **103,** 464 (1981); K. Mori, T. Ebata, *Tetrahedron Letters* **22,** 4281 (1981). Synthesis of (±)-form: K. Eiter, *Angew. Chem. Int. Ed.* **11,** 60 (1972); *idem,* **DE 2145454**; *idem,* **US 3975409** (1973, 1976 both to Bayer); H. J. Bestmann *et al., Ber.* **109,** 3375 (1976). Activity of (+)- and (±)-forms: R. T. Cardé, R. P. Webster, *J. Chem. Ecol.* **5,** 935 (1979). Acute toxicity study: M. Beroza *et al., Toxicol. Appl. Pharmacol.* **31,** 421 (1975).



Viscous colorless oil, $bp_{0.25}$ 146-148°. $[\alpha]_D^{23}$ +0.8 ±0.2° (c = 10 in CCl_4). n_D^{23} 1.4450. LD_{50} in rats (mg/kg): >34600 orally; in rabbits (mg/kg): >2025 dermally; LC_{50} (24 hr) in rainbow trout, bluegill sunfish (ppm): >100, >100 (Beroza).

USE: Insect attractant.

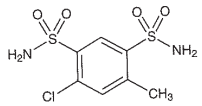
3397. Distigmine Bromide. [15876-67-2] 3,3′-[1,6-Hexanediylbis[(methylimino)carbonyl]oxy]bis[1-methylpyridinium]dibromide; 3-hydroxy-1-methylpyridinium bromide hexamethylenebis[methylcarbamate]; hexamethylenebis[methylcarbamic acid] ester of 3-hydroxy-1-methylpyridinium bromide; hexamethylenebis[*N*-methylcarbamic acid ester bromomethylate]; hexamethylenebis[*N*-methylcarbaminoyl-1-methyl-3-hydroxypyridinium bromide]; hexamarium; BC-51; Ubretid. $C_{22}H_{32}Br_2N_4O_4$; mol wt 576.33. C 45.85%, H 5.60%, Br 27.73%, N 9.72%, O 11.10%. Prepn: Schmid, **US 2789981** (1957 to Oesterr. Stickstoffwerke). Pharmacology: Hertting *et al., Arzneimittel-Forsch.* **18,** 479 (1968); Hohenegger, Lindner, *Wien. Klin. Wochenschr.* **81,** 823 (1969). Stability studies: Suzuki, Tanimura, *Yakugaku Zasshi* **90,** 762 (1970).



Crystals, dec 149°.

THERAP CAT: Cholinesterase inhibitor.

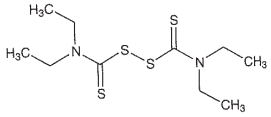
3398. Disulfamide. [671-88-5] 4-Chloro-6-methyl-1,3-benzenedisulfonamide; 5-chlorotoluene-2,4-disulfonamide; 2-chloro-4-methylbenzene-1,5-disulfonamide; 5-chloro-2,4-disulfamyltoluene; disulphamide; Disamide; Natirene 25. $C_7H_9ClN_2O_4S_2$; mol wt 284.74. C 29.53%, H 3.19%, Cl 12.45%, N 9.84%, O 22.48%, S 22.52%. Prepn: **GB 851287** (1960 to Brit. Drug Houses). Pharmacology: David, Fellowes, *J. Pharm. Pharmacol.* **12,** 65 (1960).



Non-hygroscopic cryst powder, mp 260°. uv max (ethanol): 285 nm (ε 805). Practically insol in water. Slightly sol in ethanol. Soly in abs ethanol at 25° = 1.89% w/w; in 90% ethanol = 2.23% w/w; in isopropanol = 0.35%; in chloroform = 0.001%. Sol in cold NaOH solns.

THERAP CAT: Diuretic.

3399. Disulfiram. [97-77-8] Tetraethylthioperoxydicarbonic diamide; bis(diethylthiocarbamoyl) disulfide; tetraethylthiuram disulfide; bis(diethylthiocarbamyl) disulfide; teturamin; TTD; Cronetal; Abstensil; Stopetyl; Contralin; Antadix; Antietanol; Exhoran; Ethyl Thiurad; Antabuse; Etabus; Abstinyl; Thiuranide; Esperal; Tetradine; Noxal; Tetraetil. $C_{10}H_{20}N_2S_4$; mol wt 296.54. C 40.50%, H 6.80%, N 9.45%, S 43.25%. Prepn: Bailey, **US 1796977** (1931 to Roessler and Hasslacher); Adams, Newser, **US 1782111** (1931 to Naugatuck); *cf.* Cummings, Simmons, *Ind. Eng. Chem.* **20,** 1173 (1928). Toxicity study: Child, Cramp, *Acta Pharmacol. Toxicol.* **8,** 305 (1952). Comprehensive description: N. G. Nash, R. D. Daley, *Anal. Profiles Drug Subs.* **4,** 168-191 (1975).



Crystals, mp 70°. d 1.30. Practically insol in water (0.02 g/100 ml). Sol in alcohol (3.82 g/100 ml), in ether (7.14 g/100 ml), also sol in acetone, benzene, chloroform, carbon disulfide. LD_{50} orally in rats: 8.6 g/kg (Child, Cramp).

Caution: Potential symptoms of overexposure are irritation of eyes, skin, respiratory system; sensitization dermatitis; lassitude, fatigue, tremor, restlessness, headache, dizziness; metallic taste, peripheral neuropathy; liver damage. Ingestion of alcohol after disulfiram administration causes intense vasodilation and flushing of face and neck, restlessness, anxiety; tachycardia and tachypnea; headache, nausea, vomiting, hyperpnea, chest pains, sweating, pallor, hypotension. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 122; *Clinical Toxicology of Commercial Products,* R. E. Gosselin *et al.,* Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section III, pp 159-163, 383-386.

USE: Rubber accelerator; vulcanizer; seed disinfectant; fungicide.

THERAP CAT: Alcohol deterrent.

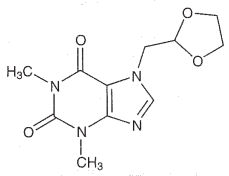
3400. Disulfoton. [298-04-4] Phosphorodithioic acid *O,O*-diethyl *S*-[2-(ethylthio)ethyl] ester; *O,O*-diethyl-*S*-ethylmercaptoethyl dithiophosphate; thiodemeton; dithiodemeton; Bay 19639; ENT-23347; Disyston. $C_8H_{19}O_2PS_3$; mol wt 274.41. C 35.02%, H 6.98%, O 11.66%, P 11.29%, S 35.06%. Homologue of phorate, *q.v.* Prepn: Schrader, Lorenz, **US 2759010**; **GB 797307** (1956, 1958 both to Bayer). Toxicity study: T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14,** 515 (1969).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 35 of 65

Crystals from ethyl acetate, mp 189-190° (Cook). Also reported as crystals from 2-propanol, mp 186-188° (Hrebabecky, Beranek); needles from methanol + ethyl acetate, mp 192-193° (Kiss). pKa 7.4. $[\alpha]_D^{25}$ +18.4° (c = 0.419 in water). uv max (in methanol): 268-269 nm (ε 8550). LD_{50} (14 day) in mice or rats (mg/kg): >1000 i.v.: >2000 s.c.; in male, female mice, male, female rats (mg/kg): >5000, >5000, 3471, 3390 orally (Shimizu).

THERAP CAT: Antineoplastic.

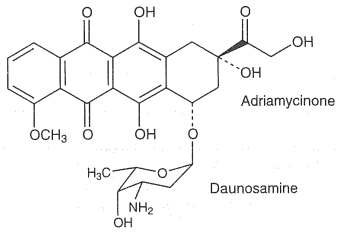
3472. Doxofylline. [69975-86-6] 7-(1,3-Dioxolan-2-ylmethyl)-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione; 7-(1,3-dioxolan-2-ylmethyl)theophylline; 2-(7′-theophyllinemethyl)-1,3-dioxolane; doxophylline; dioxyfilline; ABC-12/3; Ansimar; Maxivent; Ventax. $C_{11}H_{14}N_4O_4$; mol wt 266.25. C 49.62%, H 5.30%, N 21.04%, O 24.04%. Prepn: U. Avico *et al., Farmaco Ed. Sci.* **17,** 73 (1962). Use as bronchodilator: **BE 868556**; J. S. Franzone, T. Tamietto, **US 4187308** (1978, 1980 to Istituto Biologico Chemioterapico ABC). Pharmacology: J. S. Franzone *et al., Farmaco Ed. Sci.* **36,** 201 (1981). Pharmacodynamics and toxicity in rats: J. S. Franzone *et al., ibid.* 220. HPLC determn in pharmaceutical compositions: C. Badini *et al., Farmaco Ed. Prat.* **37,** 320 (1982). Clinical trial in obstructive pneumopathy: C. Bucca *et al., Int. J. Clin. Pharm. Res.* **11,** Suppl 1, 101 (1982).



Crystals, mp 144-145.5°. Sol in water, acetone, ethyl acetate, benzene, chloroform, dioxane, hot methanol or hot ethanol. Practically insol in ethyl ether or petr ether. LD_{50} in mice (mg/kg): 841 orally; 215.6 i.v.; in rats: 1022.4 orally, 445 i.p. (Franzone).

THERAP CAT: Bronchodilator.

3473. Doxorubicin. [23214-92-8] (8*S-cis*)-10-[(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,-12-naphthacenedione; 14-hydroxydaunomycin; NSC-123127; FI-106. $C_{27}H_{29}NO_{11}$; mol wt 543.52. C 59.66%, H 5.38%, N 2.58%, O 32.38%. Anthracycline antibiotic isolated from *Streptomyces peucetius* var *caesius:* F. Arcamone *et al.,* **ZA 68 02378** and **US 3590028** (1968 and 1971 to Farmitalia); *eidem, Biotechnol. Bioeng.* **11,** 1101 (1969). Synthesis of derivs: F. Arcamone *et al.,* **DE 1917874** (1969 to Farmitalia), *C.A.* **73,** 45799r (1970). Structural studies: F. Arcamone *et al., Tetrahedron Letters* **1969,** 1007. Synthesis from daunomycin, *q.v.: eidem, Chim. Ind. (Milan)* **51,** 834 (1969); *see also:* E. M. Acton *et al., J. Med. Chem.* **17,** 659 (1974); from 7-deoxydaunomycinone: T. H. Smith *et al.,* **US 4012448** (1977 to Stanford Res. Inst.). Biochemical comparison with daunomycin: Wang *et al., Proc. Am. Assoc. Cancer Res.* **12,** No. 62, 77 (1971). In acid environment doxorubicin breaks up into a water-insol aglycone, ***adriamycinone*** ($C_{21}H_{18}O_9$), and a water-sol basic, reducing aminosugar, ***daunosamine*** ($C_6H_{13}NO_3$), 3-amino-2,3,6-trideoxy-L-lyxohexose: A. Di Marco *et al., Cancer Chemother. Rep.* (part 1) **53,** 33 (1969). Total synthesis of adriamycinone: F. Suzuki *et al., J. Am. Chem. Soc.* **100,** 2272 (1978); regiospecific synthesis: J. S. Swenton, P. W. Reynolds, *ibid.* 6188; of daunosamine: P. M. Wovkulich, M. R. Uskonovic, *Tetrahedron* **41,** 3455 (1985). Pharmacokinetic and chemotherapeutic studies: E. Arena *et al., Arzneimittel-Forsch.* **21,** 1258 (1971). Purification: E. Oppici *et al.,* **BE 898506**; *eidem,* **GB 2133005** (both 1984 to Farmitalia). As modulator of immune response in mice: E. Mihich, M. J. Ehrke, *Transplant. Proc.* **16,** 499 (1984). Doxorubicin's cytotoxicity appears to be due to its ability to intercalate with DNA, interact with plasma membranes and take part in oxidation-reduction reactions: T. R. Tritton, G. Yee, *Science* **217,** 248 (1982); H. Simpkins *et al., Cancer Res.* **44,** 613 (1984); R. S. Youngman, E. F. Elstner, *Arch. Biochem. Biophys.* **231,** 424 (1984). In treatment of cancer of the bladder: M. Pavone-Macaluso *et al., Urology* **23,** 40 (1984); breast: D. C. Tormey *et al., Am. J. Clin. Oncol.* **7,** 231 (1984); prostate: H. Scher *et al., J. Urol.* **131,** 1099 (1984). Toxicology: C. Bertazzoli *et al., Experientia* **26,** 389 (1970); *eidem, Toxicol. Appl. Pharmacol.* **21,** 287 (1972); R. D. Olson *et al., Life Sci.* **29,** 1393 (1981). Review of properties, biosynthesis, fermentation: R. J. White, R. M. Stroshane, *Drugs Pharm. Sci.* **22,** 569-594 (1984); of efficacy: H. L. Davis, T. E. Davis, *Cancer Treat. Rep.* **63,** 809-815 (1979). *Review:* R. H. Blum, S. K. Carter, *Ann. Int. Med.* **80,** 249-259 (1974); G. Aubel-Sadron, D. Londos-Gagliardi, *Biochimie* **66,** 333-352 (1984). Comprehensive description: A. Vigevani, M. J. Williamson, *Anal. Profiles Drug Subs.* **9,** 245-274 (1980). Book: *Doxorubicin,* F. Arcamone, Ed. (Academic Press, New York, 1981) 354 pp.



mp 229-231°.

Hydrochloride. [25316-40-9] Adriacin; Adriblastina; Adriamycin; Caelyx. $C_{27}H_{29}NO_{11}.HCl$; mol wt 579.99. Orange-red colored thin needles, mp 204-205° (dec). $[\alpha]_D^{20}$ +248° (c = 0.1 in methanol). Absorption/uv max (methanol): 233, 252, 288, 479, 496, 529 nm. Sol in water, methanol, aq alcohols. Practically insol in acetone, benzene, chloroform, ethyl ether and petroleum ether. Aq solns are yellow-orange at acid pHs, orange-red at neutral pHs and violet-blue at pH >9. Aq soln unchanged after one month at 5°, but unstable at higher temperatures or at either acid or alkaline pHs. LD_{50} i.v. in mice: 21.1 mg/kg (Bertazzoli, 1970).

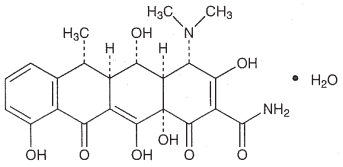
Note: Doxorubicin hydrochloride is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-70.

THERAP CAT: Antineoplastic.

3474. Doxycycline. [17086-28-1] (monohydrate); [564-25-0] (anhydrous). [4*S*-(4α,4aα,5α,5aα,6α,12aα)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate; α-6-deoxy-5-hydroxytetracycline monohydrate; α-6-deoxyoxytetracycline monohydrate; 5-hydroxy-α-6-deoxytetracycline monohydrate; GS-3065; Jenacyclin; Supracyclin; Vibramycin. $C_{22}H_{24}N_2O_8.H_2O$; mol wt 462.45. C 57.14%, H 5.67%, N 6.06%, O 31.14%. Prepn of family of 6-deoxytetracyclines: C. R. Stephens *et al., J. Am. Chem. Soc.* **80,** 5324 (1958). *See also:* McCormick, Jensen, **US 3019260** (1962 to Am. Cyanamid). Prepn, separation and configuration of 6α- and 6β-epimers: M. S. von Wittenau *et al., J. Am. Chem. Soc.* **84,** 2645 (1962); C. R. Stephens *et al., ibid.* **85,** 2643 (1963). Prepn of 6α-deoxyoxytetracycline: R. K. Blackwood *et al.,* **US 3200149** (1965 to Pfizer). ^{1}H-NMR study: M. S. von Wittenau, R. K. Blackwood, *J. Org. Chem.* **31,** 613 (1966). Biological properties: English, *Proc. Soc. Exp. Biol. Med.* **122,** 1107 (1966). Pharmacology: Fabre, *Chemotherapia* **11,** 73 (1966); Gibaldi, *ibid.* **12,** 265 (1967). Toxicity of hyclate: Goldenthal, *Toxicol. Appl. Pharmacol.* **18,** 185 (1971). Clinical trial in prophylaxis of leptospirosis: E. T. Takafuji *et al., N. Engl. J. Med.* **310,** 497 (1984). Clinical trial in periodontitis: A. M. Polson *et al., J. Periodontol.* **68,** 110, 119 (1997). *Review:* C. Edwards

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 36 of 65

in *Pharmacological and Biochemical Properties of Drug Substances* **vol. 2,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1979) pp 305-332.

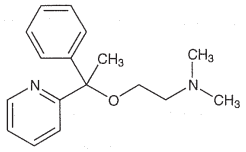


Hydrochloride hemiethanolate hemihydrate. [24390-14-5] Doxycycline hyclate; Atridox; Azudoxat; Bassado; Clinofug; Diocimex; Doryx; Doxatet; Doxicrisol; Doxychel hyclate; Doxylar; Doxytem; Duradoxal; Granudoxy; Hydramycin; Mespafin; Paldomycin; Retens; Ronaxan; Sigadoxin; Spanor; Tetradox; Unacil; Vibramycin Hyclate; Vibra-Tabs; Vibraveineuse; Vibravenös; Zadorin. $C_{22}H_{25}ClN_2O_8.\frac{1}{2}C_2H_6O.\frac{1}{2}H_2O$; mol wt 512.94. Light yellow, crystalline powder from ethanol + HCl. Chars without melting at about 201°. $[\alpha]_D^{25}$ −110° (c = 1 in 0.01*N* methanolic HCl). uv max (0.01*N* methanolic HCl): 267, 351 nm (log ε 4.24, 4.12). Sol in water. The alcohol and water of crystallization are lost by drying at 100° under reduced pressure. More active biologically than the corresponding 6β-epimer hydrochloride (Wittenau, 1962). LD_{50} i.p. in rats: 262 mg/kg (Goldenthal).

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

3475. Doxylamine. [469-21-6] *N,N*-Dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]ethanamine; 2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]pyridine; phenyl-2-pyridylmethyl-β-*N,N*-dimethylaminoethyl ether; 2-dimethylaminoethoxyphenylmethyl-2-picoline. $C_{17}H_{22}N_2O$; mol wt 270.37. C 75.52%, H 8.20%, N 10.36%, O 5.92%. Prepn: C. H. Tilford *et al., J. Am. Chem. Soc.* **70,** 4001 (1948); N. Sperber *et al., ibid.* **71,** 887 (1949). Pharmacology: B. B. Brown, H. Werner, *J. Lab. Clin. Med.* **33,** 325 (1948). GC determn: H. C. Thompson *et al., J. Chromatog. Sci.* **20,** 373 (1982). Chronic toxicity study: C. D. Jackson, B. Blackwell, *J. Am. Coll. Toxicol.* **12,** 1 (1993). Review of properties and pharmacology: T. J. Haley, *Dangerous Prop. Ind. Mater. Rep.* **2,** 17-20 (1982). Clinical evaluation as hypnotic: F. Sjöqvist, L. Lasagna, *Clin. Pharmacol. Ther.* **8,** 48 (1967); as antihistaminic for use in colds: R. Eccles *et al., J. Pharm. Pharmacol.* **47,** 990 (1995).



Liquid, $bp_{0.5}$ 137-141°. Sol in acids. Slightly volatile, darkens on exposure to light.

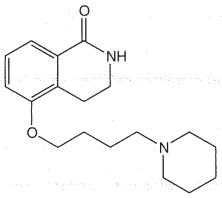
Succinate. [562-10-7] Decapryn; Gittalun; Hoggar N; Mereprine; Unisom. $C_{17}H_{22}N_2O.C_4H_6O_4$; mol wt 388.46. Crystals, mp 100-104°, sol in water. One gram dissolves in 1 ml water, 2 ml alcohol, 2 ml chloroform. Slightly sol in benzene and ether. pH (1% aq soln): 4.9 to 5.1. LD_{50} in mice, rabbits (mg/kg): 470, 250 orally; 62, 49 i.v.; in mice, male rats, female rats (mg/kg): 460, 440, 445 s.c. (Brown, Werner).

Combination with pyridoxine hydrochloride. Bendectin; Debendox. Has been used for nausea of pregnancy. Some formulations also contained dicyclomine, *q.v.* Review of therapeutic use and the issue of teratogenicity: L. J. Sheffield, R. Batagol, *Med. J. Aust.* **143,** 143-147 (1985); R. L. Brent, *Reprod. Toxicol.* **9,** 337-349 (1995).

THERAP CAT: Antihistaminic; sedative, hypnotic.

THERAP CAT (VET): Antihistaminic.

3476. DPQ. [129075-73-6] 3,4-Dihydro-5-[4-(1-piperidinyl)butoxy]-1(2*H*)-isoquinolinone. $C_{18}H_{26}N_2O_2$; mol wt 302.41. C 71.49%, H 8.67%, N 9.26%, O 10.58%. Competitive inhibitor of poly (ADP-ribose)polymerase (PARP). Prepn: M. J. Suto *et al.,* **EP 355720**; *eidem,* **US 5177075** (1990, 1993 both to Warner-Lambert). Use and effects as inhibitior: M. J. L. Eliasson *et al., Nature Med.* **3,** 1089 (1997); K. Takahashi *et al., Brain Res.* **829,** 46 (1999).



Crystals from water, mp 107-109°. Water soluble.

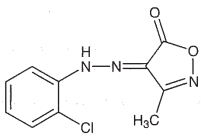
USE: Reagent for inhibition of PARP.

3477. Dragon's Blood. A resinous secretion found on the fruits of *Daemonorops propinquus* Becc., *D. draco* Blume, and probably other species of *Daemonorops, Palmae* (Rattan palms). *Habit.* Sumatra, Borneo, India. *Constit.* About 55% of a red resin contg about 12-15% of bright-yellow, amorphous dracoresene; 2-3% white amorphous dracoalban. Isoln of the main coloring matter, dracorubin: Brockmann, Haase, *Ber.* **69,** 1950 (1936). Chemical studies of resin pigments: Olaniyi *et al., J. Chem. Soc. Perkin Trans. I* **1973,** 179.

Red sticks, pieces, or cakes; vitreous fracture; makes a bright-crimson powder; odorless and almost tasteless. mp ~120° with sublimation of some benzoic acid. Insol in water; sol in alcohol.

USE: For coloring lacquers and varnishes; occasionally for coloring plasters; in photoengraving on zinc to protect metal parts against etching.

3478. Drazoxolon. [5707-69-7] 3-Methyl-4-[(2-chlorophenyl)hydrazone]-4,5-isoxazoledione; 4-(2-chlorophenylhydrazono)-3-methyl-5(4*H*)-isoxazolone; 3-methyl-4-(*o*-chlorophenylhydrazono)-5-isoxazolone; PP-781; Ganocide; Mil-Col. $C_{10}H_8ClN_3O_2$; mol wt 237.65. C 50.54%, H 3.39%, Cl 14.92%, N 17.68%, O 13.46%. Prepn: Green, Roberts, **GB 1049103** (1966 to ICI). Structure: Summers, Shields, *Chem. & Ind. (London)* **1964,** 1264. Soil degradation studies: Anderson, Horsgood, *Soil Biol. Biochem.* **3,** 271 (1971). Hydrolysis: Lehtonen *et al., Pestic. Sci.* **3,** 357 (1972). Toxicology: D. G. Clark, T. F. McElligott, *Food Cosmet. Toxicol.* **7,** 481 (1969). *Review:* Yuen, *Anal. Methods Pestic. Plant Growth Regul.* **7,** 665-673 (1973).



Yellow crystals, possessing faint odor, from methanol-benzene, mp 168°. Practically insol in water, acids, and aliphatic hydrocarbons. Sol in alkali, aromatic hydrocarbons (4%), chloroform (about 10%), ethanol (1%), ketones (5%). Stable to dilute acids and forms stable salts with alkalies. LD_{50} orally in female rats, mice: 126, 129 mg/kg (Clark, McElligott).

USE: Fungicide.

3479. Drimenin. [2326-89-8] [5a*S*-(5aα,9aβ,9bα)]-5,5a,6,7,8,9,9a,9b-Octahydro-6,6,9a-trimethylnaphtho[1,2-*c*]-furan-1(3*H*)-one. $C_{15}H_{22}O_2$; mol wt 234.33. C 76.88%, H 9.46%, O 13.66%. From bark of *Drimys winteri* Forst., *Magnoliaceae:* Appel, Dohr, *Scientia* **25,** 137 (1958); *C.A.* **54,** 4663f

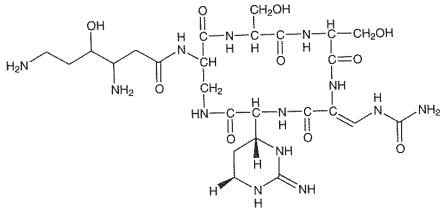
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 37 of 65

on ethylenediamine: Lundsted, Schulz, **US 2697118** (1954 to Wyandotte).

Viscous liq. $bp_{1.0}$ 190°. Miscible with water. Sol in methanol, ethanol, toluene, ethylene glycol, perchloroethylene.

USE: Cross-linking agent and catalyst in the manuf of urethan foams; in epoxy resin curing; as complexing agent, humectant, emulsifier, plasticizer.

3631. Enviomycin. [33103-22-9] Tuberactinomycin N; (*R*)-1-[(3*R*,4*R*)-4-hydroxy-3,6-diaminohexanoic acid]-6-[L-2-(2-amino-1,4,5,6-tetrahydro-4-pyrimidinyl)glycine]viomycin. $C_{25}H_{43}N_{13}O_{10}$; mol wt 685.69. C 43.79%, H 6.32%, N 26.56%, O 23.33%. Polypeptide antibiotic produced by a mutant of *Streptomyces griseoverticillatus* var. *tuberacticus*. Isoln and characterization: T. Ando *et al., J. Antibiot.* **24,** 680 (1971); A. Nagata *et al.,* in *Advan. Antimicrob. Antineopl. Chemother.* **vol. 1/2,** M. Hejzlar *et al.,* Eds. (University Park Press, Baltimore, 1972) pp 1039-1041. Prepn: J. Abe *et al.,* **DE 2133181**; *eidem,* **US 3892732** (1972, 1975 both to Toyo Brewing Co., Ltd.). Structural studies: H. Yoshioka *et al., Tetrahedron Letters* **1971,** 2043; T. Wakamiya, T. Shiba, *J. Antibiot.* **28,** 292 (1975). Pharmacology: H. Hamakawa *et al., Oyo Yakuri* **8,** 817 (1974), *C.A.* **82,** 51530y (1975). Metabolism: T. Shimizu *et al., Japan. J. Antibiot.* **27,** 279 (1974). Total synthesis: T. Shiba *et al., J. Antibiot.* **32,** 1078 (1979).

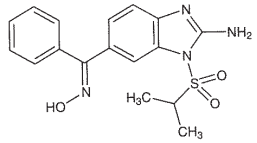


Hydrochloride. $C_{25}H_{43}N_{13}O_{10}.3HCl$. White crystalline powder, mp >245° (dec). $[\alpha]_D^{21}$ −19.1°. uv max (water, 0.1*N* HCl): 268 nm ($E_{1cm}^{1\%}$ 342); uv max (0.1*N* NaOH): 288 nm ($E_{1cm}^{1\%}$ 215). Very sol in water, slightly sol in methanol, ethanol. Insol in common organic solvents.

Sulfate. Tuberactin. $C_{50}H_{92}N_{26}O_{32}S_3$; mol wt 1665.63. White crystalline powder. Sol in water, slightly sol in usual organic solvents. LD_{50} in mice, rats (mg/kg): 485, 680 i.v. (Hamakawa).

THERAP CAT: Antibacterial (tuberculostatic).

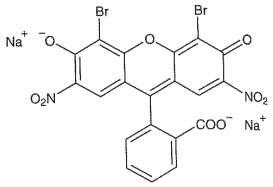
3632. Enviroxime. [72301-79-2] 6-[(Hydroxyimino)-phenylmethyl]-1-[(1-methylethyl)sulfonyl]-1*H*-benzimidazol-2-amine; (*E*)-2-amino-6-benzoyl-1-(isopropylsulfonyl)benzimidazole oxime; *anti*-2-amino-1-(isopropylsulfonyl)-6-(α-hydroxyiminobenzyl)benzimidazole; LY-122772. $C_{17}H_{18}N_4O_3S$; mol wt 358.42. C 56.97%, H 5.06%, N 15.63%, O 13.39%, S 8.95%. Benzimidazole deriv that inhibits rhinovirus multiplication. Prepn: C. J. Paget *et al.,* **DE 2638551** corresp to **US 4118742** (1977, 1978 both to Lilly). Synthesis and sepn of *syn* and *anti* isomers: J. H. Wikel *et al., J. Med. Chem.* **23,** 368 (1980). Inhibition of rhinovirus replication in organ culture: D. C. De Long, S. E. Reed, *J. Infect. Dis.* **141,** 87 (1980). Metabolic studies: J. F. Quay *et al., Fed. Proc.* **39,** 3079 (1980); C. J. Parli *et al., ibid.* 214. Activity vs rhinovirus infection in man: R. J. Phillpotts *et al., Lancet* **1,** 1342 (1981). Prophylactic activity: F. G. Haden, J. M. Gwaltney, *Antimicrob. Ag. Chemother.* **21,** 892 (1982).



Cryst from acetonitrile, mp 198-199°. uv max (methanol): 218, 290 nm (ε 45600, 27100).

***(Z)*-isomer.** Zinviroxime. Cryst from methanol, mp 182-183°. uv max (methanol): 254, 285 nm (ε 20800, 13200).

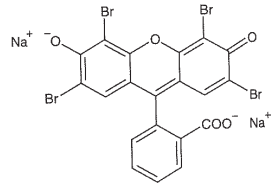
3633. Eosine I Bluish. [548-24-3] 4′,5′-Dibromo-3′,6′-dihydroxy-2′,7′-dinitrospiro[isobenzofuran-1(3*H*),9′-[9*H*]xanthen]-3-one disodium salt; 4′,5′-dibromo-2′,7′-dinitrofluorescein disodium salt; hydroxydibromodinitro-*o*-carboxyphenylfluorone sodium; C.I. Acid Red 91; C.I. 45400. $C_{20}H_6Br_2N_2Na_2O_9$; mol wt 624.06. C 38.49%, H 0.97%, Br 25.61%, N 4.49%, Na 7.37%, O 23.07%. Prepd by nitration of 4′,5′-dibromofluorescein: *Colour Index* **vol. 4** (3rd ed., 1971) p 4427.



Red powder. Freely sol in water with green fluorescence; sol in alc.

USE: Dyeing wool, cotton, and paper. In histology as a stain for epithelia, muscular fibers, nuclei, etc.

3634. Eosine Yellowish—(YS). [17372-87-1] 2′,4′,5′,7′-Tetrabromo-3′,6′-dihydroxyspiro[isobenzofuran-1(3*H*),9′-[9*H*]xanthen]-3-one disodium salt; 2′,4′,5′,7′-tetrabromofluorescein; bromoeosine; tetrabromofluorescein sol; bromofluoresceic acid; eosin; eosine; eosin Y; D & C Red No. 22; C.I. Acid Red 87; C.I. 45380. $C_{20}H_6Br_4Na_2O_5$; mol wt 691.86. C 34.72%, H 0.87%, Br 46.20%, Na 6.65%, O 11.56%. Xanthene dye capable of photodynamic generation of singlet oxygen. Prepd by bromination of fluorescein: *Colour Index* **vol. 4** (3rd ed., 1971) p 4426. Photodynamic injury to leaf tissue and inhibition of photosynthesis: J. P. Knox, A. D. Dodge, *Planta* **164,** 22; 30 (1985). *Review:* H. J. Conn's *Biological Stains,* R. D. Lillie, Ed. (Williams & Wilkins, Baltimore, 9th ed., 1977), pp 342-344.



Red crystals with bluish tinge, or brownish-red powder. Freely sol in water, less in alcohol. Insol in ether. The concd aq soln is deep brownish-red, the dilute (1:500) soln is yellowish-red with greenish fluorescence; the alcoholic soln exhibits a strong green fluorescence.

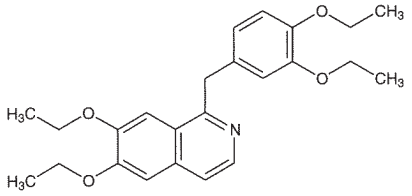
Free acid. Eosine acid; D & C Red No. 21; C.I. Solvent Red 43; C.I. 45380:2. $C_{20}H_8Br_4O_5$. Bright yellowish red. Sol in acetone, ethanol. Insol in mineral oil, toluene.

USE: In microbiological differential media. Colorant in drugs and cosmetics such as lipstick and nail-polish; dyeing wool, silk and paper; in red inks; as biological stain.

