L

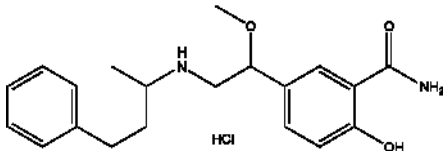
LABETALOL HYDROCHLORIDE

Therapeutic Function: Alpha-adrenergic blocker, Beta-adrenergic blocker

Chemical Name: 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino]ethyl]benzamide hydrochloride

Common Name: Ibidomide

Structural Formula:



Chemical Abstracts Registry No.: 36894-69-6; 32780-64-6 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Trandate	Allen and Hanburys	UK	1977
Trandate	Glaxo	W. Germany	1977
Labetalol	Duncan	Italy	1978
Trandate	Glaxo	Switz.	1979
Trandate	Glaxo	France	1980
Trandate	Glaxo	Japan	1983
Abetol	C.T.	Italy	-
Labelol	Elea	Argentina	-
Lamitol	Pliva	Yugoslavia	-
Lolum	Farmochimica	Italy	-
Mitalolo	Ellem	Italy	-
Normodyne	Schering	US	-
Presdate	Alfa Farm.	Italy	-

Raw Materials

5-Bromoacetylsalicylamide
N-Benzyl-N-(1-methyl-3-phenylpropyl)amine
Hydrogen

Manufacturing Process

(a) 5-Bromoacetylsalicylamide (2.6 g), N-benzyl-N-(1-methyl-3-phenylpropyl) amine (4.8 g) and methyl ethyl ketone (50 ml) were heated at reflux for 40 minutes. The solvent was removed and the residue was treated with benzene. The secondary amine hydrobromide was filtered off and discarded, and the filtrate was evaporated to dryness. The residue was treated with an excess of ethanolic hydrogen chloride when 5-[N-benzyl-N-(1-methyl-3-phenylpropyl)-glycyl]-salicylamide hydrochloride (1.15 g) crystallized out, MP 139°C to 141°C.

(b) 5-[N-benzyl-N-(1-methyl-3-phenylpropyl)glycyl]-salicylamide hydrochloride (0.75 g), 10% mixture of PdO and PtO on carbon catalyst (0.1 g) and ethanol (20 ml) were shaken at room temperature and pressure with hydrogen until uptake ceased. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was crystallized from ethanol to give 5-[1-hydroxy-2-(1-methyl-3-phenylpropyl)aminoethyl]salicylamide hydrochloride as a white solid (0.40 g), MP 188°C.

References

Merck Index 5166
DFU 1 (3) 125 (1976)
Kleeman and Engel p. 513
PDRpp.913, 1638
OCDS Vol. 3 p. 24 (1984) and 18 (8) 378 (1982)
DOT 13 (11) 493 (1977)
I.N. p. 547
REMp. 904
Lunts, L.H.C. and Collin, D.T.; US Patent 4,012,444; March 15, 1977; assigned to Allen and Hanburys Ltd. (UK)

LACTULOSE

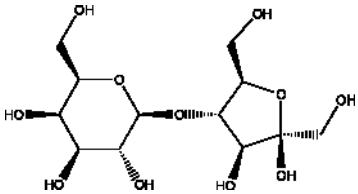
Therapeutic Function: Laxative

Chemical Name: 4-O-β-D-Galactopyranosyl-D-fructose

Common Name: -

Chemical Abstracts Registry No.: 4618-18-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Duphalac	Philips-Duphar	UK	1969
Bifiteral	Philips-Duphar	W. Germany	1971
Duphalac	Duphar	France	1972
Duphalac	Duphar	Italy	1973
Gatinar	Duphar	UK	1973
Lactulose	Nikken	Japan	1973
Cephulac	Merrell Dow	US	1976
Duphalac	Philips Roxane	US	1977
Chronulac	Merrell Dow	US	1979
Dia-Colon	Piam	Italy	-
Epalfen	Zambon	Italy	-
Laevilac	Wander	W. Germany	-
Laevolac	Laevosan	Austria	-
Monilac	Chugai	Japan	-

Raw Materials

Lactose
Sodium aluminate

Manufacturing Process

105 g of lactose monohydrate were dissolved in 500 ml of water. 48 g of $NaAlO_2$ was dissolved in 100 ml of water and was then added to the lactose solution. The mixture was then diluted to one liter to provide a pH of 11.5. The reactant concentrations of 48 g of sodium aluminate and 105 g of lactose are equivalent to a mol ratio of two mols of aluminate to one mol of lactose. The mixture was then heated to 50°C and 100 ml aliquots were removed at periodic intervals to determine the level of conversion. The reaction was terminated after three hours by adding sufficient 30% HCl to lower the pH to 4.2. The pH was then raised to neutrality, i.e., 6.5 to 7.0, with ammonium hydroxide so as to completely precipitate insoluble aluminum hydroxide. The precipitate was then removed by vacuum filtration and the filtrate was analyzed for the presence of ketose sugar by chromatographic analysis. The chromatographic analysis of the filtrate confirmed that the main component of the filtrate was lactulose and not the monosaccharide ketose sugar, fructose.

References

Merck Index 5184
Kleeman and Engel p. 513
PDR p. 1224
I.N. p. 548
REM p. 814
Guth, J.H. and Tumerman, L.; US Patent 3,546,206; December 8, 1970; assigned to Kraftco Corp.

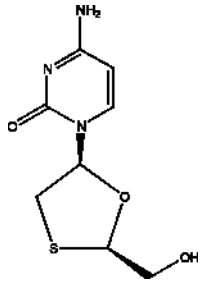
LAMIVUDINE

Therapeutic Function: Antiviral

Chemical Name: 2(1H)-Pyrimidinone, 4-amino-1-((2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-

Common Name: Lamivudine

Structural Formula:



Chemical Abstracts Registry No.: 134678-17-4

Trade Name	Manufacturer	Country	Year Introduced
Epivir (3TC)	GlaxoSmithKline	USA	-
Hepitec	Glaxo Smithkline	-	-
Heptovir	GlaxoSmithKline	Canada	-
Ladiwin	Cadila Healthcare	India	-
Ladiwin	Zydus Biogen	India	-
Lamda	Le Sante	India	-
Lamidac	Zydus Alidac	India	-
Lamivir	Cipla Limited	India	-
Lamivir-Hbv	Cipla Limited	India	-
Lamivudine	GlaxoSmithKline	USA	-
Zeffix	Glaxo Wellcome	UK	-

Raw Materials

Thiobenzoic acid
Potassium t-butoxide
1-Benzoyl glycerol
Cytosine
Trimethylsilyl chloride
4-Toluenesulfonic acid
Bromoacetaldehyde diethyl acetal
Sodium periodate
Hexamethyldisilazane

Manufacturing Process

To a solution of potassium t-butoxide (0.11 mol) in 100 ml DMF was added thiobenzoic acid (0.11 mol) and the solution partially evaporated in vacuo, benzene added in two consecutive portions and evaporated in vacuo each time. To the residual DMF solution was added bromoacetaldehyde diethyl acetal (0.1 mol) and the mixture stirred at 120°C for 15 h. After cooling, it was poured onto water (500 ml), the product extracted with ether, the extract washed with aqueous $NaHCO_3$ followed by water, then dried and the solvent removed in vacuo. The residue was distilled in vacuo to give 17.2 g of pure 2-thiobenzoyl acetaldehyde diethyl acetal, boiling point 131-133°C/0.07 mm.

The 2-thiobenzoyl acetaldehyde diethyl acetal (17.2 g) was dissolved in 100 ml THF followed by the addition of 6 g NaOH in 20 ml H_2O. The mixture was refluxed under N_2 for 15 h, then cooled and diluted with water (200 ml) and the product extracted with ether (3 x 200 ml). The extract was dried, the solvent removed in vacuo and the residue distilled to yield 7.1 g of mercaptoacetaldehyde diethylacetal.

50 g of the 1-benzoyl glycerol in a mixture of 500 ml of CH_2Cl_2 and 25 ml of H_2O was treated portionwise with 80 g of NaIO4 under vigorous stirring at room temperature. After addition, stirring was continued for 2 h after which time 100 g of $MgSO_4$ was added and stirring continued for 30 min. The mixture was filtered, the filtrate evaporated in vacuo and the residue distilled to yield 26 g of pure benzoyloxyacetaldehyde, boiling point 92-94°C/0.25 mm.

2-Benzoyloxymethyl-5-ethoxy-1,3-oxathiolane:

The mercaptoacetaldehyde diethylacetal (7 g) was mixed in 100 ml of toluene with 7 g of the above benzoyloxyacetaldehyde, a few crystals of p-toluenesulfonic acid added and the mixture place in an oil-bath at 120°C under N_2. The formed ethanol was allowed to distill over, the mixture kept at 120°C for 30 min longer than cooled and washed with aqueous $NaHCO_3$, dried and evaporated in vacuo. The residue was distilled in vacuo to yield 9.8 g of 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane as a mixture of cis- and trans-isomers, boiling point 140-143°C/0.1 mm.

Cis- and trans-2-benzoyloxymethyl-5-cytosin-1'-yl-1,3-oxathiolane:

A mixture of 2.7 g of cytosine, 30 ml of hexamethyldisilazane (HMDS) and 0.3 ml of trimethylsilyl chloride (TMSCl) was heated under reflux under dry N_2 untila clear solution resulted (3 L) and the excess reagents evaporated in vacuo. The remaining volatiles were removed under high vacuum, the solid residue taken up in 250 ml of dichlorethane and 5 g of the 2-

benzoyloxymethyl-5-ethoxy-1,3-oxathiolane in 50 ml of dichloroethane added under dry argon followed by 4.7 ml of trimethylsilyl triflate. After 3 days of heating under reflux under argon, it was cooled and poured onto 300 ml of saturated aqueous $NaHCO_3$. The organic layer was collected, the aqueous phase extracted with $CH_2Cl_2$and the combined extracts washed with water, dried and evaporated in vacuo. The residue was purified by chromatography on silica gel using CH_2Cl_2-CH_3OH 9:1 as the eluant to give 2.5 g of a pure mixture of cis- and trans-2-benzoyloxymethyl-5-cytosin-1'-yl-1,3-oxathiolane in a 1:1 ratio. These were separated as the N-acetyl derivatives.

The preceding mixture of cis- and trans-2-benzoyloxymethyl-5-cytosin-1'-yl-1,3-oxathiolane (2.5 g) in 100 ml of dry pyridine containing 0.1 g of 4-dimethylaminopyridine (DMAP) was treated with acetic anhydride (7 ml) at room temperature and after 16 h, the mixture was poured onto cold water followed by extraction with CH_2Cl_2. The extract was washed with water, dried, and evaporated in vacuo. Toluene was added to the residue, then evaporated in vacuo and the residual oil purified by chromatography on silica gel using EtOAc-CH_3OH 99:1 as the eluant to yield 1.35 g of pure trans-2-benzoyloxymethyl-5-(N^4-acetyl-cytosin-1'-yl)-1,3-oxathiolaneas the fast moving product and 1.20 g of pure cis-2-benzoyloxymethyl-5-cytosin-1'-yl-1,3-oxathiolan as the slow moving component, melting point 158-160°C.

Cis- and trans-isomers of 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane was obtained by action of methanolic ammonia at 24°C.

References

Delleau B., Nguyen-Ba N.; US Patent No. 5,047,407; 09.10.1991; Assigned to IAF BioChem International, Inc.

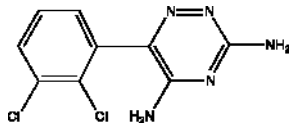
LAMOTRIGINE

Therapeutic Function: Anticonvulsant

Chemical Name: 1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-

Common Name: Lamotrigine

Structural Formula:



Chemical Abstracts Registry No.: 84057-84-1

Trade Name	Manufacturer	Country	Year Introduced
Lamepil	Innova (IPCA)	India	-
Lametec	Protech Biosystems	India	-
Lamictal	Glaxo Wellcome	-	-
Lamidus-Dt	Zydus Neurosciences	India	-
Lamitor	Torrent	India	-
Lamitor-Dt	Torrent Pharmaceuticals Ltd.	India	-
Lamotrigine	GlaxoSmithKline	-	-
Lysin	Pfizer	-	-
Vero-Lamotrigine	Okasa Pharma	Japan	-

Raw Materials

2,3-Dichlorophenylglyoxylamide
Aminoguanidine hydrochloride
Concentrated hydrochloric acid
Ethanol

Manufacturing Process

A mixture of 2,3-dichlorophenylglyoxylamide (54.5 g, 0.25 mol), aminoguanidine hydrochloride (33.15 g, 0.30 mol), ethanol (1 liter) and concentrated hydrochloric acid (4 ml) were heated under reflux for 6 hours at pH 1.5. The resulting solution was evaporated to dryness, the solid was dissolved in water (2 L; resulting pH 2.5) and the solution was basified to pH 13 by the addition of 50% aqueous sodium hydroxide (45 ml) at <15°C. The mixture was filtered, the solid washed with 0.88 N ammonia solution and dried to give (E)-2-(2',3'-dichlorophenyl)-2-(guanidinylimino)acetamide (59.5 g, 87%) m.p. 231-233°C. Recrystallisation of this product (2.2 g) from n-propanol (60 ml) afforded pure material (1.83 g, 83%), m.p. 238-239°C (decomp.).

(E)-2-(2',3'-dichlorophenyl)-2-(guanidinylimino)acetamide (0.3 g) was dissolved in ethanol (10 ml) and was irradiated by exposure to sunlight. After 5 days 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (Lamotrigine) was detected by TLC in the liquor material. Melting point of lamotrigine 218°C.