3635. Eotaxin. Chemoattractant protein that is highly selective for eosinophils. Member of the family of proinflammatory substances known as CC (or β-) chemokines. Purification and proposed role in allergic asthma: D. A. Griffiths-Johnson *et al., Biochem. Biophys. Res. Commun.* **197,** 1167 (1993); P. J. Jose *et al., J. Exp. Med.* **179,** 881 (1994). Cloning of guinea pig eotaxin: *idem et al., Biochem. Biophys. Res. Com-*

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 38 of 65

3763. Ethaverine. [486-47-5] 1-[(3,4-Diethoxyphenyl)-methyl]-6,7-diethoxyisoquinoline; 6,7-diethoxy-1-(3,4-diethoxybenzyl)isoquinoline; ethylpapaverine; Dyscural. $C_{24}H_{29}NO_4$; mol wt 395.49. C 72.89%, H 7.39%, N 3.54%, O 16.18%. Tetraethyl homolog of papaverine. Synthesis: Wolf, **US 1962224** (1934).



Crystals from alcohol + ether, mp 99-101°. Insol in water. Readily sol in hot alc; slightly in ether and chloroform.

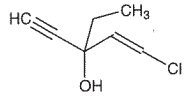
Hydrochloride. [985-13-7] Barbonin; Circubid; Diquinol; Ethabid; Isovex; Laverin; Perparin; Perperine. $C_{24}H_{29}NO_4.HCl$; mol wt 431.96. Prepn of stable solns: Hereld, **US 2971888** (1961). Crystals from abs alc, mp 186-188° (dec). One gram dissolves in about 40 ml water. pH of 1% soln 3.6; of 0.1% soln 4.6.

Acid oxalate. $C_{24}H_{29}NO_4.(COOH)_2$. Crystals from alc, soluble in hot water.

Salt with 7-iodo-8-hydroxyquinoline-5-sulfonic acid. HU 106906 (1931); v. Issekutz *et al., Arch. Exp. Pathol. Pharmakol.* **164,** 158 (1932).

THERAP CAT: Antispasmodic.

3764. Ethchlorvynol. [113-18-8] 1-Chloro-3-ethyl-1-penten-4-yl-3-ol; 5-chloro-3-ethylpent-1-yn-4-en-3-ol; ethyl β-chlorovinyl ethynyl carbinol; ethclorvynol; Placidyl; Arvynol; Serenesil; Roeridorm; Normoson. C_7H_9ClO; mol wt 144.60. C 58.14%, H 6.27%, Cl 24.52%, O 11.06%. Prepn: W. M. McLamore *et al., J. Org. Chem.* **20,** 109 (1955); Bavley, McLamore, **US 2746900** (1956 to Pfizer). Pharmacological studies: S. Y. P'an *et al., J. Pharmacol. Exp. Ther.* **114,** 326 (1955). Pharmacodynamics: Y. C. Martin, *Biochem. Pharmacol.* **16,** 2041 (1967). Evaluation as hypnotic: J. W. Middleton *et al., Curr. Ther. Res.* **8,** 391 (1966); J. H. Pattison *et al., J. Am. Geriatric Soc.* **20,** 398 (1972). Study of metabolites: J. P. Horwitz *et al., Drug Metab. Dispos.* **8,** 77 (1980).

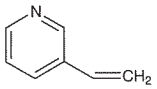


Liquid, pungent aromatic odor. Slowly darkens on exposure to light and air. d_4^{25} 1.065-1.070 (also reported as d_4^{20} 1.070). bp_{760} 173-174° (also reported as bp_{760} 181°); $bp_{0.1}$ 28.5-30°. n_D^{25} 1.4675-1.4800. Immiscible with water; miscible with most organic solvents. LD_{50} in mice (mg/kg): 290 orally; 240 s.c. (P'an).

Note: This is a controlled substance (depressant): **21 CFR,** 1308.14.

THERAP CAT: Sedative; hypnotic.

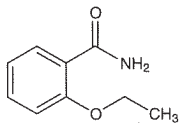
3765. 3-Ethenylpyridine. [1121-55-7] β-vinylpyridine; 3-EP. C_7H_7N; mol wt 105.14. C 79.96%, H 6.71%, N 13.32%. Combustion product of nicotine found in mainstream and sidestream smoke from cigarettes and cigars. Prepn: H. A. Iddles *et al., J. Am. Chem. Soc.* **59,** 1945 (1937). Electronic spectra: R. Abu-Eittah *et al., Int. J. Quantum Chem.* **39,** 211 (1991). Toxicology: K. D. Brunnemann *et al., Cancer Letters* **65,** 107 (1992). Use as tracer for environmental tobacco smoke exposure: M. W. Ogden, *Anal. Commun.* **33,** 197 (1996); J. M. Daisey *et al., J. Exposure Anal. Environ. Epidemiol.* **8,** 313 (1998). Rapid chromatographic determn in indoor environments: G. Bertoni *et al., Chromatographia* **43,** 296 (1996).



Light-yellow liquid. Polymerizes at room temperatures. Sol in ether, partially sol in alcohol and very slightly sol in water. uv max (cyclohexane): 278, 239 nm (ε 3320, 3920 L/mol cm); uv max (methanol): 279, 238 nm (ε 3322, 3930 L/mol cm).

USE: Tracer compound for environmental tobacco smoke.

3766. Ethenzamide. [938-73-8] 2-Ethoxybenzamide; ethbenzamide; 2-ethoxybenzenecarbonamide; salicylamide *o*-ethyl ether; Lucamide; Protopyrin; Trancalgyl. $C_9H_{11}NO_2$; mol wt 165.19. C 65.44%, H 6.71%, N 8.48%, O 19.37%. Prepn: **GB 656746** (1951 to H. Lundbeck); Shapiro *et al., J. Am. Chem. Soc.* **81,** 3728 (1959); Bryk, Osowski, **PL 47822** (1961 to Polfa), *C.A.* **61,** 5573f (1964). Metabolism: Davison *et al., J. Pharmacol. Exp. Ther.* **136,** 226 (1962). Toxicity data: Starmer *et al., Toxicol. Appl. Pharmacol.* **19,** 20 (1971).



Crystals from ethyl acetate + hexane, mp 132-134°. LD_{50} orally in mice: 1160 mg/kg (Starmer).

THERAP CAT: Analgesic.

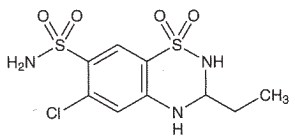
3767. Ethephon. [16672-87-0] (2-Chloroethyl)phosphonic acid; 2-chloroethanephosphonic acid; CEPA; camposan; Cerone; Ethrel; Sierra. $C_2H_6ClO_3P$; mol wt 144.49. C 16.63%, H 4.19%, Cl 24.54%, O 33.22%, P 21.44%. $ClCH_2CH_2PO(OH)_2$. Ethylene-releasing agent used to control growth and ripening of fruit crops. Prepn: Kabachnik, Rossiiskaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* **1946,** 403-410, *C.A.* **42,** 7242e (1948); *Beilstein* **EIII 4,** 1780. Toxicity data: G. Hennighausen *et al., Pharmazie* **32,** 181 (1977). Review of use in viticulture: E. Szyjewicz *et al., Am. J. Enol. Viticult.* **35,** 117-123 (1984).

Very hygroscopic needles from benzene (must be dried over P_2O_5). mp 74-75°. Freely sol in water, methanol, acetone, ethylene glycol, propylene glycol. Slightly sol in benzene, toluene. Practically insol in petr ether. Aq solns are stable below pH 3.5. Above pH 3.5 hydrolysis begins with the release of free ethylene. LD_{50} orally in mice: 2850 mg/kg (Hennighausen).

Caution: Spray formulations are quite acidic, about pH 1.0. May be irritating to exposed skin and eyes, or if inhaled.

USE: Plant growth regulator.

3768. Ethiazide. [1824-58-4] 6-Chloro-3-ethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide; 6-chloro-3-ethyl-3,4-dihydro-7-sulfamoylbenzo-1,2,4-thiadiazine 1,1-dioxide; 3-ethyl-3,4-dihydro-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide; acthiazidum. $C_9H_{12}ClN_3O_4S_2$; mol wt 325.80. C 33.18%, H 3.71%, Cl 10.88%, N 12.90%, O 19.64%, S 19.68%. Prepn: Close *et al., J. Am. Chem. Soc.* **82,** 1132 (1960); Topliss *et al., J. Org. Chem.* **26,** 3842 (1961); **GB 861367** (1961 to Ciba).

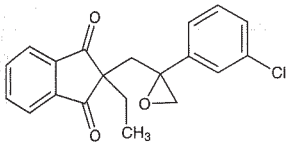


Crystals from tetrahydrofuran + chloroform, mp 269-270°. Component of ***Hypertane***.

THERAP CAT: Diuretic.

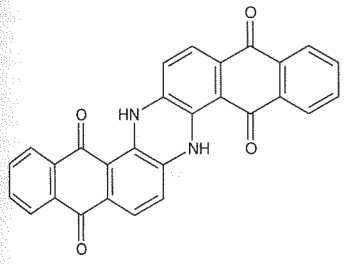
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 39 of 65

Vapor pressure at 25°: 2.8×10^{-6} Pa. LD_{50} male, female rats (mg/kg): 631, 460 orally; >2000, >2000 dermally. LC_{50} in rats (mg/l): 1.57 by inhalation (Yagi).



USE: Herbicide.

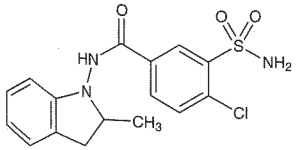
4959. Indanthrene®. [81-77-6] 6,15-Dihydro-5,9,14,18-anthrazinetetrone; *N,N'*-dihydro-1,2,1',2'-anthraquinonazine. $C_{28}H_{14}N_2O_4$; mol wt 442.42. C 76.01%, H 3.19%, N 6.33%, O 14.47%. Vat dye discovered by René Bohn (1901). Prepn: Fierz-David, Blangey, *Grundlegende Operationen der Farbenchemie* (Vienna, 5th ed., 1943) pp 304-305; Thielert, Bauman, **US 2693469** (1954 to Bayer); Sutter, Fioroni, **US 2831860** (1958 to Ciba); Kastner, **US 3138612** (1964 to Allied Chem.). Structure: Weinstein, Merrit, *J. Am. Chem. Soc.* **81,** 3759 (1959).



Blue powder, dec 470-500°. uv max on cellophane film: 278 nm. Practically insol in organic solvents. Sol in concd H_2SO_4, in dil alkali solns. ***Indanthrene Blue R***, the usual commercial grade, is extremely stable to light and heat, but sensitive to chlorine. A purer grade, which is not as sensitive to chlorine, is sold as ***Indanthrene Brilliant Blue FF***.

USE: Mainly to dye cotton.

4960. Indapamide. [26807-65-8] 3-(Aminosulfonyl)-4-chloro-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)benzamide; 4-chloro-*N*-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide; *N*-(3-sulfamyl-4-chlorobenzamido)-2-methylindoline; S-1520; SE-1520; Bajaten; Damide; Fludex; Indaflex; Indamol; Ipamix; Lozol; Natrilix; Noranat; Tandix; Veroxil. $C_{16}H_{16}ClN_3O_3S$; mol wt 365.84. C 52.53%, H 4.41%, Cl 9.69%, N 11.49%, O 13.12%, S 8.76%. Prepn: Beregi *et al.*, **FR 2003311**; *eidem*, **US 3565911** (1969, 1971, both to Sci. Union et Cie, Soc. Franc. Recherche Med.). Pharmacology: Leary *et al., Curr. Ther. Res. Clin. Exp.* **15,** 571 (1973); D. B. Campbell, R. A. Moore, *Postgrad. Med. J., Suppl.* **57,** 7 (1981). Acute toxicity data: J. Kyncl *et al., Arzneimittel-Forsch.* **25,** 1491 (1975). Symposium on pharmacology and clinical efficacy: *Am. J. Med.* **84,** Suppl. 1B, 1-111 (1988); *Am. J. Cardiol.* **65,** Suppl. H, 1H-80H (1990). Comprehensive description: T. J. DiFeo, J. E. Shuster, *Anal. Profiles Drug Subs. Excip.* **23,** 229-268 (1994).

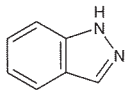


Crystals from isopropanol/water, mp 160-162°. uv max (methanol): 242, 278, 286 nm ($A^{1\%}_{1cm}$ 630, 98, 100). Sol in methanol, acetic acid, ethyl acetate. Very slightly sol in chloroform. pKa (25°) 8.8 ± 0.2. LD_{50} in rats, mice, guinea pigs (mg/kg): 393-421, 410-564, 347-416 i.p.; 394-440, 577-635, 272-358 i.v.; >3000 all species orally (Kyncl).

Hemihydrate. Pressural. $C_{16}H_{16}ClN_3O_3S.½H_2O$; mol wt 374.85.

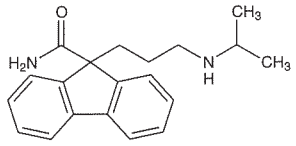
THERAP CAT: Antihypertensive; diuretic.

4961. 1*H*-Indazole. [271-44-3] Isoindazole; benzopyrazole. $C_7H_6N_2$; mol wt 118.14. C 71.17%, H 5.12%, N 23.71%. Prepn: Stephenson, *Org. Syn.*, **coll. vol. III,** 475 (1955); Ainsworth, *Org. Syn.* **39,** 27 (1959); Huisgen, Bast, *ibid.* **42,** 69 (1962).



Needles from hot water, mp 146.5°. bp_{743} 267-270°. Sol in hot water, alcohol, ether.

4962. Indecainide. [74517-78-5] 9-[3-[(1-Methylethyl)-amino]propyl]-9*H*-fluorene-9-carboxamide; 9-carbamoyl-9-(3-isopropylaminopropyl)fluorene; 9-[3-(isopropylamino)propyl]-9-(aminocarboyl)fluorene; ricainide. $C_{20}H_{24}N_2O$; mol wt 308.42. C 77.89%, H 7.84%, N 9.08%, O 5.19%. Prepn: W. B. Lacefield, R. L. Simon, **US 4197313** and **US 4452745** (1980, 1984 both to Lilly). Pharmacokinetics in animals: T. L. Lindstrom, G. W. Whitaker, *Drug Metab. Dispos.* **12,** 683 (1984). Metabolism: *eidem, ibid.* 691. LC determn in biological fluids: K. Z. Farid *et al., J. Chromatog.* **337,** 329 (1985). Toxicological studies: G. E. Sandusky, Jr., D. B. Meyers, *Fundam. Appl. Toxicol.* **5,** 175 (1985). Clinical evaluation in cardiac arrhythmias: P. F. Nestico *et al., Am. J. Cardiol.* **59,** 1332 (1987); P. J. Podrid *et al., ibid.* **61,** 764 (1988).

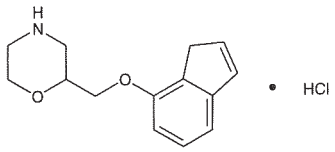


Crystals from Skelly B, mp 94-95°.

Hydrochloride. [73681-12-6] LY-135837; Decabid. $C_{20}H_{24}N_2O.HCl$; mol wt 344.89. Crystals from chloroform, mp 216.5-217°; also reported as crystals from fresh ethanol and diethyl ether, mp 203-204°. LD_{50} orally in male, female mice, rats: 100, 96, 103, 82 mg/kg (Sandusky, Meyers).

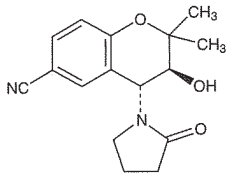
THERAP CAT: Antiarrhythmic (cardiac depressant).

4963. Indeloxazine Hydrochloride. [65043-22-3] 2-[(1*H*-Inden-7-yloxy)methyl]morpholine hydrochloride; (±)-2-[(7-indenyloxy)methyl]morpholine hydrochloride; YM-08054-1; Elen; Noin. $C_{14}H_{18}ClNO_2$; mol wt 267.76. C 62.80%, H 6.78%, Cl 13.24%, N 5.23%, O 11.95%. Serotonin uptake inhibitor. Prepn: M. Masuo *et al.*, **DE 2601703**; *eidem*, **US 4109088** (1976, 1978 both to Yamanouchi). Synthesis and resolution of isomers: T. Kojima *et al., Chem. Pharm. Bull.* **33,** 3766 (1985). Pharmacology and toxicity: S. Tachikawa *et al., Arch. Int. Pharmacodyn.* **238,** 81 (1979). Inhibition of synaptosomal uptake of serotonin and noradrenaline: M. Harada, H. Maeno, *Biochem. Pharmacol.* **28,** 2645 (1979). GLC determn in human plasma: A. G. Hayes, T. Chang, *J. Chromatog.* **272,** 176 (1983).



NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 40 of 65

et al., Arzneimittel-Forsch. **41,** 385 (1991). Clinical evaluation in hypertension: S. Suzuki *et al., ibid.* **45,** 859 (1995).



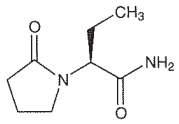
Crystals from ethyl acetate, mp 242-244°. $[\alpha]_D^{26}$ −52.2° (c = 1 in chloroform).

(+)-Form. Crystals from ethyl acetate, mp 243-245°. $[\alpha]_D^{26}$ +53.5° (c = 1 in chloroform).

(±)-Form. [94470-67-4] Cromakalim; BRL-34915. Crystals from ethyl acetate, mp 230-231°.

THERAP CAT: Antihypertensive.

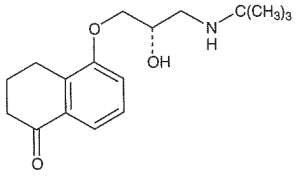
5482. Levetiracetam. [102767-28-2] (α*S*)-α-Ethyl-2-oxo-1-pyrrolidineacetamide; 2(*S*)-(2-oxopyrrolidin-1-yl)butyramide; UCB-L059; SIB-S1; Keppra. $C_8H_{14}N_2O_2$; mol wt 170.21. C 56.45%, H 8.29%, N 16.46%, O 18.80%. (*S*)-Enantiomer of the ethyl analog of piracetam, *q.v.* Prepn: J. Gobert *et al.,* **EP 162036**; *eidem,* **US 4943639** (1985, 1990 both to UCB). Pharmacological profile: A. J. Gower *et al., Eur. J. Pharmacol.* **222,** 193 (1992). HPLC determn in serum or plasma: N. Ratnaraj *et al., Ther. Drug Monit.* **18,** 154 (1996). Clinical evaluation in epilepsy: D. G. A. Kasteleijn-Nolst Trenité *et al., Epilepsy Res.* **25,** 225 (1996).



Crystals from ethyl acetate, mp 117°. $[\alpha]_D^{25}$ −90.0° (c = 1 in acetone). Readily sol in water. LD_{50} in male mice, male rats (mg/kg): 1081, 1038 i.v. (Gobert, 1990).

THERAP CAT: Anticonvulsant.

5483. Levobunolol. [47141-42-4] 5-[(2*S*)-3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone; (−)-5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone; *l*-bunolol; W-6421A. $C_{17}H_{25}NO_3$; mol wt 291.38. C 70.07%, H 8.65%, N 4.81%, O 16.47%. Nonselective β-adrenoceptor antagonist. Prepn of racemate: C. F. Schwender *et al., J. Med. Chem.* **13,** 684 (1970); J. Shavel, Jr., S. Farber, **DE 1948144**; *eidem,* **US 3641152** (1970, 1972 both to Warner-Lambert). Resolution of enantiomers: J. Shavel, Jr., C. F. Schwender, **DE 2046043**; *eidem,* **US 3649691** (1971, 1972 both to Warner-Lambert); R. D. Dennis *et al.,* **US 4463176** (1984 to Bristol Myers, Mead Johnson). Cardiovascular pharmacology, anti-arrhythmic activity of racemate and isomers: R. D. Robson, H. R. Kaplan, *J. Pharmacol. Exp. Ther.* **175,** 157, 168 (1970). Adrenoceptor blocking activity: H. R. Kaplan *et al., Eur. J. Pharmacol.* **16,** 237 (1971). Metabolism in humans: F. J. DiCarlo *et al., Clin. Pharmacol. Ther.* **22,** 858 (1977); F.-J. Leinweber *et al., Pharmacology* **16,** 70 (1978). Corneal permeability: R. D. Schoenwald, H.-S. Huang, *J. Pharm. Sci.* **72,** 1266, 1272 (1983). HPLC determn in biological fluids: H. Hengy, E. U. Kolle, *J. Chromatog.* **338,** 444 (1985); D. D. S. Tang-Liu *et al., J. Liq. Chromatog.* **9,** 2237 (1986). Clinical evaluation in hypertension: E. Arce-Gomez *et al., Curr. Ther. Res.* **19,** 386 (1976); comparison with timolol, *q.v.,* in glaucoma and ocular hypertension: A. Cinotti *et al., Am. J. Ophthalmol.* **99,** 11 (1985); D. Long *et al., ibid.* 18. *Review:* H. R. Kaplan, "Levobunolol" in *Pharmacology of Antihypertensive Drugs,* A. Scriabine, Ed. (Raven Press, New York, 1980) pp 317-323. Brief review of long-term treatment of glaucoma: G. D. Novack, *Gen. Pharmacol.* **17,** 373-377 (1986).

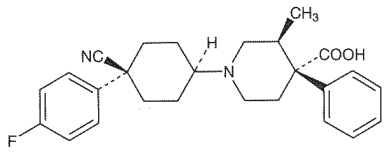


LD_{50} in male, female rats, mice (mg/kg): 700, 800, 1530, 1220 orally; 25, 28, 78, 84 i.v.; LD_{50} in male, female hamsters, dogs (mg/kg): 435, 500, 100, 100 orally (Kaplan, 1980).

Hydrochloride. [27912-14-7] W-7000A; Betagan; Vistagan; Gotensin. $C_{17}H_{25}NO_3$.HCl; mol wt 327.85. Crystals from methanol-ether, mp 209-211°. $[\alpha]_{589}^{24}$ −19.6±0.7° (c = 2.90 in methanol). uv max (NaOH): 221, 253, 310 nm (ε 24700, 9000, 2400).

THERAP CAT: Antiglaucoma.

5484. Levocabastine. [79516-68-0] [3*S*-[1(*cis*),3α,4β]]-1-[4-Cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidinecarboxylic acid; (−)-*trans*-1-[*cis*-4-cyano-4-(*p*-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid; (−)-cabastine. $C_{26}H_{29}FN_2O_2$; mol wt 420.52. C 74.26%, H 6.95%, F 4.52%, N 6.66%, O 7.61%. Histamine H_1-receptor antagonist. Prepn: R. Stokbroekx *et al.,* **EP 34415**; *eidem,* **US 4369184** (1981, 1983 both to Janssen); and pharmacology: R. A. Stokbroekx *et al., Drug Dev. Res.* **8,** 87 (1986). Pharmacology: K. Tasaka *et al., Arzneimittel-Forsch.* **40,** 1295 (1990). Clinical pharmacology: N. Rombaut *et al., Ann. Allergy* **67,** 75 (1991). Clinical trial in children with allergic conjunctivitis: M. Rimas *et al., Allergy* **45,** 18 (1990); in allergic rhinitis: M. Schata *et al., J. Allergy Clin. Immunol.* **87,** 873 (1991). Review of pharmacology and therapeutic use: K. L. Dechant, K. L. Goa, *Drugs,* **41,** 202-224 (1991).



Hydrochloride. [79547-78-7] R-50547; Levophta; Livostin. $C_{26}H_{29}FN_2O_2$.HCl; mol wt 456.99.

THERAP CAT: Antihistaminic.

5485. Levodopa. [59-92-7] 3-Hydroxy-L-tyrosine; (−)-3-(3,4-dihydroxyphenyl)-L-alanine; L-dopa; β-(3,4-dihydroxyphenyl)-L-alanine; (−)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid; Bendopa; Deadopa; Dopaflex; Dopal; Dopaidan; Dopalina; Dopar; Doparkine; Doparl; Dopasol; Dopaston; Dopastral; Cidandopa; Doprin; Eldopal; Eldopar; Eldopatec; Eurodopa; Laradopa; Maipedopa; Larodopa; Ledopa; Parda; Levopa; Veldopa (formerly Weldopa). $C_9H_{11}NO_4$; mol wt 197.19. C 54.82%, H 5.62%, N 7.10%, O 32.45%. Naturally occurring form of dopa, *q.v.,* the biological precursor of the catecholamines. Prepn from *l*-3-nitrotyrosin: Wasser, Lewandowski, *Helv. Chim. Acta* **4,** 657 (1921); from 3-(3,4-methylenedioxyphenyl)-L-alanine: Yamada *et al., Chem. Pharm. Bull.* **10,** 693 (1962); from L-tyrosine: Vorbrüggen, Krolikiewicz, *Ber.* **105,** 1168 (1972); Bretschneider *et al., Helv. Chim. Acta* **56,** 2857 (1973); from *Vicia faba* beans: Wysong, **US 3253023** (1966 to Dow Chem.); by fermentation of L-tyrosine: Sih *et al., J. Am. Chem. Soc.* **91,** 6204 (1969); Florent, Renaut, **DE 2102793** (1971 to Rhône-Poulenc), *C.A.* **75,** 108505f (1971). Sepn from racemate: Vogler, Baumgartner, *Helv. Chim. Acta* **35,** 1776 (1952); **NL 6514950**; **US 3405159** (1966, 1968 both to Merck & Co.). Molecular conformation: Becker *et al., Biochem. Biophys. Res. Commun.* **41,** 444 (1970). Metabolism studies: Shaw *et al., J. Biol. Chem.* **226,** 255 (1957); Calne *et al., Brit. J. Pharmacol.* **37,** 57 (1969). Hemodynamic effects in congestive heart failure: S. I. Rajfer *et al., N. Engl. J. Med.* **310,** 1357 (1984). Series of articles on clinical efficacy in Parkin-

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 41 of 65

Hydrochloride. [55-86-7] Caryolysine; Cloramin; Dichloren; Embichen; Embikhine; Erasol; Mustargen hydrochloride; Mustine hydrochloride; Nitrogranulogen. $C_5H_{11}Cl_2N.HCl$; mol wt 192.52. Hygroscopic leaflets from acetone or chloroform, mp 109-111°. Very sol in water; sol in alcohol. Initial pH of a 2% aq soln: 3.0-4.0. Dry crystals are stable at temps up to 40°. LD_{50} in rats (mg/kg): 1.1 i.v.; 1.9 s.c. (Anslow).

Caution: Direct contact may cause severe skin and eye irritation; injury to deeper ocular structures, particularly the iris and lens. *See Patty's Industrial Hygiene and Toxicology* **vol. 2E,** G. D. Clayton, F. E. Clayton, Eds. (John Wiley & Sons, Inc., New York, 4th ed., 1994) pp 3297-3299. Mechlorethamine hydrochloride is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-163.

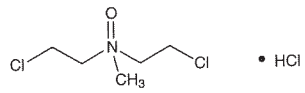
***N*-Oxide hydrochloride,** *see* separate entry

USE: Base as a gas warfare agent.

THERAP CAT: Hydrochloride as an antineoplastic.

THERAP CAT (VET): Hydrochloride has been used as an antineoplastic.

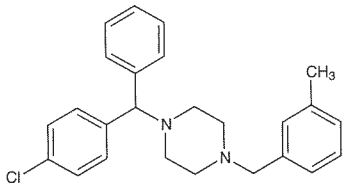
5799. Mechlorethamine Oxide Hydrochloride. [302-70-5] 2-Chloro-*N*-(2-chloroethyl)-*N*-methylethanamine *N*-oxide hydrochloride; 2,2′-dichloro-*N*-methyldiethylamine *N*-oxide hydrochloride; *N*-methyl-2,2′-dichlorodiethylamine *N*-oxide hydrochloride; methylbis(β-chloroethyl)amine *N*-oxide hydrochloride; methyldi(2-chloroethyl)amine *N*-oxide hydrochloride; Nitromin; Mitomen; Mustron. $C_5H_{12}Cl_3NO$; mol wt 208.52. C 28.80%, H 5.80%, Cl 51.01%, N 6.72%, O 7.67%. Prepd by treating 2,2′-dichloro-*N*-methyldiethylamine with hydrogen peroxide and acetic anhydride in ether, followed by shaking with 10% hydrochloric acid: Aiko *et al., J. Pharm. Soc. Japan* **72,** 1297 (1952, English Text), *C.A.* **47,** 1289 (1953). *Cf.* Stahmann, Bergmann, *J. Org. Chem.* **11,** 586 (1946).



Prisms from acetone, mp 109-110°. Sol in water.

THERAP CAT: Antineoplastic.

5800. Meclizine. [569-65-3] 1-[(4-Chlorophenyl)phenylmethyl]-4-[(3-methylphenyl)methyl]piperazine; 1-(*p*-chloro-α-phenylbenzyl)-4-(*m*-methylbenzyl)piperazine; 1-(*p*-chlorobenzhydryl)-4-(*m*-methylbenzyl)diethylenediamine; meclozine; parachloramine. $C_{25}H_{27}ClN_2$; mol wt 390.96. C 76.80%, H 6.96%, Cl 9.07%, N 7.17%. 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).



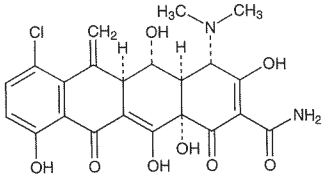
bp_2 230°.

Dihydrochloride monohydrate. [31884-77-2] UCB-5062; Ancolan; Antivert; Bonamine; Bonine; Calmonal; Peremesin; Postafen; Sea-Legs. $C_{25}H_{27}ClN_2.2HCl.H_2O$; mol wt 481.90. Freely sol in chloroform, pyridine; slightly sol in dil acids, alc. Practically insol in water (0.1 gm/100 ml), ether.

THERAP CAT: Antiemetic.

THERAP CAT (VET): Antiemetic.

5801. Meclocycline. [2013-58-3] [4*S*-(4α,4aα,5α,5aα,12aα)]-7-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-2-naphthacenecarboxamide; 7-chloro-6-methylene-5-hydroxytetracycline; GS-2989; NSC-78502. $C_{22}H_{21}ClN_2O_8$; mol wt 476.87. C 55.41%, H 4.44%, Cl 7.43%, N 5.87%, O 26.84%. Semi-synthetic antibiotic derived from tetracycline, *q.v.* Prepn: R. K. Blackwood *et al.,* **US 2984686** (1961 to Pfizer); *eidem, J. Am. Chem. Soc.* **83,** 2773 (1961); of the free base and 5-sulfosalicylate salt: *eidem, ibid.* **85,** 3943 (1963). *In vitro* study: L. Lucca, G. Vittadini, *G. Ital. Chemioter.* **26,** 203 (1979). ^{13}C-NMR study: E. Mazzola *et al., J. Pharm. Sci.* **69,** 229 (1980). Toxicity study: F. Bernardi *et al., G. Ital. Chemioter.* **17,** 276 (1970).

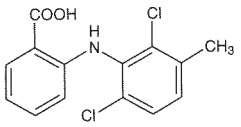


uv max (methanol, 0.01*N* HCl): 245, 347 nm (log ε 4.34, 410). LD_{50} in mice (mg/kg): >5000 orally, 425 i.p. (Bernardi).

5-Sulfosalicylate. [73816-42-9] Meclan; Mecloderm; Meclosorb; Meclutin; Traumatociclina. $C_{29}H_{27}ClN_2O_{14}S$; mol wt 695.05. uv max (methanol, 0.01*N* HCl): 239, 268, 346 nm (log ε 4.46, 4.07, 4.11).

THERAP CAT: Antibacterial.

5802. Meclofenamic Acid. [644-62-2] 2-[(2,6-Dichloro-3-methylphenyl)amino]benzoic acid; *N*-(2,6-dichloro-*m*-tolyl)-anthranilic acid; meclophenamic acid; CI-583; INF-4668; Arquel. $C_{14}H_{11}Cl_2NO_2$; mol wt 296.15. C 56.78%, H 3.74%, Cl 23.94%, N 4.73%, O 10.80%. Prepn: Scherrer, Short, **DE 1149015** *C.A.* **61,** 1801d (1964) and **US 3313848** (1963, 1967 to Parke, Davis); Juby *et al., J. Med Chem.* **11,** 111 (1968). Pharmacology and toxicology: Winder *et al., J. Pharmacol. Exp. Ther.* **148,** 422 (1965); Winder, *Ann. Phys. Med.* **1966,** 7; Kaump, *ibid.* 16. Series of articles on structure-activity relationships, mechanism of action, clinical studies: *Arzneimittel-Forsch.* **33,** 619-680 (1983). Effect on prostaglandin E receptor binding: M. C. P. Rees *et al., Lancet* **2,** 541 (1988).



White crystals from acetone-water, mp 257-259°; also reported as mp 248-250°. Soly (mg/ml): water 0.03; 0.1*N* NaOH 28. pH of satd aq soln: ~6.9.

Sodium salt monohydrate. Lenidolor; Meclodol; Meclomen; Movens. $C_{14}H_{10}Cl_2NNaO_2.H_2O$; mol wt 336.15. mp 289-291°. Soly in water: 15 mg/ml (slightly turbid). pH 8.7.

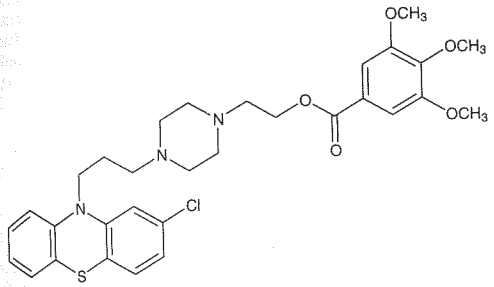
THERAP CAT: Anti-inflammatory; antipyretic.