References

Winter R.G., Sawler D.A., Germain A.; US Patent No. 5,912,345; 06.15.1999; Assigned to Glaxo Wellcome Inc. (Research Triangle Park, NC)
Winter R.G. et al.; US Patent No. 5,047,407; June 15, 1999; Assigned to Glaxo Wellcome Inc. (Research Triangle Park, NC)

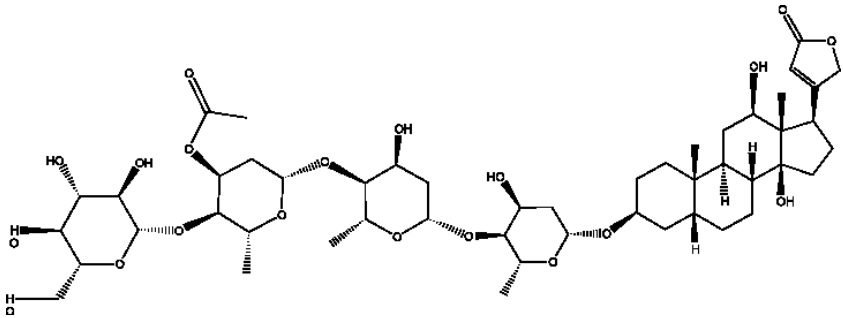
LANATOSIDE C

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((O-beta-D-glucopyranosyl-(1-4)-O-3-O-acetyl-2,6-dideoxy-beta-D-ribo-hexopyranosyl-(1-4)-O-2,6-dideoxy-beta-D-ribo-hexopyranosyl-(1-4)-2,6-dideoxy-beta-D-ribo-hexopyranosyl) oxy)-12,14-dihydroxy-, (3beta,5beta,12beta)-

Common Name: Celanidum; Glycoside C from Digitalis lanata; Lanatoside C

Structural Formula:



Chemical Abstracts Registry No.: 17575-22-3

Trade Name	Manufacturer	Country	Year Introduced
Lanatozid C	Biofarm	-	-
Cedigalan	Zdravle	-	-

Raw Materials

Dry leaves of digitalis lanata
Lead hydroxide
Tannin

Manufacturing Process

2000 parts of dry leaves of digitalis lanata are finely ground with 500 parts of sodium chloride, they are then wetted with 1000 parts of water and extracted with 30,000 parts of chloroform. The filtered extract is completely evaporated in vacuum at a low temperature and to the remaining residue are added 1000 parts of dry ether and the whole mixture is left under the ether until the thick viscous mass has been transformed into a hard body. The ether is then poured away and the residue is digested with 1000 parts of ether for about 2 hours under a reflux condenser. After cooling down the mixture, it is filtered, and the residue obtained, which is now in form of a brittle mass, which is then dried in vacuum in order to completely eliminate the remaining ether present, and pulverized. The pulverized mass is advantageously subjected once more to the treatment with ether. The yellow greenish powder thus obtained is then dissolved in 1000 parts of methyl alcohol and to the solution, so obtained a fine suspension of 30 parts lead hydroxide in 1000 parts water is added with stirring. The solution obtained is neutralized, stirred for about 2 hours, and

filtered, and the clear yellowish filtrate is preferably treated again with a small quantity of tannin precipitating substance. The clear filtrate thus obtained is concentrated in vacuum at a low temperature to about 200 parts, whereby the difficultly soluble portion of the glucoside mixture precipitates. The solution is then filtered. The precipitate is dissolved in a small quantity of methyl alcohol and is treated with a small quantity of water whereby the new product begins to precipitate in a crystalline form. By repeated crystallization from methyl alcohol, without addition of water, the glucoside may be obtained in the form of a perfectly pure compound; it does not change its properties even on further recrystallization. The glucoside, freshly crystallized from methyl alcohol and dried in vacuo, had MP: 248°C with decomposition, when heated rapidly. At 230°-235°C, the substance begins to sinter and becomes quite soft; the melting point, therefore, is not well defined.

References

GB Patent No. 357,926; March 1, 1930; Chemiche Fabrik Sandoz of Basle, Switzerland
Wander A. AG., Bern (Schweiz); S.P. No. 245219; Oct. 31, 1946

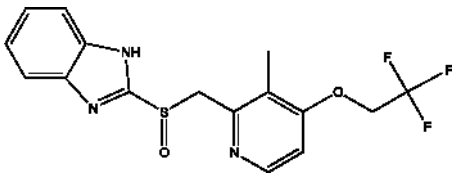
LANSOPRAZOLE

Therapeutic Function: Antiulcer

Chemical Name: 1H-Benzimidazole, 2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-

Common Name: Lansoprazole

Structural Formula:



Chemical Abstracts Registry No.: 103577-45-3

Trade Name	Manufacturer	Country	Year Introduced
Acilanz	Themis Pharmaceuticals Ltd.	India	-
Lams OD	Recon Healthcare Ltd.	India	-
Lancid	Brown and Burk Pharmaceuticals Ltd.	India	-
Lansoptol	Krka	Slovenia	-
Lansoprazole	Chemo Iberica	Spain	-
Lansoprazole	Wyeth Pharmaceuticals	-	-
Lanzap	Dr. Reddy's Laboratories Ltd.	India	-

Raw Materials

Diethyl azodicarboxylate
Triphenylphosphine
Sodium hypochlorite
2-Hydroxymethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine
2-Mercaptobenzimidazole
Tetramethyl-1-piperidinyloxy free radical
Tetrabutylammonium chloride

Manufacturing Process

Preparation of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylthio-1H-benzimidazole:

A mixture of 6.63 g of 2-hydroxymethyl-3-methyl-4-(2,2,2-trifluoroethoxy) pyridine (30 mmol), 4.5 g of 2-mercaptobenzimidazol (30 mmol) and 8.67 g of triphenylphosphine (33 mmol) was dissolved in 100 ml of tetrahydrofuran, 5.75 g of diethyl azodicarboxylate (33 mmol) dissolved in 30 ml of tetrahydrofuran was added dropwise thereto at room temperature, and stirred for 1 hour. The reaction mixture was concentrated under a reduced pressure, the resulting residue was combined with 100 ml of ethylacetate, and extracted twice with 50 ml portions of 1 N HCl. The aqueous layer was then washed with 50 ml of diethylether; neutralized with 1 N NaOH to adjust the pH to 7. The resulting precipitates were filtrated, washed with water, and dried, to obtain 10.06 g of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylthio-1H-benzimidazole as a white solid (yield: 95%), m.p.142-144°C.

4.46 g of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylthio-1H-benzimidazole (12 mmol) and 18.74 mg of tetramethyl-1-piperidinyloxy free radical (1 mol %, used as a catalyst) were dissolved in 40 ml of tetrahydrofuran, and combined with 166.76 mg of tetrabutylammonium chloride (5 mol %) dissolved in 20 ml of distilled water. The resulting mixture was cooled to 0°C and 13.6 ml of NaOCl (12%, 2.2 equivalent) dissolved in 20 ml of distilled water was added thereto over 2 hours at 0°C, stirred for 10 min, and then for additional 10 min at 20°C. Then, the reaction mixture was extracted with 40 ml of ethylacetate and the organic layer was washed with sat. $NaHCO_3$ (30 ml) and then with sat. brine (30 ml), dried over anhydrous $MgSO_4$, and the solvent was removed therefrom. The resulting crude product as recrystallized from acetone/hexane, to obtain 3.99 g of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulphinyl-1H-benzimidazol (lansoprazole) as a white-light brown solid (yield: 90%), melting point 164-165°C (decomposition).

References

Moon Y.-H. et al.; US Patent No. 6,423,846; 07.23.2002; Assigned to Hanmi Pharm. Co., Ltd. (KR)

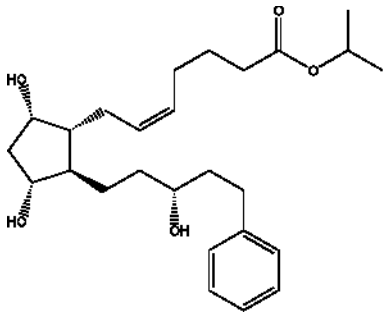
LATANOPROST

Therapeutic Function: Antiglaucoma

Chemical Name: 5-Heptenoic acid, 7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((3R)-3-hydroxy-5-phenylpentyl)cyclopentyl)-, 1-methylethyl ester, (5Z)-

Common Name: Latanoprost

Structural Formula:



Chemical Abstracts Registry No.: 130209-82-4

Trade Name	Manufacturer	Country	Year Introduced
Latanoprost	Pharmacia and Upjohn	USA	-
Latanoprost	Milmet Pharma Ltd.	India	-
Xalatan	Pharmacia and Upjohn	USA	-
Xalatan	Pharmacia India (P) Ltd.	India	-

Raw Materials

Lithium chloride
Triethylamine
2-Iodopropane
Cesium carbonate
Platinum on carbon
Chlorodiisopinocampheylborane, (-)-
Potassium hydroxide
tris(Hydroxymethyl)aminomethane
Dimethyl-(2-oxo-4-phenylbutyl)phosphonate
(1S,5R,6R,7R)-6-Formyl-7-(benzyloxy)-2-oxabicyclo[3.3.0]octan-3-one

Manufacturing Process

Lithium chloride (2.6 g) is dissolved in THF (170 mL). Dimethyl-(2-oxo-4-phenylbutyl)phosphonate (7.87 g) and triethylamine (4.3 mL) are added. The mixture is stirred and cooled to -10°C. A solution of the Corey aldehyde benzoate, (1S,5R,6R,7R)-6-formyl-7-(benzyloxy)-2-oxabicyclo[3.3.0]octan-3-one (8.42 g) in THF (75 mL) is added to the reaction mixture over three hours. The resulting mixture is stirred for 18 hours at -10°C. At the end of this time, methyl t-butyl ether (MTBE) (100 mL) is added and the mixture warmed to 0-20°C. Sodium bisulfite (38%, 100 mL) is added and the two-phase mixture was stirred for 10 min. The phases are separated and the organic phase is washed with saturated aqueous sodium bicarbonate solution (100 mL). The organic phase is separated and concentrated under reduced pressure to a volume of <100 mL. Ethyl acetate (200 mL) is added and the

mixture is concentrated to a volume of 50 mL. MTBE (100 mL) is added and the mixture is allowed to cool to 20-25°C for 1 hour. The mixture is then cooled to -20°C for 2 hours. The solids were filtered, washed with MTBE and dried on a nitrogen to give [3aR-[3aα,4α(E),5β,6aα]]-5-(benzoyloxy) hexahydro-4-(3-oxo-5-phenyl-1-pentenyl)-2H-cyclopenta[b]furan-2-one, m.p. 117-118°C.

[3aR-[3aα,4α(E),5β,6aα]]-5-(Benzoyloxy)hexahydro-4-(3-oxo-5-phenyl-1-pentenyl)-2H-cyclopenta[b]furan-2-one(10.0 g, 0.0247 mole) in THF (100 mL) is cooled to -38 to -42°C and is added a solution of (-)-chlorodiisopinocampheylborane (2 M in hexane; 43 mL) is added at <-35°C. When the addition is complete, the mixture is stirred at -38 to -42°C for 18 hours. At this time acetone (12.7 mL) is added and the mixture is allowed to warm to 20-25°C and stirred for two hours. MTBE (100 mL) is added and then a solution of sodium bicarbonate (10 g) in water (150 mL) is added. The two phase mixture is stirred for 15 min. The phases are separated and the organic phase is washed with water (100 mL) and concentrated in vacuum. MTBE (300 mL) is added and the mixture then concentrated. Acetonitrile (100 mL) is added and the mixture is again concentrated. Acetonitrile (150 mL) and heptane (100 mL) are added. The two-phase mixture is stirred for 5 min and then allowed to settle. The phases are separated. The acetonitrile phase is extracted with heptane. The acetonitrile phase is concentrated. A portion of the concentrate is purified by chromatography (silica gel, heptane/ethyl acetate, 1/1) to give [3aR-[3aα,4a(1E,3S),5β,6aα]]-5-(benzoyloxy)hexahydro-4-(3 -hydroxy-5-phenyl-1-pentenyl)-2H-cyclopenta[b]furan-2-one, m.p. 78-81°C.

[3aR-[3aα,4a(1E,3S),5β,6aα]]-5-(Benzoyloxy)hexahydro-4-(3-hydroxy-5-phenyl-1-pentenyl)-2H-cyclopenta[b]furan-2-oneis dissolved in THF (125 mL). Platinum on carbon catalyst (5%, 1 g) and triethylamine (3.4 mL) are added. The mixture is purged with nitrogen and then and the mixture is stirred vigorously under 5 psi hydrogen at 20°C. When the reaction was complete as measured by HPLC, the reaction is purged with nitrogen. The mixture is filtered over celite. The filtrate is concentrated under reduced pressure to give the crude product. A portion of the product is purified by chromatography (silica gel, heptane/ethyl acetate, 1/1) to give [3aR-[3aα,4a(1E,3S),5β,6aα]]-5-(benzoyloxy)hexahydro-4-(3-hydroxy-5-phenyl-1-pentyl)-2H-cyclopenta[b]furan-2-one, m.p. 68-70°C.

A mixture of potassium hydroxide in methanol (300 ml) and water (5 mL) is added to [3aR-[3aα,4a(1E,3S),5β,6aα]]-5-(benzoyloxy)hexahydro-4-(3 -hydroxy-5-phenyl-1-pentyl)-2H-cyclopenta[b]furan-2-one. The mixture is stirred and heated in an 80°C for 2 hours. When the reaction is complete, the mixture is concentrated under reduced pressure. Water (100 mL) and MTBE (100 mL) are added and the mixture stirred at 20-25°C for 15 min. The phases are allowed to separate. The product is in the aqueous phase and the organic phase is removed. The pH of the aqueous phase is adjusted to 1 to 1.5 by the addition of hydrochloric acid (3 N, about 60 mL are required). The solution is stirred at 20-25°C. After 30 min, MTBE (100 mL) is added and the mixture stirred for 12 hours. The phases are separated and the aqueous phase extracted once with MTBE (50 mL). The MTBE phases are combined and washed with sodium carbonate (1 N, 50 mL). The MTBE mixture is stirred with a solution of potassium hydroxide (2.8 g, 42.5 mmole) in water (100 mL) for 30 min. The phases are separated and the aqueous phase is added to a slurry

of citric acid monohydrate (8.90 g) and ethyl acetate (100 mL). The mixture is stirred for 15 min and the phases are separated. The aqueous phase is extracted with ethyl acetate. The combined organic phases are dried over anhydrous sodium sulfate (8.90 g) for 15 min. The ethyl acetate extract is concentrated under reduced pressure to a volume of 100 mL. Ethyl acetate (200 mL) is added and the mixture is again concentrated to a volume of 100 mL. The resulting slurry is stirred at 0-5°C for 30 min. The solids are filtered and washed with heptane/ethyl acetate (1/1, 35 mL), then dried on a nitrogen to give 2-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]acetic acid.

2-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl] cyclopentyl]aceticacid (4.80 g) and toluene (100 mL) are stirred and the slurry heated to reflux for 30 min. Then the toluene is slowly distilled at atmospheric pressure to remove water. After about 1 hour of distillation, all acid is dissolved. The solution is then distilled to a volume of about 50 mL. The mixture is then cooled to about 80°C and ethyl acetate (25 mL) is added. The mixture is then cooled to 30C and heptane (20 mL) is added. The mixture is seeded with a small amount of [3aR-[3aα,4α(R),5β,6aα]]-hexahydro-5-hydroxy-4-(3-hydroxy-5-phenylpentyl)-2H-cyclopenta[b]furan-2-one. The mixture is stirred at about 30°C for 10 min, during which time crystallization occurred. Heptane (30 mL) is added over 15 min. The slurry is cooled to 20-25°C and stirred for 1 hour. The product is filtered and dried under nitrogen to give [3aR-[3aα,4α(R),5β,6aα]]-hexahydro-5-hydroxy-4-(3-hydroxy-5-phenylpentyl)-2H-cyclopenta[b]furan-2-one, m.p. 69-71°C.