THERAP CAT (VET): Anti-inflammatory.

5803. Meclofenoxate. [51-68-3] (4-Chlorophenoxy)-acetic acid 2-(dimethylamino)ethyl ester; dimethylaminoethyl *p*-chlorophenoxyacetate; centrophenoxine; meclofenoxane; acephen; ANP-235; Analux; Cetrexin; Proseryl. $C_{12}H_{16}ClNO_3$; mol wt 257.72. C 55.93%, H 6.26%, Cl 13.76%, N 5.43%, O 18.62%. Prepn: Rumpf, Thuillier, **FR M398** (1962 to Centre Nat'l. Recherche Sci.), *C.A.* **57,** 16768e (1962); Thuillier *et al., Compt. Rend.* **249,** 2081 (1959); Thuillier, Rumpf, *Bull. Soc. Chim. France* **1960,** 1786. Pharmacology: Petkov, *C.A.* **65,** 20717g (1966); Liberman, *Farmakol. Toksikol.* **30,** 409 (1967). Auxin activity: Conti, *Boll. Chim. Farm.* **107,** 325 (1968).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 42 of 65

6166. Metofenazate. [388-51-2] 3,4,5-Trimethoxybenzoic acid 2-[4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-1-piperazinyl]ethyl ester; 2-[4-[3-(2-chlorophenothiazin-10-yl)propyl]-1-piperazinyl]ethyl 3,4,5-trimethoxybenzoate; *N*-[β-(3,4,5-trimethoxybenzoyloxy)ethyl]-*N*′-[γ-(3-chloro-10-phenothiazinyl)propyl]piperazine; methophenazine; perphenazine 3,4,5-trimethoxybenzoate. $C_{31}H_{36}ClN_3O_5S$; mol wt 598.16. C 62.25%, H 6.07%, Cl 5.93%, N 7.03%, O 13.37%, S 5.36%. Prepn: *Magy. Kém. Lapja* **17,** 169 (1962), *C.A.* **57,** 11314d (1962); Toldy *et al., Acta Chim. Acad. Sci. Hung.* **42,** 351 (1964).

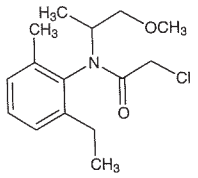


Crystals from ethanol, mp 102-107°.

Difumarate. [522-23-6] Frenolon. $C_{31}H_{36}ClN_3O_5S.2C_4H_4O_4$; mol wt 830.31.

THERAP CAT: Antipsychotic.

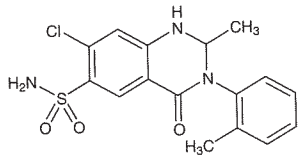
6167. Metolachlor. [51218-45-2] 2-Chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide; 2-chloro-6′-ethyl-*N*-(2-methoxy-1-methylethyl)acet-*o*-toluidide; α-chloro-2′-ethyl-6′-methyl-*N*-(1-methyl-2-methoxyethyl)-acetanilide; metelilachlor; CGA-24705; Dual. $C_{15}H_{22}ClNO_2$; mol wt 283.80. C 63.48%, H 7.81%, Cl 12.49%, N 4.94%, O 11.27%. Selective pre-emergence herbicide. Prepn: C. Vogel, R. Aebi, **DE 2328340**; *eidem,* **US 3937730** (1973, 1976 both to Ciba-Geigy). Metabolism: L. L. McGahen, J. M. Tiedje, *J. Agr. Food Chem.* **26,** 414 (1978). ELISA determn: T. S. Lawruk *et al., J. Agric. Food Chem.* **41,** 1426 (1993). *Review:* G. Chesters *et al., Rev. Environ. Contam. Toxicol.* **110,** 1-74 (1989); of biological activity and field trials: H. R. Gerber *et al., Proc. 12th Brit. Weed Cont. Conf.* 787-794 (1974).



Colorless liquid. $bp_{0.001}$ 100°. n_D^{20} 1.5301. Vapor pressure at 20°: 1.3×10^{-5} mm Hg. Soly in water at 20°: 530 ppm. Sol in most organic solvents. Partition coefficient (octanol/water): 2,800. LD_{50} in rats (mg/kg): 2780 orally; >3170 dermally (Gerber).

USE: Herbicide.

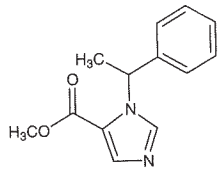
6168. Metolazone. [17560-51-9] 7-Chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazolinesulfonamide; 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide; 2-methyl-3-*o*-tolyl-6-sulfamyl-7-chloro-1,2,3,4-tetrahydro-4-quinazolinone; SR-720-22; Diulo; Metenix; Mykrox; Oldren; Xuret; Zaroxolyn. $C_{16}H_{16}ClN_3O_3S$; mol wt 365.84. C 52.53%, H 4.41%, Cl 9.69%, N 11.49%, O 13.12%, S 8.76%. Prepn: B. V. Shetty, **US 3360518** (1967 to Wallace & Tiernan); B. V. Shetty *et al., J. Med. Chem.* **13,** 886 (1970). Pharmacology: E. Belair *et al., Arch. Int. Pharmacodyn. Ther.* **177,** 71 (1969); E. J. Belair, *Res. Comm. Chem. Pathol. Pharmacol.* **2,** 98 (1971). HPLC determn in urine: D. Farthing *et al., J. Chromatog.* **534,** 228 (1990). Clinical evaluations as diuretic in chronic renal disease: R. Schoonees *et al., N.Y. State J. Med.* **71,** 566 (1971); in hypertension: C. L. Curry *et al., Clin. Ther.* **9,** 47 (1986); in congestive heart failure: A. Kiyingi *et al., Lancet* **335,** 29 (1990).



Crystals from ethanol or butanol, mp 252-254°. LD_{50} in mice (mg/kg): >5000 orally; >1500 i.p. (Shetty, 1967).

THERAP CAT: Diuretic; antihypertensive.

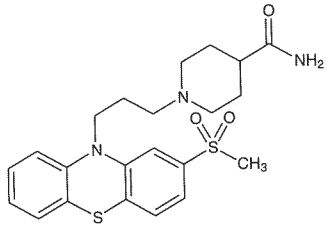
6169. Metomidate. [5377-20-8] 1-(1-Phenylethyl)-1*H*-imidazole-5-carboxylic acid methyl ester; 1-(α-methylbenzyl)-imidazole-5-carboxylic acid methyl ester; methyl 1-(α-methylbenzyl)imidazole-5-carboxylate; methoxymol; methomidate. $C_{13}H_{14}N_2O_2$; mol wt 230.26. C 67.81%, H 6.13%, N 12.17%, O 13.90%. Injectable hypnotic related to etomidate, *q.v.* Prepn: **BE 662474**; E. F. Godefroi, C. A. M. van der Eijcken, **US 3354173** (1965, 1967 both to Janssen); E. F. Godefroi *et al., J. Med. Chem.* **8,** 220 (1965). Anaesthetic effect of combination with azaperone, *q.v.*: J. F. F. Callear, J. F. E. Van Gestel, *Vet. Rec.* **92,** 284 (1973); of combination with fentanyl, *q.v.*: W. Erhardt, *J. Small Animal Pract.* **19,** 401 (1978); C. J. Green, *Lab. Animal* **15,** 171 (1981).



Hydrochloride. R-7315; Hypnodil. $C_{13}H_{14}N_2O_2.HCl$; mol wt 266.73. Crystals from methanol-ether, mp 173-174°. LD_{50} i.v. in rats: 50 mg/kg (Godefroi).

THERAP CAT (VET): Hypnotic.

6170. Metopimazine. [14008-44-7] 1-[3-[2-(Methylsulfonyl)-10*H*-phenothiazin-10-yl]propyl]-4-piperidinecarboxamide; 1-[3-[2-(methylsulfonyl)phenothiazin-10-yl]propyl]isonipecotamide; 10-[3-(4-carbamoylpiperidino)propyl]-2-(methanesulfonyl)phenothiazine; 1-[3-[2-(methylsulfonyl)phenothiazin-10-yl]propyl]-4-piperidinecarboxamide; EXP-999; RP-9965; Vogalene. $C_{22}H_{27}N_3O_3S_2$; mol wt 445.61. C 59.30%, H 6.11%, N 9.43%, O 10.77%, S 14.39%. Prepn: Jacob, Robert, **DE 1092476** (to Rhône-Poulenc), *C.A.* **56,** 8723h (1962). Toxicity study: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* **18,** 185 (1971).



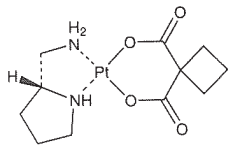
Solid, mp 170-171°. LD_{50} in male rats (mg/kg): 976 orally, 1080 s.c. (Goldenthal).

THERAP CAT: Antiemetic.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 43 of 65

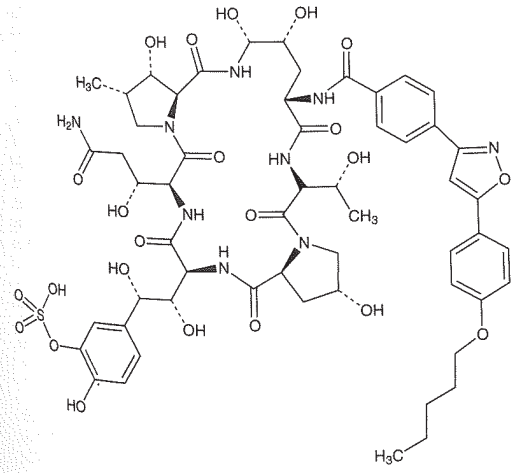
Cryst solid. Soly in deionized water: 0.0454 mg/ml at 37°.
Note: This is a controlled substance (anabolic steroid): **21 CFR,** 1308.13, as defined in 1300.01.
THERAP CAT (VET): Anabolic; androgen.

6198. Miboplatin. [103775-75-3] (*SP*-4-3)-[1,1-Cyclobutanedi(carboxylato-κO)(2−)][(1*R*,2*R*)-2-pyrrolidinemethanamine-$\kappa N^1,\kappa N^2$]platinum; (−)-*cis*-[(*R*)-2-(aminomethyl)pyrrolidine](1,1-cyclobutanedicarboxylato)platinum; (−)-(*R*)-1,1-cyclobutanedicarboxylato(2-aminomethylpyrrolidine)platinum-(II). $C_{11}H_{18}N_2O_4Pt$; mol wt 437.35. C 30.21%, H 4.15%, N 6.41%, O 14.63%, Pt 44.60%. Cytotoxic platinum complex. Prepn: M. Honda *et al.*, **EP 176005**; *eidem*, **US 4822892** (1986, 1989 both to Chugai); K. Morikawa *et al.*, *J. Pharm. Sci.* **80,** 837 (1991). Comparative antitumor and nephrotoxic activities of isomers: T. Matumoto *et al.*, *Brit. J. Cancer* **64,** 41 (1991). Mechanism of action studies: M. Itoh *et al.*, *Chem. Pharm. Bull.* **37,** 2825 (1989); M. Akaboshi *et al.*, *Japan. J. Cancer Res.* **85,** 106 (1994). Clinical evaluation: K. Tamura *et al.*, *Cancer* **66,** 2059 (1990). Acute toxicity: M. Suzuki *et al.*, *Yakuri to Chiryo* **20,** S743 (1992), *C.A.* **117,** 124096 (1992).



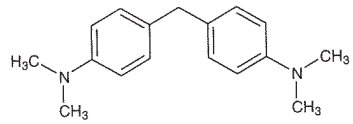
Monohydrate. DWA-2114R; Neoplat. Colorless crystals from water, mp 248-254°. $[\alpha]_D^{20}$ −40.1° (c = 0.4 in water). LD_{50} in male, female mice, rats (mg/kg): 150, 155, 107, 135 i.v. (Suzuki).
THERAP CAT: Antineoplastic.

6199. Micafungin. [235114-32-6] 1-[(4*R*,5*R*)-4,5-Dihydroxy-N^2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4*S*)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]pneumocandin A0. $C_{56}H_{71}N_9O_{23}S$; mol wt 1270.29. C 52.95%, H 5.63%, N 9.92%, O 28.97%, S 2.52%. Semisynthetic echinocandin antifungal; inhibits 1,3-β-glucan synthase. Prepn (stereochem unspec): H. Ohki *et al.*, **WO 96 11210**; *eidem*, **US 6107458** (1996, 2000 both to Fujisawa). Synthesis and antifungal activity: M. Tomishima *et al.*, *J. Antibiot.* **52,** 674 (1999). Antifungal spectrum *in vitro*: S. Tawara *et al.*, *Antimicrob. Ag. Chemother.* **44,** 57 (2000). Review of pharmacology and therapeutic potential: A. H. Groll, T. J. Walsh, *Curr. Opin. Anti-infect. Invest. Drugs* **2,** 405-412 (2000).



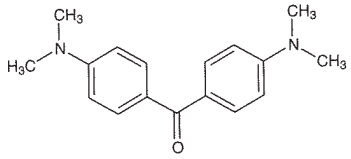
Sodium salt. [208538-73-2] FK-463. $C_{56}H_{70}N_9NaO_{23}S$; mol wt 1292.27. Water soluble lipopeptide.
THERAP CAT: Antifungal.

6200. Michler's Base. [101-61-1] 4,4′-Methylenebis(*N*,*N*-dimethylbenzenamine); 4,4′-methylenebis(*N*,*N*-dimethylaniline); bis(*p*-dimethylaminophenyl)methane; 4,4′-tetramethyldiaminodiphenylmethane; tetra-base; Arnold's base. $C_{17}H_{22}N_2$; mol wt 254.37. C 80.27%, H 8.72%, N 11.01%. Prepd by heating dimethylaniline with 40% formaldehyde and concd HCl: Mekel, **DE 1026322** (1958 to BASF); Hey, Sanderson, *J. Chem. Soc.* **1960,** 3203; from dimethylaniline + diacetylperoxide: Horner *et al.*, *Ann.* **626,** 1 (1959); from dimethylaniline + *tert*-butylperbenzoate: Sosnovsky, Yang, *J. Org. Chem.* **25,** 899 (1960).



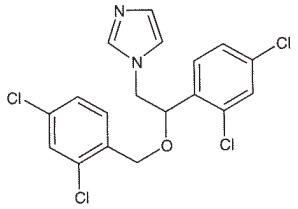
Lustrous leaflets, mp 90-91°. Sublimes without decompn. bp 390°; $bp_{0.1}$ 155-157°. Insol in water. Sol in benzene, ether, carbon disulfide, acids; slightly sol in cold alcohol; more sol in hot alcohol.
Note: This substance is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-149.
USE: Has been used in manufacture of dyes. As reagent for lead: *Deut. med. Wochschr.* **52,** 1855 (1926).

6201. Michler's Ketone. [90-94-8] Bis[4-(dimethylamino)phenyl]methanone; 4,4′-bis(dimethylamino)benzophenone; tetramethyldiaminobenzophenone. $C_{17}H_{20}N_2O$; mol wt 268.35. C 76.09%, H 7.51%, N 10.44%, O 5.96%. Prepn from dimethylaniline + phosgene: Michler, *Ber.* **9,** 716 (1876); Michler, Dupertius, *ibid.* 1900; from dimethylaniline, $AlCl_3$ and CCl_4: Fierz, Koechlin, *Helv. Chim. Acta* **1,** 218 (1918).



White to greenish leaflets, mp 172°. bp >360° with decompn. Practically insol in water. Sol in alcohol, warm benzene; very slightly sol in ether.
Note: This substance is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-153.
USE: In manuf of dyes and pigments.

6202. Miconazole. [22916-47-8] 1-[2-(2,4-Dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1*H*-imidazole; 1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]imidazole. $C_{18}H_{14}Cl_4N_2O$; mol wt 416.14. C 51.95%, H 3.39%, Cl 34.08%, N 6.73%, O 3.84%. Prepn: E. F. Godefroi *et al.*, *J. Med. Chem.* **12,** 784 (1969); E. F. Godefroi, J. Heeres, **DE 1940388**; *eidem*, **US 3717655** (1970, 1973 to Janssen). Clinical evaluation: Brugmans *et al.*, *Arch. Dermatol.* **102,** 428 (1970); Godts *et al.*, *Arzneimittel-Forsch.* **21,** 256 (1971). *Review:* P. Janssen, W. Van Bever, in *Pharmacological and Biochemical Properties of*



NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 44 of 65

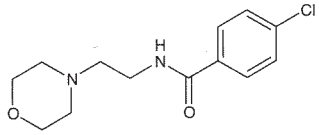
Insol in diethyl ether, petr ether, water, acid soln. Stable for 4 hrs in 50% aq methanol at pH 3-12. The solid antibiotic stored at 25° and 37° and low relative humidity shows no activity loss for 5 mos. Stable for 3 mos at 25°, 100% relative humidity; for 2 mos at 37°, 100% relative humidity. LD_{50} i.p. in mice: >1000 mg/kg (DE 2140674).

1-Methyl deriv, *see* Aurodox

5,6-Dihydromocimycin. $C_{43}H_{62}N_2O_{12}$; mol wt 798.96. Isoln from *S. ramocissimus* and properties: H. Jongsma *et al.*, **DE 2658977** (1977 to Gist-Brocades), *C.A.* **87,** 135078y (1977); *see also* C. Vos *et al.*, **US 4062948** (1977 to Gist-Brocades). Pale yellow solid, dec begins at 123°. $[\alpha]_D^{20}$ −85° (1% methanolic soln). uv max (methanol/water): 233.5, 267, 291, 333 nm (ε 63000, 23000, 19000, 18000). Solubility similar to mocimycin in most solvents.

USE: Animal growth promotant.

6247. Moclobemide. [71320-77-9] 4-Chloro-*N*-[2-(4-morpholinyl)ethyl]benzamide; *p*-chloro-*N*-(2-morpholinoethyl)benzamide; Ro-11-1163; Aurorix; Manerix; Moclamine. $C_{13}H_{17}ClN_2O_2$; mol wt 268.74. C 58.10%, H 6.38%, Cl 13.19%, N 10.42%, O 11.91%. Reversible monoamine oxidase A (MAO-A) inhibitor. Prepn: W. Burkard, P.-C. Wyss, **DE 2706179**; **US 4210754** (1977, 1980 both to Hoffmann-La Roche). Gas chromatography: K. P. Maguire *et al.*, *J. Chromatog.* **278,** 429 (1983). Human pharmacokinetics: F. A. Wiesel *et al.*, *Eur. J. Clin. Pharmacol.* **28,** 89 (1985). Clinical study: J. K. Larsen *et al.*, *Acta Psychiat. Scand.* **70,** 254 (1984). Review of pharmacology: W. P. Burkard *et al.*, *J. Pharmacol. Exp. Ther.* **248,** 391-399 (1989); of neurochemical profile: M. DaPrada *et al.*, *ibid.* 400-414.



Crystals from isopropanol, mp 137°. LD_{50} in rats (mg/kg): 707 orally (Burkard, Wyss).

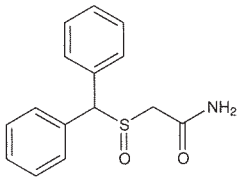
Hydrochloride. $C_{13}H_{18}Cl_2N_2O_2$. Crystals from isopropanol, mp 208°.

THERAP CAT: Antidepressant.

6248. Modacrylic Fibers. A generic term for acrylic fibers composed of a long chain synthetic polymer containing 35-85% of acrylonitrile units such as ***Dynel*** and ***Verel***. *See:* R. W. Moncrieff, *Man-Made Fibres* (Wiley, New York, 4th ed., 1963) p 9. *Review:* Kennedy in *Encyclopedia of Polymer Science and Technology* **vol. 8,** N. M. Bikales, Ed. (Interscience, New York, 1968) pp 812-839.

USE: In pile fabrics, carpeting, paint rollers.

6249. Modafinil. [68693-11-8] 2-[(Diphenylmethyl)-sulfinyl]acetamide; 2-(benzhydrylsulfinyl)acetamide; CRL-40476; Provigil. $C_{15}H_{15}NO_2S$; mol wt 273.36. C 65.91%, H 5.53%, N 5.12%, O 11.71%, S 11.73%. α_1-Adrenergic agonist. Prepn: L. Lafon, **DE 2809625**; *eidem,* **US 4177290** (1978, 1979 both to Lab. Lafon). Effects on vigilance: F. Goldenberg, J. S. Weil, *Sleep (Stuttgart)* **8,** 343 (1988); on normal sleep: B. Saletu *et al.*, *Int. J. Clin. Pharmacol. Res.* **9,** 183 (1989). Clinical evaluation in hypersomnia and narcolepsy: H. Bastuji, M. Jouvet, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **12,** 695 (1988).

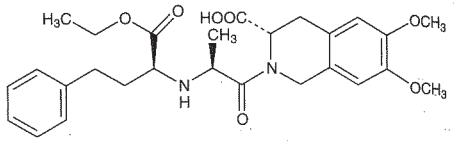


Crystals from methanol, mp 164-166°.

Note: This is a controlled substance (stimulant): **21 CFR,** 1308.14.

THERAP CAT: CNS Stimulant.

6250. Moexipril. [103775-10-6] (3*S*)-2-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid; RS-10085. $C_{27}H_{34}N_2O_7$; mol wt 498.57. C 65.04%, H 6.87%, N 5.62%, O 22.46%. Angiotensin converting enzyme (ACE) inhibitor; dimethoxy analog of quinapril, *q.v.* Prepn: M. L. Hoefle, S. Klutchko, **EP 49605**; *eidem,* **US 4344949** (both 1982 to Warner-Lambert); S. Klutchko *et al.*, *J. Med. Chem.* **29,** 1953 (1986). Pharmacology: O. Edling *et al.*, *J. Pharmacol. Exp. Ther.* **275,** 854 (1995). GC-MS determn in plasma: W. Hammes *et al.*, *J. Chromatog. B* **670,** 81 (1995). Clinical trials in hypertension: W. B. White *et al.*, *J. Human Hypertens.* **8,** 917 (1994); M. Stimpel *et al.*, *Cardiology* **87,** 313 (1996).

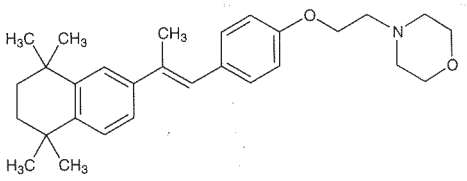


Hydrochloride. [82586-52-5] CI-925; RS-10085-197; SPM-925; Fempress; Perdix; Univasc. $C_{27}H_{34}N_2O_7$.HCl; mol wt 535.04. Crystals from ethanol + ethyl ether, mp 141-161°. $[\alpha]_D^{23}$ +34.2° (c = 1.1 in ethanol).

Diacid hydrochloride. [82586-57-0] Moexiprilat hydrochloride. $C_{25}H_{30}N_2O_7$.HCl. Prepd as the monohydrate; crystals from THF + ethanol, mp 145-170°. $[\alpha]_D^{23}$ +37.8° (c = 1.1 in methanol).

THERAP CAT: Antihypertensive.

6251. Mofarotene. [125533-88-2] 4-[2-[4-[(1*E*)-2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]phenoxy]ethyl]morpholine; Ro 40-8757. $C_{29}H_{39}NO_2$; mol wt 433.62. C 80.33%, H 9.07%, N 3.23%, O 7.38%. Anticancer aromatic analog of retinoic acid (arotinoid). Prepn: M. Klaus *et al.*, **EP 331983**; *eidem,* **US 4940707** (1989, 1990 both to Hoffmann-La Roche). Mode of action study: J. F. Eliason *et al.*, *Blood* **86,** 4516 (1995). Pharmacokinetics: B. Vallès *et al.*, *Eur. J. Drug Metab. Pharmacokinet.* **20,** 49 (1995). HPLC determn in plasma: R. Wyss *et al.*, *J. Chromatog. A.* **729,** 315 (1996). Mechanism of growth inhibition on pancreatic cancer cells: S. Kawa *et al.*, *Int. J. Cancer* **72,** 906 (1997). Clinical pharmacology in combination with cisplatin and etoposide: L. van Zuylen *et al.*, *Anti-Cancer Drugs* **10,** 361 (1999).



White crystals from ethyl acetate/hexane, mp 107-109°.

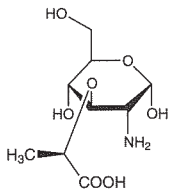
THERAP CAT: Antineoplastic.

6252. Mofebutazone. [2210-63-1] 4-Butyl-1-phenyl-3,5-pyrazolidinedione; 4-butyl-1-phenyl-3,5-dioxopyrazolidine; 2-phenyl-3,5-dihydroxy-4-butylpyrazolidine; monophenylbutazone; Arcomonol Tablets; Mobutazon; Mobuzon; Mofesal; Monazan; Monobutyl; Monorheumetten; Reumatox. $C_{13}H_{16}N_2O_2$; mol wt 232.28. C 67.22%, H 6.94%, N 12.06%, O 13.78%. Prepn: Büchi *et al.*, *Helv. Chim. Acta* **36,** 75 (1953); **GB 839057** (1960 to Comm. Farm. Milanese). Toxicity data: Schoetensack, *Arch. Exp. Pathol. Pharmakol.* **233,** 365 (1958).

Crystals from ethanol + water, mp 102-103°. uv max (ethanol): 240, 275 nm ($E_{1cm}^{1\%}$ 443, 245). LD_{50} i.v. in mice: 600 mg/kg (Schoetensack).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 45 of 65

Org. Chem. **27,** 3581 (1962); *eidem, Biochem. Prepn.* **10,** 109 (1963); T. Osawa, R. W. Jeanloz, *J. Org. Chem.* **30,** 448 (1965). Review of peptidoglycan structure: H. J. Rogers, *Ann. N.Y. Acad. Sci.* **235,** 29-51 (1974). Use to determine bacterial levels in mammalian tissues: J. Gilbart *et al., J. Microbiol. Methods* **5,** 271 (1986); in airborne dust: A. Fox *et al., Appl. Environ. Microbiol.* **59,** 4354 (1993).

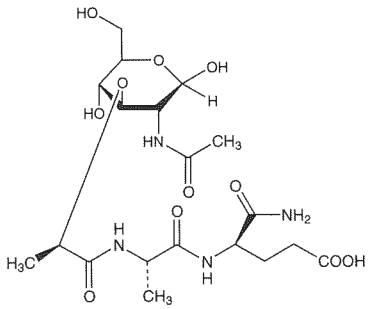


Crystals from water, mp 152-154° (dec); $[\alpha]_D^{25}$ +103° (c = 0.26 in water) (Matsushima, Park). Also reported as crystals from 90% ethanol, mp 160-162° (dec); $[\alpha]_D^{22}$ +146° (6 minutes) → +116° (31 hrs) (c = 0.57 in water) (Osawa, Jeanloz).

***N*-Acetylmuramic acid.** [10597-89-4] (*R*)-2-(Acetylamino)-3-*O*-(1-carboxyethyl)-2-deoxy-D-glucose. $C_{11}H_{19}NO_8$; mol wt 293.27. Crystals from ethyl acetate + methanol, mp 119-121°. $[\alpha]_D^{20}$ +56° (10 minutes) → +40° (24 hrs) (c = 0.68 in water).

USE: As chemical marker for the detection of bacterial contamination.

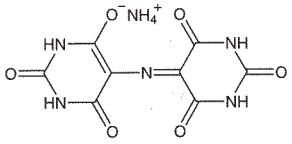
6329. Muramyl Dipeptide. [53678-77-6] N^2-[*N*-(*N*-Acetylmuramoyl)-L-alanyl]-D-α-glutamine; *N*-acetylmuramyl-L-alanyl-D-isoglutamine; 2-acetamido-2-deoxy-3-*O*-(D-2-propionyl-L-alanyl-D-isoglutamine)-D-glucopyranose; MDP. $C_{19}H_{32}N_4O_{11}$; mol wt 492.48. C 46.34%, H 6.55%, N 11.38%, O 35.74%. Synthetic immunoadjuvant corresponding to the smallest immunologically active glycopeptide subunit of the bacterial cell wall. Prepn: A. Adam *et al.,* **DE 2450355**; *eidem,* **US 4235771** (1975, 1980 both to Agen. Nat. Valor. Recher.); C. Merser *et al., Biochem. Biophys. Res. Commun.* **66,** 1316 (1975); P. Lefrancier *et al., Int. J. Pep. Prot. Res.* **9,** 249 (1977). Structure-activity relationships: F. Ellouz *et al., Biochem. Biophys. Res. Commun.* **59,** 1317 (1974); A. Adam *et al., ibid.* **72,** 339 (1976). Review of immunoregulating activity: L. Chedid *et al., Prog. Allergy* **25,** 63-105 (1978). Tissue distribution in mice: M. Parant *et al., Int. J. Immunopharmacol.* **1,** 35 (1979). Potentiation of antitumor immunity: S. Sone *et al., J. Biol. Resp. Mod.* **3,** 185 (1984); A. E. Eggers, *ibid.* **7,** 229 (1988).



Crystals from methanol-acetone-ether. $[\alpha]_D^{25}$ +44° (acetic acid).

USE: Immunological adjuvant.

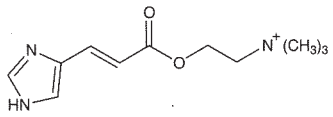
6330. Murexide. [3051-09-0] 5-[(Hexahydro-2,4,6-trioxo-5-pyrimidinyl)imino]-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione monoammonium salt; 5,5′-nitrilodibarbituric acid monoammonium salt; acid ammonium purpurate; ammonium purpurate. $C_8H_8N_6O_6$; mol wt 284.19. C 33.81%, H 2.84%, N 29.57%, O 33.78%. Prepn from alloxan + NH_3: Hartley, *J. Chem. Soc.* **87,** 1791 (1905); Schwartz, Handritschk, **DD 17589** (1959), *C.A.* **55,** 3630a (1961); from alloxantin + ammonium acetate: Davidson, *J. Am. Chem. Soc.* **58,** 1821 (1936). Structure: Hartley, *J. Chem. Soc.* **87,** 1796 (1905); Winslow, *J. Am. Chem. Soc.* **61,** 2089 (1939); Schreiber, *Mitt. Deut. Pharm. Ges.* **28,** 20 (1958).



Purple-red crystals with green metallic luster. Absorption max in water: 520 nm. Sparingly sol in cold water, more in hot water; practically insol in alcohol, ether. The H_2O soln is deep purple and the aq NaOH soln is deep blue.

USE: Indicator for complexometric titrations.

6331. Murexine. [20284-40-6] 2-[[3-(1*H*-Imidazol-4-yl)-1-oxo-2-propenyl]oxy]-*N,N,N*-trimethylethanaminium; β-(4-imidazolyl)acrylcholine; urocanylcholine. $[C_{11}H_{18}N_3O_2]^+$. Neuromuscular blocker found, often in very large quantities, in the median zone of the hypobranchial body of *Murex trunculus* and of other related species of mollusks: Erspamer, Dordoni, *Ric. Sci. Ricostr.* **16,** 1114 (1946); *Arch. Int. Pharmacodyn.* **74,** 263 (1947); Erspamer, *ibid.* **76,** 308 (1948). Isoln: *idem, Experientia* **4,** 226 (1948); M. Roseghini *et al., Eur. J. Biochem.* **12,** 468 (1970); J. E. Blankenship *et al., Comp. Biochem. Physiol.* **51C,** 129 (1975). Synthesis: Pasini *et al., Ann.* **578,** 6 (1952); Pasini, Coda, **US 2956061** (1960 to Società Farmaceutici). Structure: V. Erspamer, O. Benati, *Science* **117,** 161 (1953). Effect on vertebrate and invertebrate muscles: J. C. de Freitas, *Comp. Biochem. Physiol.* **56C,** 57 (1977).



The base is instantly hydrolyzed by water; unstable both in acid or alkaline media.

Chloride. Extremely hygroscopic crystals. uv max (pH 4.5): 280-282 nm.

Chloride hydrochloride. Hygroscopic microcrystalline powder, mp 219-221° (dec); shows the same uv max as the chloride.

6332. Muromonab CD3. [140608-64-6] OKT3; Orthoclone OKT3. Murine monoclonal IgG_{2a} antibody directed against the CD3 surface antigen on mature T-cells; designed as a specific T-cell inhibitor for treatment of transplant rejection. Prepn: P. C. Kung *et al., Science* **206,** 347 (1979); P. C.-S. Kung, G. Goldstein, **EP 18795**; *eidem,* **US 4361549** (1980, 1982 both to Ortho Pharm.). Clinical study in renal transplant: G. Goldstein *et al., N. Engl. J. Med.* **313,** 337 (1985); in heart transplant: M. P. Macris *et al., J. Heart Transpl.* **8,** 281 (1989). Review of development and mechanism of action: G. Goldstein, *Transpl. Proc.* **19,** Suppl. 1, 1-6 (1987); of pharmacology and clinical use in transplantation: M. A. Hooks *et al., Pharmacotherapy* **11,** 26-37 (1991); M. I. Wilde, K. L. Goa, *Drugs* **51,** 865-894 (1996).

THERAP CAT: Immunosuppressant.

6333. Muscalure. [27519-02-4] (*Z*)-9-Tricosene; *cis*-tricos-9-ene. $C_{23}H_{46}$; mol wt 322.61. C 85.63%, H 14.37%. Sex pheromone of the female common house fly, *Musca domestica* L. Isoln and synthesis: Carlson *et al., Science* **174,** 76 (1971). Alternate syntheses: Eiter, *Naturwiss.* **59,** 468 (1972); Cargill, Rosenblum, *J. Org. Chem.* **37,** 3971 (1972); Gribble *et al., Chem. Commun.* **1973,** 735; Ho, Wong, *Can. J. Chem.* **52,** 1923 (1974); K. Abe *et al., Bull. Chem. Soc. Japan* **50,** 2792 (1977); V. N. Odinokov *et al., Tetrahedron Letters* **23,** 1371 (1982).

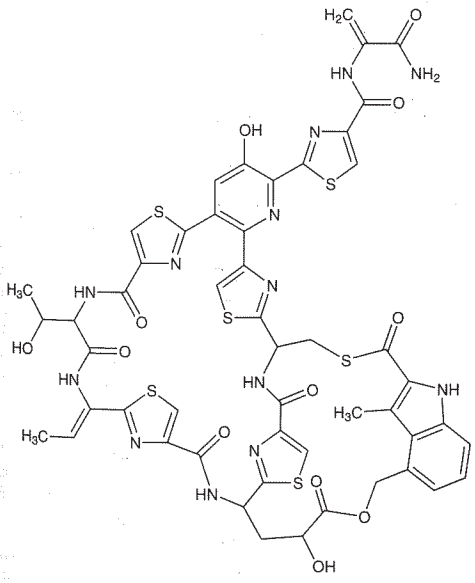
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 46 of 65

Camphorsulfonate. [25333-79-3] Tulisan. $C_{22}H_{23}NO_7 \cdot C_{10}H_{16}O_4S$; mol wt 645.73. Contains 35.97% camphosulfonic acid. Prepn: Maillard, **US 3108106** (1963 to Jacques Logeais). Crystals, mp 188-191°. $[\alpha]_D^{33}$ +32.7° (c = 4.56 in water). Freely sol in water. Sol in methanol, ethanol. Slightly sol in ethyl acetate. Practically insol in ether.

***dl*-Form.** [6035-40-1] *dl*-Narcotine; gnoscopine. Long needles from methanol, mp 232° (dec). pK 7.8. Freely sol in carbon disulfide, hot chloroform; sol in ~1500 parts alcohol; sparingly sol in benzene, water.

THERAP CAT: Antitussive.

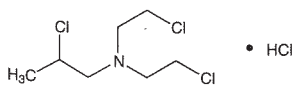
6753. Nosiheptide. [56377-79-8] Multhiomycin; RP-9671; Primofax. $C_{51}H_{43}N_{13}O_{12}S_6$; mol wt 1222.37. C 50.11%, H 3.55%, N 14.90%, O 15.71%, S 15.74%. Polythiazole antibiotic produced by *Streptomyces actuosus.* Isoln and characterization: S. Pinnert *et al.*, **FR 1392453**; *eidem,* **US 3155581** (1961, 1964 both to Rhône-Poulenc); F. Benazet *et al., Experientia* **36,** 414 (1980). NMR determination of mol wt and elemental formula: H. Depaire *et al., Tetrahedron Letters* **1977,** 1397, 1401. Structure and configuration: T. Prange *et al., Nature* **265,** 189 (1977); C. Pascard *et al., J. Am. Chem. Soc.* **99,** 6418 (1977). Biosynthetic study: D. P. Houck *et al., ibid.* **109,** 1250 (1987). Identity with multhiomycin: T. Endo, H. Yonehara, *J. Antibiot.* **31,** 623 (1978). Mode of action: E. Cundliffe, J. Thompson, *J. Gen. Microbiol.* **126,** 185 (1981). *Review:* F. Benazet *et al., Experientia* **36,** 414-416 (1980).



Yellow needles, mp 310-320° (dec). $[\alpha]_D^{20}$ +38° (c = 1 in pyridine). uv max (water/DMF): 242, 322 nm ($E_{1cm}^{1\%}$ 525, 229). Sol in chloroform, dioxane, pyridine, DMF, DMSO; slightly sol in methanol, ethanol, ethyl acetate, benzene. Insol in water and petr ether.

THERAP CAT (VET): Antibacterial; growth promotant.

6754. Novembichin. [1936-40-9] 2-Chloro-*N,N*-bis(2-chloroethyl)propanamine hydrochloride; 2-chloropropyldi(2-chloroethyl)amine hydrochloride; Novoembichin; Embichin 7; Embikhin 7. $C_7H_{15}Cl_4N$; mol wt 255.02. C 32.97%, H 5.93%, Cl 55.61%, N 5.49%. Prepn: Ford-Moore *et al., J. Chem. Soc.* **1946,** 819; E. Wilson, M. Tishler, *J. Am. Chem. Soc.* **73,** 3635 (1951).

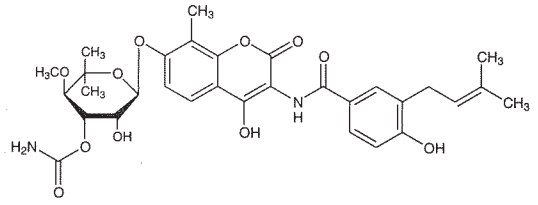


Crystals from chloroform + ethanol, mp 78-79.4°.

Free base. Colorless oil, bp 114°.

THERAP CAT: Antineoplastic.

6755. Novobiocin. [303-81-1] *N*-[7-[[3-*O*-(Aminocarbonyl)-6-deoxy-5-*C*-methyl-4-*O*-methyl-β-L-*lyxo*-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2*H*-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)benzamide; crystallinic acid; streptonivicin; PA-93; U-6591. $C_{31}H_{36}N_2O_{11}$; mol wt 612.62. C 60.78%, H 5.92%, N 4.57%, O 28.73%. Antibiotic substance produced by *Streptomyces spheroides:* Kaczka *et al., J. Am. Chem. Soc.* **77,** 6404 (1955); Wolf, **US 3000873** (1961 to Merck & Co.); Stammer, Miller; Miller; Wallick, **US 3049475**; **US 3049476**; **US 3049534** (all 1962 to Merck & Co.). By *Streptomyces niveus:* Hoeksema *et al., J. Am. Chem. Soc.* **77,** 6710 (1955); *Antibiot. & Chemother.* **6,** 143 (1956); French, **US 3068221** (1962 to Upjohn). Structure: Shunk *et al., J. Am. Chem. Soc.* **78,** 1770 (1956); Hoeksema *et al., ibid.* 2019; Walton *et al., ibid.* **82,** 1489 (1960). Conformation: Golding, Richards, *Chem. & Ind. (London)* **1963,** 1081. Revised configuration: O. Achmatowicz *et al., Tetrahedron* **32,** 1051 (1976). Synthesis: Stammer, **US 2925411** (1960); Walton, Spencer, **US 2966484** (1960 to Merck & Co.); Vaterlaus *et al., Helv. Chim. Acta* **47,** 390 (1964). Conversion of ***isonovobiocin*** to novobiocin: Caron *et al.*, **US 2983723** (1961 to Upjohn). Antiviral activity: Chang, Weinstein, *Antimicrob. Ag. Chemother.* **1970,** 165. Efficacy in canine respiratory infections: B. W. Maxey, *Vet. Med. Small Anim. Clin.* **75,** 89 (1980). Mechanism of action studies: Smith, Davis, *J. Bacteriol.* **93,** 71 (1967); H. T. Wright *et al., Science* **213,** 455 (1981); I. W. Althaus *et al., J. Antibiot.* **41,** 373 (1988). *Review:* Brock in *Antibiotics,* **vol. 1,** R. Gottlieb, P. Shaw, Eds. (Springer-Verlag, New York, 1967) pp 651-665; M. J. Ryan, *ibid.* **vol. 5**(pt. 1), F. E. Hahn, Ed. (1979) pp 214-234.



Pale yellow orthorhombic crystals from ethanol. *Sensitive to light.* d 1.3448. Dec at 152-156° (a rarer modification dec 174-178°). Acid reaction: pKa_1 4.3; pKa_2 9.1. $[\alpha]_D^{24}$ −63.0° (c = 1 in ethanol). uv max (0.1*N* NaOH; 0.1*N* methanolic HCl; pH 7 phosphate buffer): 307; 324; 390 nm ($E_{1cm}^{1\%}$ 600, 390, 350 resp.). Sol in aq soln above pH 7.5. Practically insol in more acidic solns. Sol in acetone, ethyl acetate, amyl acetate, lower alcohols, pyridine. Additional soly data: Weiss *et al., Antibiot. & Chemother.* **7,** 374 (1957).

Monosodium salt. [1476-53-5] Albamycin; Cathomycin; Inamycin; Robiocina. $C_{31}H_{35}N_2NaO_{11}$; mol wt 634.60. Minute crystals, dec 220°. $[\alpha]_D^{24}$ −38° (c = 2.5 in 95% ethanol); $[\alpha]_D^{24}$ −33° (c = 2.5 in water). Freely sol in water. A 100 mg/ml soln has a pH of 7.5 and a half-life of ~30 days at 25° and several months at 4°. Soly data: Weiss *et al., loc. cit.* Properties: Birlova, Traktenberg, *Antibiotiki* **13,** 997 (1968).

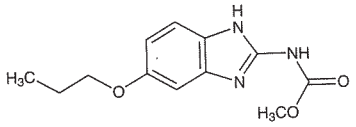
THERAP CAT: Antibacterial.

THERAP CAT (VET): Antimicrobial.

6756. Novoldiamine. [140-80-7] N^1,N^1-Diethyl-1,4-pentanediamine; 1-diethylamino-4-aminopentane; 4-amino-1-diethylaminopentane; 2-amino-5-diethylaminopentane; δ-diethylamino-α-methylbutylamine; δ-diethylaminoisopentylamine. $C_9H_{22}N_2$; mol wt 158.28. C 68.29%, H 14.01%, N 17.70%. Prepd commercially from 2-diethylaminoethanol and ethyl acetoacetate. 2-Chlorotriethylamine (formed by the action of thionyl chloride on the alcohol) is condensed with the sodium derivative of ethyl acetoacetate to yield an intermediate ester, which is hydrolyzed and decarboxylated to ***novol ketone*** (5-diethylamino-2-pentanone). This is hydrogenated in the presence of

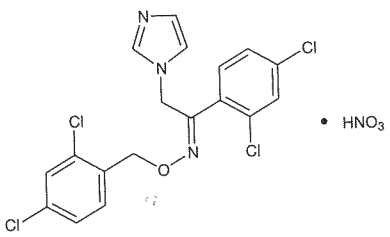
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 47 of 65

oxyamino)benzimidazole; SKF-30310; Anthelcide EQ; Equitac. $C_{12}H_{15}N_3O_3$; mol wt 249.27. C 57.82%, H 6.07%, N 16.86%, O 19.26%. Prepn: **GB 1123317** corresp to P. P. Actor, J. F. Pagano, **US 3574845** (1968, 1971 both to SK & F). Comparative anthelmintic effects in mice: C. S. Karunakaron, D. A. Denham, *J. Parasitol.* **66,** 929 (1980). Clinical studies in foals and horses: J. H. Drudge *et al., Am. J. Vet. Res.* **42,** 526 (1981); E. T. Lyons *et al., ibid.* 685; D. K. Hass *et al., ibid.* **43,** 534 (1982).



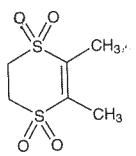
Cryst, mp 230-230.5°.
THERAP CAT (VET): Anthelmintic.

7006. Oxiconazole Nitrate. [64211-46-7] (*Z*)-1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone *O*-[(2,4-dichlorophenyl)methyl]oxime mononitrate; 2′,4′-dichloro-2-(imidazol-1-yl)acetophenone *O*-(2,4-dichlorobenzyl)oxime nitrate; Sgd-301-76; Ro-13-8996; Gyno-Myfungar; Myfungar; Oceral; Oxistat. $C_{18}H_{14}Cl_4N_4O_4$; mol wt 492.15. C 43.93%, H 2.87%, Cl 28.81%, N 11.38%, O 13.00%. Broad spectrum topical antimycotic agent. Prepn: G. Mixich *et al.,* **DE 2657578**; *eidem,* **US 4124767** (1977, 1978 both to Siegfried). Stereospecific synthesis of *(E)-, (Z)*-isomers, ^{1}H NMR study: G. Mixich, K. Thiele, *Arzneimittel-Forsch.* **29,** 1510 (1979). GLC determn in plasma: M. Zell, L. Herzfeld, *J. Chromatog.* **229,** 111 (1982). *In vitro* and *in vivo* antifungal activity: A. Polak, *Arzneimittel-Forsch.* **32,** 17 (1982). Study of skin, nail penetration: G. Stueltgen, E. Bauer, *Mykosen* **25,** 74 (1982). Comparison of antifungal imidazoles: W. H. Beggs, *IRCS Med. Sci.* **11,** 677 (1983).



Crystals from ethanol, mp 137-138°.
THERAP CAT: Antifungal.

7007. Oxidimethiin. [55290-64-7] 2,3-Dihydro-5,6-dimethyl-1,4-dithiin 1,1,4,4-tetraoxide; tetrathiin; UBI-N252; Harvade. $C_6H_{10}O_4S_2$; mol wt 210.27. C 34.27%, H 4.79%, O 30.44%, S 30.50%. Prepn: A. D. Brewer *et al.,* **FR 2228429** corresp to **US 3920438** (1974, 1975 to Uniroyal). Activity: R. W. Neidermyer *et al., Proc. Brit. Weed Control Conf., 12th* **3,** 959 (1974). Crystal structure: S. K. Arora *et al., Acta Crystallogr.* **B34,** 2918 (1978).

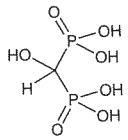


Long white needles from water, mp 166-168°.
USE: Plant growth regulator.

7008. Oxidized Cellulose. Absorbable cellulose; cellulosic acid; polyanhydroglucuronic acid; Oxycel; Hemo-Pak. A cellulose of varied carboxyl content retaining the fibrous structure. Prepd by oxidizing cellulose with nitrogen dioxide; Yackel, Kenyon, *J. Am. Chem. Soc.* **64,** 121 (1942).

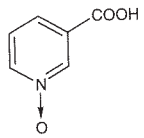
The degree of oxidation is sufficiently high to make the product sol in dil alk solns. Insol in water or acidic solns.
THERAP CAT: Hemostatic (local).
THERAP CAT (VET): Hemostatic (local).

7009. Oxidronic Acid. [15468-10-7] (Hydroxymethylene)bisphosphonic acid; (hydroxymethylene)diphosphonic acid; HDP; HMDP. $CH_6O_7P_2$; mol wt 192.00. C 6.26%, H 3.15%, O 58.33%, P 32.26%. Bisphosphonate similar to etidronic acid, *q.v.* Prepn: O. T. Quimby, **FR 1506840**; *idem,* **US 3422137** (1967, 1969 both to Procter & Gamble); of sodium salt: *idem et al., J. Org. Chem.* **32,** 4111 (1967). Prepn of ^{99m}Tc-complex: J. A. Bevan, **EP 7676**; *idem,* **US 4247534** (1980, 1981 both to Procter & Gamble); and osteotropic properties: T. S. T. Wang *et al., J. Nucl. Med.* **21,** 767 (1980). Biodistribution: J. A. Bevan *et al., ibid* 961. Radiochemical purity: W. Majewski *et al., J. Nucl. Med. Technol.* **11,** 23 (1983). Clinical evaluation as skeletal imaging agent: P. A. Domstad *et al., Radiology* **136,** 209 (1980). Diagnostic use in Paget's disease: A. Evans *et al., Eur. J. Nucl. Med.* **18,** 757 (1991); for localization of bone metastases: F. Tenenbaum *et al., ibid* **20,** 1168 (1993).



Sodium salt. [14255-61-9] Disodium monohydroxy methylene diphosphonate; oxidronate sodium. $CH_4Na_2O_7P_2$. Crystals from methanol/water (6/1), mp 297-300°.
^{99m}Tc-complex. [72945-61-0] Technetium ^{99m}Tc oxidronate; TechneScan HDP; Osteoscan-HDP.
THERAP CAT: ^{99m}Tc-complex as diagnostic aid (radioactive imaging agent).

7010. Oxiniacic Acid. [2398-81-4] 3-Pyridinecarboxylic acid 1-oxide; nicotinic acid 1-oxide; 3-carboxypyridine *N*-oxide. $C_6H_5NO_3$; mol wt 139.11. C 51.80%, H 3.62%, N 10.07%, O 34.50%. Prepn: Clemo, Koenig, *J. Chem. Soc.* **1949,** S231; Taylor, Crovetti, *J. Org. Chem.* **19,** 1633 (1954). Mass spectrum: Bild, Hesse, *Helv. Chim. Acta* **50,** 1885 (1967). Therapeutic effect: Debay, Thery, **BE 618968** (1962), *C.A.* **58,** 12375e (1963).

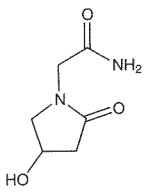


Needles, mp 254-255° (dec). Slightly soluble in cold water, more sol in hot water, hot glacial acetic acid, hot methanol, less sol in ethanol. Insol in light petroleum, benzene, chloroform. uv max (0.1*N* H_2SO_4): 220, 260 nm (ε 22400, 10200).
Ethanolamine salt. [36296-31-8] Ethanolamine oxiniacate; Novacyl. $C_6H_5NO_3.C_2H_7NO$; mol wt 200.19.
THERAP CAT: Antihyperlipoproteinemic.

7011. Oxiracetam. [62613-82-5] 4-Hydroxy-2-oxo-1-pyrrolidineacetamide; 2-(4-hydroxypyrrolidin-2-on-1-yl)acetamide; hydroxypiracetam; CT-848; ISF-2522; Neuractiv; Neuromet. $C_6H_{10}N_2O_3$; mol wt 158.15. C 45.57%, H 6.37%, N 17.71%, O 30.35%. Analog of piracetam, *q.v.*, with psychostimulant activity. Prepn: G. Pifferi, M. Pinza, **DE 2635853**; *eidem,* **US 4118396** (1977, 1978 both to I.S.F.); *eidem, Farmaco*

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 48 of 65

Ed. Sci. **32,** 602 (1977). Effect on learning and memory in animals and prepn of enantiomers: S. Banfi *et al., ibid.* **39,** 16 (1984). Effect in animals with cerebral impairment: S. Banfi *et al., Pharmacol. Res. Commun.* **16,** 67 (1984). Pharmacokinetics in humans: E. Perucca *et al., Eur. J. Drug Metabol. Pharmacokinet.* **9,** 267 (1984). Clinical evaluation in organic brain syndrome: B. Saletu *et al., Neuropsychobiology* **13,** 44 (1985).



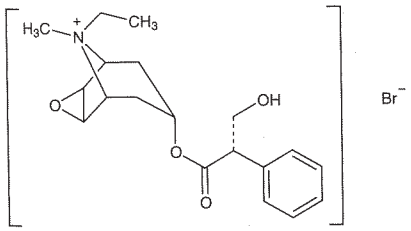
White, microcrystalline powder from methanol, mp 165-168°.

***(R)*-Form.** Crystals from acetone + water, mp 135-136°. $[\alpha]_D$ +36.2° (c = 1.00 in water).

***(S)*-Form.** Crystals from acetone + water, mp 135-136°. $[\alpha]_D$ −36.0° (c = 1.00 in water).

THERAP CAT: Nootropic.

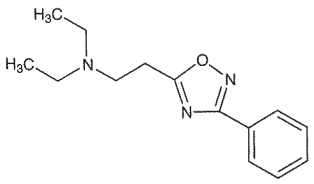
7012. Oxitropium Bromide. [30286-75-0] [7(*S*)-(1α,2β,4β,5α,7β)]-9-Ethyl-7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide; (8r)-6β,7β-epoxy-8-ethyl-3α-hydroxy-1α*H*,5α*H*-tropanium bromide (−)-tropate; (−)-*N*-ethylnorscopolamine methobromide; Ba-253; Ba-253-BR-L; Oxivent; Tersigat; Ventilat. $C_{19}H_{26}BrNO_4$; mol wt 412.32. C 55.35%, H 6.36%, Br 19.38%, N 3.40%, O 15.52%. Anticholinergic bronchodilating agent. Prepn: K. Zeile *et al.,* **US 3472861** (1969 to Boehringer, Ing.). Comparison with fenoterol, *q.v.*: D. Nolte, *Respiration* **36,** 32 (1978); with ipratropium bromide, *q.v.*: J. Lulling *et al., ibid.* **42,** 188 (1981). Efficacy in bronchial asthma: H. M. Beumer *et al., Int. J. Clin. Pharmacol. Ther. Toxicol.* **19,** 168 (1981); in exercise-induced asthma: K. Larsson, *Respiration* **43,** 57 (1982).



Crystals, mp 203-204° (dec). $[\alpha]_D^{21}$ −25° (c = 2.0 in water).

THERAP CAT: Bronchodilator.

7013. Oxolamine. [959-14-8] *N,N*-Diethyl-3-phenyl-1,2,4-oxadiazole-5-ethanamine; 5-(2-diethylaminoethyl)-3-phenyl-1,2,4-oxadiazole; 3-phenyl-5-(β-diethylaminoethyl)-1,2,4-oxadiazole; 683-M. $C_{14}H_{19}N_3O$; mol wt 245.32. C 68.54%, H 7.81%, N 17.13%, O 6.52%. Prepn: **DE 1097998** (1961 to Angelini Francesco), *C.A.* **56,** 11598h (1962). Teratogenicity studies of oxolamine citrate: L. Nilsson, *Arzneimittel-Forsch.* **17,** 781 (1967).



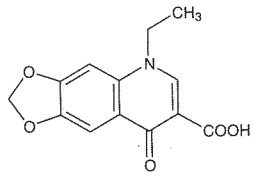
Liquid, $bp_{0.4}$ 127°.

Hydrochloride. [1219-20-1] $C_{14}H_{19}N_3O.HCl$. Crystals, mp 153-154°.

Citrate. [1949-20-8] AF-438; Bredon; Broncatar; Perebron; Prilon; Flogobron; Oxarmin. $C_{14}H_{19}N_3O.C_6H_8O_7$; mol wt 437.44. Crystals, slightly sol in water, alcohol. uv max (aq soln): 239 nm (ε 260), 273, 283 nm.

THERAP CAT: In inflammatory conditions of respiratory tract.

7014. Oxolinic Acid. [14698-29-4] 5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid; 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid; 1-ethyl-6,7-methylenedioxy-4-quinolone-3-carboxylic acid; W-4565; Emyrenil; Inoxyl; Nidantin; Ossian; Oxoboi; Pietil; Prodoxol; Urinox; Uritrate; Uro-Alvar; Urotrate; Uroxin; Uroxol; Utibid. $C_{13}H_{11}NO_5$; mol wt 261.23; C 59.77%, H 4.24%, N 5.36%, O 30.62%. Quinolone antibacterial. Prepn: Kaminsky, Meltzer, **US 3287458** (1966 to Warner-Lambert); *eidem, J. Med. Chem.* **11,** 160 (1968). Pharmacology: Turner *et al., Antimicrob. Ag. Chemother.* **1967,** 475 sqq. Metabolism studies: DiCarlo *et al., Arch. Biochem. Biophys.* **127,** 503 (1968); Crew *et al., Xenobiotica* **1,** 193 (1971). Use in urinary tract infections: S. Kalowski *et al., Med. J. Aust.* **21,** 345 (1979); E. Anza *et al., Minerva Med.* **70,** 2333 (1979). Mechanism of action study: H. T. Wright *et al., Science* **213,** 455 (1981). Brief review of therapeutic use: R. Glickman *et al., Am. J. Hosp. Pharm.* **36,** 1077-1079 (1979).

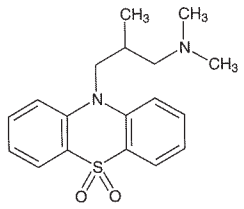


Crystals from DMF, mp 314-316° (dec). LD_{50} in mice, rats (mg/kg): >6000, >2000 orally (Turner).

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

7015. Oxomemazine. [3689-50-7] *N,N,β*-Trimethyl-10*H*-phenothiazine-10-propanamine 5,5-dioxide; 10-(3-dimethylamino-2-methylpropyl)phenothiazine 5,5-dioxide; 3-(9,9-dioxo-10-phenothiazinyl)-2-methyl-1-dimethylaminopropane; RP-6847; Dysedon. $C_{18}H_{22}N_2O_2S$; mol wt 330.45. C 65.43%, H 6.71%, N 8.48%, O 9.68%, S 9.70%. Prepn: Jacob, Robert, **US 2972612** (1961 to Rhône-Poulenc).



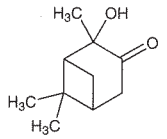
Crystals from heptane, mp 115°.

Hydrochloride. Doxergan; Imakol. $C_{18}H_{22}N_2O_2S.HCl$; mol wt 366.91. Crystals from ethanol + isopropanol, mp 250°.

7016. Oxonic Acid. [937-13-3] 1,4,5,6-Tetrahydro-4,6-dioxo-1,3,5-triazine-2-carboxylic acid; allantoxanic acid; 5-azaorotic acid; *s*-triazine-2,4-dione-6-carboxylic acid; 2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazine-6-carboxylic acid. $C_4H_3N_3O_4$; mol wt 157.08. C 30.58%, H 1.92%, N 26.75%, O 40.74%. Formed during alkaline oxidation of uric acid with H_2O_2 or $KMnO_4$. Prepn and structure: Brandenberger, *Helv. Chim. Acta* **37,** 641 (1954); Brandenberger, Brandenberger, *ibid.* **37,** 2207 (1954); Piskala, Gut, *Coll. Czech. Chem. Commun.* **27,** 1572 (1962). Metabolism: Chelbova *et al., Biochem. Pharmacol.* **19,** 2785 (1970); Cihak, Sorm, *ibid.* **21,** 607 (1972).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 49 of 65

7045. Oxypinocamphone. [10136-65-9] 2-Hydroxy-2,-6,6-trimethylbicyclo[3.1.1]heptan-3-one; 2-hydroxy-3-pinanone; 2-hydroxypinocamphone; Camphostene; Oxypinone. $C_{10}H_{16}O_2$; mol wt 168.23. C 71.39%, H 9.59%, O 19.02%. Prepn of *l*-form: Kuwata, *J. Am. Chem. Soc.* **59,** 2509 (1937); Harispe *et al., Bull. Soc. Chim. France* **1964,** 1035; of *dl*-form: Kuwata, *loc. cit.* Stereochemistry: Carlson *et al., Tetrahedron Letters* **1968,** 5941.

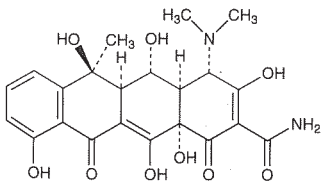


***dl*-Form.** Crystals, mp 38.5-39.0°.

***l*-Form.** Crystals from ether + petr ether, mp 35.5-36.5°. $[\alpha]_D^{25}$ −18.56° (c = 14.44 in alcohol).

THERAP CAT: Respiratory insufficiency.

7046. Oxytetracycline. [79-57-2] [4*S*-(4α,4aα,5α,5aα,-6β,12aα)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide; glomycin; riomitsin; hydroxytetracycline. $C_{22}H_{24}N_2O_9$; mol wt 460.43. C 57.39%, H 5.25%, N 6.08%, O 31.27%. Antibiotic substance isolated from the elaboration products of the actinomycete, *Streptomyces rimosus,* grown on a suitable medium: Finlay *et al., Science* **111,** 85 (1950). Isoln: Regna, Solomons, *Ann. N.Y. Acad. Sci.* **53,** 221 (1950); Regna *et al., J. Am. Chem. Soc.* **73,** 4211 (1951). Production from *Streptomyces rimosus:* Sobin *et al.,* **US 2516080** (1950 to Pfizer). Isoln from *S. xanthophaeus:* Brockmann, Musso, *Naturwiss.* **41,** 451 (1954); Brockmann *et al.,* **DE 913687** (1954 to Bayer), *C.A.* **53,** 4662h (1959). Solubility data: Weiss *et al., Antibiot. & Chemother.* **7,** 374 (1957). Structure: Hochstein *et al., J. Am. Chem. Soc.* **74,** 3708 (1952). Abs config: Dobrynin *et al., Tetrahedron Letters* **1962,** 901. Stereochemistry: Schach von Wittenau *et al., J. Am. Chem. Soc.* **87,** 134 (1965). Total synthesis of the *dl*-form: H. Muxfeldt *et al., ibid.* **101,** 689 (1979).



Stability: Oxytetracycline crystals show no loss in potency on heating for 4 days at 100°, the hydrochloride crystals show <5% inactivation after 4 mos at 56°. Aq solns of the hydrochloride at pH 1.0 to 2.5 are stable for at least 30 days at 25°. Solns at pH 3.0 to 9.0 show no detectable loss in potency on storage at 5° for at least 30 days. Half-life in hours of aq oxytetracycline solns at 37°: pH 1.0 = 114; pH 2.5 = 134; pH 4.6 = 45; pH 5.5 = 45; pH 7.0 = 26; pH 8.5 = 33; pH 10.0 = 14.

Dihydrate. Abbocin; Berkmycen; Imperacin; Oxydon; Oxymycin; Terralon-LA; Terramycin; Unimycin. Needles from water or methanol, dec 181-182°. $[\alpha]_D^{25}$ −196.6° (0.1*N* HCl); $[\alpha]_D^{25}$ −2.1° (0.1*N* NaOH); $[\alpha]_D^{25}$ +26.5° (methanol). uv max (pH 4.5 phosphate buffer 0.1*M*): 249, 276, 353 nm ($E_{1cm}^{1\%}$ 240, 322, 301). Soly in water at 23°: pH 1.2 = 31,400 γ/ml, pH 2.0 = 4600 γ/ml, pH 3.0 = 1400 γ/ml; pH 5.0 = 500 γ/ml, pH 6.0 = 700 γ/ml, pH 7.0 = 1100 γ/ml, pH 9.0 = 38,600 γ/ml. Soly in abs ethanol 12,000 γ/ml, in 95% ethanol 200 γ/ml.

Hydrochloride. [2058-46-0] Alamycin; Duphacycline; Engemycin; Geomycin; Macocyn; Occrycetin; Oxlopar; Oxycyclin; Oxy-Dumocyclin; Oxylag; Oxytetrin; Terraject; Tetran; Tetra-Tablinen; Toxinal; Vendarcin. Yellow platelets from water. Very soluble in water (1 g/ml). Concd aq solns at neutral pH hydrolyze on standing and deposit crystals of oxytetracycline. Soly in abs ethanol: 12,000 γ/ml, in 95% ethanol: 33,000 γ/ml.

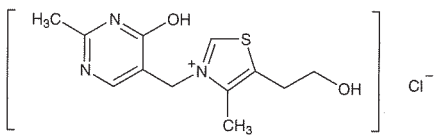
Disodium salt dihydrate. $C_{22}H_{22}N_2Na_2O_9.2H_2O$. Yellow crystals; darkens on standing. Soly in abs alc: 8,000 γ/ml, in methanol: 1500 γ/ml.

USE: To treat lethal yellowing in palm trees.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

7047. Oxythiamine. [582-36-5] 3-[(1,4-Dihydro-2-methyl-4-oxo-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride; 5-(2-hydroxyethyl)-3-[(4-hydroxy-2-methyl-5-pyrimidinyl)methyl]-4-methylthiazolium chloride. $C_{12}H_{16}ClN_3O_2S$; mol wt 301.80. C 47.76%, H 5.34%, Cl 11.75%, N 13.92%, O 10.60%, S 10.62%. Prepn: F. Bergel, A. R. Todd, *J. Chem. Soc.* **1937,** 1504; M. Soodak, L. R. Cerecedo, *J. Am. Chem. Soc.* **66,** 1988 (1944). Improved prepn: H. N. Rydon, *Biochem. J.* **48,** 383 (1951). Thiamine antagonist activity: A. J. Eusebi, L. R. Cerecedo, *Science* **110,** 162 (1949); L. J. Daniel, L. C. Norris, *Proc. Soc. Exp. Biol. Med.* **72,** 165 (1949); and distribution in tissues: C. J. Gubler, D. S. Murdock, *J. Nutr. Sci. Vitaminol.* **28,** 217 (1982). Proposed mechanism of action: S. A. Strumilo *et al., Biomed. Biochim. Acta* **43,** 159 (1984). Determn by HPLC: B. C. Hemming, C. J. Gubler, *J. Liq. Chromatog.* **3,** 1697 (1980).