[3aR-[3aα,4α(R),5β,6aα]]-Hexahydro-5-hydroxy-4-(3-hydroxy-5-phenylpentyl)-2H-cyclopenta[b]furan-2-one(1.0 g, 3.3 mmoles) is dissolved in methylene chloride (3 mL) and the mixture is placed in a sealable pressure tube. Add 1.0 mL of a mixture of trichloracetic acid (0.27 g) in methylene chloride (10 mL) followed by ethyl vinyl ether (6.3 mL). The pressure tube is closed and heated to 45°C for about 8 hours. At this time, triethylamine (0.12 mL) is added and the mixture is stirred for 10 min. The mixture is then concentrated under reduced pressure to give [3aR-[3aα,4α(R),5β,6aα]]-hexahydro-5-hydroxy-4-(3-hydroxy-5-phenylpentyl)-2H-cyclopenta[b]furan-2-one.

[3aR-[3aα,4α(R),5β,6aα]]-Hexahydro-5-hydroxy-4-(3-hydroxy-5-phenylpentyl)-2H-cyclopenta[b]furan-2-oneis dissolved in THF (14 mL) and the mixture cooled to -40°C. Using a syringe pump, diisobutyl aluminum hydride DIBAL (1.0 M, 3.78 mL in toluene) is added over 15 min. The mixture is stirred for 15 min after the completion of the addition, then ethyl acetate (0.38 mL) is added. The mixture is poured into a solution of potassium sodium tartarate (10 g in 30 mL of water) and warmed to 20-25°C. The two phase mixture is heated to 45°C for 1 hour and then cooled. The phases are separated and the organic phase is concentrated to give (3aR,4R,5R,6aS)-5-(1-ethoxyethoxy)-4-[(3R)-3-(1-ethoxyethoxy)-5-phenylpentyl]hexahydro-2H-cyclopenta[b]furan-2-ol.

(3aR,4R,5R,6aS)-5-(1-Ethoxyethoxy)-4-[(3R)-3-(1-ethoxyethoxy)-5-phenylpentyl]hexahydro-2H-cyclopenta[b]furan-2-olis dissolved in dry THF (10 mL) and added to a mixture containing potassium 5-(triphenylphosphoranylidene)pentaonate (prepared from 4-carboxybutyltriphenylphosphonium bromide and potassium t-butoxide solution

in THF at 0°C, the resulting solution is then cooled to -10°C) at -10 to -5°C. The resulting mixture is stirred for about 3 hours at -5°C. Water (30 mL; 0°C) is added over 10 min, then ethyl acetate (20 mL) and aqueous tris (hydroxymethyl)aminomethane solution (10 mL) is added. The phases are separated and the organic phase is washed with aqueous tris(hydroxymethyl) aminomethane solution. The aqueous phases are combined and washed once with ethyl acetate, MTBE is added to the combined aqueous phases. The mixture is acidified to pH 3 with aqueous phosphoric acid (40%). The organic phase is separated and concentrated under reduced pressure to 20 mL. Solids (5-diphenylphosphinopentanoic acid) crystallized. MTBE (50 mL) is added and the slurry concentrated under reduced pressure to a volume of 20 mL. The solid is filtered and washed with MTBE (100 mL). The filtrate is concentrated under reduced pressure to give 7-[(1R,2R,3R,5S)-3-(1-ethoxyethoxy)-5-hydroxy-2-[(3R)-3-(1-ethoxyethoxy)-5- phenylpentyl]cyclopentyl-5-heptenoic acid.

7-[(1R,2R,3R,5S)-3-(1-Ethoxyethoxy)-5-hydroxy-2-[(3R)-3-(1-ethoxyethoxy)-5-phenylpentyl]cyclopentyl-5-heptenoic acid is dissolved in THF (30 mL). Water (15 mL) and phosphoric acid (85 wt %; 0.67 mL) are added and the mixture is heated to reflux for about 2 hours. The mixture is cooled and MTBE (30 mL) is added. The phases are separated. The organic phase is washed once with saline (100 mL). The organic phase is concentrated under reduced pressure. MTBE (3 times 50 mL) is added and concentrated under reduced pressure to give (5Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoic acid (Latanoprost Acid).

Latanoprost acid is dissolved in DMF (10 mL) and added to a slurry of cesium carbonate (1.6 g) in DMF (10 mL). 2-Iodopropane (0.49 mL) is added and the slurry is heated to 45°C for about 6 hours. When the reaction is complete, MTBE (40 mL) and water (50 mL) are added and the mixture is stirred for 15 min. The phases are separated and the aqueous phase is washed with MTBE (20 mL). The organic phases are combined and concentrated. The concentrate is chromatographed (silica gel) eluting with MTBE. The appropriate fractions are pooled and concentrated to give (5Z)-(9CI)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoic acid 1-methylethyl ester (Latanoprost).

References

Henegar K.E.; US Patent No. 6,689,901; Feb. 10, 2004; Assigned to Pharmacia and Upjohn Company (Kalamazoo, MI)

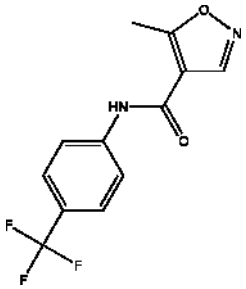
LEFLUNOMIDE

Therapeutic Function: Immunosuppressive, Antiarthritic

Chemical Name: 4-Isoxazolecarboxamide, 5-methyl-N-(4-(trifluoromethyl) phenyl)

Common Name: Leflunomide

Structural Formula:



Chemical Abstracts Registry No.: 75706-12-6

Trade Name	Manufacturer	Country	Year Introduced
Arava	Aventis Pharma Deutschland	Germany	-
Arava	Aventis Pharmaceuticals	USA	-
Arava	Hoechst Marion Roussel	Germany	-
Leflunomide	Torrent	-	-

Raw Materials

Diketene
Acetic anhydride
Sodium hydroxide
5-Methylisoxazole-4-carboxylic acid chloride
Orthoformic acid triethyl ester
Hydroxylamine hydrochloride
4-Trifluoromethylaniline
Trifluoromethylaniline

Manufacturing Process

In US Patent No. 4,284,786 is described two methods of preparation of 5-methylisoxazole-4-carboxylic-(4-trifluoromethyl)-anilide.

The method 1

A mixture of 0.55 mole of diketene (46.3 g) and 30 ml of acetonitrile is added dropwise, at 75°C, to a solution of 0.5 mole of 4-trifluoromethylaniline (30.6 g) in 150 ml of acetonitrile. The mixture is heated to boiling under reflux for 2.5 hours. When it has cooled to room temperature, the crystals which are precipitated are filtered off, washed with cold ethanol and dried. This gives 79.1 g (64.5% of theory) of crystalline acetoacetic acid-4-trifluoromethylanilide, melting point (after recrystallization from ethanol) 155°C.

The acetonitrile phase is evaporated to dryness under reduced pressure. The crystalline residue (42.1 g) is recrystallized from 80 ml of ethanol. This gives a further 24.1 g (19.7% of theory) of crystals. Melting point (after recrystallization from ethanol) 155°C. Total yield: 84.2% of theory.

0.75 mole of acetoacetic acid 4-trifluoromethylanilide (183.9 g) is boiled under reflux for 1.5 hours with 0.83 mole of orthoformic acid triethyl ester (123 g) and 2.25 mole of acetic anhydride (229.7 g). After the mixture has cooled to room temperature, the crystals which have precipitated are filtered off and washed first with a small amount of acetic anhydride and then with petroleum ether. This gives 116.1 g (51.4% of theory) of crystalline 2-ethoxymethyleneacetoacetic acid 4-trifluoromethylanilide, melting point (after recrystallization from toluene) 124-125°C.

The combined filtrates are concentrated under reduced pressure. The crystals of the crystal paste which thereupon remains are filtered off, washed first with a small amount of acetic anhydride and then with petroleum ether and dried. A further 56.1 g (24.8% of theory) of crystals are thus obtained. Melting point (after recrystallization from toluene) 124-125°C. Total yield: 76.2% of theory.

A solution 0.1 mole of 2-ethoxymethyleneacetoacetic acid 4-trifluoromethylanilide (30.1 g) in 60 ml of ethanol is added dropwise at 5-10°C to the mixture of 0.11 mole of hydroxylamine hydrochloride (7.65 g) in 50 ml of water and 0.11 mole of sodium hydroxide (4.4 g) in 10 ml of water. The mixture is heated under reflux for 15 min. The crystals which are precipitated after cooling are filtered off, washed with water and dried. 19.6 g (72.6% of theory) of crystalline 5-methylisoxazole-4-carboxylic acid 4-trifluoromethyl-anilide are thus obtained, melting point (after recrystallization from toluene) 166.5°C.

The method 2

0.1 mole of 5-methylisoxazole-4-carboxylic acid chloride (14.6 g) and 20 ml of a 5 N potassium hydroxide solution are added dropwise to 0.1 mole of trifluoromethylaniline (16.1 g), suspended in 150 ml of water, in such a way that the pH of the reaction mixture does not rise above 5. The mixture is subsequently shaken with 150 ml of methylene chloride. The methylene chloride phase is washed with water and, after drying with sodium sulfate is, evaporated to dryness under reduced pressure. This gives 24.4 g (90.2% of theory) of a crystalline 5-methylisoxazole-4-carboxylic acid 4-trifluoromethyl-anilide, melting point (after recrystallization from toluene) 166.5°C.

References

Kammerer, F.-J., Schleyerbach R.; US Patent No. 4,284,786; August 18, 1981; Assigned: Hoechst Aktiengesellschaft (Frankfurt am Main, DE)

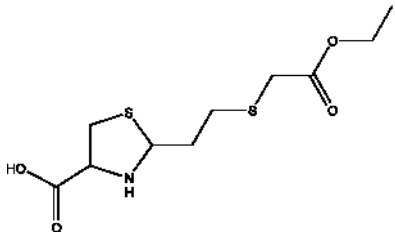
LETOSTEINE

Therapeutic Function: Mucolytic

Chemical Name: 4-Carboxythiazolidinyl-2-ethylmercapto-acetic acid ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53943-88-7

Trade Name	Manufacturer	Country	Year Introduced
Viscotiol	Carlo Erba	France	1979
Viscotiol	Carlo Erba	Switz.	1980
Viscotiol	I.S.F.	Italy	1981

Raw Materials

Acrolein
Thioglycolic acid
Cysteine hydrochloride

Manufacturing Process

In an Erlenmeyer flask placed in an ice bath, and under a well-ventilated hood, a solution of 0.1 mol of acrolein in 100 ml of ether was introduced, With the aid of a bromine ampoule, 0.1 mol (= 11 ml) of the ethyl ester of thioglycolic acid containing 0.5 ml of triethylamine was added drop by drop.

One hour after completion of the addition, there was added 0.1 mol (15.6 g) of chlorhydrate of cysteine in alcoholic solution. The chlorhydrate of the expected derivative, which appeared in the form of a thick oil, was precipitated by addition of 0.1 mol (10 g) of potassium acetate in aqueous solution. The abundant precipitate obtained was filtered and washed in water and ether. The product was recrystallized in a minimum of absolute alcohol.

References

DFU 4 (10) 729 (1979)
Kleeman and Engel p. 516
DOT 16 (4) 109 (1980)
I.N. p. 553
Chodkiewicz, M.X.; US Patent 4,032,534; June 28, 1977; assigned to Ferlus-Chimie SA

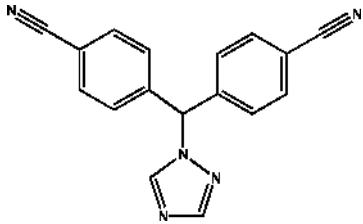
LETROZOLE

Therapeutic Function: Antineoplastic

Chemical Name: Benzonitrile, 4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis-

Common Name: Letrozole

Structural Formula:



Chemical Abstracts Registry No.: 112809-51-5

Trade Name	Manufacturer	Country	Year Introduced
Femara	Novartis Pharmaceuticals	-	-
Letrozole	Novartis Pharmaceuticals	-	-
Lets	Samarth Pharma Pvt. Ltd.	India	-
Letzole	VHB Life Sciences	India	-

Raw Materials

4-Bromomethylbenzonitrile
1H-1,2,4-Triazole
tert-BuOK
p-Fluorobenzinitrile

Manufacturing Process

From 4-bromomethylbenzonitrile and 1H-[1,2,4]triazole was obtained 4-[1,2,4]triazol-1-ylmethylbenzonitrile. Treatment of that with strong base (tert-BuOK) results in formation of the anion by removal of the relatively acidic benzyl proton. This anion was condensed with p-fluorobenzinitrile to give benzhydryl tetrazole (Letrozole).

References

Lang M. et al.; J. Ster; Biochem. Mol. Biol. 1993, V.44, P. 421
The Medical Letter, 1998, V 20, P.53-54
Org. Chem. Drug. Synth., V 6, P.86

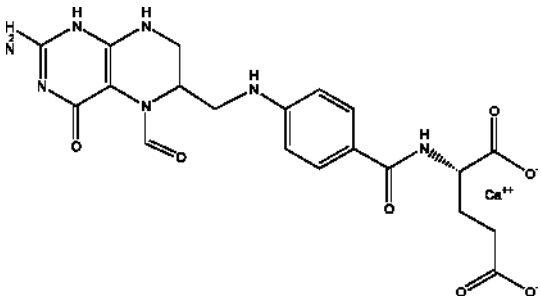
LEUCOVORIN CALCIUM

Therapeutic Function: Antidote (folic acid antagonists), Antianemic

Chemical Name: Glutamic acid, N-(p-(((2-amino-5-formyl-5,6,7,8-tetrahydro-3-hydroxy-6-pteridinyl)methyl)amino)benzoyl)-, calcium salt (1:1), L-

Common Name: Calcio folinato; Calcium folinate; Leucovorin calcium

Structural Formula:



Chemical Abstracts Registry No.: 1492-18-8; 58-05-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Leucovorin calcium	AstraZeneca	-	-
Leucovorin calcium	ROX	-	-
Wellcovorin	Immunex Corporation	-	-
Wellcovorin	Glaxo Wellcome	-	-

Raw Materials

5,10-Methenyl-5,6,7,8-tetrahydrofolic acid, chloride hydrochloride dihydrate
N,N-Diethylethanolamine

Manufacturing Process

5,10-Methenyl-5,6,7,8-tetrahydrofolic acid, chloride hydrochloride dihydrate (20 g) was added in one portion to 100 ml water at 60°C followed by N,N-diethylethanolamine (14.9 g) which adjusted the pH to 6. The mixture was maintained at reflux for 5 hours and the pH kept between 5.7 and 6.2 by addition of N,N-diethylethanolamine. The mixture was cooled, synthetic magnesium silicate (15 g) added and slurried, and filtered through celite and diluted with 40 ml SD3A (95% ethanol with 5% methanol). The filtrate was kept at -5°C for 16 hours, aqueous calcium chloride (4.0 g) was added dropwise to the cold filtrate, and the precipitate filtered, washed with SD3A (100 ml) and with ethyl acetate (100 ml) and dried under reduced pressure.

Yield of calcium leucovorin 91%.

References

Shive W.; US Patent No. 2,741,608; 04.10.1956; Assigned to Research Corporation
Wisowaty J.C., Swaringen R.A., Yeowell D.A.; US Patent No. 4,500,711; 02.19.1985; Assigned to Burroughs Wellcome Co. (Research Triangle Park, NC)

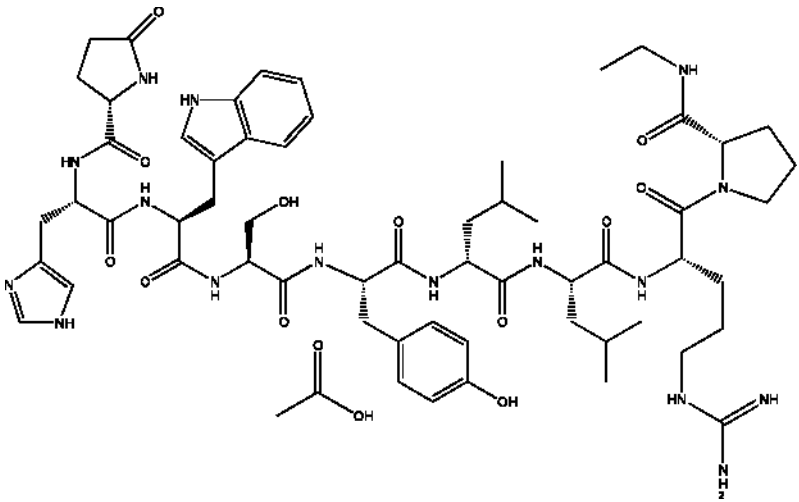
LEUPROLIDE ACETATE

Therapeutic Function: Antineoplastic

Chemical Name: 1-9-Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamide)-L-deglycinamide, monoacetate

Common Name: Leuprolide acetate; Leuprorelin acetate

Structural Formula:



Chemical Abstracts Registry No.: 74381-53-6; 53714-56-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Eligard	Atrix Laboratories, Inc.	-	-
Lupride	Inca (Sun)	India	-
Lupride Depot	Inca (Sun)	India	-
Lupron	TAP Pharmaceuticals	-	-
Viadur	ALZA Corp.	-	-

Raw Materials

Boc-Arg(Tos)	Chloromethylated divinylbenzene-styrene copolymer
Boc-Leu	Hydrogen fluoride
Boc-Tyr(Cl_2Bzl)	Boc-Ser(Bzl)
Boc-Trp	Boc-His(DNP)
pGlu	Dicyclohexylcarbodiimide
Boc-D-Leu	N-Ethyl dinitroaniline

Manufacturing Process

5-Oxo-L-prolyl-L-histidyl-L-tryptophanyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-L-prolylethylamideacetate was prepared by using of Boc strategy on a 2%-crosslinking chloromethylated divinylbenzene-styrene copolymer in a the Merrifield automatic sintesizer apparatus. 4.6 g of this resin/aminoacid material is used for the synthesis of the desired nonapeptide. Each N-blocked aminoacid is added in a three-fold access and allowed to couple to them, existing aminoacid-resin ester in the usual coupling cycle. Ordinarily the solvent used for the coupling reaction is dichloromethane or, when the solubility of the blocked aminoacid is low, a mixture of dichloromethane and DMF. Coupling is effected by the addition of a solution of dicyclohexylcarbodiimide in dichloromethane at a 2.9 fold excess. The sequence used for deprotection, neutralization and coupling of the next aminoacid is done in a fully automatic system. In this manner, the peptide is assembled using in turn Boc-Arg(Tos), Boc-Leu, Boc-D-Leu, Boc-Tyr(Cl_2Bzl), Boc-Ser(Bzl), Boc-Trp, Boc-His(DNP), and pGlu wherein all aminoacids are in the L-form except in the leucine so designated. A 250 mg sample of the above is placed in a hydrogen fluoride reaction with 250 mg vessel of anisole and about 5 ml of anhydrous hydrogen fluoride is distilled into it. After 1 hour at 0°C, the hydrogen fluoride is removed with a stream of dry nitrogen and the residue is taken up in 1% acetic acid. This solution is extracted with ether, and the aqueous phase applied to a 1 time 30 cm column of a highly basic ion exchange resin (marketed by Bio-Rad as AGl resin) in the acetate form. The product is eluted with 0.1 N acetic acid and localized using thin-layer chromatography ($CHCl_3$/MeOH/32% HOAc: 120/90/40, silica gel G, Cl_2/tolidine). The product bearing solution is lyophilized, rechromatographed on a Sephadex G-25 (marketed by Pharmacia of Uppsala, Sweden) column. The product eluted is collected and lyophilized to yield a fluffy white solid. An aminoacid analysis shows the expected ratio of all desired aminoacids assembled in the above fashion.

References

Adjei A.L., Johnson E.S., Kesterson J.W.; US Patent No. 4,897,256; 01.30.1990; Assignd to Abbott Laboratories (Abbott Park, IL)

Gendrich R.L., Rippel R.H., Seely J.H.; US Patent No. 4,005,063; 01.25.1977; Assigned: Abbott Laboratories (North Chicago, IL)

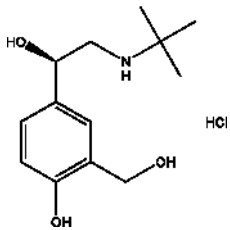
LEVALBUTEROL HYDROCHLORIDE

Therapeutic Function: Bronchodilator

Chemical Name: 1,3-Benzenedimethanol, α^1-(((1,1-dimethylethyl)amino) methyl)-4-hydroxy-, hydrochloride, (α^1R)-

Common Name: Levalbuterol hydrochloride; Levosalbutamol hydrochloride; (R)-Albuterol hydrochloride; (R)-Salbutamol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 50293-90-8; 34391-04-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Xopenex	Sepracor Inc.	USA	-

Raw Materials

Methyl 5-acetylsalicylate
t-Butylamine
Palladium on carbon
Hydrobromic acid
Borane-dimethyl sulfide

Manufacturing Process

Preparation of 5-glyoxyloyl-salicylic acid methyl ester hydrate using aqueous HBr

To a 3-neck flask immersed in an oil bath containing a solution of 40 g (0.206 mole) methyl 5-acetylsalicylate in 6 ml methylene chloride is charged with 82 ml of isopropanol. The solution is distilled to remove excess methylene chloride. When the internal temperature reaches 77°C, 126 ml (1.77 mole or 8.6 equivalents) of DMSO is added to the reaction mixture and the temperature of the mixture is increased to a temperature of 85° to 90°C. Then 33 ml (0.29 mole or 1.4 equivalents) of HBr (aqueous, 48%) is added to the mixture over a period of 20 minutes (exothermic), and the bath temperature is maintained at 95° to 100°C. As the addition of HBr nears completion distillation is initiated and dimethysulfide and isopropanol are distilled off. The mixture is stirred and the volume of the distillate monitored. After distillation of 82 ml of solvent, 20 ml of isopropanol is added slowly to maintain a steady rate of distillation. After the reaction completed as

determined by high performance liquid chromatography (HPLC), the reaction mixture is quenched with 70 ml of 2.4 N H_2SO_4, the temperature of the reaction mixture is allowed to drop to 75°C and residual isopropanol is distilled off under vacuum. After a total of 165 ml distillate is collected, the title compound begins to precipitate. A mixture of 30 ml of acetonitrile and 70 ml of water is added slowly at 75°C with stirring. After 30 minutes of stirring, the reaction mixture is cooled to 15°C over a period of 90 minutes to complete the precipitation. The reaction mixture is filtered and the cake is washed with three 300 ml portions of water. The cake is dried in a draft oven at 50°C for 16 hours to give 39.5 g of the title compound (85% yield).

Preparation of albuterol from 5-glyoxyloyl-salicylic acid methyl ester

To a solution of 5-glyoxyloylsalicylic acid methyl ester hydrate (50 g, 0.221 mol) in ethylene glycol diethyl ether, 440 mL is added tertiary butylamine (16.2 g, 0.221 mol) at room temperature. The resulting light orange solution is stirred for 5 min until a clear solution is formed. The clear solution is then heated to reflux. Water and DME are distilled off azeotropically. After a total of 200 ml of distillate are collected, the solution is cooled to 25°C. The reaction mixture is slowly added to a solution containing 49 mL (0.49 mol) of 10.0 M borane-dimethyl sulfide in 220 mL of ethylene glycol diethyl ether (DME) at 70°C. The resulting reaction mixture is further refluxed for 2.5 hrs. After the reaction is completed as monitored by HPLC, excess DME is removed via vacuum distillation. The residue containing complexes of boron and arylethanolamine is subsequently cooled to 0°C. Quenching of the residue with 300 mL methanol gives the methylborate of arylethanolamine. The borate is then removed by azeotropic distillation as trimethylborate, leaving behind the desired arylethanolamine in the reaction mixture. An additional 300 ml of methanol and acetic acid (85 mL) are added to ensure the complete removal of trimethylborate via vacuum distillation to near dryness. The residue containing the boron-free arylethanolamine is cooled to 25°C and concentrated sulfuric acid (10.4 g, 0.221 mole) in water (64 mL) is added following by 570 ml of isopropyl alcohol. Albuterol sulfate is precipitated out as a white solid. After the reaction mixture is stirred at room temperature for 12 hrs and 0°C for 30 min the albuterol sulfate is filtered, washed with isopropyl alcohol (two 50 mL portions) and dried at 50°C for 12 hrs to give 49.75 g of the title compound (78% yield) as racemate.

The optically pure albuterol may be prepared by resolving a mixture of enantiomers methyl benzoate albuterol precursors which prepared by procedures well known to persons skilled in the art. The starting material 4-benzyl albuterol is commercially available from Cipla (Bombay, India).

(-)-D-Dibenzoyltartaric acid (D-DBTA) (32.2 g, 90 mmol, 1.0 eq) is added to a hot solution of racemic 4-benzyl albuterol (29.6 g, 90 mmol, 1.0 eq) in 180 mL of anhydrous denatured ethanol (type 3A, denatured with 5 vol % 2-propanol). The resulting solution is refluxed for 15 min and cooled to room temperature over 40 min and seeded with 99% ee (R)-4-benzyl albuterol D-DBTA salt. The mixture is cooled to 5°-10°C and stirred for 1 hour. The white solid is collected by filtration and dried at 40°C and 28 inches of Hg for 1 hour to give (R)-4-benzyl albuterol D-DBTA salt (31.8 g, 50% yield, 83.6% ee). The solid is redissolved in 240 mL of ethanol at 55°-60°C and the solution is cooled to room temperature and stirred at room temperature for 2 hours and at 0°-5°C for 1 hour. The resulting solid is collected by filtration and dried at

40°C and 28 inches of Hg for 2 hours as (R)-4-benzyl albuterol D-DBTA salt (22.9 g, 37.1% yield, 99.3% ee). The salt (22.9 g) is then treated with 204 mL of 5 wt % aq. Na_2CO_3 solution in 570 mL of ethyl acetate. The solid is worked-up, and recrystallization from 30 mL of ethyl acetate and 30 mL of n-heptane gives optically pure (R)-4-benzyl albuterol free base as a white powder (10.1 g, 34.1% yield from racemic compound 99.6% ee and 99.8% purity).

A mixture of (R)-4-benzyl albuterol as a free base (3.2 g, 9.73 mmol) and 10% Pd/C (0.64 g) in 24 mL of ethanol (denatured with 5 vol % 2-propanol) is shaken on a Parr-hydrogenator under 50 psi of hydrogen at room temperature for 3 hours. The catalyst is removed by filtration and the filtrate is concentrated to ca. 9 mL in volume containing crude (R)-albuterol and treated with anhydrous HCl in ether (1.0 M, 9.5 mL, 0.98 eq) at 0°-5°C. After 30 min at room temperature, 9 mL of methyl t-butyl ether (MTBE) is added, the resulting mixture is stirred at room temperature for 30 min and at 0°-5°C for 2 hours. The white solid (R)-albuterol hydrochloride is collected by filtration and recrystallized from 25 mL of ethanol and 12.5 mL of MTBE to give pure (R)-albuterol hydrochloride (2.17 g, 80.9% yield, 99.6% purity), white powder.

References

Tann C. et al.; US Patent No. 5,283,359; Feb. 1, 1994; Assigned to Schering Corp., Kenilworth, N.J.