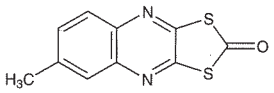
Hydrochloride. $C_{12}H_{16}ClN_3O_2S.HCl$. Flat needles grouped in rosettes, dec 195°. uv max (acid soln): 265, 258, 228, 223 nm; (alkaline soln): 268, 260, 228, 221 nm. Does not give the thiochrome reaction.

Diphosphate. Crystals, mp 127-129°.

Monophosphoric acid ester. Hygroscopic crystals, dec 185-186°.

Triphosphoric acid ester. Minute crystals, dec 245-255°.

7048. Oxythioquinox. [2439-01-2] 6-Methyl-1,3-dithiolo[4,5-*b*]quinoxalin-2-one; dithiocarbonic acid cyclic *S,S*-(6-methyl-2,3-quinoxalinediyl) ester; 6-methyl-2,3-quinoxalinedithiol cyclic *S,S*-dithiocarbonate; 6-methyl-2-oxo-1,3-dithio[4,5-*b*]quinoxaline; chinomethionat(e); quinomethionate; Bayer 36205; Forstan; Morestan. $C_{10}H_6N_2OS_2$; mol wt 234.30. C 51.26%, H 2.58%, N 11.96%, O 6.83%, S 27.37%. Prepn and review (in English) of chemical and fungicidal properties and toxicology: F. Grewe, H. Kaspers, *Pflanzenschutz Nachr. Bayer* **18** (1), 1-23 (1965), *C.A.* **64,** 5689h (1966). Toxicity study: T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14,** 515 (1969).



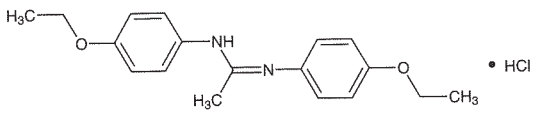
Yellow crystals from benzene, mp 172°. Practically insol in water. Freely sol in DMF. Sol in hot benzene, toluene, dioxane. Slightly sol in methanol, ethanol, acetone. LD_{50} in male, female rats (mg/kg): 1800, 1100 orally (Gaines).

USE: Acaricide; agricultural fungicide.

7049. Oxytocin. [50-56-6] Alpha-hypophamine; ocytocin; Intertocine-S; Perlacton; Pitocin; Syntocinon; Orasthin; Oxystin; Partocon; Synpitan; Uteracon. $C_{43}H_{66}N_{12}O_{12}S_2$; mol wt 1007.20. C 51.28%, H 6.61%, N 16.69%, O 19.06%, S 6.37%. The principal uterus-contracting and lactation-stimulating hormone of the posterior pituitary gland. Isoln: Pierce *et*

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 50 of 65

drochloride. $C_{18}H_{23}ClN_2O_2$; mol wt 334.85. C 64.57%, H 6.92%, Cl 10.59%, N 8.37%, O 9.56%. Prepn: **DE 79868**; **DE 80568**.



Monohydrate. [6153-19-1] Faintly bitter crystals producing transient numbness of the tongue. Stable in air. When anhydr, mp 190-192°. One gram dissolves in 50 ml water. Freely sol in boiling water, alcohol, chloroform. Insol in ether. Incompatible with alkalies and their carbonates and the usual alkaloidal reagents. Aq solns are stable and are not dec by boiling.

THERAP CAT: Topical anesthetic (ophthalmic).

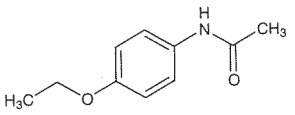
THERAP CAT (VET): Ocular anesthetic.

7280. Phenacemide. [63-98-9] *N*-(Aminocarbonyl)benzeneacetamide; (phenylacetyl)urea; phenacetylurea; Epiclase; Phacetur; Phenurone; Phetylureum. $C_9H_{10}N_2O_2$; mol wt 178.19. C 60.66%, H 5.66%, N 15.72%, O 17.96%. $C_6H_5CH_2CONHCONH_2$. Prepd by the action of aq NH_3 on phenacetylurethan: Basterfield, Greig, *Can. J. Res.* **8,** 454 (1933); of phenacetyl chloride on urea: Spielman *et al., J. Am. Chem. Soc.* **70,** 4189 (1948). Toxicity study: K. Nakamura *et al., Arzneimittel-Forsch.* **18,** 524 (1968).

Crystals from alcohol, mp 212-216°. Very slightly sol in water; slightly sol in alcohol, benzene, chloroform, ether. LD_{50} in mice, rats (mmol/kg): 5.54, >10 orally (Nakamura).

THERAP CAT: Anticonvulsant.

7281. Phenacetin. [62-44-2] *N*-(4-Ethoxyphenyl)acetamide; *p*-acetophenetidide; *p*-ethoxyacetanilide; acetophenetidin; *para*-acetphenetidin; acet-*p*-phenetidin; *p*-acetophenetide. $C_{10}H_{13}NO_2$; mol wt 179.22. C 67.02%, H 7.31%, N 7.82%, O 17.85%. Prepn: *Beilstein* **vol. XIII,** 461. Improved process: Eaker, Campbell, **US 2887513** (1959 to Monsanto). *Monograph:* P. K. Smith, *Acetophenetidin* (Interscience, New York, 1958) 180 pp. Toxicity: Boyd, *Toxicol. Appl. Pharmacol.* **1,** 240 (1959). Review of toxicity and metabolism studies: L. Fishbein, *IARC Sci. Publ.* **40,** 287-310 (1981). Epidemiologic study of renal morbidity and mortality: U. C. Dubach *et al., N. Engl. J. Med.* **308,** 357 (1983). Evaluation of renal effects: D. P. Sandler *et al., ibid.* **320,** 1238 (1989).



Slightly bitter, cryst scales or powder. mp 134-135°. One gram dissolves in 1310 ml cold water, 82 ml boiling water; 15 ml cold alcohol, 2.8 ml boiling alcohol; 14 ml chloroform, 90 ml ether; sol in glycerol. Gives a pasty mass with phenol, chloral hydrate or pyrocatechol, strong acids or alkalies, salicylic acid, oxidizers, iodine, spirit nitrous ether. LD_{50} orally in rats: 1.65 g/kg (Boyd).

Note: Component of ***APC*** tablets, analgesic mixture also containing aspirin and caffeine. Analgesic mixtures containing phenacetin have been listed as known human carcinogens; phenacetin is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-4, III-180.

THERAP CAT: Analgesic, antipyretic.

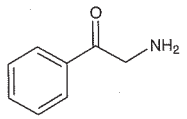
THERAP CAT (VET): Analgesic, antipyretic.

7282. Phenacetolin. [1340-26-7] Degener's indicator. Reaction product of concd H_2SO_4 and glacial acetic acid on phenol.

Yellowish-brown powder. Slightly sol in water; sol in alc.

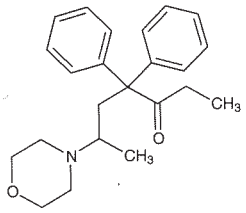
USE: Has been employed as indicator, particularly for mixtures of alkali hydroxides and carbonates; the yellow color changes to red when hydroxide is neutralized, and again to yellow when carbonate is fully dec by acid; was also used for determining alkalinity of water. The indicator soln is prepd by digesting 1 g with 100 ml warm alcohol and filtering after cooling; 2-3 drops used for 100 ml liquid.

7283. Phenacylamine. [613-89-8] 2-Amino-1-phenylethanone; 2-aminoacetophenone; α-aminoacetophenone; ω-aminoacetophenone. C_8H_9NO; mol wt 135.16. C 71.09%, H 6.71%, N 10.36%, O 11.84%. Prepn from α-phenylethylamine: H. E. Baumgarten, J. M. Petersen, *J. Am. Chem. Soc.* **82,** 459 (1960); *eidem, Org. Syn.* **coll. vol. V,** 909 (1973).



Hydrochloride. $C_8H_9NO.HCl$. Crystals from isopropanol + HCl, dec 188.5°.

7284. Phenadoxone. [467-84-5] 6-(4-Morpholinyl)-4,4-diphenyl-3-heptanone; 6-tetrahydrooxazine-4,4-diphenyl-3-heptanone; heptazone; morphodone. $C_{23}H_{29}NO_2$; mol wt 351.48. C 78.60%, H 8.32%, N 3.99%, O 9.10%. Prepn: M. Bockmühl, G. Ehrhart, *Ann.* **561,** 52 (1948). Comparison with other analgesics: C. A. Winter, L. Flataker, *J. Pharmacol. Exp. Ther.* **98,** 305 (1950). HPLC determn: I. Jane *et al., J. Chromatog.* **323,** 191 (1985).



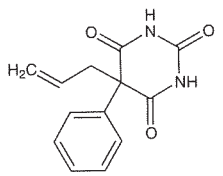
mp 75-76°.

Hydrochloride. [545-91-5] Hoechst 10600; CB-11; Hepagin; Heptalgin; Heptalin; Heptone; Supralgin. $C_{23}H_{29}NO_2.HCl$; mol wt 387.95. Crystals, mp 224-225° (some decompn). pKa (25°): 6.7 in 40% alcohol. pH of 1% aq soln 4.1; of 5% aq soln 3.7. The free base begins to precipitate when the pH is raised to 5.5. uv max (abs alcohol): 260, 295 nm. Soly (g/100 ml) in water: 10 at 25°; 80 at the bp; in methanol: 27; in abs ethanol: 24; in chloroform: 50. Slightly sol in acetone. Almost insol in benzene, ethyl acetate. LD_{50} i.v. in mice: 47.5 mg/kg (Winter, Flataker).

Note: This is a controlled substance (opiate): **21 CFR,** 1308.11.

THERAP CAT: Analgesic (narcotic).

7285. Phenallymal. [115-43-5] 5-Phenyl-5-(2-propenyl)-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione; 5-allyl-5-phenylbarbituric acid; 5-phenyl-5-allylbarbituric acid; phenallymalum; alphenal; prophenal; Alphenate; Allofenyl; Fenallymal. $C_{13}H_{12}N_2O_3$; mol wt 244.25. C 63.93%, H 4.95%, N 11.47%, O 19.65%. Its methods of prepn are similar to those used for phenobarbital: Slotta, *Grundriss der modernen Arzneistoff-Synthese* (Stuttgart, 1931) p 45. Metabolism: D. J. Harvey *et al., Res. Commun. Chem. Pathol. Pharmacol.* **4,** 247 (1972); *eidem, Drug Metab. Dispos.* **5,** 527 (1977).

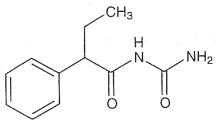


NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 51 of 65

Wohl, *Ber.* **39,** 1953 (1906); ethyl bromide: White *et al., J. Am. Chem. Soc.* **46,** 965 (1924); ethyl *p*-toluenesulfonate: Finzi, *Ann. Chim. Applicata* **15,** 41 (1925); diethyl sulfate or triethyl phosphate: Noller, Dutton, *J. Am. Chem. Soc.* **55,** 424 (1933). Toxicity data: Binet, *Rev. Med. Suisse Rom.* **15,** 561 (1895).

Oily liquid. d_4^{20} 0.967; mp −30°; bp 171-173°; n_D^{20} 1.507. Practically insol in water. Freely sol in alcohol, ether. MLD in rats (mg/kg): 3500-4000 s.c. (Binet).

7309. Pheneturide. [90-49-3] *N*-(Aminocarbonyl)-α-ethylbenzeneacetamide; (2-phenylbutyryl)urea; α-phenyl-α-ethylacetylurea; *N*-(α-phenylbutyryl)urea; α-ethyl-α-phenylacetylurea; ethylphenacemide; EPA; PBU; Benuride. $C_{11}H_{14}N_2O_2$; mol wt 206.24. C 64.06%, H 6.84%, N 13.58%, O 15.52%. Prepd by heating α-phenylbutyric acid chloride with urea: **DE 249241** (1912 to Bayer); *Chem. Zentr.* **1912,** II, 396; *Frdl.* **10,** 1165. From α-phenylbutyric acid chloride, urea, and antipyrine: Gold-Aubert, *Helv. Chim. Acta* **41,** 1512 (1958); **CH 374644** (1964 to Labs. Sapos). Pharmacokinetics: R. L. Galeazzi *et al., J. Pharmacokinet. Biopharm.* **7,** 453 (1979). Toxicity: M. J. Orloff *et al., Neurology* **1,** 377 (1951). Clinical studies: J. C. Bowe, *Brit. J. Clin. Pract.* **27,** 174 (1973); F. B. Gibberd *et al., J. Neurol. Neurosurg. Psychiat.* **45,** 1113 (1982).



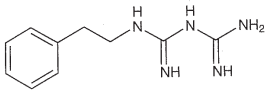
***dl*-Form.** Needles from ethanol, mp 149-150°.

***d*-Form.** Needles from ethanol, mp 168-169°. $[\alpha]_D^{17}$ +54.0° (c = 1 in ethanol); $[\alpha]_D^{22}$ +53.8° (c = 1 in acetone); +48.2° (c = 1 in dioxane).

***l*-Form.** Crystals from 50% ethanol, mp 162-163°. $[\alpha]_D^{30}$ −51.6° (c = 1 in ethanol).

THERAP CAT: Anticonvulsant.

7310. Phenformin. [114-86-3] *N*-(2-Phenylethyl)imidodicarbonimidic diamide; 1-phenethylbiguanide; phenethyldiguanide; *N'*-β-phenethylformamidinyliminourea; fenformin; fenormin; β-PEBG; PEDG. $C_{10}H_{15}N_5$; mol wt 205.26. C 58.51%, H 7.37%, N 34.12%. Prepn: Shapiro *et al., J. Am. Chem. Soc.* **81,** 2220 (1959); Shapiro, Freedman, **US 2961377**; **US 3057780** (1960, 1962 both to U.S.V.). Metabolism: R. Beckmann, *Diabetologia* **3,** 368 (1967). Association with lactic acidosis in diabetic patients: R. I. Misbin, *Ann. Int. Med.* **87,** 591 (1977). Toxicity study: G. Proske *et al., Arzneimittel-Forsch.* **12,** 314 (1962). Comprehensive description: J. E. Moody, *Anal. Profiles Drug Subs.* **4,** 319-332 (1975). Review of phenformin-induced lactic acidosis: M. E. McGuinness, R. L. Talbert, *Annals Pharmacother.* **27,** 1183-1187 (1993).

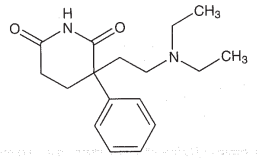


Hydrochloride. [834-28-6] Azucaps; DBI; DBI-TD; Debeone-DT; Debinyl; Dibein; Dibotin; Dipar; Feguanide; Glucopostin; Insoral; Lentobetic; Meltrol; Normoglucina. $C_{10}H_{15}N_5$.HCl; mol wt 241.73. Crystals from isopropanol, mp 175-178°. Sol in water; pH (0.1*M* aq soln): 6.7. LD_{50} in mice (mg/kg): 19 i.v., 450 orally; in rats: 1050 orally; in guinea pigs: 47 orally, 19 s.c. (Proske).

Caution: Associated with the development of lactic acidosis. *See* M. J. Ellenhorn, D. G. Barceloux, *Medical Toxicology: Diagnosis and Treatment of Human Poisoning* (Elsevier, New York, 1988) pp 449-453.

THERAP CAT: Antidiabetic.

7311. Phenglutarimide. [1156-05-4] 3-[2-(Diethylamino)ethyl]-3-phenyl-2,6-piperidinedione; 2-(2-diethylaminoethyl)-2-phenylglutarimide; α-phenyl-α-(diethylaminoethyl)glutarimide; 3-phenyl-3-(β-diethylaminoethyl)-2,6-dioxopiperidine. $C_{17}H_{24}N_2O_2$; mol wt 288.38. C 70.80%, H 8.39%, N 9.71%, O 11.10%. Anticholinergic. Prepn: Tagmann *et al., Helv. Chim. Acta* **35,** 1235 (1952); **37,** 185 (1954); Hoffmann, Tagmann, **US 2664424** (1953 to Ciba).

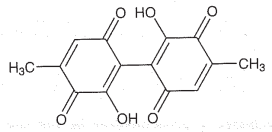


Crystals from isopropanol, mp 125-127°. Can also be crystallized from a mixture of ethyl acetate and ligroin.

Hydrochloride. [1674-96-0] Aturbane; Aturbal. $C_{17}H_{24}N_2O_2$.HCl; mol wt 324.85. Crystals from methanol + ethyl acetate, dec 168-172°, also 176-177°. Freely sol in water. Dec by alkali.

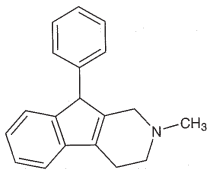
THERAP CAT: Antiparkinsonian.

7312. Phenicin. [128-68-7] 2,2′-Dihydroxy-4,4′-dimethyl[bi-1,4-cyclohexadien-1-yl]-3,3′,6,6′-tetrone; 3,3′-dihydroxy-5,5′-dimethyl-2,2′-bi-*p*-benzoquinone; phoenicin. $C_{14}H_{10}O_6$; mol wt 274.23. C 61.32%, H 3.68%, O 35.01%. Fungal pigment produced by *Penicillium phoeniceum* and *P. rubrum:* Friedheim, *Helv. Chim. Acta* **21,** 1464 (1938); Charollais *et al., Arch. Sci. (Geneva)* **16,** 474 (1963). Synthesis: Posternak *et al., Helv. Chim. Acta* **26,** 2031 (1943); Musso, Beecken, *Ber.* **92,** 1416 (1959); J. Kalamar *et al., Helv. Chim. Acta* **57,** 2368 (1974). Biosynthesis: E. Steiner *et al., ibid.* 2377.



Yellowish-brown crystals from alc, mp 230-231°. uv max (chloroform): 268, 406 nm (log ε 4.52, 3.36). Sparingly sol in water; freely sol in chloroform, acetic acid, hot alcohol. Very acidic solns are yellow, turning red at pH 1.6-3.6 and violet at pH 4.9-6.

7313. Phenindamine. [82-88-2] 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine; 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene; 1,2,3,4-tetrahydro-2-methyl-9-phenyl-2-azafluorene; Nu-1504. $C_{19}H_{19}N$; mol wt 261.36. C 87.31%, H 7.33%, N 5.36%. Prepn: J. T. Plati, W. Wenner, **US 2470108** (1949 to Hoffmann-La Roche). Pharmacology: G. Lehmann, *J. Pharmacol. Exp. Ther.* **92,** 249 (1948); W. Schallek, *ibid.* **105,** 291 (1952).

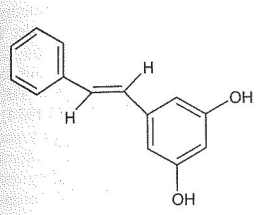


Crystals from ether, mp 90-91°, d 1.17.

Hydrogen tartrate. [569-59-5] Pernovin; Thephorin. $C_{19}H_{19}N.C_4H_6O_6$; mol wt 411.45. Crystals, mp 160°. Soly: about 2.5% in water; sparingly sol in propylene glycol. Insol in 95% ethanol, glycerol, ether. LD_{50} in mice (mg/kg): 27 i.v., 170 i.p., 265 orally (Schallek).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 52 of 65

A. A. Loman, L. R. Snowdon, *Can. J. Chem.* **48,** 1554 (1970). Biosynthesis: Birch, *Fortschr. Chem. Org. Naturst.* **14,** 186 (1957). Toxicological study: K. O. Frykholm, *Nature* **155,** 454 (1945). Use as antimicrobial agent: E. H. Sheers, **DE 1952451**; *idem,* **US 3577230** (1970, 1971 both to Arizona Chem. Co.). Deterrent to feeding behavior of snowshoe hare: J. P. Bryant *et al., Science* **222,** 1023 (1983).

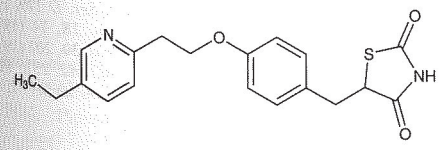


Fine needles from glacial acetic acid, mp 155.5-156°. uv max (ethanol): 305 nm (log ε 4.49). Practically insol in water. Sol in benzene, acetone, chloroform, glacial acetic acid.

Monomethyl ether. $C_{15}H_{14}O_2$. Crystals, mp 122-123°. uv max (ethanol): 303 nm (log ε 4.26). More sol in benzene than pinosylvin. Also sol in methanol, glacial acetic acid.

Dimethyl ether. $C_{16}H_{16}O_2$. Crystals from methanol-water, mp 55-56°. uv max (ethanol): 305 nm (log ε 4.39).

7533. Pioglitazone. [111025-46-8] 5-[[4-[2-(5-Ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione; (±)-5-[*p*-[2-(ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; AD-4833. $C_{19}H_{20}N_2O_3S$; mol wt 356.45. C 64.02%, H 5.66%, N 7.86%, O 13.47%, S 9.00%. Insulin sensitizer. Prepn: K. Meguro, T. Fujita, **EP 193256**; *eidem,* **US 4687777** (1986, 1987 both to Takeda); T. Sohda *et al., Arzneimittel-Forsch.* **40,** 37 (1990). Pharmacology: H. Ikeda *et al., ibid.* 156. HPLC determn in serum: W. Z. Zhong, D. B. Lakings, *J. Chromatog.* **490,** 377 (1989). Mechanism of action: C. Hofmann *et al., Endocrinology* **129,** 1915 (1991); M. Kobayashi *et al., Diabetes* **41,** 476 (1992). Effect on adipocyte differentiation: T. Sandouk *et al., Am J. Physiol.* **264,** C1600 (1993). Clinical evaluation in noninsulin-dependent diabetes: R. Kawamori *et al., Diabetes Res. Clin. Pract.* **41,** 35 (1998).

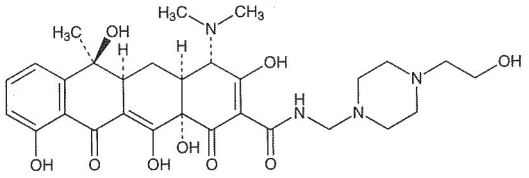


Colorless needles from DMF + water, mp 183-184°.

Hydrochloride. [112529-15-4] U-72107A; Actos. $C_{19}H_{20}N_2O_3S.HCl$; mol wt 392.91. Colorless prisms from ethanol, mp 193-194°. Sol in DMF; slightly sol in ethanol; very slightly sol in acetone, acetonitrile. Practically insol in water; insol in ether.

THERAP CAT: Antidiabetic.

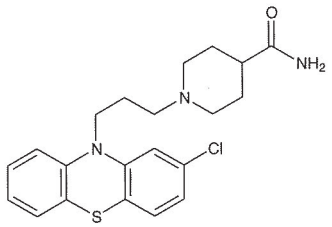
7534. Pipacycline. [1110-80-1] [4*S*-(4α,4aα,5aα,6β,12aα)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-*N*-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]-6-methyl-1,11-dioxo-2-naphthacenecarboxamide; *N*-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]tetracycline; *N*-[4-(β-hydroxyethyl)diethylenediamino-1-methyl]tetracycline; mepicycline; mepiciclina; Ambra-Vena; Sieromicin; Valtomicina. $C_{29}H_{38}N_4O_9$; mol wt 586.63. C 59.37%, H 6.53%, N 9.55%, O 24.55%. Semi-synthetic broad spectrum antibiotic related to tetracycline. Prepn: Pedrazzoli *et al., Boll. Chim. Farm.* **98,** 516 (1959), *C.A.* **54,** 3856a (1960); Gradnik *et al.,* **GB 888968** corresp to **US 3149114** (1962 and 1964 to E.R.A.S.M.E.). Properties: *eidem, Pharm. Acta Helv.* **35,** 529 (1960). Pharmacokinetic studies: A. Scalvini, A. Delmonte, *Gazz. Med. Ital.* **131,** 1 (1972).



Yellow cryst powder, dec 162-163°. $[\alpha]_D^{20}$ −195° (c = 0.5). $[\alpha]_D^{20}$ −175° (c = 0.5 in methanol). uv max (10 γ/ml 0.1*N* HCl): 286, 355 nm. pH of 2% aq soln, 7.2-7.4. Freely sol in water, methanol, formamide; slightly sol in ethanol, isopropanol. Practically insol in ether, benzene, chloroform. Sensitive to light, heat, and air. LD_{50} i.v. in white mice: 188 mg/kg (Scalvini, Delmonte).

THERAP CAT: Antibacterial.

7535. Pipamazine. [84-04-8] 1-[3-(2-Chloro-10*H*-phenothiazin-10-yl)propyl]-4-piperidinecarboxamide; 1-[3-(2-chlorophenothiazin-10-yl)propyl]isonipecotamide; 10-[3-(4-carbamoylpiperidin-1-yl)propyl]-2-chlorophenothiazine; 2-chloro-10-[3-(4-carbamoylpiperidinyl)propyl]phenothiazine; 10-[3-(4-carbamoylpiperidino)propyl]-2-chlorophenothiazine; SC-9387; Nausidol; Mornidine. $C_{21}H_{24}ClN_3OS$; mol wt 401.96. C 62.75%, H 6.02%, Cl 8.82%, N 10.45%, O 3.98%, S 7.98%. Prepn: Cusic *et al.,* **US 2957870** (1960 to Searle).

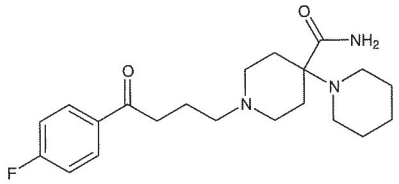


Crystals from 2-propanol + petr ether, mp about 139°.

Hydrochloride. Crystals, mp about 196-197° with formation of bubbles.

THERAP CAT: Antiemetic.

7536. Pipamperone. [1893-33-0] 1′-[4-(4-Fluorophenyl)-4-oxobutyl]-[1,4′-bipiperidine]-4′-carboxamide; 1′-[3-(*p*-fluorobenzoyl)propyl]-[1,4′-bipiperidine]-4′-carboxamide; 1-(*p*-fluorophenyl)-4-(4-piperidino-4-carbamoylpiperidino)-1-butanone; 1-[γ-(4-fluorobenzoyl)propyl]-4-piperidinopiperidine-4-carboxamide; 4′-fluoro-4-[*N*-[4-(*N*-piperidino)-4-carbamido]-piperidino]butyrophenone; floropipamide; R-3345. $C_{21}H_{30}FN_3O_2$; mol wt 375.48. C 67.17%, H 8.05%, F 5.06%, N 11.19%, O 8.52%. Prepn of the dihydrochloride by reaction of γ-chloro-4-fluorobutyrophenone and 4-piperidinopiperidine-4-carboxamide: Janssen, **BE 610830** (1962 to Janssen), *C.A.* **57,** 13740b (1962).



Dihydrochloride. [2448-68-2] Dipiperon; Piperonil; Propitan. $C_{21}H_{30}FN_3O_2.2HCl$; mol wt 448.41. Crystals, mp 124.5-126.0°.

THERAP CAT: Antipsychotic.

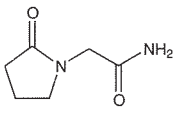
7537. Pipazethate. [2167-85-3] 10*H*-Pyrido[3,2-*b*]-[1,4]benzothiadiazine-10-carboxylic acid 2-(2-piperidinoeth-

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 53 of 65

Colorless cryst, mp 86-87°. Practically insol in water. Sol in dil aq acids and most organic solvents. uv max (methanol): 245, 285 nm (ε 8200, 20000) (Vollmer). LD_{50} in mice, rats (mg/kg): 1070, 3256 orally (Herrmann).
THERAP CAT: Choleretic.

7568. Pipsyl Chloride. [98-61-3] 4-Iodobenzenesulfonyl chloride; *p*-iodophenyl sulfonyl chloride. Usually prepd from iodide ion and *p*-diazobenzenesulfonic acid, followed by treatment with phosphorus pentachloride. A 5-10-fold excess reacts quantitatively with amino acids as indicated by the disappearance of amino nitrogen. Radioactive pipsyl chloride is used in the analysis of proteins: Keston *et al., J. Am. Chem. Soc.* **68,** 1390 (1946).

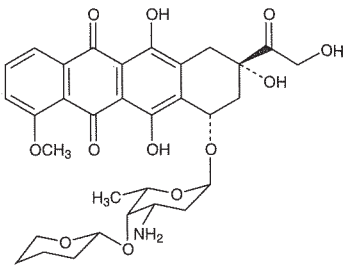
7569. Piracetam. [7491-74-9] 2-Oxo-1-pyrrolidineacetamide; 2-pyrrolidoneacetamide; 2-pyrrolidinoneacetamide; 2-ketopyrrolidine-1-ylacetamide; 1-acetamido-2-pyrrolidinone; UCB-6215; Avigilen; Axonyl; Cerebroforte; Encetrop; Gabacet; Genogris; Geram; Nootron; Nootrop; Nootropil; Nootropyl; Norzetam; Normabraïn; Pirroxil. $C_6H_{10}N_2O_2$; mol wt 142.16. C 50.69%, H 7.09%, N 19.71%, O 22.51%. Prepn: H. Morren, **NL 6509994**; *eidem,* **US 3459738** (1966, 1969 both to U.C.B.). Pharmacology: Giurgea *et al., Arch. Int. Pharmacodyn. Ther.* **166,** 238 (1967); Giurgea, Moyersoons, *ibid.* **188,** 401 (1970); Giurgea *et al., Psychopharmacologia* **20,** 160 (1971). Metabolism and biochemical studies: Gobert, *J. Pharm. Belg.* **27,** 281 (1972). Clinical studies: W. J. Oosterveld, *Arzneimittel-Forsch.* **30,** 1947 (1980); G. Chouinard *et al., Psychopharmacol. Bull.* **17,** 129 (1981); in dyslexia: M. Di Ianni *et al., J. Clin. Psychopharmacol.* **5,** 272 (1985).



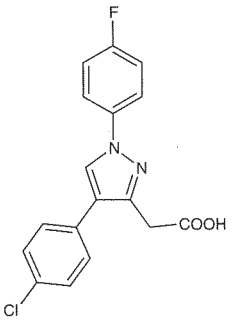
Crystals from isopropanol, mp 151.5-152.5°.
THERAP CAT: Nootropic.

7570. Pirarubicin. [72496-41-4] (8*S*,10*S*)-10-[[3-Amino-2,3,6-trideoxy-4-*O*-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]-α-L-*lyxo*-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione; 4′-*O*-tetrahydropyranyl doxorubicin; (2″*R*)-4′-*O*-tetrahydropyranyladriamycin; (8*S*,10*S*)-10-[[3-amino-2,3,6-trideoxy-4-*O*-(tetrahydro-2*H*-pyran-2-yl)-α-L-*lyxo*-hexopyranosyl]oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione; tepirubicin; THP; THP-ADM; THP-adriamycin; 1609-RB; Pinorubicin; Theprubicin; Therarubicin. $C_{32}H_{37}NO_{12}$; mol wt 627.63. C 61.24%, H 5.94%, N 2.23%, O 30.59%. Structural analog of doxorubicin, *q.v.* Prepn of (2″*R*) and (2″*S*)-diastereomers: H. Umezawa *et al., J. Antibiot.* **32,** 1082 (1979); H. Umezawa *et al.,* **EP 14853**; *eidem,* **US 4303785** (1980, 1981 both to Microbiochem. Res. Found. Japan). Absolute configuration: H. Umezawa *et al., J. Antibiot.* **37,** 1094 (1984). HPLC determn in biological fluids: Y. Matsushita *et al., J. Antibiot.* **36,** 880 (1983). Preliminary toxicology: D. Dantchev *et al., ibid.* **32,** 1085 (1979). *In vitro* antitumor activity: T. Tsuruo *et al., Cancer Res.* **42,** 1462 (1982); *in vivo* activity: T. Hisamatsu *et al., Japan. J. Cancer Res.* **76,** 1008 (1985). Cellular uptake and inhibition of DNA synthesis: S. Kunimoto *et al., J. Antibiot.* **36,** 312 (1983); and cytostatic activity: S. Kunimoto *et al., ibid.* **37,** 1697 (1984). Pharmacokinetics and tissue distribution: H. Iguchi *et al., Cancer Chemother. Pharmacol.* **15,** 132 (1985). Clinical pharmacology: A. A. Miller, C. G. Schmidt, *Cancer Res.* **47,** 1461 (1987). Clinical studies in breast cancer: G. Mathe *et al., Biomed. Pharmacother.* **40,** 376 (1986); in leukemia and malignant lymphoma: R. Ohno *et al., Cancer Chemother. Pharmacol.* **20,** 230 (1987). Brief review of early clinical evaluations: H. Majima, K. Ohta, *Biomed. Pharmacother.* **41,** 237-243 (1987).

Red solid, mp 188-192° (dec). $[\alpha]_D^{25}$ 175 ±25° (c = 0.2 in $CHCl_3$). uv and visible max (methanol): 234, 252, 290, 498, 531.5, 580 nm ($E_{1cm}^{1\%}$ 480, 350, 110, 140, 100, 45). Sol in ethyl acetate, chloroform, and ethanol; slightly sol in water, *n*-hexane, petr ether. Ethanolic and acidic solutions are red in color; give a positive ninhydrin reaction and do not reduce Fehling's solution. LD_{50} i.v. in mice: 27.8 mg/kg (Umezawa, 1979).
THERAP CAT: Antineoplastic.