Gao Y. et al.; US Patent No. 5,545,745; Aug. 13, 1996; Assigned to Sepracor, Inc. (Marlborough, MA)

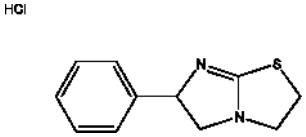
LEVAMISOLE HYDROCHLORIDE

Therapeutic Function: Antiinflammatory

Chemical Name: L-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole hydrochloride

Common Name: L-Tetramisole hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 16695-80-5; 14769-73-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Solaskil	Specia	France	1971
Ergamisol	Janssen	Italy	1978
Ascaryl	Abic	Israel	-
Meglum	Bago	Argentina	-
Niratic-Pur-On	Vet. Med. Handel	W. Germany	-
Tramisol	Lederle	US	-
Vermisol	Andreu	Spain	-

Raw Materials

1,2-Dibromoethane
Potassium hydroxide
Hydrogen chloride
DL-2-Thio-1-phenyl-imidazolidine
d-10-Gamphorsulfonic acid
Sodium hydroxide

Manufacturing Process

To a stirred and refluxed suspension of 17 parts of 1,2-dibromoethane, 7.8 parts of sodium hydrogen carbonate and 50 parts of 2-propanol is added a mixture of 3.4 parts of dl-2-thio-1-phenyl-imidazolidine, 9 parts of a 20% potassium hydroxide solution in 40 parts of 2-propanol over a period of about 1 hour. After the addition is complete, the whole is stirred and refluxed for an additional 3 hours. The reaction mixture is evaporated. To the residue are added 18 parts of a 15% potassium hydroxide solution. The whole is extracted with toluene. The extract is dried and evaporated. The oily residue is dissolved in acetone and gaseous hydrogen chloride is introduced into the solution. The precipitated solid salt is filtered off and recrystallized from 2-propanol, yielding dl-2,3,5,6-tetrahydro-6-phenyl-imidazo[2,1-b]thiazole hydrochloride; melting point 264°C to 266°C.

dl-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole hydrochloride, 188 g (0.785 mol), is suspended in a mixture of 500 ml of water and 500 ml of methylene chloride. The suspension is stirred mechanically while 20% sodium hydroxide solution is added until the solution is basic. Ice is added from time to time to keep the temperature below the boiling point of the methylene chloride. The methylene chloride layer is separated, washed with water, dried over potassium carbonate and evaporated. The oily residue crystallizes with the evolution of the heat when poured into a beaker containing 100 ml of ether. The free base is washed with ether. The yield of dl-6-phenyl-2,3,5,6-tetrahydroimidazo[2,-b]thiazole is 151.4 g (0.746 mol), 94%. The product has a melting point of 90°C.

A solution of 204.3 g (1 mol) of dl-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole and 232.3 g (1 mol) of d-10-camphorsulfonic acid in 1,750 ml of chloroform is allowed to crystallize overnight at -28°C. The solvate is recovered by filtration and washed with ice cold chloroform (400 ml). The solvate is dried (decomposed) under nitrogen 7 hours and then in air overnight. The yield of d(+)6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole d-10-camphorsulfonate is 202.5 g (0.464 mol) 92.8%, melting point 139°C to 140°C $[\alpha]_D^{25}$+ 82.6 (C = 16, H_2O).

A solution of 150 g (0.344 mol) of d(+)6-phenyl-2,3,5,6-tetrahydroimidazo

[2,1-b]thiazole, d-10-camphorsulfonate in water is treated with 15.5 g (0.378 mol) of 98% sodium hydroxide and the liberated base extracted with chloroform. The chloroform solution is washed with water followed by sodium chloride solution and dried over magnesium sulfate. Evaporation of the solvent left 72.1 g of residue which crystallized shortly. The free base hereby obtained has a melting point of 60°C to 61.5°C and an optical rotation $[\alpha]_D^{25}$+ 85.1 (C = 10, $CHCl_3$).

The free base d(+)6-phenyl-2,3,5.6-tetrahydroimidazo[2.1-b]thiazole is dissolved in 112 ml of acetone and 178 ml of isopropanolic hydrogen chloride is added all at once. The hydrochloride crystallizes at once. After cooling to below 0°C, the salt is recovered by filtration and washed with acetone. The product weighs 75.2 g (0.312 mol), 91%, from the camphorsulfonate, melting point 227°C to 227.5°C $[\alpha]_D^{25}$+ 123.1 (C = 15, H_2O).

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Bullock, M.W.; US Patent 3,463,786; August 26, 1969; assigned to American Cyanamid Co. Dewar, R.A., Maier, V.E. and Ingram, M.A.; US Patent 3,579,530; May 18, 1971; assigned to Imperial Chemical Industries of Australia and New Zealand Ltd.
Dewilde, F. and Frot, G.G.; US Patent 3,646,051; February 29, 1972; assigned to Rhone-Poulenc SA

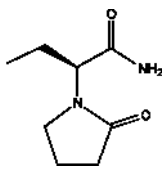
LEVETIRACETAM

Therapeutic Function: Antiepileptic, Nootropic

Chemical Name: 1-Pyrrolidineacetamide, α-ethyl-2-oxo-, (αS)-

Common Name: Levetiracetam

Structural Formula:



Chemical Abstracts Registry No.: 102767-28-2

Trade Name	Manufacturer	Country	Year Introduced
Keppra	UCB Pharma	Belgium	-
Levetiracetam	UCB Pharma	Belgium	-

Raw Materials

(+/-)-α-Ethyl-2-oxo-1-pyrrolidineacetic acid
(R)-(+)-α-Methyl-benzylamine
Triethylamine
Ethyl chloroformate

Manufacturing Process

(a) Preparation of the (R)-α-methyl-benzylamine salt of (S)-α-ethyl-2-oxo-1-pyrrolidineacetic acid

8.7 kg (50.8 moles) of racemic ()-α-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 21.5 liters of anhydrous benzene in a 50 liter reactor. To this suspension is added gradually a solution containing 3.08 kg (25.45 moles) of (R)-(+)-α-methyl-benzylamine and 2.575 kg (25.49 moles) of triethylamine in 2.4 liters of anhydrous benzene. This mixture is then heated to reflux temperature until complete dissolution. It is then cooled and allowed to crystallize for a few hours. 5.73 kg of the (R)-α-methyl-benzylamine salt of (S)-α-ethyl-2-oxo-1-pyrrolidineacetic acid are thus obtained. Melting point: 148°-151°C. Yield: 77.1%.

This salt may be purified by heating under reflux in 48.3 liters of benzene for 4 hours. The mixture is cooled and filtered to obtain 5.040 kg of the desired salt. Melting point: 152°-153.5°C. Yield: 67.85%.

(b) Preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetic acid

5.04 kg of the salt obtained in (a) above are dissolved in 9 liters of water. 710 g of a 30% sodium hydroxide solution are added slowly so that the pH of the solution reaches 12.6 and the temperature does not exceed 25°C. The solution is stirred for a further 20 minutes and the α-methylbenzylamine liberated is extracted with a total volume of 18 liters of benzene. The aqueous phase is then acidified to a pH of 1.1 by adding 3.2 liters of 6 N hydrochloric acid. The precipitate formed is filtered off, washed with water and dried. The filtrate is extracted repeatedly with a total volume of 50 liters of dichloromethane. The organic phase is dried over sodium sulfate and filtered and evaporated to dryness under reduced pressure. The residue obtained after the evaporation and the precipitate isolated previously, are dissolved together in 14 liters of hot dichloromethane. The dichloromethane is distilled and replaced at the distillation rate, by 14 liters of toluene from which the product crystallizes. The mixture is cooled to ambient temperature and the crystals are filtered off to obtain 2.78 kg of (S)-α-ethyl-2-oxo-1-pyrrolidineacetic acid. Melting point: 125.9°C. $[\alpha]_D^{20}$ = -26.4° (c = 1, acetone). Yield: 94.5%.

(c) Preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide

34.2 g (0.2 mole) of (S)-α-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 225 ml of dichloromethane cooled to -30°C. 24.3 g (0.24 mole) of triethylamine are added dropwise over 15 minutes. The reaction mixture is then cooled to -40°C and 24.3 g (0.224 mole) of ethyl chloroformate are added over 12 minutes. Thereafter, a stream of ammonia is passed through the mixture for 4 ½ hours. The reaction mixture is then allowed to return to ambient temperature and the ammonium salts formed are removed by filtration and washed with dichloromethane. The solvent is distilled off under reduced pressure. The solid residue thus obtained is dispersed in 55 ml toluene and the dispersion is stirred for 30 minutes and then filtered. The product is recrystallized from 280 ml of ethyl acetate in the presence of 9 g of 0.4 nm molecular sieve in powder form 24.6 g of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide are obtained. Melting point: 115°-118°C. $[\alpha]_D^{25}$ = -89.7° (c = 1, acetone). Yield: 72.3%.

References

Gobert et al.; US Patent No. 4,696,943; Sep. 29, 1987; Assigned to USB Societe Anonyme, Brusseles, Belgium

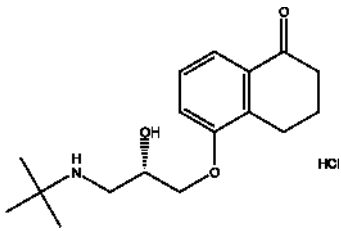
LEVOBUNOLOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 1(2H)-Naphthalenone, 3,4-dihydro-5-((2S)-3-(tert-butylamino)-2-hydroxypropoxy)-, hydrochloride

Common Name: Levobunolol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 27912-14-7; 47141-42-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Betagan	Allergan	India	-
Betagan Liquifilm	Allergan	Australia	-
Betagen	Ferraz	-	-
Sab-Levobunolol	Sabex Inc.	-	-

Raw Materials

Potassium hydroxide
t-Butylamine
5-Hydroxy-3,4-dihydro-1(2H)-naphthalenone
Tetrabutylammonium bromide
(R)-(-)-Epichlorhydrine

Manufacturing Process

9.62 g (59 mmoles) 5-hydroxy-3,4-dihydro-1(2H)-naphthalenone, 67 ml toluene, 0.36 g (1.1 mmoles) tetra-n-butylammonium bromide, 4.51 g (68 mmoles) 85% potassium hydroxide and 20 ml (254 mmoles) (R)-(-)-epichlorhydrine were placed in an appropriate flask fitted with efficient mechanical stirring, and the mixture was heated under reflux for two hours. The mixture was allowed to cool to 30°C, 50 ml toluene and 50 ml water were added and the mixture was vigorously stirred. The organic phase was removed and the aqueous phase extracted with 25 ml toluene. The combined organic phases were concentrated at reduced pressure, 31 ml (300 mmoles) tert-butylamine, 45 ml ethanol and 3 ml deionized water were added, and the solution was heated under reflux for one hour. The mixture was allowed to cool to 40°C and the volatile products were distilled at reduced pressure. Toluene (9 ml) was added to the residue and volatiles were distilled at reduced pressure. (S)-5-(2,3-Epoxypropoxy)-3,4-dihydro-1(2H)-naphthalenone with an optical purity greater than 95% was obtained. Toluene (75 ml) was added to the product, and then, 10 ml of 35% (w/v) hydrochloric acid and 110 ml water, and the mixture was stirred for fifteen minutes. The organic phase was decanted and the aqueous one was extracted with 50 ml toluene. The aqueous phase was basified by addition of a solution of 5.1 g sodium hydroxide in 150 ml water and extracted twice with toluene (100 and 50 ml, respectively). The combined organic extracts were dried with anhydrous sodium sulfate, decolorized with active charcoal and filtered.

To the above toluenic solution containing levobunolol as free base, 16 ml ethanol and the stoichiometric amount of hydrogen chloride were added. The stirred mixture was cooled below 10°C and kept at this temperature for one hour. The precipitated solid was filtered, washed with toluene, recrystallized twice from 43 ml ethanol and dried to give 10.0 g (51% yield) of (-)-3,4-dihydro-5-(3-(tert-butylamino)-2-hydroxypropoxy)-1(2H)-naphthalenone hydrochloride (levobunolol hydrochloride) having a rotary power at 25°C below -19°.

References

Camps G.P. et al.; CA Patent No. 2,119,052, Dec. 25, 1994; Medichem SA (ES)
Stampa D.D.C. et al.; US Patent No. 5,426,227; June 20, 1995; Assigned to Medichem S.A.

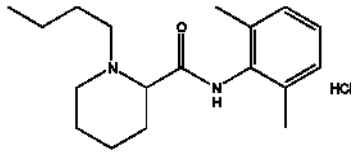
LEVOBUPIVACAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, (2S)-

Common Name: Levobupivacaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 27262-48-2; 27262-47-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Chirocaine	Abbott Laboratories	-	-
Chirochaine	Darwin Discovery	-	-

Raw Materials

Pipecolic acid
Amberlite
2,6-Dimethylaniline
Tartaric acid, L-
Phosphorus pentachloride
n-Butyl bromide

Manufacturing Process

Synthesis of L-pipecolic acid 2,6-xylidide (Patent US 4,695,576)

130 g of pipecolic acid and 158.6 g of Laevo (+)-tartaric acid are dissolved under stirring in 2 L 95% ethyl alcohol and 125 ml water at 80°C. The solution is allowed to cool to room temperature and after two days the crystallized D-pipecolic-tartrate is separated. The L-pipecolic-tartrate remains in solution. The filtrate is evaporated and dissolved in 5% acetic acid. Finally the solution is treated with Amberlite IR 45* in an ion exchanger. The eluate thus obtained is evaporated and the resulting crystalline residue is dried with potassium hydroxide in vacuo. The product obtained consists of L-pipecolic acid $[\alpha]_D^{24}$ = -26.2°(C = 5, H_2O).

4 g of phosphorus pentachloride was added to a suspension of 4 g of L-pipecolic acid hydrochloride in 40 ml acetylchloride. The initial reaction is effected at a temperature of about 35°C under stirring for 2 hours. The chlorination is completed by adding during a time period of about 10 minutes an additional two grams of phosphorus pentachloride and stirring over a further period of 4 hours while maintaining the suspension at a temperature of about 35°C. The resulting L-pipecolic acid chloride hydrochloride is filtered and washed with toluene and acetone. The crystalline residue is then dried in vacuo, m.p. 155°C.

A mixture of 2.7 ml 2,6-dimethylaniline, 4 ml acetone, and 4 ml N-

methylpyrrolidone is gradually added under stirring for 2 hours at 70°C to a suspension of 4 g of L-pipecolic acid chloride hydrochloride. This yields a crystalline product, which is filtered, washed with acetone and dried. This crystalline product is then dissolved in water and the base is precipitated by the addition of ammonia. The base is then extracted by the use of toluene and is recovered by evaporation. The base is recrystallized from a mixture of hexane and ethanol to yield L-pipecolic acid 2,6-xylidide. The melting point of this compound is 129-130°C.

Preparation of L-N-n-butylpipecilic acid 2,6-xylidide may de carried out by analogy with the preparation of L-N-n-propylpipecolic acid 2,6-xylidide (Patent US 5,777,124).

n-Butylbromide and potassium carbonate are added to a solution of L-pipecolic acid 2,6-xylidide dissolved in isopropyl alcohol. Thereafter, 5 ml of water is added to the mixture and the reaction is carried out for 4 hours at 72°C.

To complete the reaction, a further 0.8 ml n-butylbromide are added under continuous stirring and heating for 4 hours. The residue is treated with a mixture of 250 ml toluene and an equal amount of water at 50°C. The toluene layer is separated and washed three times with 100 ml warm water (40°C). A 175 ml portion of the toluene is removed by evaporation and the remainder is stored at +5°C for 6 hours to achieve crude crystalline L-N-n-butylpipecilic acid 2,6-xylidide. The crystalline product is separated by filtration, washed with some cooled toluene and dried at 70°C. Recrystallization may be carried from toluene. This product is dissolved in 100 ml ethanol and neutralized with concentrated hydrochloric acid. Ethanol is removed by evaporation and the hydrochloride product obtained is vacuum dried. Finally the latter is recrystallized from isopropyl alcohol.

References

Ekenstam B.T., Bovin Ch.; US Patent No. 4,695,576; Sep. 22, 1987; Assigned to Astra Lake Medel, Aktiebolag, Sweden
Zavareh H.Sh., Frampton G.A.Ch.; US Patent No. 5,777,124; Jul. 7, 1998; Assigned to Chiroscience Limited, Camdridge, United Kingdom

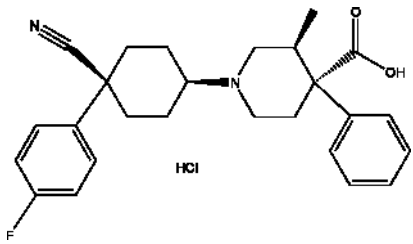
LEVOCABASTINE HYDROCHLORIDE

Therapeutic Function: Antihistaminic

Chemical Name: 4-Piperidinecarboxylic acid, 1-(cis-4-cyano-4-(4-fluorophenyl)cyclohexyl)-3-methyl-4-phenyl-, monohydrochloride, (3S,4R)-

Common Name: Levocabastine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 79547-78-7; 79516-68-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Livostin	Janssen-Cilag	Belgium	-
Livostin	Novartis	-	-

Raw Materials

Ethyl acrylate
Palladium on charocal
3-Methyl-5-phenylpiperidine-4-carboxylic acid benzyl ester
p-Fluorophenylacetonitrile
Sodium methoxide

Manufacturing Process

4-Cyano-4-(4-fluorophenyl)-heptanedioic acid diethyl ester is obtained by addition of ethyl acrylate to the anion from p-fluorophenylacetonitrile. By base catalyzed cyclization of these diester (sodium methoxide, 60°C, xylene) is synthesized an intermediate that after decarboethoxylation gives 1-(4-fluorophenyl)-4-oxycyclohexanecarbonitrile. By condensation of 3-methyl-5-phenylpiperidine-4-carboxylic acid benzyl ester and 1-(4-fluorophenyl)-4-oxycyclohexanecarbonitrile under reductive hydrogenation conditions (palladium-on-charcoal catalyst, 50°C, in ethanol) is prepared benzyl ester 4-piperidinecarboxylic acid, 1-(4-cyano-4-(4-fluorophenyl)cyclohexyl)-3-methyl-4-phenyl-, (3S-(1(cis),3α,4β))-. The benzyl protecting group is then removed by hydrogenation method and 4-piperidinecarboxylic acid, 1-(4-cyano-4-(4-fluorophenyl)cyclohexyl)-3-methyl-4-phenyl-, (3S-(1(cis),3α,4β))- obtained is transformed into 4-piperidinecarboxylic acid, 1-(4-cyano-4-(4-fluorophenyl) cyclohexyl)-3-methyl-4-phenyl-, hydrochloride, (3S-(1(cis), 3α,4β))-(Levocabastine hydrochloride).

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Stokbroekx R. A. et al.; Patent U.S. 4,369,184, January 18, 1983; Assigned to Janssen Pharmaceutica N.V. (Beerse, BE)
Stokbroekx R. A. et al.; Drug Dev. Res., 1986, 8, 87
G. Vanden Bussche, Drugs of the Future, 1986, 11, 841

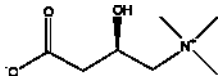
LEVOCARNITINE

Therapeutic Function: Appetite stimulant

Chemical Name: 1-Propanaminium, 3-carboxy-2-hydroxy-N,N,N-trimethyl-, inner salt, (2R)-

Common Name: Carnitine; L-Carnitine; Levocarnitine; Vitamin B_T

Structural Formula:



Chemical Abstracts Registry No.: 541-15-1

Trade Name	Manufacturer	Country	Year Introduced
Carnitene	Sigma Tau Industrie Farmaceutiche Riunite	Italy	-
Carnitor	Sigma Tau	Italy	-
Levocarnitine	Shire Pharmaceuticals	-	-

Raw Materials

Trimethylamine
Potassium iodide
Ethyl 4-chloro-3-oxobutyrate
Dichloro(p-cymene)ruthenium(II) dimer
Tetramethylammonium iodide
(+)-[2,2',5,5'-Tetramethyl-3,3'-bis(diphenylphosphino)]-4,4'-bithiophene

Manufacturing Process

a) Preparation of $[RuI_2p\text{-cymene}]_2$

Two g of $[RuCl_2p\text{-cymene}]_2$ and 50 ml of methylene chloride are placed under nitrogen in a flask; 66 mg of tetramethylammonium iodide and subsequently an aqueous solution (50 ml) containing 10.2 mg of KI are added to the solution. The mixture is left under vigorous stirring and in an inert atmosphere for approximately 15 hours at ambient temperature. The phases are separated. The aqueous phase is extracted with 2 times 40 ml of CH_2Cl_2. The gathered organic phases are washed with 3 x 40 ml of H_2O, dried on Na_2SO_4 and filtered on fume silica (dicalite). A red-brown solution is obtained which is vacuum-dried. 3.07 g of $[RuI_2p\text{-cymene}]_2$ are obtained.

b) Preparation of {[Ru (p-cymene) I (+)-TMBTP] I}

155 mg of $[RuI_2p\text{-cymene}]_2$ and 204 mg of (+)-TMBTP are placed under nitrogen in a flask, and the mixture of 80 ml of CH_2Cl_2 fvand 30 ml of MeOH degassed with nitrogen is added. The mixture is left at reflux under stirring for

1.5 h; it is then cooled and concentrated at reduced pressure. The dark red solid consisting of {[Ru (p-cymene) I (+)-TMBTP] I} is used as such in the enantioselective hydrogenation processes.

c) Preparation of ethyl (+)-(R)-4-chloro-hydroxybutyrate

14 kg of ethyl 4-chloro-3-oxobutyrate (titre 88%) and 6.2 g of {[Ru (p-cymene) I (+)-TMBTP] I}, are placed under argon in a 200-liter reactor, in 143 L of ethyl alcohol. The mixture is heated at 116°C and pressurized with hydrogen at 5-6 bar. Temperature rises up to 124°C and the reaction goes to completion within about 1 hour. The mixture is cooled, concentrated at reduced pressure, and the residue, analyzed with gaschromatography, has a 81% titre of ethyl (+)-(R)-4-chloro-3-hydroxybutyrate, with an e.e. of 96.7% reaction yield: 94%.

d) Preparation of L-carnitine

400 g of crude ethyl (+)-(R)-4-chloro-3-hydroxybutyrate, above prepared and 1 L of 45% trimethylamine in H_2O are placed in a 2-liter reactor. The reaction mixture is heated to 80°C and kept at this temperature for 15 h. After cooling and removing the excess of trimethylamine under nitrogen flow, the aqueous solution is extracted with 1.9 L of methylene chloride and analyzed with HPLC. L-carnitine is obtained with 75% yield.

References

Tiniti M. et al.; US Patent No. 6,566,552 B2; May 20, 2003; Assigned to Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Roma

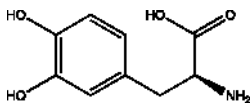
LEVODOPA

Therapeutic Function: Antiparkinsonian

Chemical Name: 3-Hydroxy-L-tyrosine

Common Name: β-(3,4-Dihydroxyphenyl)-α-alanine; 2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid

Structural Formula:



Chemical Abstracts Registry No.: 59-92-7

Trade Name	Manufacturer	Country	Year Introduced
Larodopa	Roche	US	1970
Dopar	Norwich Eaton	US	1970
Dopaidan	De Angeli	Italy	1970
Larodopa	Roche	W. Germany	1970
Larodopa	Roche	UK	1970
Larodopa	Roche	France	1970
Larodopa	Roche	Italy	1970
Brocadopa	Brocades	UK	1970
Levodopa	SKF	US	1971
Bendopa	I.C.N.	US	1971
Larodopa	Roche	Japan	1972
Biodopa	DDR Pharm	US	-
Ceredopa	Merckle	W. Germany	-
Cidandopa	Cidan	Spain	-
Dehdopa	De Angeli	Brazil	-
Dopacin	I.C.N.	Brazil	-
Dopaflex	EGYT	Hungary	-
Dopaidan	De Angeli	Italy	-
Dopalfher	Fher	Spain	-
Doparkin	Farmos	Finland	-
Doparkine	Armstrong	Argentina	-
Doparl	Kyowa	Japan	-
Dopasol	Daiichi	Japan	-
Dopason	Yurtoglu	Turkey	-
Dopaston	Sankyo	Japan	-
Eldopar	Weifa	Norway	-
Eldopatec	Labatec	Switz.	-
Eurodopa	Castejon	Spain	-
Levopa	Arco	Switz.	-
Maipedopa	Maipe	Spain	-
Medidopa	Medica	Finland	-
Novedopa	Torlan	Spain	-
Parkidopa	Farmos	Finland	-
Parmedin	Kwizda	Austria	-
Prodopa	Faulding	Australia	-
Syndopa	Sankyo	Japan	-
Weldopa	Smith and Nephew	UK	-

Raw Materials

Velvet beans
Acetic acid

Manufacturing Process

A charge of 1,000 g of ground velvet beans was extracted with 9 liters of 1% aqueous acetic acid at room temperature over a 20-hour period with occasional stirring during the first 4 hours. The liquor was decanted and the

bean pulp slurry was vacuum filtered through a cake of acid-washed diatomaceous earth in a Buechner funnel. The decanted liquor was combined with the filtrate and concentrated under vacuum and a nitrogen atmosphere to a volume of 900 ml. After treating with acid-washed activated carbon, the concentrate was then filtered through acid-washed diatomaceous earth.

After concentrating the filtrate to approximately 400 ml, solids started crystallizing out at which time the filtrate was cooled by refrigerating at 5°C for several hours. Filtration gave 18.7 g of L-Dopa, MP 284° to 286°C (dec.); $[\alpha]_D$ 8.81° (1% solution in aqueous 4% HCl). The infrared spectrum and paper chromatography indicated very good L-Dopa according to US Patent 3,253,023.

Various synthetic routes are also described by Kleeman and Engel.

References

Merck Index 5298
Kleeman and Engel p. 520
PDR pp. 1210, 1489
DOT 9 (6) 247 (1973) and 10 (9) 317, 332 (1974)
I.N. p. 555
REM p, 930
Wysong, D.V.; US Patent 3,253,023; May 24, 1966; assigned to The Dow Chemical Company
Krieger, K.H., Lago, J. and Wantuck, J.A.; US Patent 3,405,159; October 8, 1968; assigned to Merck and Co.,Inc.

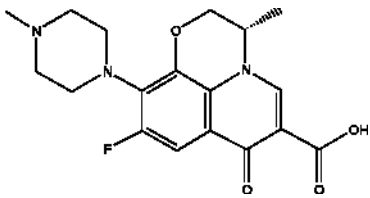
LEVOFLOXACIN

Therapeutic Function: Antibacterial

Chemical Name: 7H-Pyrido(1,2,3-de)-1,4-benzoxazine-6-carboxylic acid, 2,3-dihydro-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (S)-

Common Name: Levofloxacin; (S)-Ofloxacin

Structural Formula:



Chemical Abstracts Registry No.: 100986-85-4

Trade Name	Manufacturer	Country	Year Introduced
Fynal-500	Mankind Pharma Pvt. Ltd.	India	-
Levaquin	Hoechst Marion Roussel	-	-
Levoday	Recon Healthcare Ltd.	India	-
Levoff	Biochem Pharma Industries	-	-
Levoflox	Protech Biosystems	India	-
Levofloxacin	Hoechst Marion Roussel	-	-
Levo-Fq Inj.	Venus Remedies Limited	India	-
Levox	Claris Life Sciences	India	-
Lf	Finecure Pharma	India	-
Lofel	East African (I) Remedies Pvt. Ltd.	-	-
Lotor	Emcure Pharmaceuticals Ltd.	India	-
Loxof	Rexcel Pharmaceuticals	India	-
Qure	Aristo Pharmaceutical Ltd.	India	-
Tavanic	Aventis Pasteur	-	-
Tavanic	Hoechst Marion Roussel	Germany	-
T-Livo	Taurus Laboratories Pvt Ltd.	India	-
Voxin	Panacea Biotec Ltd.	India	-

Raw Materials

2,3-Difluoro-6-nitrophenol	1-Acetoxy-3-chloro-2-propane
Nickel Raney	Lipoprotein lipase
Thionyl chloride	3,5-Dinitrobenzoyl chloride
Acetic anhydride	Diethyl ethoxymethylenemalonate
N-Methylpiperazine	Boron trifluoride ethyl etherate

Manufacturing Process

()-3-Acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine (m.p. 73-74°C) was synthesized by hydrogenation of a compound prepared from 2,3-difluoro-6-nitrophenol, 1-acetoxy-3-chloro-2-propane and potassium iodide. The hydrogenation was carried out on Raney nickel. The resulting compound was dissolved in THF, and 3,5-dinitrobenzoyl chloride and pyridine were added thereto, followed by heating at 60°C for 3 hours. The mixture was concentrated, and the concentrate was dissolved in ethyl acetate, washed successively with diluted hydrochloric acid, an aqueous solution of sodium bicarbonate and water, dried over anhydrous sodium sulfate and concentrated. Addition of n-hexane to the concentrate caused precipitation of yellow crystals of a racemate. The yield of 3,5-dinitrobenzoyl derivative of the ()-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine 3.93 g.

To 2.0 ml of Amberlite XAD 7 was added 2.0 ml of a 0.05 M phosphoric acid buffer (pH 7.0) having dissolved therein 20 mg of lipoprotein lipase, and the system was allowed to stand at room temperature for 18 hours to thereby adsorb the enzyme onto the resin. The resin was filtered. A solution of 250 mg of 3,5-dinitrobenzoyl derivative of ()-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine as a substrate in 25 ml of a mixed solvent of benzene and n-hexane (4:1 by volume) was added to the resin, followed by

allowing to react at 37°C for 4 hours. It was obtained 117 mg of a 3,5-dinitrobenzoyl derivative of the (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine and 65 mg of a derivative of the (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine.