7571. Pirazolac. [71002-09-0] 4-(4-Chlorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazole-3-acetic acid; ZK-76604. $C_{17}H_{12}ClFN_2O_2$; mol wt 330.75. C 61.73%, H 3.66%, Cl 10.72%, F 5.74%, N 8.47%, O 9.67%. Prepn: **BE 844972**; H. Ahrens *et al.,* **US 4042706** (both 1977 to Schering AG); H. Biere *et al., Eur. J. Med. Chem.-Chim. Ther.* **17,** 27 (1982). Pharmacokinetics: U. Täuber *et al., Eur. J. Drug Metabol. Pharmacokinet.* **10,** 41 (1985). Effect on arachidonic acid metabolism in human synovia: M. Kurowski *et al., Curr. Med. Res. Opin.* **10,** 494 (1987). Preliminary clinical trial in rheumatoid arthritis: D. Symmons *et al., ibid.* **9,** 542 (1985).

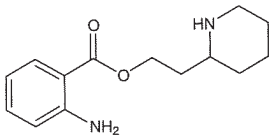


Crystals from ethanol + water, mp 148-149°. Also reported as second crystalline modification from toluene, mp 135-136°.
THERAP CAT: Anti-inflammatory.

7572. Pirbuterol. [38677-81-5] α^6-[[(1,1-Dimethylethyl)amino]methyl]-3-hydroxy-2,6-pyridinedimethanol; 2-hydroxymethyl-3-hydroxy-6-(1-hydroxy-2-*tert*-butylaminoethyl)pyridine. $C_{12}H_{20}N_2O_3$; mol wt 240.30. C 59.98%, H 8.39%, N 11.66%, O 19.97%. Analog of albuterol, *q.v.*, with β_2-adrenergic stimulating activity. Prepn: W. E. Barth, **DE 2204195**; *idem,* **US 3700681** (both 1972 to Pfizer). Stability study: P. C. Bansal, D. C. Monkhouse, *J. Pharm. Sci.* **66,** 819 (1977). Biotransformation: H. M. McIlhenny, M. S. D. Ghaly, *Fed. Proc.* **38,** 1130 (1979). Pharmacokinetics and cardiopulmonary effects in dogs: J. W. Constantine *et al., J. Pharmacol. Exp. Ther.* **208,** 371 (1979). Comparative study in respiratory disease: A. J. Dyson, A. D. Mackay, *Brit. J. Dis. Chest* **74,** 70 (1980). Use in treatment of cardiac failure: N. A. Awan *et al., Clin. Res.* **28,** 17A (1980); W. S. Colucci *et al., N. Engl. J. Med.* **305,** 185 (1981); G. I. Nelson *et al., Eur. Heart J.* **3,** 238 (1982); K. T. Weber *et al., Circulation* **66,** 1262 (1982). Review of pharmacology and efficacy in bronchospastic disease: D. M. Richards, R. N. Brogden, *Drugs* **30,** 6-21 (1985).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 54 of 65

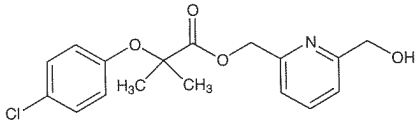
ter; 2-piperidineethanol anthranilate; β-(2-piperidyl)ethyl *o*-aminobenzoate; PT-14; Lucaine. $C_{14}H_{20}N_2O_2$; mol wt 248.32. C 67.71%, H 8.12%, N 11.28%, O 12.89%. Prepn: Walter, Fosbinder, *J. Am. Chem. Soc.* **61,** 1713 (1939); **US 2229533** (1941 to Maltbie Chem.).



Hydrochloride. $C_{14}H_{21}ClN_2O_2$. Crystals from abs alcohol, mp 209-211°.

THERAP CAT: Anesthetic (local).

7578. Pirifibrate. [55285-45-5] 2-(4-Chlorophenoxy)-2-methylpropanoic acid [6-(hydroxymethyl)-2-pyridinyl]methyl ester; 2,6-pyridinedimethanol mono-*p*-chlorophenoxyisobutyrate; EL-466; Bratenol. $C_{17}H_{18}ClNO_4$; mol wt 335.79. C 60.81%, H 5.40%, Cl 10.56%, N 4.17%, O 19.06%. Hypolipemic agent related structurally to clofibrate, *q.v.* Prepn: D. Humbert, R. Ratouis, **DE 2432322**; *eidem,* **US 3971798** (1975, 1976 both to Roussel). Multicenter study in hyperlipoproteinemias: A. J. Domingo *et al., Clin. Ther.* **3,** 219 (1980).

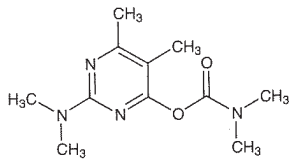


Crystals from isopropyl ether, mp 46°. LD_{50} in mice (mg/kg): 915-1098 i.p. (Humbert, Ratouis, 1975).

Hydrochloride. $C_{17}H_{18}ClNO_4.HCl$. Crystals, mp 110°. LD_{50} (calculated as base) in mice (mg/kg): 1098-1281 i.p. (Humbert, Ratouis, 1975).

THERAP CAT: Antihyperlipoproteinemic.

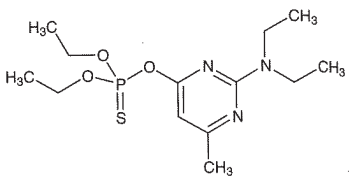
7579. Pirimicarb. [23103-98-2] Dimethylcarbamic acid 2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl ester; 2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl dimethylcarbamate; 5,6-dimethyl-2-dimethylamino-4-dimethylcarbamoyloxypyrimidine; PP-062; ENT-27766; Aphox; Fernos; Pirimor. $C_{11}H_{18}N_4O_2$; mol wt 238.29. C 55.44%, H 7.61%, N 23.51%, O 13.43%. Selective aphicide. Prepn: F. L. C. Baranyovits *et al.,* **ZA 67 01588**; *eidem,* **US 3493574** (1968, 1970 to ICI). Activity: F. L. C. Baranyovits, R. Ghosh, *Chem. & Ind. (London)* **1969,** 1018. Degradn in soil: I. R. Hill, *ACS Symp. Ser.* **29,** 358 (1976). GLC analysis: P. D. Bland, *J. Assoc. Off. Anal. Chem.* **64,** 1315 (1981).



Crystalline solid, mp 90.5°. Vapor pressure at 30°: 3×10^{-5} mm Hg. Soly in water at 25°: 2.7 g/l. Sol in most organic solvents. Dec by prolonged boiling with acids or alkali. Aq solns are unstable to light. LD_{50} orally in female rats: 147 (mg/kg) (Baranyovits, Ghosh).

USE: Insecticide.

7580. Pirimiphos-ethyl. [23505-41-1] *O*-[2-(Diethylamino)-6-methyl-4-pyrimidinyl]phosphorothioic acid *O,O*-diethyl ester; *O,O*-diethyl *O*-[2-(diethylamino)-6-methyl-4-pyrimidinyl]phosphorothioate; PP-211; Primicid. $C_{13}H_{24}N_3O_3PS$; mol wt 333.39. C 46.83%, H 7.26%, N 12.60%, O 14.40%, P 9.29%, S 9.62%. Broad spectrum contact and fumigant insecticide. Prepn: B. K. Snell, S. P. Sharpe, **GB 1205000** (1970 to ICI), *C.A.* **74,** 52482f (1971). Efficacy against wireworms: C. E. Lilly, *J. Econ. Entomol.* **66,** 1205 (1973). Persistence and degradn in soil: D. L. Suett, *Pestic. Sci.* **6,** 385 (1975). Review of properties and analytical methods: D. J. W. Bullock, *Anal. Methods Pestic. Plant Growth Regul.* **8,** 171-184 (1976).



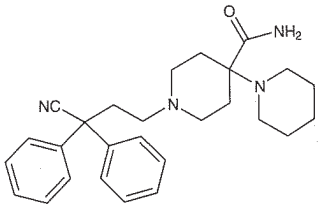
Straw-colored liquid, dec >130°. d^{20} 1.14; n_D^{25} 1.520. Vapor pressure at 25°: 2.9×10^{-4} mm Hg. Miscible with most organic solvents. Soly in water (30°): 1 ppm. Weakly basic. uv max (methanol): 248 nm (ε 21300). LD_{50} in rats, mice, guinea pigs (mg/kg); 140-200, 105, 50-150 orally; dermally in rats: 1000-2000 mg/kg (Bullock).

***O,O*-Dimethyl analog.** [29232-93-7] Pirimiphos-methyl; PP-511; Actellic; Actellifog; Blex; Dominator; Silosan. $C_{11}H_{20}N_3O_3PS$; mol wt 305.34. Straw-colored liquid, d^{30} 1.157; n_D^{25} 1.527. Vapor press at 30°: $\sim1\times10^{-4}$ mm Hg. Soly in water at 30°: 5 mg/l.

USE: Insecticide.

THERAP CAT (VET): Ectoparasiticide.

7581. Piritramide. [302-41-0] 1′-(3-Cyano-3,3-diphenylpropyl)-[1,4′-bipiperidine]-4′-carboxamide; 1-(3,3-diphenyl-3-cyanopropyl)-4-piperidino-4-piperidinecarboxamide; 2,2-diphenyl-4-(4-piperidino-4-carbamoylpiperidino)butyronitrile; pirinitramide; A-65; R-3365; Dipidolor; Piridolan. $C_{27}H_{34}N_4O$; mol wt 430.58. C 75.31%, H 7.96%, N 13.01%, O 3.72%. Prepn: **BE 606850**; P. A. J. Janssen, **US 3080366** (1961, 1963 both to Janssen). Crystal structure: C. Humblet *et al., Acta Crystallogr.* **B33,** 1615 (1977).



Crystals from acetone, mp 149-150°.

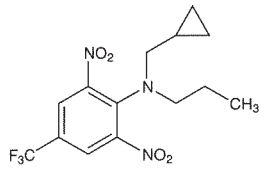
Note: This is a controlled substance (opiate): **21 CFR,** 1308.11.

THERAP CAT: Analgesic (narcotic).

7582. Piritrexim. [72732-56-0] 6-[(2,5-Dimethoxyphenyl)methyl]-5-methylpyrido[2,3-*d*]pyrimidine-2,4-diamine; 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*]pyrimidine; BW-301U; NSC-351521. $C_{17}H_{19}N_5O_2$; mol wt 325.36. C 62.76%, H 5.89%, N 21.52%, O 9.83%. Lipid soluble dihydrofolate reductase inhibitor. Prepn: E. M. Grivsky *et al., J. Med. Chem.* **23,** 327 (1980); E. M. Grivsky *et al.,* **EP 21292** (1981 to Wellcome); E. M. Grivsky, **US 4959474** (1990 to Burroughs Wellcome). Biochemistry and antitumor activity: D. S. Duch *et al., Cancer Res.* **42,** 3987 (1982). Cytotoxicity: I. W. Taylor *et al., ibid* **45,** 978 (1985). Pharmacology and toxicology: C. W. Sigel *et al., NCI Monogr.* **5,** 111 (1987). Antipneumocystis and antitoxoplasma activities: J. A. Kovacs *et al., Antimicrob. Ag. Chemother.* **32,** 430 (1988). HPLC determn in plasma: R. G. Foss, C. W. Sigel, *J. Pharm. Sci.* **71,** 1176 (1982). Determn by protein binding assay in plasma: J. L. Woolley, Jr., *et al., ibid* **78,** 749 (1989). Crystal structure

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 55 of 65

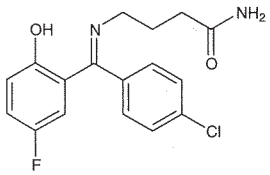
L. L. Maravetz, US **3546295** (1969, 1970 to Esso). Persistence in soil: J. M. Kennedy *et al., Weed Sci.* **25,** 373 (1977). Field trial: R. E. Frans *et al., Arkansas, Agric. Exp. Stn., Mimeogr. Ser.* **249,** 1 (1977). Soil degradn: N. D. Camper *et al., J. Environ. Sci. Health* **B15,** 457 (1980). GC determn in biological samples: T. R. Edgerton *et al., J. Anal. Toxicol.* **9,** 15 (1985).



Yellow-orange crystals or liquid, mp 33-36°. Soly in water at 20°: 0.1 mg/l. Readily sol in most organic solvents.

USE: Herbicide.

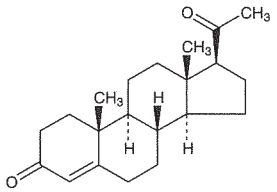
7863. Progabide. [62666-20-0] 4-[[(4-Chlorophenyl)(5-fluoro-2-hydroxyphenyl)methylene]amino]butanamide; 4-[[α-(*p*-chlorophenyl)-5-fluorosalicylidene]amino]butyramide; 4-[[α-(*p*-chlorophenyl)-5-fluoro-2-hydroxybenzylidene]amino]butyramide; halogabide; SL-76.002; Gabren(e). $C_{17}H_{16}ClFN_2O_2$; mol wt 334.78. C 60.99%, H 4.82%, Cl 10.59%, F 5.67%, N 8.37%, O 9.56%. Gamma-aminobutyric acid (GABA) antagonist with anti-epileptic activity. Prepn: J.-P. Kaplan *et al.,* **DE 2634288**; *eidem,* **US 4094992** (1977, 1978 to Synthelabo); *eidem, J. Med. Chem.* **23,** 702 (1980). Use as analgesic: J.-P. Kaplan, **US 4361583** (1982 to Synthelabo). Pharmacokinetics: I. Johno *et al., J. Pharm. Sci.* **71,** 633 (1982). HPLC determn in biological fluids: P. Padovani *et al., J. Chromatog.* **308,** 229 (1984). Double-blind clinical trial in therapy resistant epilepsy: P. Loiseau *et al., Epilepsia* **24,** 703 (1983); in spasticity: K. Mondrup, E. Pedersen, *Acta Neurol. Scand.* **69,** 200 (1984).



Crystals from cyclohexane and toluene, mp 133-135°; possible second crystalline form, mp 142.5° (Kaplan, *J. Med. Chem.*). uv max in methanol: 332, 250, 210 (ε 4200, 10800, 24000). LD_{50} i.p. in mice: 900 mg/kg (Kaplan).

THERAP CAT: Anticonvulsant.

7864. Progesterone. [57-83-0] Pregn-4-ene-3,20-dione; Δ^4-pregnene-3,20-dione; corpus luteum hormone; luteohormone; Corlutina; Corluvite; Crinone; Cyclogest; Gestiron; Gestone; Lipo-Lutin; Lutocyclin M; Lutromone; Progestasert; Progestin; Progestogel; Progestol; Progeston; Prolidon; Proluton; Syngesterone; Utrogestan. $C_{21}H_{30}O_2$; mol wt 314.46. C 80.21%, H 9.62%, O 10.18%. Active principle of the corpus luteum, secreted during the latter half of the menstrual cycle. If pregnancy ensues, secretion continues. Exerts an antiovulatory effect when administered during days 5 to 25 of the normal menstrual cycle. Isoln from corpus luteum of pregnant sows: Butenandt, Westphal, *Ber.* **67,** 1440 (1934); Wintersteiner, Allen, *J. Biol. Chem.* **107,** 321 (1934). Structure: Butenandt *et al., Ber.* **67,** 1611 (1934). Synthesis of DL-form: Johnson *et al., J. Am. Chem. Soc.* **93,** 4332 (1971). Prepn from other steroids in review by W. H. Strain in Gilman's *Organic Chemistry* **vol. II** (Wiley, New York, 2nd ed., 1943) pp 1487-1489. Numerous patents, e.g., **US 2379832**; **US 2232438**; **US 2314185**. Anesthetic effect and toxicity: H. Selye, *Proc. Soc. Exp. Biol. Med.* **46,** 116 (1941). Review of physiology: Csapo, *Sci. Am.* **198,** 40-46 (April, 1958); Rothchild, *Vitam. Horm. (New York)* **23,** 209-327 (1965). Book: *Progesterone and Progestins,* C. W. Bardin *et al.,* Eds. (Raven Press, New York, 1982) 462 pp.



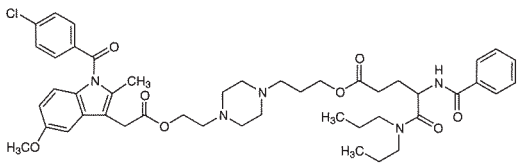
Exists in two cryst forms of equal physiologic activity and which are readily interconverted. The α-form is orthorhombic (prisms from dil alc) with a:b:c = 0.750:1:0.905. Crystals show (011), (110), (010). Poor (011) cleavage. d^{23} 1.166. mp 127-131°. The β-form is orthorhombic (needles) with a:b:c = 0.563:1:0.275. Crystals acicular with parallel extinction and negative elongation. Cleavage on (001) and (110). d^{20} 1.171. mp 121°. $[\alpha]_D^{20}$ +172 to +182° (c = 2 in dioxane). uv max: 240 nm. Insol in water. Sol in alcohol, acetone, dioxane, concd H_2SO_4. Sparingly sol in vegetable oils. 1 mg = 1 I.U.

Note: This substance is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-191.

THERAP CAT: Progestogen.

THERAP CAT (VET): Progestogen. Has been used to control habitual abortion, to suppress or synchronize estrus.

7865. Proglumetacin. [57132-53-3] 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid 2-[4-[3-[[4-(benzoylamino)-5-(dipropylamino)-1,5-dioxopentyl]oxy]propyl]-1-piperazinyl]ethyl ester; (±)-*N*-[2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetoxy]ethyl]-*N'*-[3-(*N*-benzoyl-*N',N'*-di-*n*-propyl-DL-isoglutaminoyl)oxypropyl]piperazine. $C_{46}H_{58}ClN_5O_8$; mol wt 844.45. C 65.43%, H 6.92%, Cl 4.20%, N 8.29%, O 15.16%. Deriv of indomethacin, *q.v.* Prepn: F. Makovec *et al.,* **DE 2535799** corresp to **US 3985878** (both 1976 to Rotta). Series of articles on pharmacology, mechanism of action, safety: *Arzneimittel-Forsch.* **29,** 1116-1129 (1979). Bioavailability study: A. A. Bignamini, P. L. Casula, *Curr. Med. Res. Opin.* **6,** 299 (1979). Clinical evaluation: J. Münzenberg, S. Tachibana, *Pharmatherapeutica* **2,** 279 (1980); P. Loizzi *et al., ibid.* 285. Mutagenicity study: R. Vidal y Plana *et al., Farmaco Ed. Prat.* **33,** 543 (1978). Toxicity data for dimaleate: A. L. Rovati *et al., Arzneimittel-Forsch.* **29,** 1116 (1979).



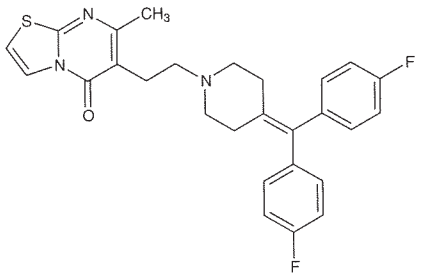
Dimaleate. [59209-40-4] Protacine; CR-604; Afloxan; Miridacin; Protaxon; Proxil. $C_{46}H_{58}ClN_5O_8.2C_4H_4O_4$; mol wt 1076.59. Crystals from ethanol, mp 146-148°. LD_{50} in male mice, rats (mg/kg): 262, 450 orally (Rovati).

THERAP CAT: Anti-inflammatory.

7866. Proglumide. [6620-60-6] 4-(Benzoylamino)-5-(dipropylamino)-5-oxopentanoic acid; DL-4-benzamido-*N,N*-dipropylglutaramic acid; *N*-benzoyl-*N',N'*-di-*n*-propyl-DL-isoglutamine; xylamide; CR-242; W-5219; Milid; Milide; Promid. $C_{18}H_{26}N_2O_4$; mol wt 334.41. C 64.65%, H 7.84%, N 8.38%, O 19.14%. Prepn: **NL 6510006**; **ZA 65 04065** (both 1966 to Rotta), *C.A.* **65,** 3793b (1966). Pharmacological activity: A. L. Rovati *et al., Minerva Med.* **58,** 3653 (1967); T. Umetzu *et al., Eur. J. Pharmacol.* **64,** 69 (1980). Pharmacokinetic study: A. A. Bignamini *et al., Arzneimittel-Forsch.* **29,** 639 (1979). Clinical study in duodenal ulcer: W. Bergemann *et al., Med. Klin.* **76,** 226 (1981). Cholecystokinin receptor antagonist activity: W. F. Hahne *et al., Proc. Nat. Acad. Sci. USA* **78,** 6304 (1981). Selective blockade of cholecystokinin CNS effects: L. A. Chiodo, B. S. Bunney, *Science* **219,** 1449 (1983).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 56 of 65

termn in plasma and pharmacokinetics: P. Timmerman *et al, Biomed. Environ. Mass Spectrom.* **18,** 498 (1989). Clinical studies: G. Nappi *et al., Headache* **30,** 439 (1990); G. Bersani *et al., Acta Psychiat. Scand.* **83,** 244 (1991); J. M. Monti *et al., Sleep* **16,** 647 (1993).

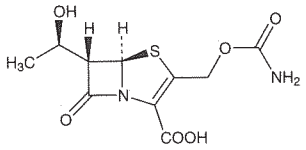


Crystals from acetonitrile, mp 145.5°. LD_{50} in male, female mice, rats, dogs (mg/kg): 28.2, 28.2, 20.0, 22.2, 24.1, 33.2 i.v.; 626, 993, 956, 515, ~1280, 640-1280 orally (Awouters).

L-Tartrate. [93076-39-2] $C_{27}H_{25}F_2N_3OS.C_4H_6O_6$. Solid from 2-propanol, mp 198.7°.

THERAP CAT: Anxiolytic; antidepressant.

8319. Ritipenem. [84845-57-8] (5*R*,6*S*)-3-[[(Aminocarbonyl)oxy]methyl]-6-[(1*R*)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid; (5*R*,6*S*,8*R*)-6α-hydroxyethyl-2-carbamoyloxymethyl-2-penem-3-carboxylic acid; (5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-3-(hydroxymethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-carbamate. $C_{10}H_{12}N_2O_6S$; mol wt 288.28. C 41.66%, H 4.20%, N 9.72%, O 33.30%, S 11.12%. Prepn: M. Alpegiani *et al.,* **DE 3245270**; M. Foglio *et al.,* **US 4482565** (1983, 1984 both to Carlo Erba). Synthesis: G. Franceschi *et al., J. Antibiot.* **36,** 938 (1983). Total synthesis: W. Cabri *et al., Tetrahedron Letters* **34,** 3491 (1993). Toxicity study: M. Brughera *et al., J. Antimicrob. Chemother.* **23,** Suppl. C, 129 (1989). Series of articles on synthesis, *in vitro* activity, metabolism: *ibid.,* 1-204 (1989). Clinical pharmacokinetics of acid and ester forms: S. R. Norrby *et al., ibid.* **25,** 371 (1990); A. M. Lovering *et al., ibid.* **29,** 179 (1992). HPLC determn in serum and urine: R. Mendez *et al., J. Chromatog.* **579,** 115 (1992).

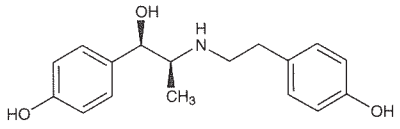


Sodium salt. [84845-58-9] FCE-22101. $C_{10}H_{11}N_2NaO_6S$; mol wt 310.26. $[\alpha]_D^{20}$ +140°. uv max (H_2O): 258, 306 nm (ε 4150, 6030). LD_{50} in male, female mice, male, female rats (mg/kg): 3872, 4393, 2000, 2201 i.v. (Brughera).

Acetoxymethyl ester. [87238-52-6] Ritipenem acoxil; FCE-22891. $C_{13}H_{16}N_2O_8S$; mol wt 360.34. LD_{50} in male, female mice, male, female rats (mg/kg): 4363, 6167, >5000, >5000 orally (Brughera).

THERAP CAT: Antibacterial.

8320. Ritodrine. [26652-09-5] (α*S*)-*rel*-4-Hydroxy-α-[(1*R*)-1-[[2-(4-hydroxyphenyl)ethyl]amino]ethyl]benzenemethanol; *erythro*-*p*-hydroxy-α-[1-[(*p*-hydroxyphenethyl)amino]-ethyl]benzyl alcohol; *N*-[2-(*p*-hydroxyphenyl)ethyl]-*N*-[2-(*p*-hydroxyphenyl)-2-hydroxy-1-methylethyl]amine; 1-(4-hydroxyphenyl)-2-[2-(4-hydroxyphenyl)ethylamino]propanol; *N*-(*p*-hydroxyphenylethyl)-4-hydroxynorephedrine. $C_{17}H_{21}NO_3$; mol wt 287.35. C 71.06%, H 7.37%, N 4.87%, O 16.70%. β_2-Adrenergic agonist. Prepn: **BE 660244** (1965 to N.V. Philips); Claassen *et al.,* **US 3410944** (1968 to No. Am. Philips). Clinical investigations: Coutinho *et al., Am. J. Obstet. Gynecol.* **104,** 1053 (1969); Landesman *et al., ibid.* **110,** 111 (1971); Wesselius-De Casparis *et al., Brit. Med. J.* **3,** 144 (1971). Clinical efficacy in treatment of preterm labor: J. F. Larsen *et al., Obstet. Gynecol.* **67,** 607 (1986).

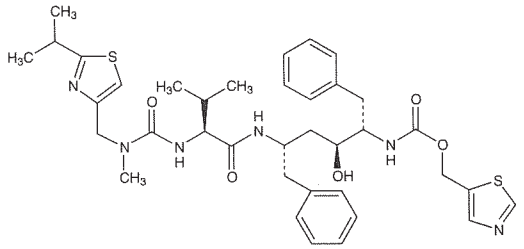


Base. Resinous mass, mp 88-90°.

Hydrochloride. [23239-51-2] DU-21220; Miolene; Prempar; Pre-Par; Utemerin; Utopar; Yutopar. $C_{17}H_{21}NO_3.HCl$; mol wt 323.82. mp 193-195° (dec) from ethanol-ether. uv max: 267.5 nm (ε 3310).

THERAP CAT: Tocolytic.

8321. Ritonavir. [155213-67-5] (5*S*,8*S*,10*S*,11*S*)-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester; (2*S*,3*S*,5*S*)-5-[*N*-[[*N*-methyl-*N*-[(2-isopropyl-4-thiazolyl)methyl]amino]carbonyl]valinyl]amino]-2-[*N*-[(5-thiazolyl)methoxycarbonyl]amino]-1,6-diphenyl-3-hydroxyhexane; A-84538; Abbott 84538: ABT-538; Norvir. $C_{37}H_{48}N_6O_5S_2$; mol wt 720.96. C 61.64%, H 6.71%, N 11.66%, O 11.10%, S 8.90%. Peptidomimetic HIV-1 protease inhibitor. Prepn: D. J. Kempf *et al.,* **WO 94 14436**; *eidem,* **US 5541206** (1994, 1996 both to Abbott). Antiretroviral spectrum, pharmacokinetics: *idem et al., Proc. Nat. Acad. Sci. USA* **92,** 2484 (1995). Structural model for drug resistance: M. Markowitz *et al., J. Virol.* **69,** 701 (1995). HPLC determn in biological fluids: R. M. W. Hoetelmans *et al., J. Chromatog. B* **705,** 119 (1998). Review of clinical experience: A. P. Lea, D. Faulds, *Drugs* **52,** 541-546 (1996). Clinical trial with nucleoside analogs in HIV-infected children: S. A. Nachman *et al., J. Am. Med. Assoc.* **283,** 492 (2000).



THERAP CAT: Antiviral.

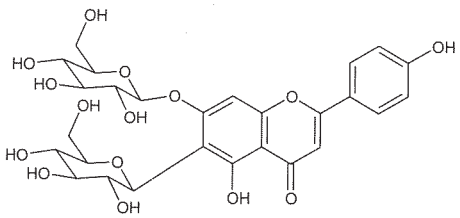
8322. Rituximab. [174722-31-7] Anti-(human CD20 antigen) immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 γ_1-chain) disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer; IDEC-C2B8; Mabthera; Rituxan. Genetically engineered chimeric murine-human monoclonal antibody directed against the CD20 antigen found on normal and malignant B lymphocyte surfaces. Contains murine light and heavy-chain variable regions and γ_1 heavy-chain and κ light chain human constant regions. Composed of 2 heavy chains of 451 amino acids and 2 light chains of 213 amino acids; approx mol wt 145 kD. Prepn: D. R. Anderson *et al.,* **WO 94 11026**; *eidem,* **US 5763137** (1994, 1998 both to IDEC); M. E. Reff *et al., Blood* **83,** 435 (1994). HPLC determn of product purity: K. G. Moorhouse *et al., J. Pharm. Biomed. Anal.* **16,** 593 (1997). Clinical pharmacokinetics: N. L. Berinstein *et al., Ann. Oncol.* **9,** 995 (1998). Clinical trial in lymphoma: P. McLaughlin *et al., J. Clin. Oncol.* **16,** 2825 (1998); in combination with CHOP chemotherapy: M. S. Czuczman *et al., ibid.* **17,** 268 (1999). Review of clinical studies: C. A. White, *Cancer Biother. Ra-*

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 57 of 65

Crystals from acetonitrile, mp 189.5°. Poorly sol in water.
THERAP CAT: Antifungal.

8440. Saponaria. Soapwort; soaproot; fuller's herb; bruisewort; bouncing bet. *Saponaria officinalis* L., *Caryophyllaceae*; herbaceous perennial plant having sharp-pointed leaves and large pale pink flowers. Habit. Europe to Middle Asia; naturalized in U.S. *Constit.* Saponins, saponarin, saporins, *q.q.v.* Produces soapy lather when bruised and agitated with water. Root has been used in traditional medicine as antitussive or as a wash for skin irritations. Brief review: M. Wichtl, N. G. Bisset, *Herbal Drugs and Phytopharmaceuticals,* English Ed. (CRC Press, Boca Raton, 1994) pp 453-454.

8441. Saponarin. [20310-89-8] 6-β-D-Glucopyranosyl-7-(β-D-glucopyranosyloxy)-5-hydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one. $C_{27}H_{30}O_{15}$; mol wt 594.52. C 54.55%, H 5.09%, O 40.37%. From leaves of *Saponaria officinalis* L., *Caryophyllaceae:* Barger, *J. Chem. Soc.* **89,** 1210 (1906); from *Hibiscus syriacus* L., *Malvaceae:* Nakoaki, *J. Pharm. Soc. Japan* **64,** 304 (1944), *C.A.* **46,** 108d (1952); from *Lemna (Spirodela) oligorrhiza* Kurz., *Lemnaceae:* Jurd *et al., Arch. Biochem. Biophys.* **67,** 284 (1957). Structure: Seikel, Geissman, *ibid.* **71,** 17 (1957). Revised structure: Hörhammer *et al., Tetrahedron Letters* **1965,** 1707. On acidic hydrolysis yields the aglycone, ***saponaretin***.



Monohydrate. Pale yellow granules, mp 228°. $[\alpha]_D$ −7.9° (aq pyridine). uv max (ethanol): 335, 272 nm. Practically insol in cold water. Sparingly sol in hot water, alcohol; sol in alkalies with yellow color and in concd H_2SO_4 with blue fluorescence; sol in pyridine.

8442. Saponins. Sapogenin glycosides. A type of glycoside widely distributed in plants. Each saponin consists of a sapogenin which constitutes the aglucon moiety of the molecule, and a sugar. The sapogenin may be a steroid or a triterpene and the sugar moiety may be glucose, galactose, a pentose, or a methylpentose. Poisonous towards the lower forms of life and used for killing fish by the aborigines of South America. *Review and bibliography:* R. J. McIlroy, *The Plant Glycosides* (Edward Arnold & Co., London, 1951) Chapter IX; Y. Birk, I. Peri in *Toxic Const. Plant Foodst.,* I. E. Liener, Ed. (Academic Press, New York, 2nd ed., 1980) pp 161-182.

Bitter taste. All saponins foam strongly when shaken with water. They form oil-in-water emulsions and act as protective colloids.

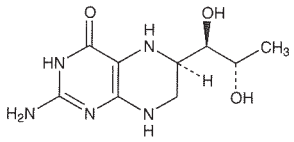
Caution: Although practically non-toxic to man upon oral ingestion, they act as powerful hemolytics when injected into the blood stream, dissolving the red corpuscles even at extreme dilutions.

8443. Saporins. Single chain ribosome inactivating proteins (type 1 RIPs); found in the seeds, leaves and roots of the soapwort plant, *Saponaria officinalis* L., *Caryophyllaceae.* Used to produce targeted immunotoxins by conjugating with a specific monoclonal antibody or other cell receptor ligand. At least 7 isoforms have been identified. Saporin-6 is the most abundant and is often referred to as "saporin". Isoln from seeds: F. Stirpe *et al., Biochem. J.* **216,** 617 (1983). Purification and distribution in plant tissues: J. M. Ferreras *et al., Biochim. Biophys. Acta* **1216,** 31 (1993). Production by plant cell culture: A. Di Cola *et al., Plant Cell Rep.* **17,** 55 (1997). Review of use as neural lesioning tools: R. G. Wiley, *Trends Neurosci.* **15,** 285-290 (1992); in model for Alzheimer's disease: R. Schliebs *et al., Prog. Brain Res.* **109,** 253-264 (1996). Discussion of therapeutic potential in cancer: D. J. Flavell, *Curr. Top. Microbiol. Immunol.* **234,** 57-61 (1998).

Saporin-6. [166944-16-7] SO6. Isoform constituting 7% of the total seed protein. Composed of 259 amino acid residues; mol wt 29 kDa. Review of isoln, properties and production by recombinant technology: M. R. Soria *et al., Targeted Diagn. Ther.* **7,** 193-212 (1992). Crystal structure: C. Savino *et al., Acta Crystallogr.* **D54,** 636 (1998). pI >9.5. LD_{50} i.p. in mice: 4 mg/kg (Stirpe).
USE: Biological research tool.

8444. Sapphire. [1317-82-4] The corundum modification of aluminum oxide, Al_2O_3. Mined in Montana, Siam, Burma, Ceylon. The highest priced variety of the native gem has the blue color of cornflowers. Easily prepd synthetically. Hydrothermal synthesis: Laudise, Ballman, *J. Am. Chem. Soc.* **80,** 2655 (1958).
USE: In jewelry, as phonograph needles, industrial abrasive, watch and instrument bearings.

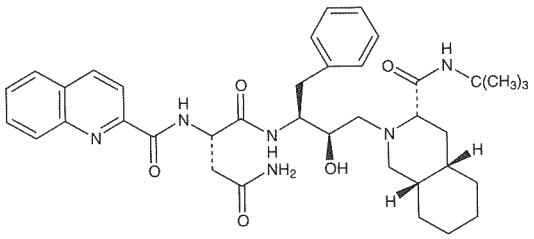
8445. Sapropterin. [62989-33-7] (6*R*)-2-Amino-6-[(1*R*,-2*S*)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1*H*)-pteridinone; (6*R*)-L-*erythro*-tetrahydrobiopterin; dapropterin; *R*-THBP; 6*R*-BH_4. $C_9H_{15}N_5O_3$; mol wt 241.25. C 44.81%, H 6.27%, N 29.03%, O 19.90%. Natural cofactor of the aromatic amino acid hydroxylases required for catecholamine and serotonin biosynthesis. Identification of cofactor activity: S. Kaufman, *Proc. Nat. Acad. Sci. USA* **50,** 1085 (1963). Prepn of (6*R,S*)-BH_4: B. Schircks *et al., Helv. Chim. Acta* **61,** 2731 (1978). Chromatographic separation of diastereoisomers: S. W. Bailey, J. E. Ayling, *J. Biol. Chem.* **253,** 1598 (1978). Absolute configuration of natural isomer: W. L. F. Armarego *et al., Aust. J. Chem.* **35,** 785 (1982). Stereospecific synthesis: S. Matsuura *et al., Heterocycles* **23,** 3115 (1985); H. Sakai, T. Kanai, **EP 191335**; *eidem,* **US 4713454** (1986, 1987 both to Shiratori; Suntory). Bioavailability: G. Kapatos, S. Kaufman, *Science* **212,** 955 (1981). Effect on neurotransmitter monoamine biosynthesis: S. Miwa *et al., Arch. Biochem. Biophys.* **239,** 234 (1985). LC determn in biological samples: Y. Tani, T. Ishihara, *Life Sci.* **46,** 373 (1990). Therapeutic potential in hyperphenylalaninemia: S. Kaufman, *J. Nutr. Sci. Vitaminol,* Suppl., 601 (1992).



pK′ 5.05. uv max (0.1 *N* HCl): 265 nm (ε 14000).
Dihydrochloride. [69056-38-8] SUN-0588; Biopten. $C_9H_{15}N_5O_3.2HCl$; mol wt 314.17. Crystals from HCl, mp 245-246° (dec). $[\alpha]_D^{25}$ −6.81° (c = 0.665 in 0.1 *M* HCl). uv max (2 *M* HCl): 264 nm (ε 16770).
THERAP CAT: In treatment of hyperphenylalaninemia.

8446. Saquinavir. [127779-20-8] (2*S*)-N^1[(1*S*,2*R*)-3-[(3*S*,-4a*S*,8a*S*)-3-[[(1,1-Dimethylethyl)amino]carbonyl]octahydro-2(1*H*)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]butanediamide; (*S*)-*N*-[(α*S*)-α-[(1*R*)-2-[(3*S*,4a*S*,8a*S*)-3-(*tert*-butylcarbamoyl)octahydro-2(1*H*)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamido-succinamide; *N*-*tert*-butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[*N*-(2-quinolylcarbonyl)-L-asparaginyl]-amino]butyl](4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide; Ro-31-8959. $C_{38}H_{50}N_6O_5$; mol wt 670.84. C 68.04%, H 7.51%, N 12.53%, O 11.92%. Selective HIV protease inhibitor. Prepn: J. A. Martin, S. Redshaw, **EP 432695**; *eidem,* **US 5196438** (1991, 1993 both to Hoffmann-LaRoche); K. E. B. Parkes *et al., J. Org. Chem.* **59,** 3656 (1994). *In vitro* HIV proteinase inhibition: N. A. Roberts *et al., Science* **248,** 358 (1990). Antiviral properties: J. C. Craig *et al., Antiviral Res.* **16,** 295 (1991); S. Galpin *et al., Antiviral Chem. Chemother.* **5,** 43-45 (1994). Clinical evaluation of tolerability and activity: V. S. Kitchen *et al., Lancet* **345,** 952 (1995). Brief review of clinical evaluations: N. A. Roberts, *Int. Antiviral News* **3** (1), 2-3 (1995).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 58 of 65

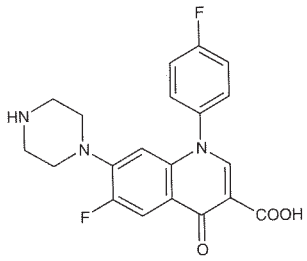


White crystalline solid. $[\alpha]_D^{20}$ −55.9° (c = 0.5 in methanol). Soly (21°): 0.22 g/100 ml water.

Methanesulfonate salt. [149845-06-7] Saquinavir mesylate; Ro-31-8959/003; Fortovase; Invirase. $C_{38}H_{50}N_6O_5.CH_3SO_3H$; mol wt 766.96.

THERAP CAT: Antiviral.

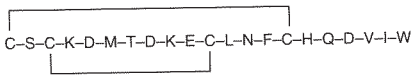
8447. Sarafloxacin. [98105-99-8] 6-Fluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. $C_{20}H_{17}F_2N_3O_3$; mol wt 385.36. C 62.33%, H 4.45%, F 9.86%, N 10.90%, O 12.46%. Fluorinated quinolone antibacterial. Prepn: D. T. W. Chu, **EP 131839**; *idem*, **US 4730000** (1985, 1988 both to Abbott); D. T. W. Chu *et al., J. Med. Chem.* **28,** 1558 (1985); H. Narita *et al.*, **JP Kokai 85 237069** (1985 to Toyama). Comparative *in vitro* antibacterial spectrum: A. Digranes, W. L. Dibb, *Chemotherapy* **34,** 298 (1988). *In vivo* antibacterial activity: P. B. Fernandes *et al., Antimicrob. Ag. Chemother.* **29,** 201 (1986). HPLC determn: J. F. Bauer *et al., Pharm. Res.* **7,** 1177 (1990).



Monohydrochloride. [91296-87-6] Abbott 56620; A-56620. $C_{20}H_{17}F_2N_3O_3.HCl$; mol wt 421.83. mp as monohydrate >275°.

THERAP CAT (VET): Antibacterial.

8448. Sarafotoxins. SRTx. Family of vasoactive toxins isolated from the venom of the Israeli burrowing asp, *Atractaspis engaddensis*. Several isoforms exist, all are closely related in structure and biological activity to the mammalian endothelins, *q.v.*; both families show highly conserved sequences of 21 amino acids with 2 fixed disulfide bridges. Isoln: E. Kochva *et al., Toxicon.* **20,** 581 (1982). Purification of a-c: C. Takasaki *et al., ibid.* **26,** 543 (1988); of d: A. Bdolah *et al., FEBS Letters* **256,** 1 (1989). Structure-activity study: A. M. Doherty *et al., J. Cardiovasc. Pharmacol.* **17,** Suppl 7, S59 (1991). Conformational stability: A. R. Atkins *et al., Int. J. Peptide Protein Res.* **44,** 372 (1994). Review of structure and evolution: E. Kochva *et al., Toxicon.* **31,** 541-568 (1993); of biological activity: M. Sokolovsky in *Toxins and Signal Transduction*, Y. Gutman, P. Lazarovici, Eds. (Harwood Academic Publishers, Netherlands, 1997) pp 53-67.



C–S–C–K–D–M–T–D–K–E–C–L–N–F–C–H–Q–D–V–I–W

Sarafotoxin A

8449. Saralasin. [34273-10-4] 1-(*N*-Methylglycine)-5-L-valine-8-L-alanineangiotensin II; *N*-[1-[*N*-[*N*-[*N*-[*N*-[*N*^{2}-(*N*-methylglycyl)-L-arginyl]-L-valyl]-L-tyrosyl]-L-valyl]-L-histidyl]-L-prolyl]-L-alanine; 1-sar-8-ala-angiotensin II. $C_{42}H_{65}N_{13}O_{10}$; mol wt 912.04. C 55.31%, H 7.18%, N 19.96%, O 17.54%. A specific antagonist of angiotensin II. Prepn: Sipos *et al.*, **DE 2127393** corresp to **US 3751404** (1972, 1973 to Norwich Pharmacal). Activity studies: Pals *et al., Circ. Res.* **29,** 673 (1971); Pals, Fulton, *Arch. Int. Pharmacodyn. Ther.* **204,** 20 (1973); Solomon, Buckley, *J. Pharm. Sci.* **63,** 1109 (1974); Streeten *et al., N. Engl. J. Med.* **292,** 657 (1975). Comprehensive review of the acetate: C. T. Huang *et al.*, in *Pharmacological and Biochemical Properties of Drug Substances* **vol. 3,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1981) pp 176-225.

Sar–Arg–Val–Tyr–Val–His–Pro–Ala

Hydrated acetate. [39698-78-7] Saralasin acetate; P-113; Sarenin. Described as $C_{42}H_{65}N_{13}O_{10}.xC_2H_4O_2.xH_2O$. Fluffy white powder, mp 256°. Sol in water, 5% aq dextrose, 90-95% aq alcohol. LD_{50} i.v. in male mice: 1171 mg/kg (Huang).

THERAP CAT: Antihypertensive, diagnostic aid (renin-dependent hypertension).

8450. Sarcosine. [107-97-1] *N*-Methylglycine; *N*-methylaminoacetic acid; Sar; *N*-methylglycocoll; methylaminoethanoic acid. $C_3H_7NO_2$; mol wt 89.09. C 40.44%, H 7.92%, N 15.72%, O 35.92%. CH_3NHCH_2COOH. Has been found in starfish and sea urchins: A. Kossel, S. Edlbacher, *Z. Physiol. Chem.* **94,** 264 (1915); in rock lobsters: L. Novellie, H. M. Schwartz, *Nature* **173,** 450 (1954). Formation from caffeine by dec with barium hydroxide: Paulmann, *Arch. Pharm.* **232,** 601 (1894). Prepd on a large scale from formaldehyde, sodium cyanide, and methylamine: Eschweiler, *Ann.* **279,** 39 (1894); Baumann, *J. Biol. Chem.* **21,** 563 (1915); Caverly, **US 2720540** (1955 to du Pont); Leake, Brakebill, **US 3009954** (1961 to Allied Chem.). Synthesis: M. Ebata *et al., Bull. Chem. Soc. Japan* **39,** 2535 (1966). Review of syntheses: T. Shirai, *Synthetic Production and Utilization of Amino Acids*, T. Kaneko *et al.*, Eds. (Wiley, New York, 1974) pp 184-186.

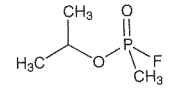
Orthorhombic, deliquescent crystals from dil methanol. Dec 212°. Sweetish taste. pK_1' 2.23; pK_2' 10.01. Sol in water: 5 ml of a satd aq soln contain 2.1412 g sarcosine. Slightly sol in alc.

Sodium salt. Usually sold as aq soln, pH 12.0.

Hydrochloride. $C_3H_7NO_2.HCl$. Needles from alcohol, dec 171°. Freely sol in water; slightly sol in alcohol, ether.

USE: Intermediate in the synthesis of antienzyme agents for toothpaste.

8451. Sarin. [107-44-8] Methylphosphonofluoridic acid 1-methylethyl ester; isopropoxymethylphosphoryl fluoride; isopropylmethylphosphonofluoridate; GB. $C_4H_{10}FO_2P$; mol wt 140.09. C 34.29%, H 7.19%, F 13.56%, O 22.84%, P 22.11%. Nerve gas; potent cholinesterase inhibitor similar in structure and activity to soman and tabun, *q.q.v.* Prepn: Holmstedt, *Acta Physiol. Scand.* **25,** suppl. 90, p 106 (1951); *Protar* **14,** 113 (1948); **16,** 131 (1950). Additional syntheses: Schrader, *B.I.O.S.* **714,** 41 (1947); B. C. Saunders, *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine* (Cambridge, 1957) p 92 sqq; Bryant *et al., J. Chem. Soc.* **1960,** 1553. Absolute configuration: Benschop *et al., Rec. Trav. Chim.* **87,** 387 (1968). Toxicity study: B. Holmstedt, *Pharmacol. Rev.* **11,** 567 (1959). Brief review: Schrader, *Die Entwicklung neuer insektizider Phosphorsäure-Ester* (Verlag Chemie, Weinheim, 1963) p 4; B. L. Harris in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 5** (Wiley-Interscience, New York, 4th ed., 1993) pp 795-816.



NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 59 of 65

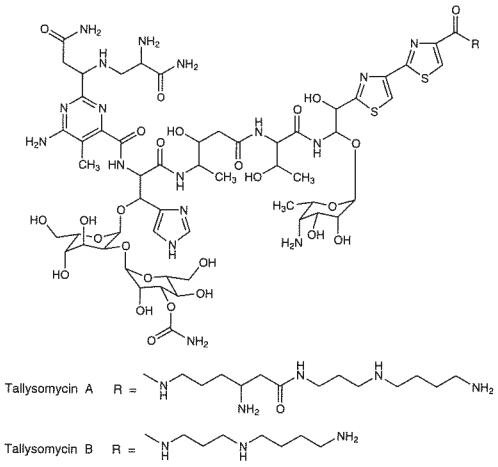
The term horse tallow is generally no longer admitted. ***Oleo stock*** is the highest grade of beef tallow. Contains (as glycerides): Oleic acid (37-43%), palmitic (24-32%), stearic (20-25%), myristic (3-6%), linoleic (2-3%). Minor constituents are cholesterol, arachidonic, elaidic, and vaccenic acids. Perhaps the most observed characteristic of tallow is its titer (solidif pt) which ranges from 40° to 46°.

9132. Tallow Alcohol. A name for commercial mixtures of *n*-octadecanol and *n*-hexadecanol.

Fatty crystalline mass, mp 46-47°.

USE: Defoaming agent, emollient, intermediate for surface active agents.

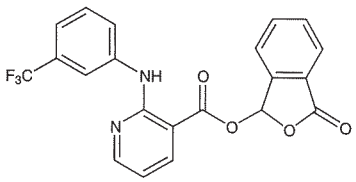
9133. Tallysomycin. [67995-68-0] Talisomycin; BU-2231. Antitumor antibiotic complex and third generation analog of bleomycins, *q.v.*, produced by *Streptoalloteichus hindustanus* E 465-94. Prodn, isoln, properties of the major components, tallysomycins A and B: H. Kawaguchi *et al.*, **BE 845513**; *eidem*, **US 4051237** (both 1977 to Bristol-Myers); *eidem, J. Antibiot.* **30,** 779 (1977). Structure of A and B, based on originally proposed bleomycin structure: M. Konishi *et al., ibid.* 789; *cf.* bleomycin for revised structure. Antitumor activity: H. Imanishi *et al., ibid.* **31,** 667 (1978). Radioimmunoassay: A. Broughton *et al., Cancer Treat. Rep.* **63,** 1829 (1979). Pharmacokinetics: J. E. Strong *et al., ibid.* 1821. ^{13}C-NMR spectra of tallysomycin and its zinc complex: F. T. Greenaway *et al., Org. Magn. Reson.* **13,** 270 (1980). Biosynthetic derivs: T. Miyaki *et al., J. Antibiot.* **34,** 658, 665 (1981). Relative pulmonary toxicity: A. Broughton *et al., Cancer Treat. Rep.* **64,** 659 (1980). *Review:* S. T. Crooke *et al., Recent Results Cancer Res.* **76,** 83-90 (1981).



Tallysomycin A. [65057-90-1] N^1-[4-Amino-6-[[3-[(4-aminobutyl)amino]propyl]amino]-6-oxohexyl]-13-[(4-amino-4,6-dideoxy-α-L-talopyranosyl)oxy]-19-demethyl-12-hydroxybleomycinamide; BU-2231A. $C_{68}H_{110}N_{22}O_{27}S_2$; mol wt 1731.89. The term "talisomycin" has also been used to refer to tallysomycin A. White amorphous solid. No definite mp; gradually dec >210°. Sol in water, methanol, DMF; slightly sol in ethanol. Practically insol in other organic solvents. $[\alpha]_D^{23}$ −21° (c = 0.5 in water). uv max (water): 290 nm ($E_{1cm}^{1\%}$ 67). LD_{50} s.c. in mice: 28 mg/kg (**US 4051237**).

Tallysomycin B. [65057-91-2] N^1-[3-[(4-Aminobutyl)amino]propyl]-13-[(4-amino-4,6-dideoxy-α-L-talopyranosyl)oxy]-19-demethyl-12-hydroxybleomycinamide; talisomycin B; BU-2231B. $C_{62}H_{98}N_{20}O_{26}S_2$; mol wt 1603.71. Mp, soly similar to tallysomycin A. $[\alpha]_D^{23}$ −19° (c = 0.5 in water). uv max (water): 289.5 ($E_{1cm}^{1\%}$ 77). LD_{50} s.c. in mice: >50 mg/kg (**US 4051237**).

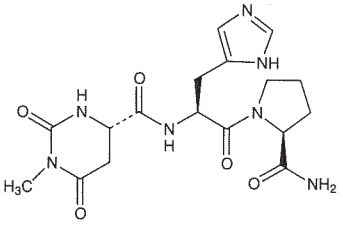
9134. Talniflumate. [66898-62-2] 2-[[3-(Trifluoromethyl)phenyl]amino]-3-pyridinecarboxylic acid 1,3-dihydro-3-oxo-1-isobenzofuranyl ester; phthalidyl 2-(3-trifluoromethylanilino)nicotinate; phthalidyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate; BA-7602-06; Somalgen. $C_{21}H_{13}F_3N_2O_4$; mol wt 414.33. C 60.88%, H 3.16%, F 13.76%, N 6.76%, O 15.45%. Deriv of niflumic acid, *q.v.* Prepn: **BE 858864** (1978 to Bago), *C.A.* **89,** 109104 (1978); S. Bago, **US 4168313** (1979). Synthesis and pharmacologic study: M. Los *et al., Farmaco Ed. Sci.* **36,** 372 (1981).



White or pale yellow crystalline powder, mp 165-166°. uv max (chloroform): 287, 357 nm (ε 25600, 7800). LD_{50} orally in rats: 12000 mg/kg (Los).

THERAP CAT: Anti-inflammatory; analgesic.

9135. Taltirelin. [103300-74-9] *N*-[[(4*S*)-Hexahydro-1-methyl-2,6-dioxo-4-primidinyl]carbonyl]-L-histidyl-L-prolinamide; (*S*)-*N*-(1-methyl-4,5-dihydroorotyl)-L-histidyl-L-prolinamide. $C_{17}H_{23}N_7O_5$; mol wt 405.41. C 50.36%, H 5.72%, N 24.18%, O 19.73%. Analog of thyrotropin releasing hormone (TRH) *q.v.* with pronounced CNS activity. Prepn: H. Sugano *et al.*, **EP 168042**; *eidem*, **US 4665056** (1986, 1987 both to Tanabe Seiyaku): M. Suzuki *et al., J. Med. Chem.* **33,** 2130 (1990). Radioimmunoassay determn in plasma and urine: S. Morikawa *et al., J. Pharm. Biomed. Anal.* **16,** 1267 (1998). CNS pharmacology: M. Yamamura *et al., Japan J. Pharmacol.* **53,** 451 (1990). Effect on motor neuron survival: Y. Iwasaki *et al., Neurolog. Res.* **19,** 613 (1997). Review of pharmacology, toxicology, and clinical trials: K. Kinoshita *et al., CNS Drug Rev.* **4,** 25-41 (1998).



Crystals from water as the hemiheptahydrate, mp 72-75°. $[\alpha]_D^{25}$ −13.6° (c = 1 in water).

Tetrahydrate. [201677-75-0] TA-0910; Ceredist. $C_{17}H_{21}N_7O_5.4H_2O$; mol wt 475.45. White, odorless crystals, mp 72-75°. Sol in water, acetic acid, ethanol. Slightly sol in methanol, acetonitrile. $[\alpha]_D^{23}$ −13.6°. LD_{50} in mice, rats (mg/kg): >5000, >5000 orally; in mice, male, female rats (mg/kg): >2000, 799, 946 i.v. (Kinoshita).

THERAP CAT: In treatment of spinocerebellar degeneration.

9136. Tamarind. Partially dried ripe fruit of *Tamarindus indica* L., *Leguminosae,* preserved in sugar or syrup. *Habit.* East Indies, India, Africa; naturalized in West Indies. *Constit.* The pulp contains about 10% tartaric acid, also some citric and malic acids; 25-40% invert sugar, pectin. *Review:* Rao, Srivastava, in *Industrial Gums,* R. L. Whistler, Ed. (Academic Press, New York, 2nd ed., 1973) pp 369-411.

USE: The pulp as souring agent in Indian curries. The seed kernel powder with water as sizing agent.

9137. Tamoxifen. [10540-29-1] (*Z*)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine; 1-*p*-β-dimethyl-

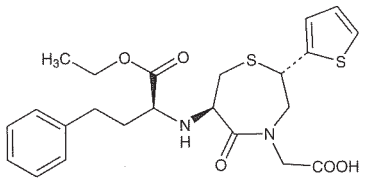
NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 60 of 65

Crystalline solid, mp 30.0-30.5°. Optimum stability at pH 5-7. Sol in acetonitrile, carbon tetrachloride, ether, dichloroethane, toluene. Almost insol in water, hexane. LD_{50} in male, female rats (mg/kg): 8600, 13000 orally (Gaines).

Caution: Potential symptoms of overexposure are eye irritation, blurred vision; dizziness, confusion; dyspnea; salivation; abdominal cramps, nausea, diarrhea, vomiting. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 296.

USE: Insecticide.

9215. Temocapril. [111902-57-9] (2*S*,6*R*)-6-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5*H*)-acetic acid; (+)-(2*S*,6*R*)-6-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5*H*)-acetic acid, 6-ethyl ester. $C_{23}H_{28}N_2O_5S_2$; mol wt 476.62. C 57.96%, H 5.92%, N 5.88%, O 16.78%, S 13.46%. Angiotensin-converting enzyme (ACE) inhibitor. Hydrolyzed *in vivo* to the active diacid metabolite. Prepn: H. Yanagisawa *et al.*, **EP 161801**; *eidem*, **US 4699905** (1985, 1987 both to Sankyo); *idem et al., J. Med. Chem.* **30,** 1984 (1987). Pharmacology: K. Oizumi *et al., Japan. J. Pharmacol.* **48,** 349 (1988). GC/MS determn in human plasma and urine: H. Shioya *et al., J. Chromatog.* **496,** 129 (1989). Clinical evaluation: M. Arita *et al., Clin. Exp. Pharmacol. Physiol.* **21,** 195 (1994); and pharmacokinetics: S. Tokunaga *et al., Drug Invest.* **7,** 161 (1994). *Review:* H. Koike *et al., Ann. Rep. Sankyo Res. Lab.* **44,** 1-81 (1992).



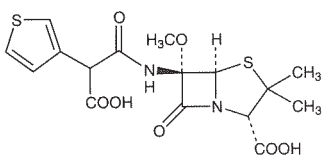
Cryst powder, mp 168°. $[\alpha]^{23}$ +40° (c = 1.1 in DMF).

Hydrochloride. [110221-44-8] CS-622; Acecol. Solid from ethanol/ethyl acetate, mp 187° (dec). $[\alpha]_D^{25}$ +47.7° (c = 1 in DMF). LD_{50} in mice, rats, dogs (mg/kg): >5000, >5000, >800 orally (Koike).

Diacid. [110221-53-9] Temocaprilat; RS-5139. $C_{21}H_{24}N_2O_5S_2$; mol wt 448.56. Solid from ethanol, mp 246° (dec). $[\alpha]_D^{25}$ +63.4° (c = 1 in DMF).

THERAP CAT: Antihypertensive.

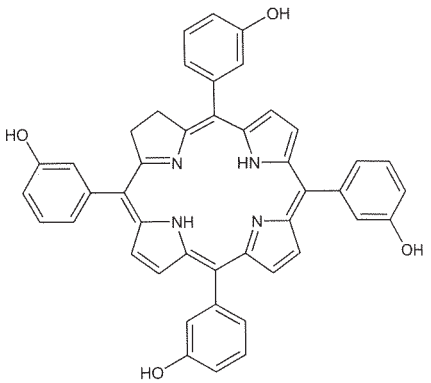
9216. Temocillin. [66148-78-5] (2*S*,5*R*,6*S*)-6-[(Carboxy-3-thienylacetyl)amino]-6-methoxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; (6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid. $C_{16}H_{18}N_2O_7S_2$; mol wt 414.46. C 46.37%, H 4.38%, N 6.76%, O 27.02%, S 15.47%. Semi-synthetic injectable penicillin deriv with high activity vs a large number of gram-negative bacteria, but with little activity vs gram-positive organisms. Prepn: J. P. Clayton, P. H. Bentley, **DE 2600866** (1976 to Beecham), *C.A.* **86,** 55420t (1977); P. H. Bentley *et al., J. Chem. Soc. Perkin Trans. I* **1979,** 2455. *In vitro* antibacterial activity and β-lactamase susceptibility: I. Phillips *et al., J. Antimicrob. Chemother.* **10,** 271 (1982). Comparison to other penicillins vs *H. influenzae* and intestinal gram-negative rods: H. Y. Chen, J. D. Williams, *ibid.* 279. Pharmacokinetics and tissue penetration in healthy volunteers: R. M. Brown *et al., ibid.* 295. *In vivo* and *in vitro* comparison to ampicillin: R. Yogev *et al., Antimicrob. Ag. Chemother.* **23,** 182 (1983). Series of articles on microbiology, pharmacology and clinical studies: *Drugs* **29,** Suppl. 5, 1-243 (1985).



Disodium salt. [61545-06-0] BRL-17421; Temopen. $C_{16}H_{16}N_2Na_2O_7S_2$; mol wt 458.42. Amorphous solid.

THERAP CAT: Antibacterial.

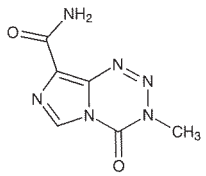
9217. Temoporfin. [122341-38-2] 3,3′,3″,3‴-(2,3-Dihydro-21*H*,23*H*-porphine-5,10,15,20-tetrayl)tetrakisphenol; 2,3-dihydro-5,10,15,20-tetra(*m*-hydroxyphenyl)porphyrin; 5,10,15,-20-tetra(*m*-hydroxyphenyl)chlorin; *m*-THPC; dihydro meta-HK7; EF-9; Foscan. $C_{44}H_{32}N_4O_4$; mol wt 680.75. C 77.63%, H 4.74%, N 8.23%, O 9.40%. Second generation systemic photosensitizing agent. Prepn: R. Bonnett, M. C. Berenbaum, **EP 337601**; *eidem*, **US 4992257** (1989, 1991 both to Efamol Holdings); R. Bonnett *et al., Biochem. J.* **261,** 277 (1989). NMR study: *idem et al., J. Chem. Soc., Perkin Trans.* **2,** 1839 (1994). Toxicology study: R. B. Veenhuizen *et al., Int. J. Cancer* **59,** 830 (1994). HPLC determn in plasma and tissue: M. Barberi-Heyob *et al., J. Chromatog. B* **688,** 331 (1997). Clinical pharmacokinetics: T. Glanzmann *et al., Photochem. Photobiol.* **67,** 596 (1998). Clinical evaluation in photodynamic therapy of malignancies: J.-F. Savary *et al., Arch. Otolaryngol. Head Neck Surg.* **123,** 162 (1997).



Purple solid from methanol/water. Absorption max (methanol): 284, 306, 415, 516, 543, 591, 650 nm (ε 16900, 15600, 146000, 11000, 7300, 4400, 22400 l/mol-cm). Sol in polar solvents.

THERAP CAT: Antineoplastic (photosensitizer).

9218. Temozolomide. [85622-93-1] 3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-*d*]-1,2,3,5-tetrazine-8-carboxamide; 8-carbamoyl-3-methylimidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one; methazolastone; M & B 39831; CCRG-81045; NSC-362856; Temodal; Temodar. $C_6H_6N_6O_2$; mol wt 194.15. C 37.12%, H 3.11%, N 43.29%, O 16.48%. Imidazotetrazine alkylating agent. Prepn: E. Lunt *et al.*, **DE 3231255** (1983 to May & Baker); *eidem*, **US 5260921** (1993 to Cancer Res. Campaign Technol.); M. F. G. Stevens *et al., J. Med. Chem.* **27,** 196 (1984). Crystal structure and structure-activity study: P. R. Lowe *et al., ibid.* **35,** 3377 (1992). Synthesis: Y. Wang *et al., J. Org. Chem.* **62,** 7288 (1997). HPLC determn in plasma and urine: F. Shen *et al., J. Chromatog. B* **667,** 291 (1995). Review of pharmacology and clinical efficacy in melanoma and brain tumor: E. S. Newlands *et al., Cancer Treat. Rev.* **23,** 35-61 (1997).

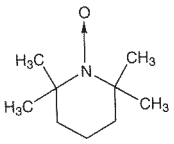


Crystals from dichloromethane, mp 212° (dec). uv max (95% ethanol): 327 nm.

THERAP CAT: Antineoplastic.

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 61 of 65

9219. TEMPO. [2564-83-2] 2,2,6,6-Tetramethyl-1-piperidinyloxy; 2,2,6,6-tetramethylpentamethylene nitroxide. $C_9H_{18}NO$; mol wt 156.24. C 69.19%, H 11.61%, N 8.96%, O 10.24%. Stable nitroxide free radical used as reversible capping agent in "living" free radical polymerizations and as catalyst for selective oxidation of alcohols. Prepn: E. G. Ruzantsev *et al., Bull. Acad. Sci. USSR Div. Chem. Sci.* **1962,** 2152. Crystal structure: Z. Ciunik, *J. Mol. Struct.* **412,** 27 (1997). Thermal stability: M. V. Ciriano *et al., J. Am. Chem. Soc.* **121,** 6375 (1999). Effect of acids on reaction rates: M. V. Baldovi *et al., Macromolecules* **29,** 5497 (1996). Use in oxidation of alcohols: M. Zhao *et al., J. Org. Chem.* **64,** 2564 (1999); in production of aminyl radicals: W. Huang *et al., J. Am. Chem. Soc.* **121,** 3939 (1999); in polymerization: L. I. Gabaston *et al., Polymer* **40,** 4505 (1999).



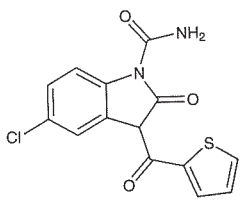
Monoclinic dark red crystals, mp 36-40°. Flash pt: 67°C (Acros Organics Data Sheet).

USE: In organic chemistry as a radical trap, a catalyst and in polymerization mediation.

9220. Tenecteplase. [191588-94-0] 103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanineplasminogen activator (human tissue-type); TNK-tPA; Metalyse. Genetically engineered variant of human tissue plasminogen activator (t-PA), *q.v.*; expressed in Chinese hamster ovary cells. mol wt ~65 kDa. Constructed by oligonucleotide-directed mutagenesis at 3 specific sites. Prepn: W. F. Bennett *et al.,* **WO 93 24635** (1993 to Genentech); B. A. Keyt *et al., Proc. Nat. Acad. Sci. USA* **91,** 3670 (1994). Pharmacology: C. R. Benedict *et al., Circulation* **92,** 3032 (1995). Clinical pharmacokinetics: N. B. Modi *et al., Thromb. Haemost.* **79,** 134 (1998). Clinical trial in acute myocardial infarction: ASSENT-2 Investigators, *Lancet* **354,** 716 (1999).