In 135 ml THF was dissolved 3.03 g of a 3,5-dinitrobenzoyl derivative of (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine, and 135 ml of ethanol and 30 ml of 1.0 N potassium hydroxide were added to the solution. After 30 min 3 ml of acetic acid was added thereto for neutralization. The mixture was concentrated. The solid was subjected to column chromatography using 40 g of silica gel and eluted with chloroform/methanol to obtain 1.17 g of (-)-7,8-difluoro-2,3-dihydro-3-hydroxymethyl-4H-[1,4]benzoxazine; $[\alpha]_D^{22}$ = -14.1° (c = 1.80, $CHCl_3$).

To 1.17 g of (-)-7,8-difluoro-2,3-dihydro-3-hydroxymethyl-4H-[1,4] benzoxazine was added 2.77 g of thionyl chloride in pyridine. The reaction mixture was concentrated and the concentrate was subjected to column chromatography using 40 g of silica gel and eluted with chloroform to obtain 1.18 g of the reaction product as a colorless oily product. This product was dissolved in 30 ml of dimethyl sulfoxide, and 0.41 g of sodium borohydride was added thereto, followed by heating at 80-90°C for 1 hour. The reaction mixture was dissolved in 500 ml of benzene, washed with water to remove the dimethyl sulfoxide, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was subjected to column chromatography using 40 g of silica gel and eluted with benzene to obtain 0.80 g of (-)-7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine as a colorless oily product; $[\alpha]_D^{25}$ = -9.6° (c = 2.17, $CHCl_3$). Optical Purity: >99% e.e.

To 1.13 g of (-)-7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine was added 1.58 g of diethyl ethoxymethylenemalonate, and the mixture was stirred at 130-140°C for 70 min. The reaction mixture was subjected to column chromatography using 50 g of silica gel and eluted with chloroform to obtain 2.47 g of diethyl [(-)-7,8-difluoro-3-methyl-2,3-dihydro-4H-[1,4] benzoxazin-4-yl]methylenemalonate. This product was dissolved in 5 ml of acetic anhydride, and 10 ml of a mixture of acetic anhydride and concentrated sulfuric acid (2/1 by volume) with stirring under ice-cooling, followed by stirring at 50-60°C for 40 min. To the reaction mixture were added ice and an aqueous solution of sodium bicarbonate, and the product was extracted three times with 150 ml portions of chloroform. The combined extract was washed with water, dried over anhydrous sodium sulfate and concentrated. The precipitate was washed with a small amount of diethyl ether to yield 1.32 g of (-)-ethyl 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4] benzoxazine-6-carboxylate.

In 12 ml of acetic acid was dissolved 1.20 g of the resulting compound, and 25 ml of concentrated hydrochloric acid was added, followed by refluxing at 120-130°C for 90 min. Upon allowing the reaction mixture to stand at room temperature, colorless crystals were precipitated, which were collected by filtration and washed successively with a small amount of water, ethanol and diethyl ether to obtain 0.96 g of (-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid.

In 30 ml of diethyl ether was suspended 324 mg of the resulting compound,

and a large excess of boron trifluoride ethyl etherate was added thereto, followed by stirring at room temperature for 30 min to form a chelate compound. The product was collected by filtration and washed with a small amount of diethyl ether to obtain 373 mg of a powder. The powder was dissolved in 7 ml of dimethyl sulfoxide, and 136 mg of N-methylpiperazine and 228 mg of triethylamine were added thereto, followed by stirring at room temperature for 17 hours. The reaction mixture was concentrated to dryness under reduced pressure, and to the solid were added 15 ml of 95% methanol and 0.31 ml of triethylamine. The resulting mixture was refluxed for 3 hours. The reaction mixture was concentrated under reduced pressure, and the residue was filtered and washed successively with a small amount of ethanol and diethyl ether to obtain 350 mg of a white powder. Recrystallization from a mixed solvent of ethanol and thick aqueous ammonia gave 230 mg of S-(-)-ofloxacin (Levofloxacin).

Melting Point: 225-227°C (with decomposition); $[\alpha]_D^{23}$ = -76.9° (c = 0.39, 0.05 N NaOH).

References

Hayakawa I. et al.; US Patent No. 5,053,407; Oct. 1, 1991; Assigned to Daiichi Pharmaceutical Co., Ltd.

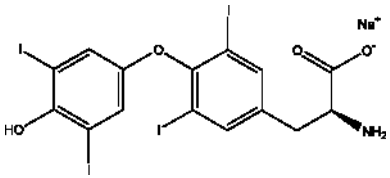
LEVOTHYROXINE SODIUM

Therapeutic Function: Thyroid hormone

Chemical Name: L-3,3',5,5'-Tetraiodothyronine sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 55-03-8; 51-48-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Synthroid	Flint	US	1953
Letter	Armour	US	1965
Eltroxin	Glaxo	UK	-
Euthyrox	Merck	W. Germany	-
Eutirox	Bracco	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Levaxin	Nyegaard	Norway	-
Levothyrox	Merck Clevenot	France	-
Levotiron	Abdi Ibrahim	Turkey	-
Ro-Thyroxine	Robinson	US	-
Syntaroid	Travenol	US	-
Thevier	Glaxo	W. Germany	-
Thyradin-S	Teikoku Zoki	Japan	-
Thyraplex	Erco	Denmark	-
Thyrex	Sanabo	Austria	-

Raw Materials

Manganese sulfate
Sodium hydroxide
Hydrochloric acid
N-Acetyl-L-diiodotyrosinamide
Acetic acid

Manufacturing Process

A 9.30 g portion of N-acetyl-L-diiodotyrosinamide was suspended in 100 ml of 0.05M boric acid (H_3BO_3) and 100 ml of 95% ethanol, and the solid was dissolved by adjusting the pH to 10.5 with 2N sodium hydroxide (NaOH). A 15% (by weight) portion of manganese sulfate monohydrate was added and the solution heated at 44°C under conditions of oxygenation while being agitated mechanically. After approximately 24 hours of incubation, the precipitated product was collected and separated from the catalyst, providing the amide of N-acetyl-L-thyroxine in 30.6% yield. On hydrolysis (removal of both amide functions), achieved by refluxing in glacial acetic acid-hydrochloric acid (approximately 2:1), L-thyroxine is obtained. It was isolated as the sodium salt, containing approximately 5 molecules of water of hydration.

References

Merck Index 5303
Kleeman and Engel p. 525
PDR p. 993
OCDS Vol. 1 p. 97 (1977)
I.N. p. 558
REM p. 980
Anthony, P.Z. and Ginger, L.G.; US Patent 2,889,364; June 2, 1959;assigned to Baxter Laboratories, Inc.

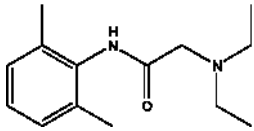
LIDOCAINE

Therapeutic Function: Local anesthetic, Antiarrhythmic

Chemical Name: 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide

Common Name: Lignocaine

Structural Formula:



Chemical Abstracts Registry No.: 137-58-6; 73-78-9 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Xylocaine	Astra	US	1949
Anestacon	Contal	US	1967
Octocaine	Novocol	US	1980
Clinicaine	Johnson and Johnson	US	1982
Anestacain	Farmos	Finland	-
Anestecidan	Cidan	Spain	-
Baylocaine	Bay	US	-
Cidancaina	Cidan	Spain	-
Cito-Optadren	Fischer	Switz.	-
Dolicaine	Reid-Provident	US	-
Dulicaine	Dulcis	Monte Carlo	-
Duncaine	Duncan Flockhart	UK	-
Esracain	Hillel	Israel	-
Leotesin-N	Showa	Japan	-
Lida-Mantal	Dome	US	-
Lidocain	Bristol	US	-
Lidocard	Orion	Finland	-
Lidocaton	Pharmaton	Switz.	-
Lidocor	Gebro	Austria	-
Lido Pen	Survival Tech.	US	-
Lignane	Propan-Lipworth	S. Africa	-
Neo-Novutox	Braun	W. Germany	-
Ortoderm ina	Tiber	Italy	-
Qualigens	Qualipharma	Switz.	-
Rapidocaine	Sintetica	Switz.	-
Sedodent	Belupo Ltd.	Yugoslavia	-
Xylanaest	Gebro	Austria	-
Xylesin	Amino	Switz.	-
Xylestesin	Espe	W. Germany	-
Xylocard	Hassle	Sweden	-
Xylocitin	Jenapharm	E. Germany	-
Xyloneural	Gebro	Austria	-
Xylonor	Septodont	France	-
Xylotox	Willows-Francis	UK	-

Raw Materials

2,6-Xylidine
Chloroacetyl chloride
Diethylamine

Manufacturing Process

One mol of 2,6-xylidine is dissolved in 800 ml glacial acetic acid. The mixture is cooled to 10°C, after which 1.1 mol chloracetyl chloride is added at one time. The mixture is stirred vigorously during a few moments after which 1,000 ml half-saturated sodium acetate solution, or other buffering or alkalizing substance, is added at one time. The reaction mixture is shaken during half an hour. The precipitate formed which consists of ω-chloro-2,6-dimethyl-acetanilide is filtered off, washed with water and dried. The product is sufficiently pure for further treatment. The yield amounts to 70 to 80% of the theoretical amount.

One mole of the chloracetyl xylidide thus prepared and 2.5 to 3 mols diethyl amine are dissolved in 1,000 ml dry benzene. The mixture is refluxed for 4 to 5 hours. The separated diethyl amine hydrochloride is filtered off. The benzene solution is shaken out two times with 3N hydrochloric acid, the first time with 800 ml and the second time with 400 ml acid. To the combined acid extracts is added an approximately 30% solution of sodium hydroxide until the precipitate does not increase.

The precipitate, which sometimes is an oil, is taken up in ether. The ether solution is dried with anhydrous potassium carbonate after which the ether is driven off. The remaining crude substance is purified by vacuum distillation. During the distillation practically the entire quantity of the substance is carried over within a temperature interval of 1° to 2°C. The yield approaches the theoretical amount. MP 68° to 69°C. BP 180° to 182°C at 4 mm Hg; 159° to 160°C at 2 mm Hg. (Procedure is from US Patent 2,441,498.)

References

Merck Index 5310
DFU 8 (12) 1021 (1983)
Kleeman and Engel p. 526
PDR pp. 607, 888, 1569
OCDS Vol. 1 p. 16 (1977); 2, 95, 449 (1980) 813, 40 (1984)
I.N. p. 559
REM p. 1051
Lofgren, N.M. and Lundqvist, B.J.; US Patent 2,441,498; May 11, 1948; assigned to AB Astra, Sweden
Brown, C.L.M. and Poole, A.; US Patent 2,797,241; June 25, 1957

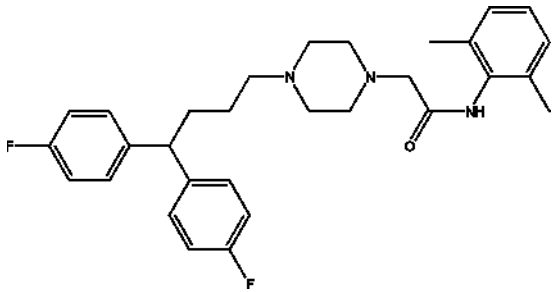
LIDOFLAZINE

Therapeutic Function: Coronary vasodilator

Chemical Name: 4-[4,4-Bis(4-fluorophenyl)butyl]-N-(2,6-dimethylphenyl)-1-piperazineacetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3416-26-0

Trade Name	Manufacturer	Country	Year Introduced
Clinium	Janssen	W. Germany	1969
Corflazine	Cassenne	France	1972
Clinium	Janssen	Italy	1974
Clinium	Janssen	UK	1980
Anginin	Yurtoglu	Turkey	-
Clavidene	Corvi	Italy	-
Clinium	McNeil	US	-
Klinium	Esteve	Spain	-
Klintab	Eczacibasi	Turkey	-

Raw Materials

1-[4,4-(Di-p-fluorophenyl)butyl]piperazine
N-(2-Chloroacetyl)-2,6-dimethylaniline

Manufacturing Process

A mixture of 6.6 parts 1-[4,4-di-(4-fluoro-phenyl)butyl]-piperazine, 4.33 parts N-(2-chloro-acetyl)-2,6-dimethyl-aniline, 3.2 parts sodium carbonate, a few crystals of potassium iodide in 200 parts 4-methyl-2-pentanone is stirred and refluxed for 70 hours. After cooling there are added 70 parts water. The organic layer is separated, dried over potassium carbonate, filtered and evaporated. The oily residue is dissolved in 80 parts diisopropylether and the solution is filtered hot. After cooling the filtrate at 0°C. the formed solid is filtered off and recystallired from 80 parts ether, yielding 1-[4,4-di-(4-fluoro-phenyl)butyl]-4-[(2,6-dimethylanilino-carbonyl)-methyl]-piperazine; MP 159°C to 161°C.

References

Merck Index 5311
Kleeman and Engel p. 526
OCDS Vol. 1 p. 279 (1977)
DOT 2 (4) 118 (1966) and 6 (1) 21 (1970)
I.N. p. 560
Hermans, H.K.F. and Schaper, W.K.A.; US Patent 3,267,164; August 16, 1966; assigned to Janssen Pharmaceutica N.V. (Belgium)

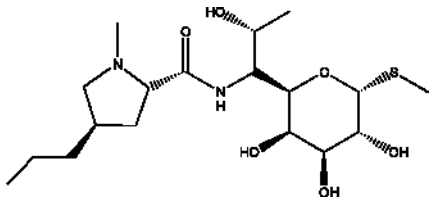
LINCOMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Methyl 6,8-dideoxy-6-(1-methyl-4-propyl-2-pyrrolidinecarboxamido)-1-thio-D-erythro-D-galacto-octopyranoside

Common Name: Lincoinensin

Structural Formula:



Chemical Abstracts Registry No.: 154-21-2; 859-18-7 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Lincocin	Upjohn	UK	1964
Lincocin	Upjohn	US	1965
Lincocine	Upjohn	France	1966
Albiotic	Upjohn	W. Germany	1966
Lincocin	Upjohn	Italy	1966
Cillimicina	Albert Pharma	Spain	-
Cillimycin	Hoechst	W. Germany	-
Lincolcina	Atral	Portugal	-
Mycivin	Boots	UK	-

Raw Materials

Bacterium Streptomyces lincolnensis
Nutrient medium

Manufacturing Process

As described in US Patent 3,086,912, the process comprises cultivating Streptomyces lincolnensis var. lincolnensis in an aqueous nutrient medium containing a source of assimilable carbohydrate and assimilable nitrogen under aerobic conditions until substantial activity is imparted to the medium by production of lincolnensin and isolating the lincolnensin so produced.