THERAP CAT: Thrombolytic.

9221. Tenidap. [120210-48-2] (*Z*)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indole-1-carboxamide; 5-chloro-2,3-dihydro-2-oxo-3-(2-thienylcarbonyl)-1*H*-indole-1-carboxamide; 5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide; CP-66248. $C_{14}H_9ClN_2O_3S$; mol wt 320.76. C 52.42%, H 2.83%, Cl 11.05%, N 8.73%, O 14.96%, S 10.00%. Inhibitor of 5-lipoxygenase and interleukin-1 (IL-1) activity. Prepn: S. B. Kadin, **EP 156603**; *idem,* **US 4556672** (both 1985 to Pfizer). Effect on 5-lipoxygenase activity *in vitro:* K. Fogh *et al., Arch. Dermatol. Res.* **280,** 430 (1988). Effect on IL-1 activity in patients with rheumatoid arthritis: B. McDonald *et al., Arthritis Rheum.* **31,** Suppl., S52 (1988). Clinical evaluation: P. Katz *et al., ibid.* S52.

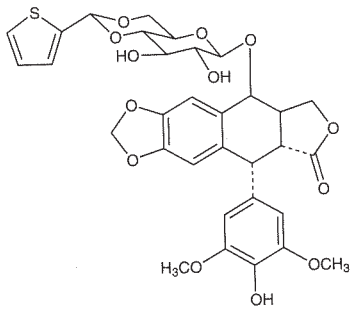


Fluffy, yellow crystals from acetic acid, mp 230° (dec).

Sodium salt. [119784-94-0] CP-66248-2. $C_{14}H_8ClN_2NaO_3S$; mol wt 342.74. Crystals from methanol-isopropanol, mp 237-238°.

THERAP CAT: Anti-inflammatory.

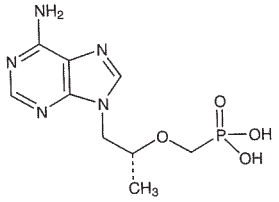
9222. Teniposide. [29767-20-2] [5*R*-[5α,5aβ,8aα,9β-(*R**)]]-5,8,8a,9-Tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-*O*-(2-thienylmethylene)-β-D-glucopyranosyl]oxy]-furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one; 4′-demethylepipodophyllotoxin 9-(4,6-*O*-2-thenylidene-β-D-glucopyranoside); 4′-demethylepipodophyllotoxin-β-D-thenylidine glucoside; ETP; NSC-122819; VM-26; Vehem-Sandoz; Vumon. $C_{32}H_{32}O_{13}S$; mol wt 656.66. C 58.53%, H 4.91%, O 31.67%, S 4.88%. Semi-synthetic derivative of podophyllotoxin, *q.v.* Prepn: A. Von Wartburg, **ZA 66 07585**; C. Keeler-Juslen *et al.,* **US 3524844** (1968, 1970 both to Sandoz). Mechanism of action: H. Stählen, *Eur. J. Cancer* **6,** 303 (1970). Pharmacology: M. Hacker, D. Roberts, *Cancer Res.* **37,** 3287 (1977); S. M. Sieber *et al., Teratology* **18,** 31 (1978); T. J. Vietti *et al., Cancer Treat. Rep.* **62,** 1313 (1978). Metabolism: L. Allen, *Drug Metab. Rev.* **8,** 119 (1978); *Cancer Res.* **38,** 2549 (1978). Clinical studies: N. M. Gadel-Mawla *et al., Cancer Treat. Rep.* **62,** 993 (1978); R. E. Bellet *et al., ibid.* 445. Studies on delayed toxicity in mice after i.p. injections: M. Hacker, D. Roberts, *Cancer Res.* **35,** 1756 (1975); H. Stählin, *Eur. J. Cancer* **12,** 925 (1976). Review of pharmacology, pharmacokinetics and assay methods: P. I. Clark, M. L. Slevin, *Clin. Pharmacokinet.* **12,** 223-252 (1987). Comprehensive description: J. J. Kettenes-van den Bosch *et al., Anal. Profiles Drug Subs.* **19,** 575-600 (1990).



Crystals from abs ethanol, mp 242-246°. $[\alpha]_D^{20}$ −107° (9:1 chloroform/methanol). uv max (methanol): 283 nm ($E_{1cm}^{1\%}$ 64.1). pKa 10.13.

THERAP CAT: Antineoplastic.

9223. Tenofovir. [147127-20-6] [[(1*R*)-2-(6-Amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid; (*R*)-9-(2-phosphonomethoxypropyl)adenine; (*R*)-PMPA; GS-1278. $C_9H_{14}N_5O_4P$; mol wt 287.21. C 37.64%, H 4.91%, N 24.38%, O 22.28%, P 10.78%. Acyclic phosphonate nucleotide analog; reverse transcriptase inhibitor. Prepn: I. Rosenberg *et al., Coll. Czech. Chem. Commun.* **53,** 2753 (1988); A. Holy *et al., ibid.* **60,** 1390 (1995); L. M. Schultze *et al., Tetrahedron Letters* **39,** 1853 (1998). Prepn of ester prodrug: M. N. Arimilli *et al., Antivir. Chem. Chemother.* **8,** 557 (1997); *idem et al.,* **WO 98 04569**; *eidem,* **US 5922695** (1998, 1999 both to Gilead Sci.). Antiretroviral activity *in vitro:* J. Balzarini *et al., Biochem. Biophys. Res. Commun.* **219,** 337 (1996). Metabolism and pharmacokinetics of prodrugs: J.-P. Shaw *et al., Pharm. Res.* **14,** 1824 (1997). Clinical evaluation in HIV-infected patients: S. G. Deeks *et al., Antimicrob. Ag. Chemother.* **42,** 2380 (1998).



Crystals from boiling water + ethanol, mp 279°. $[\alpha]_D$ +21° (c = 1 in 0.1M HCl).

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 62 of 65

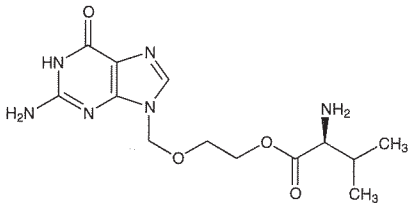
V

9965. Vaccenic Acid. [693-72-1] (11*E*)-11-Octadecenoic acid; *trans*-Δ^{11}-octadecenoic acid. $C_{18}H_{34}O_2$; mol wt 282.46. C 76.54%, H 12.13%, O 11.33%. $CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$. Found in butterfat and in other animal fats. Growth-promoting factor for rats. Isoln: Bertram, *Biochem. Z.* **197,** 433 (1928). Synthesis: Böeseken, Hoagland, *Rec. Trav. Chim.* **46,** 632 (1927); Ahmad *et al., J. Am. Chem. Soc.* **70,** 3391 (1948). Configuration and ir spectrum: Rao, Daubert, *ibid.* 1102.

Platelets from acetone, mp 43-44°; n_D^{60} 1.4439; n_D^{70} 1.4402. Neutralization equivalent 282.5; iodine no. 89.9.

Methyl ester. $C_{19}H_{36}O_2$. bp_3 172-173°.

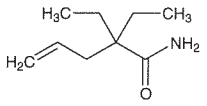
9966. Valacyclovir. [124832-26-4] L-Valine 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl ester; L-valine ester with 9-[(2-hydroxyethoxy)methyl]guanine; valaciclovir; ValACV. $C_{13}H_{20}N_6O_4$; mol wt 324.33. C 48.14%, H 6.22%, N 25.91%, O 19.73%. L-Valine ester prodrug of acyclovir, *q.v.* Prepn: T. A. Krenitsky *et al.,* **EP 308065**; L. M. Beauchamp, **US 4957924** (1989, 1990 both to Wellcome). Evaluation as prodrug: L. M. Beauchamp *et al., Antiviral Chem. Chemother.* **3,** 157 (1992). Clinical pharmacokinetics: S. Weller *et al., Clin. Pharmacol. Ther.* **54,** 595 (1993). Review of pharmacology and clinical efficacy in herpes virus infections: C. M. Perry, D. Faulds, *Drugs* **52,** 754-772 (1996). Clinical trial to prevent cytomegalovirus disease in renal transplantation: D. Lowance *et al., N. Engl. J. Med.* **340,** 1462 (1999).



Hydrochloride. [124832-27-5] 256U; BW-256U87; BW-256; Valtrex. Crystalline solid, occurs as hydrate. uv max (water): 252.8 nm (ε 8530). Soly in water: 174 mg/ml.

THERAP CAT: Antiviral.

9967. Valdetamide. [512-48-1] 2,2-Diethyl-4-pentenamide; diethylallylacetamide; Novonal. $C_9H_{17}NO$; mol wt 155.24. C 69.63%, H 11.04%, N 9.02%, O 10.31%. Description: Bockmühl, Schaumann, *Deut. Med. Wochenschr.* **54,** 270 (1928). Pharmacokinetics and metabolism: H. Uehleke, M. Brinkschulte-Freitas, *Arch. Pharmacol.* **302,** 11 (1978). TLC determn in urine: E. Klug, P. Toffel, *Arzneimittel-Forsch.* **29,** 1651 (1979).



White powder, mp 75-76°. Sol in 120 parts water; freely sol in alcohol, ether.

THERAP CAT: Sedative, hypnotic.

9968. *n*-Valeraldehyde. [110-62-3] Pentanal; valeral; valeric aldehyde. $C_5H_{10}O$; mol wt 86.13. C 69.72%, H 11.70%, O 18.58%. $CH_3(CH_2)_3CHO$. Prepn: Lieben, Rossi, *Ann.* **159,** 70 (1871); Olsen, **US 2548171** (1951 to GAF); Sisti *et al., J. Org. Chem.* **27,** 279 (1962). Toxicity study: H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30,** 470 (1969).

Liquid, bp 102-103°. d_4^{20} 0.8095. n_D^{20} 1.3944. Very slightly sol in water; miscible with many organic solvents. LD_{50} orally in rats: 5.66 ml/kg (Smyth).

Caution: Potential symptoms of overexposure are irritation of eyes, skin, nose, throat. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 326.

USE: In flavoring compds, resin chemistry, rubber accelerators.

9969. Valerian. Dried rhizome and roots of *Valeriana officinalis* L., *Valerianaceae. Habit.* Europe, Northern Asia; naturalized in eastern U.S. *Constit.* Volatile oil (~1%); valerine (valerianin) and chatinine (alkaloids); valeric, formic and malic acids; tannin, resin.

Component of ***Valerbé***.

THERAP CAT: Sedative.

9970. Valeric Acid, Normal. [109-52-4] Pentanoic acid; valerianic acid; propylacetic acid. $C_5H_{10}O_2$; mol wt 102.13. C 58.80%, H 9.87%, O 31.33%. $CH_3(CH_2)_3COOH$. Obtained by decompn of *n*-propylmalonic acid: Fürth, *Monatsh.* **9,** 308 (1888); from *n*-butyl chloride: Gilman, Kirby, *Org. Syn.* **coll. vol. I,** 363 (2nd ed., 1941). Industrial synthesis by oxidation of amyl alcohol or by fermentation processes. Toxicity study: L. Orö, A. Wretlind, *Acta Pharmacol. Toxicol.* **18,** 141 (1961).

Colorless liquid; unpleasant odor; d_4^{20} 0.939; mp −34.5°; bp 186-187°; bp_{23} 96°; n_D^{20} 1.4086. Sol in 30 parts water; freely sol in alcohol, ether. LD_{50} i.v. in mice: 1290 ±53 mg/kg (Orö, Wretlind).

Ethyl ester. Ethyl *n*-valerate. $C_7H_{14}O_2$. Liquid. d_4^{20} 0.877. bp 145-146°. n_D^{20} 1.3732. Insol in water. Misc with alcohol, ether.

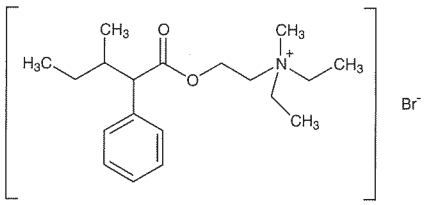
USE: Intermediate in perfumery.

9971. Valeronitrile. [110-59-8] Pentanenitrile; 1-butyl cyanide; 1-cyanobutane. C_5H_9N; mol wt 83.13. C 72.24%, H 10.91%, N 16.85%. $CH_3(CH_2)_3CN$. Prepn: A. Lieben, A. Rossi, *Ann.* **158,** 137 (1871); W. Kantlehner *et al., ibid.* **1980,** 389; H. G. Thomas, H. D. Greyn, *Synthesis* **1990,** 129. Acute toxicity and metabolism: H. Tanii, K. Hashimoto, *Arch. Toxicol.* **55,** 47 (1984). Comparative toxicity of aliphatic nitriles: M. A. Wallig *et al., Food Chem. Toxicol.* **26,** 149 (1988).

bp_{15} 45-47°. $bp_{739.3}$ 140.4°. bp 141°. d^0 0.8164. n_D^{20} 1.3962. Log P (*n*-octanol/water): 0.94. LD_{50} orally in male mice: 2.297 mmol/kg (Tanii).

USE: Solvent.

9972. Valethamate Bromide. [90-22-2] *N,N*-Diethyl-*N*-methyl-2-[(3-methyl-1-oxo-2-phenylpentyl)oxy]ethanaminium bromide; 3-methyl-2-phenylvaleric acid diethyl(3-hydroxyethyl)methylammonium bromide ester; 2-phenyl-3-methylvaleric acid β-(diethylamino)ethyl ester bromomethylate; 3-methyl-2-phenylvaleric acid 2-diethylaminoethyl ester methyl bromide; 2-diethylaminoethyl 2-phenyl-3-methylvalerate methyl bromide; diethyl(2-hydroxyethyl)methylammonium 3-methyl-2-phenylvalerate bromide; Resitan; Epidosin. $C_{19}H_{32}BrNO_2$; mol wt 386.37. C 59.06%, H 8.35%, Br 20.68%, N 3.63%, O 8.28%. Anticholinergic. Prepn: Stühmer, Funke, **DE 969245**; **DE 971136**; **DE 1112989** (all 1958 to Kali-Chemie); Martin, Habicht, **DE 1091124**; **US 2987517** (1960, 1961 both to Cilag-Chemie).



Crystals from ethanol + ether or acetone, mp 100-101°. Freely sol in water, very sol in alcohol. Practically insol in ether. Aq solns are stable to storage; 0.6% ampuled solns showed no loss after one year at room temp.

THERAP CAT: Antispasmodic.

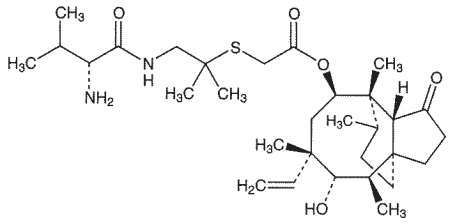
9973. Valganciclovir. [175865-60-8] L-Valine 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl ester; 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)-methoxy]-3-hydroxypropanyl-L-valinate. $C_{14}H_{22}N_6O_5$; mol wt 354.36. C 47.45%, H 6.26%, N 23.72%, O 22.58%. Valine ester prodrug of ganciclovir, *q.v.* Prepn: J. J. Nestor *et al.,* **EP 694547**; *eidem,* **US 6083953** (1996, 2000 both to Hoffmann-La

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 63 of 65

Practically insol in water. Freely sol in petr ether, ether, benzene, chloroform, glacial acetic, butyl acetate, acetone. Active *in vitro* against *Mycobacterium tuberculosis.*

USE: Insecticide, nematocide, Patterson, Wright, **US 3520973** (1970 to Am. Cyanamid).

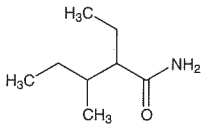
9977. Valnemulin. [101312-92-9] [[2-[[(2*R*)-2-Amino-3-methyl-1-oxobutyl]amino]-1,1-dimethylethyl]thio]acetic acid (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl ester; 14-*O*-[1-(D-2-amino-3-methylbutyrylamino)-2-methylpropan-2-ylthioacetyl]mutilin. $C_{31}H_{52}N_2O_5S$; mol wt 564.83. C 65.92%, H 9.28%, N 4.96%, O 14.16%, S 5.68%. Semisynthetic antibiotic; derivative of pleuromutilin, *q.v.* Prepn: H. Berner, H. Vyplel, **EP 153277**; *eidem,* **US 4675330** (1985, 1987 both to Sandoz). Comparative *in vitro* activity vs porcine bacterial pathogens: I. A. Aitken *et al., Vet. Rec.* **144,** 128 (1999). Pharmacokinetics in pigs: S. Horkovics-Kovats, F. Schatz, *J. Pharm. Med.* **6,** 149 (1996). Efficacy vs *Mycoplasma gallisepticum* in chickens: F. T. W. Jordan *et al., Avian Dis.* **42,** 738 (1998).



Hydrochloride. [133868-46-9] Econor. $C_{31}H_{52}N_2O_5S.HCl$; mol wt 601.29.

THERAP CAT (VET): Antibacterial.

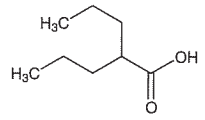
9978. Valnoctamide. [4171-13-5] 2-Ethyl-3-methylpentanamide; 2-ethyl-3-methylvaleramide; α-ethyl-β-methylvaleramide; valmethamide; McN-X-181; Axiquel; Nirvanil. $C_8H_{17}NO$; mol wt 143.23. C 67.08%, H 11.96%, N 9.78%, O 11.17%. Isomer of valpromide, *q.v.* Prepn: Freifelder *et al., J. Org. Chem.* **26,** 203 (1961). GLC determn in plasma: M. Bialer, B. Hoch, *J. Chromatog.* **337,** 408 (1985). Clinical pharmacokinetics: M. Bialer *et al., Eur. J. Clin. Pharmacol.* **38,** 289 (1990).



Crystals, mp 113.5-114°. Sol in water.

THERAP CAT: Anxiolytic.

9979. Valproic Acid. [99-66-1] 2-Propylpentanoic acid; 2-propylvaleric acid; di-*n*-propylacetic acid; Convulex; Depakene; Mylproin. $C_8H_{16}O_2$; mol wt 144.21. C 66.63%, H 11.18%, O 22.19%. Antiepileptic; increases levels of γ-aminobutyric acid (GABA) in the brain. Prepn: B. S. Burton, *Am. Chem. J.* **3,** 385 (1882); E. Oberreit, *Ber.* **29,** 1998 (1896); M. Tiffeneau, Y. Deux, *Compte Rend.* **212,** 105 (1941). Anticonvulsant activity: H. Meunier *et al., Thérapie* **18,** 435 (1963). Toxicity data: Jenner *et al., Food Cosmet. Toxicol.* **2,** 327 (1964). Comprehensive description: Z. L. Chang, *Anal. Profiles Drug Subs.* **8,** 529-556 (1979). Review of teratogenicity studies: H. Nau *et al., Pharmacol. Toxicol.* **69,** 310-321 (1991). Review of pharmacology and clinical experience in epilepsy: E. M. Rimmer, A. Richens, *Pharmacotherapy* **5,** 171-184 (1985); in psychiatric disease: D. R. P. Guay, *ibid.* **15,** 631-647 (1995); in migraine prophylaxis: C. E. Shelton, J. F. Connelly, *Ann. Pharmacother.* **30,** 865-866 (1996). Review of pharmacodynamics and mechanisms of action: W. Löscher, *Prog. Neurobiol.* **58,** 31-59 (1999).



Colorless liquid with characteristic odor. bp 219.5°. $n_D^{24.5}$ 1.425. d_4^0 0.9215. pKa 4.6. Very sol in organic solvents. Soly in water: 1.3 mg/ml. LD_{50} orally in rats: 670 mg/kg (Jenner).

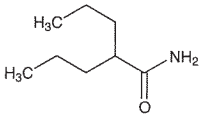
Sodium salt (1:1). [1069-66-5] Sodium valproate; Depacon; Depakin; Dépakine; Epilim; Ergenyl; Leptilan; Orfiril. $C_8H_{15}NaO_2$; mol wt 166.19. White, odorless, crystalline, deliquescent powder. pKa 4.8. Hygroscopic. One gram is sol in 0.4 ml water; 1.5 ml ethanol; 5 ml methanol. Practically insol in common organic solvents. LD_{50} orally in mice: 1700 mg/kg (Meunier).

Sodium salt (2:1). [76584-70-8] Sodium hydrogen bis(2-propylpentanoate); divalproex sodium; valproate semisodium; Abbott 50711; Depakote; Valcote. $C_{16}H_{31}NaO_4$; mol wt 310.40.

Magnesium salt. Depamag. $C_{16}H_{30}MgO_4$; mol wt 310.71.

THERAP CAT: Anticonvulsant; antimanic; antimigraine.

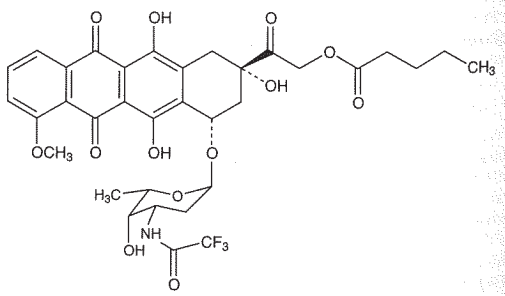
9980. Valpromide. [2430-27-5] 2-Propylpentanamide; 2-propylvaleramide; 2-propylpentamide; dipropylacetamide; Depamide. $C_8H_{17}NO$; mol wt 143.23. C 67.08%, H 11.96%, N 9.78%, O 11.17%. Prodrug of valproic acid, *q.v.* Prepn: E. Fischer, A. Dilthey, *Ber.* **35,** 844 (1902); M. Tiffeneau, Y. Deux, *Compt. Rend.* **212,** 105 (1941). GC determn in plasma: M. Pokrajac *et al., Pharm. Acta Helv.* **67,** 237 (1992). Review of pharmacology and clinical activity: M. Bialer, *Clin. Pharmacokinet.* **20,** 114-122 (1991).



White, odorless and bitter crystalline powder, mp 125-126°. Practically insol in water.

THERAP CAT: Anticonvulsant.

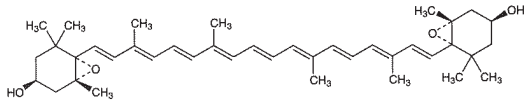
9981. Valrubicin. [56124-62-0] Pentanoic acid 2-[(2*S*,4*S*)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoroacetyl)amino]-α-L-lyxo-hexopyranosyl]oxy]-2-naphthacenyl]-2-oxoethyl ester; *N*-trifluoroacetyladriamycin-14-valerate; AD-32; NSC-246131; Valstar. $C_{34}H_{36}F_3NO_{13}$; mol wt 723.64. C 56.43%, H 5.01%, F 7.88%, N 1.94%, O 28.74%. Semisynthetic doxorubicin, *q.v.*, analog. Prepn: M. Israel *et al., Cancer Res.* **35,** 1365 (1975); M. Israel, E. J. Modest, **US 4035566** (1977 to S. Farber Cancer Inst.). TLC determn in biological samples: B. Barbieri *et al., J. Chromatog.* **163,** 195 (1979). Clinical pharmacokinetics: R. E. Greenberg *et al., Urology* **49,** 471 (1997). Clinical trial in refractory bladder cancer: G. Steinberg *et al., J. Urol.* **163,** 761 (2000). Review of pharmacology and clinical development: C. Doehn, *Curr. Opin. Oncol. Endocrin. Metab. Invest. Drugs* **1,** 407-415 (1999); S. V. Onrust, H. M. Lamb, *Drugs Aging* **15,** 69-75 (1999).



NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 64 of 65

Purplish-black needles, prisms. Practically insol in water; slightly sol in alcohol; moderately sol in dioxane.

10059. Violaxanthin. [126-29-4] 5,6:5′,6′-Diepoxy-5,5′,6,6′-tetrahydro-β,β-carotene-3,3′-diol; zeaxanthin diepoxide. $C_{40}H_{56}O_4$; mol wt 600.87. C 79.96%, H 9.39%, O 10.65%. Widely distributed carotenoid pigment. Formed in plants from zeaxanthin. Isoln from yellow pansies *(Viola tricolor):* Kuhn, Winterstein, *Ber.* **64,** 326 (1931). Structure: Karrer *et al., Helv. Chim. Acta* **14,** 1044 (1931); **16,** 977 (1933); **19,** 1024 (1936); **27,** 1684 (1944). Partial synthesis: Karrer, Jucker, *ibid.* **28,** 300 (1945). Abs config: Bartlett *et al., J. Chem. Soc. (C)* **1969,** 2527. Isoln from *Viola tricolor* and configuration of the 15-*cis*-isomer: P. Molnar, J. Szabolcs, *Phytochemistry* **19,** 623 (1980).



Orange prisms from methanol, reddish-brown acicular crystals from CS_2. mp 200°. $[\alpha]_{Cd}^{20}$ +35° (c = 0.08 in chloroform). Absorption max (in alc): 471.5, 442.5, 417.5 nm. Sol in alcohol, methanol, carbon disulfide, ether; almost insol in petr ether.

15-*cis*-Isomer. Irregular yellow plates from benzene/petrol, mp 109°. uv max (benzene): 479, 448, 423, 337 nm (log ε 4.91, 4.98, 4.83, 4.77). Friction causes crystals to form orange prisms.

10060. Viologen. A term coined by Michaelis to designate the chlorides of certain quaternary bases derived from γ,γ′-dipyridyl. Presently used as dichlorides, dibromides and diiodides. Prepn: Michaelis, *Biochem. Z.* **250,** 564 (1932); Michaelis, Hill, *J. Am. Chem. Soc.* **55,** 1481 (1933); *J. Gen. Physiol.* **16,** 859-873 (1933). Viologens are useful as oxidation-reduction indicators because their potential range is very negative. In contrast to other redox indicators, the color is exhibited by the reduced form, whereas usually the oxidized form is the colored one and secondly, the redox potential of these substances is independent of pH. Review of electrochemistry: C. L. Bird, A. T. Kuhn, *Chem. Soc. Rev.* **10,** 49-82 (1981).

Ethyl viologen. 1,1-Diethyl-4,4′-bipyridinium; *N,N′*-diethyl-γ,γ′-dipyridylium. Normal potential at 30°: −0.449 volts.

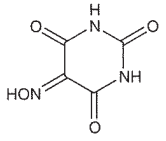
Benzyl viologen. 1,1′-Bis(phenylmethyl)-4,4′-bipyridinium; *N,N′*-dibenzyl-γ,γ′-dipyridylium. Normal potential at 30°: −0.359 volts.

Betaine viologen. *N,N′*-Dibetaine-γ,γ′-dipyridylium. Normal potential at 30°: −0.444 volts.

Dimethyl analog, *see* Paraquat

USE: As biological oxidation-reduction indicators.

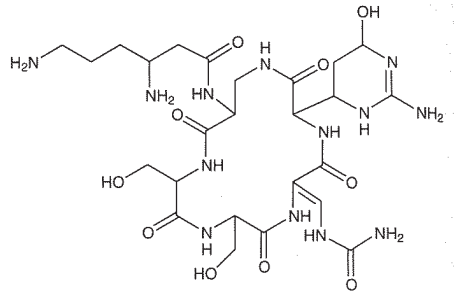
10061. Violuric Acid. [87-39-8] 2,4,5,6(1*H*,3*H*)-Pyrimidinetetrone 5-oxime; alloxan 5-oxime; 5-isonitrosobarbituric acid; 5-(hydroxyimino)barbituric acid. $C_4H_3N_3O_4$; mol wt 157.08. C 30.58%, H 1.92%, N 26.75%, O 40.74%. Known to exist as a mixture of keto-enol tautomers. Prepd from alloxan and hydroxylamine: Cresole, *Ber.* **16,** 1133 (1883); Guinchard, *Ber.* **32,** 1723 (1899).



Orthorhombic crystals, dec 240-241°. pK 4.7. Sparingly sol in water to a violet-colored soln; sol in alcohol. With $FeCl_3$ produces blue color.

USE: Analytical reagent for chromatographic separation of cations. Forms chelates: Leermakers, Hoffman, *J. Am. Chem. Soc.* **80,** 5663 (1958).

10062. Viomycin. [32988-50-4] Celiomycin; florimycin; tuberactinomycin B. $C_{25}H_{43}N_{13}O_{10}$; mol wt 685.69. C 43.79%, H 6.32%, N 26.56%, O 23.33%. Polypeptide antibiotic produced by various *Streptomyces* species including *S. puniceus, S. floridae, S. vinaceus.* Isoln: A. C. Finlay *et al., Am. Rev. Tuberc.* **63,** 1 (1951); Bartz *et al., ibid.* 4. Production: Marsh *et al.,* **US 2633445** (1953 to Ciba); Freaney, **US 2828245** (1958 to C.S.C.). Purification and chemical characterization: T. Kitagawa *et al., Chem. Pharm. Bull.* **20,** 2176 (1972). Proposed structure: Yoshioka *et al., Tetrahedron Letters* **1971,** 2043. Alternate structure: B. W. Bycroft *et al., ibid.* **1968,** 5901; *eidem, Experientia* **27,** 501 (1971); *eidem, J. Chem. Soc., Perkin Trans. I* **1972,** 820, 827. Confirmed structure: Noda *et al., J. Antibiot.* **25,** 427 (1972); T. Kitagawa *et al., Chem. Pharm. Bull.* **20,** 2215 (1972). X-ray crystallography: B. W. Bycroft, *Chem. Commun.* **1972,** 660. Biosynthesis: J. H. Carter II *et al., Biochemistry* **13,** 1221, 1227 (1974). Toxicological study: H. Keller *et al., Arzneimittel-Forsch.* **6,** 61 (1956). Enzyme immunoassay for determn in body fluids: T. Kitagawa *et al., Chem. Pharm. Bull.* **30,** 2487 (1982).



Sulfate. [37883-00-4] Viocin. Hygroscopic plates, mp 266° (dec). $[\alpha]_D^{18}$ −29.5° (c = 1 in H_2O). uv max (water or 0.1*N* HCl; 0.1*N* NaOH): 268 nm (log ε 4.4); 285 nm (log ε 4.2). LD_{50} in mice (mg/kg): 240 i.v. (Finlay); 1750 s.c. (Keller). Sol in water. Relatively insol in most organic solvents. Solns adjusted to pH 5-6 are quite stable. Soly data: Weiss *et al., Antibiot. & Chemother.* **7,** 374 (1957).

Pantothenate sulfate. [1401-79-2] Vionactan; Viothenat. $C_{25}H_{43}N_{13}O_{10}.C_9H_{17}NO_5.H_2SO_4$; mol wt 1003.01. Prepn: H. Keller, H. Mückter, **DE 1011800** (1957 to Grünenthal), *C.A.* **53,** 13519c (1959). Crystals, mp 242° (dec).

Hydrochloride. Hygroscopic plates, mp 270° (dec). $[\alpha]_D^{18}$ −16.6° (c = 1 in H_2O). uv max (water; 0.1*N* HCl; 0.1*N* NaOH): 268 nm (log ε 4.5); 268 nm (log ε 4.4); 285 nm (log ε 4.3).

THERAP CAT: Antibacterial (tuberculostatic).

10063. VIP. [37221-79-7] Vasoactive intestinal polypeptide; vasoactive intestinal peptide. Neuroactive polypeptide gastrointestinal hormone, related to glucagon and secretin, *q.q.v.* It exhibits a wide variety of biological activities, including relaxation of systemic and vascular smooth muscle and stimulation of the exocrine pancreas, of secretion of insulin and of cyclic-AMP formation in the small intestine. Initially isolated from porcine upper intestinal wall: S. I. Said, V. Mutt, *Science* **169,** 1217 (1970); *eidem, Eur. J. Biochem.* **28,** 199 (1972). Porcine VIP is a 28-residue peptide having an *N*-terminal seryl sequence: M. Bodanszky *et al., Proc. Nat. Acad. Sci. USA* **70,** 382 (1973); V. Mutt, S. I. Said, *Eur. J. Biochem.* **42,** 581 (1974). Synthesis: M. Bodanszky *et al., J. Am. Chem. Soc.* **96,** 4973 (1974); *see also* S. I. Said *et al.,* **US 3862927** (1975). Solid-phase synthesis: D. H. Coy, J. Gardner, *Int. J. Peptide Protein Res.* **15,** 73 (1980); R. Colombo, *Experientia* **38,** 773 (1982). Isoln of chicken VIP: A. Nilsson, *FEBS Letters* **47,** 284 (1974). Amino acid sequence: *idem, ibid.* **60,** 322 (1975). Synthesis of C-terminal fragment: M. Bodanszky *et al., Bioorg. Chem.* **5,** 339 (1976). Solid-phase synthesis: R. Colombo, *Int. J. Peptide Protein Res.* **19,** 71 (1982). Multiple immunoreactive forms of VIP have also been found in human colonic mucosa: R. Dimaline, G. J. Dockray, *Gastroenterology* **75,** 387 (1978). The

NOVARTIS EXHIBIT 1549
Novartis v. Regents, IPR2023-01347
Page 65 of 65