References

Merck Index 5328
Kleeman and Engel p. 527
PDR p. 1847
DOT 2 (2) 62 (1966)
I.N. p. 561
REM p. 1212
Bergy, M.E., Herr, R.R. and Mason, D.J.; US Patent 3,086,912; April 23, 1963;assigned to The Upjohn Company
Bergy, ME, Herr, R.R. and Mason, D.J.; US Patent 3,155,580; November 3, 1964; assigned to The Upjohn Company
Argoudelis, A.D., Bannister, B., Hoeksema, H., Kagan, F. and Magerlein, B.J.; US Patent 3,380,992; April 30, 1968;assigned to The Upjohn Company
Jariwala, S.L.; US Patent 4,091204; May 23, 1978; assigned to The Upjohn Company

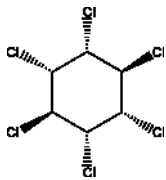
LINDANE

Therapeutic Function: Pediculicide, Scabicide

Chemical Name: 1α,2α,3β,4α,5α,6β-Hexachlorocyclohexane

Common Name: γ-BHC

Structural Formula:



Chemical Abstracts Registry No.: 58-89-9

Trade Name	Manufacturer	Country	Year Introduced
Kwell	Reed Carnrick	US	1952
Gamene	Barnes Hind	US	1975
Escabiol	Stiefel	US	1979
Scabene	Stiefel	US	1981

Trade Name	Manufacturer	Country	Year Introduced
Bicide	Fischer	Israel	-
Gambex	Continental Ethicals	S. Africa	-
HCH-Salbe	VEB Leipziger Arz.	E. Germany	-
Jacutin	Hermal	W. Germany	-
Malice Shampoo	Restan	S. Africa	-
Quellada	Stafford-Miller	UK	-

Raw Materials

Benzene
Chlorine

Manufacturing Process

Chlorine gas was gradually passed into 660 parts of benzene contained in a lead-lined reaction vessel until 890 parts of the gas had been absorbed. The mixture was stirred continuously and the temperature maintained at 15°C to 20°C.

The supply of chlorine was then interrupted and the precipitated solid filtered off and dried. In weight, it was found to be equivalent to 900 parts. The mother liquid was then mixed with 330 parts of benzene and the mixture again treated with 890 parts of chlorine in the manner described.

After filtering the reaction mixture resulting from the second chlorination, the filtrate was again mixed with a smaller quantity of benzene and again chlorinated in a similar manner. In this way, a continuous process for the preparation of benzene hexachloride resulted.

That benzene hexachloride isomer mixture is then the raw material for lindane production. The production of lindane per se is not a chemical synthesis operation but a physical separation process. It is possible to influence the gamma isomer content of benzene hexachloride to an extent during the synthesis process. Basically, however, one is faced with the problem of separating a 99%-plus purity gamma isomer from a crude product containing perhaps 12 to 15% of the gamma isomer. The separation and concentration process is done by a carefully controlled solvent extraction and crystallization process. One such process is described by R.D. Donaldson et al. Another description of hexachlorocyclohexane isomer separation is given by R.H. Kimball.

References

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PDR pp. 1444, 1606, 1779
I.N. p. 561
REM pp. 1239, 1253
Donaldson, R.D. et al; US Patent 2,767,223; October 16, 1956; assigned to Allied Chemical and Dye Corp.
Kimball, R.H.; US Patent 2,767,224; October 16, 1956; assigned to Hooker Electrochemical Co.

Hay,J.K. and Webster, K.C.; US Patent 2,502,258; March 28, 1950; assigned to Imperial Chemical Industries, Ltd.
Hardie, T.; US Patent 2,218,148; October 15, 1940; assigned to Imperial Chemical Industries, Ltd.

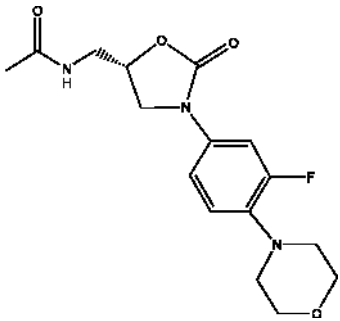
LINEZOLID

Therapeutic Function: Antibacterial

Chemical Name: Acetamide, N-(((5S)-3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-

Common Name: Linezolid

Structural Formula:



Chemical Abstracts Registry No.: 165800-03-3

Trade Name	Manufacturer	Country	Year Introduced
Linosept	Eros Pharma Ltd. (A div. of Microlabs)	India	-
Linospan	Cipla Limited	India	-
Zivox	Pharmacia and Upjohn	USA	-
Zyvox	Pharmacia and Upjohn	USA	-
Zyvoxam	Pharmacia and Upjohn	USA	-

Raw Materials

Butyl lithium
t-Amyl alcohol
Citric acid
Triethylamine
Salicylaldehyde
Morpholine
Sodium azide
S-(+)-3-Chloro-1,2-propanediol
Methanesulfonyl chloride
Potassium t-butoxide
4-Nitrobenzenesulfonyl chloride
Hydrochloric acid
Diisopropylethylamine
Benzyl chloroformate

(R)-Glycidyl butyrate Palladium on carbon
N-Carbobenzoxy-3-fluoro-4-morpholinylaniline

Manufacturing Process

The 1st method of synthesis (Patent US 5,837,870)

N-Carbobenzoxy-3-fluoro-4-morpholinylaniline (3.00 mmol, 1.000 eq) and tetrahydrofuran (3.5 ml) were agitated and cooled. The lithium t-amylate mixture [prepared in THF at 25°C from t-amyl alcohol (0.66 ml, 6.03 mmol, 2.00 eq) and butyl lithium (1.8 ml, 2.5 M in hexanes, 4.55 mmol, 1.5 eq)] is then added to the carbamate mixture at less than 8°C and rinsed in with THF (1 ml).

Tetrahydrofuran (3.2 ml) and S-(+)-3-chloro-1,2-propanediol (0.299 ml, 3.58 mmol, 1.19 eq) are mixed. The mixture of THF (3.2 ml) and S-(+)-3-chloro-1,2-propanediol (0.299 ml, 3.58 mmol, 1.19 eq) is cooled to -16°C and potassium t-butoxide (3.2 ml, 1.0 M) in THF (3.2 mmol, 1.07 eq) is added at less than -10°C. The resulting slurry is stirred at -14-0°C for 1 hour. Then added to the lithium anion mixture while maintaining both mixtures at 0°C, then rinsed in with THF (2 ml). The resultant slurry is stirred at 20-23°C for 2 hour and then cooled to 6°C and a mixture of citric acid monohydrate (0.4459 g, 2.122 mmol, 0.705 eq) in water (10 ml) is added. The resultant liquid phases are separated and the lower aqueous phase is washed with ethyl acetate (12 ml). The organic layers are combined and solvent is removed under reduced pressure until a net weight of 9.73 g remains. Heptane (10 ml) and water (5 ml) are added and solvent is removed 4-nitrobenzenesulfonyl chloride y reduced pressure until a total volume of 5 ml remains. The precipitated product is collected by vacuum filtration and washed with water (7 ml). The solids are dried in a stream of nitrogen to give (R)-[N-3-(3-fluoro-4-(4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol.

To a slurry of (R)-[N-3-(3-fluoro-4-(4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol (43.0 g, 145 mmol) and triethylamine (36 g, 355 mmol) in methylene chloride (450 ml) at 0°C is added a mixture of 4-nitrobenzenesulfonyl chloride (32 g, 145 mmol) in methylene chloride (55 ml). The mixture is stirred in a 0°C bath for 30 min and then quenched with hydrochloric extracted again with methylene chloride (200 ml). The combined organic extracts are then concentrated column chromatographed (silica gel, methanol/methylene chloride 1-2/98-99, about 8 L). The appropriate fractions are combined and concentrated to give the (R)-[N-3-(3-fluoro-4-(4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol 4-nitrobenzenesulfonate ester.

A mixture of (R)-[N-3-(3-fluoro-4-(4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methanol 4-nitrobenzenesulfonate ester, isopropanol (149 ml), acetonitrile (245 ml), salicylaldehyde (13.7 ml, 129 mmol) and aqueous ammonia (30%, 257 ml, 4.02 mol), is heated to 40°C and stirred at 39-42°C for 24 hours. The mixture is then cooled to -22°C and the precipitate collected by vacuum filtration, washed with water (10 ml) and dried to give the (S)-[N-3-(3-fluoro-4-(4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methylamine salicylaldehyde imine.

(S)-[N-3-(3-Fluoro-4-(4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]

methylaminesalicylaldehyde imine (1.0068 g, 2.521 mmol) is slurried in water (10 ml) and 37% aqueous hydrochloric acid (0.417 ml, 5.04 mmol) and stirred at 20-25°C for 15 hours. Toluene (10 ml) is added and the phases separated; then, the organic phase is washed with hydrochloric acid (1 M, 5 ml) and the combined aqueous phases are washed with toluene (10 ml). The toluene wash is back-extracted with hydrochloric acid (1 M, 5 ml). The combined aqueous phases are then adjusted to pH 13.0 with aqueous sodium hydroxide (50%, 1.83 g, 22.9 mmol). To the resultant slurry is then added methylene chloride (10 ml) and sodium chloride (1 g) and the phases separated. The aqueous phase is then washed with methylene chloride (10 ml). To the combined organic phases is then added acetic anhydride (0.472 ml, 5.00 mmol) while maintaining 24-27°C. The mixture is stirred 40 min, then water is added (5 ml). The phases are separated and the aqueous phase is washed with methylene chloride (5 ml). The combined organic phases are concentrated and ethyl acetate (25 ml) is added. The mixture is warmed to 70°C and then the resultant mixture is slowly cooled to -25°C. The precipitate is collected by vacuum filtration, washed with ethyl acetate (5 ml) and dried to give the (S)-[[N-3-(3-fluoro-4-(4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methyl]acetamide, HPLC major component (99.93 area % at 254 nm detection) retention time = 0.97 min, column Zorbax RX-C8, mobile phase 650 ml acetonitrile, 1.85 ml triethylamine, 1.30 ml acetic acid and sufficient water to make 1000 ml; flow rate = 3 ml/min.

The 2 th method of synthesis (Patent U.S. 5,688,792)

A solution of 19.9 g of morpholine, 14.8 g of diisopropylethylamine and 28.7 g of 3,4-difluoronitrobenzene in 100 mL of ethylacetate was refluxed under nitrogen for 4 hours. The mixture was allowed to cool to room temperature overnight, then 100 mL of ethyl acetate, 150 mL of methylene chloride, and 150 mL of water were added, and the aqueous layer extracted with methylene chloride and ethyl acetate. The combined organic layers were dried (Na_2SO_4) to give a yellow solid. This was recrystallized from acetone-water to give 3-fluoro-4-morpholinyl-nitrobenzene as a yellow solid, m.p. = 112-113°C.

To a suspension of 36.56 g of 3-fluoro-4-morpholinyl-nitrobenzene and 48.84 g of ammonium formate in 110 mL of tetrahydrofuran and 440 mL of methanol under nitrogen was added 0.524 g of 10% palladium on carbon. After stirring the mixture for 3 hours, the mixture was filtered through diatomaceous earth, and the filter pad was washed with ethyl acetate. The filtrate was concentrated to a volume of about 450 mL and then 200 mL of water was added. This was extracted with 300 mL of ethyl acetate, then the organic layer was washed with of water and then with brine, dried ($MgSO_4$), and concentrated to give a brown solid of 3-fluoro-4-morpholinyl-aniline.

To a solution of 28.91 g of 3-fluoro-4-morpholinyl-aniline and 27.88 g of sodium bicarbonate in 500 mL of acetone and 250 mL of water at 0°C was added 28.68 g of benzyl chloroformate. After stirring the mixture for 1.5 hours, the mixture was poured onto 1 L of ice and water, and the ice allowed to melt. The precipitated solid was collected by filtration and washed with of water, and then dried in a vacuum oven at 75°C to give a gray-purple solid. This was recrystallized from acetone-water to give a cream-colored solid of N-carbobenzyloxy-3-fluoro-4-morpholinylaniline, m.p. = 123-124°C.

To a solution of 39.01 g of N-carbobenzyloxy-3-fluoro-4-morpholinylaniline in

550 mL of THF at -78°C under nitrogen was added 77 mL of 1.6 M n-butyl lithium/hexane via syringe over 30 min, and the mixture stirred for an additional 40 min. At that time, a solution of 18.32 g of (R)-glycidyl butyrate in 30 mL of THF was added over 30 min, and after 1.5 hours, the flask was removed from the dry ice bath, and allowed to come to ambient temperature. After stirring the mixture overnight, 20 ml of saturated aqueous ammonium chloride was added, followed by 500 mL of water, and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with 200 mL of brine and dried ($MgSO_4$) to give a light purple solid. This is triturated with 1200 mL of 1:1 ethyl acetate/hexanes (v:v), then recrystallized from ethyl acetate/hexanes to give a white solid of (R)-N-[[3-(3-fluoro-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol, m.p. 110-113°C.

To a solution of 13.28 g of (R)-N-[[3-(3-fluoro-4-morpholinyl]phenyl)-2-oxo-5-oxazolidinyl]methanol and 8.71 g of triethylamine in 100 mL of methylene chloride at 0°C under nitrogen was added 7.4 g of methanesulfonyl chloride over 4 min. The mixture was allowed to stir at 0°C for 30 min, then allowed to warm to ambient temperature. A white solid of (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methane sulfonate was precipitated and dried in a vacuum, m.p. = 183-184°C.

To a solution of (R)-N-[[3-(3-fluoro-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methane sulfonate (9.05 g) in 200 mL of DMF was added 6.367 g of sodium azide, and the mixture heated at 85°C overnight. The mixture was cooled and poured into 500 mL of water and 150 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried ($MgSO_4$), and concentrated in vacuum. The brown oil of (R)-N-[[3-(3-fluoro-4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]azide, containing some DMF, was utilized without further purification.

A flask containing the crude (R)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]azide (24.2 mmol) in 500 mL of ethyl acetate was evacuated and filled with nitrogen (three times). Then 0.602 g of 10% palladium/carbon was added and the flask again evacuated and filled with nitrogen (three times), then with hydrogen from a balloon (four times). The mixture was stirred for 17 hours, then a fresh balloon of hydrogen was attached. After a period of 5 hours, the flask was evacuated and filled with nitrogen (three times), and 16 mL of pyridine and 10 mL of acetic anhydride were added. After a period of 2.5 hours, the mixture was filtered over diatomaceous earth, washing the pad with ethyl acetate, and the filtrate concentrated in vacuo to give a brown gummy solid. The residue was purified by chromatography (silica gel column, eluting with a gradient of 2-10% methanol/ethyl acetate (v/v); the combined proper fractions gave an off white solid, which was triturated with ethyl acetate and dried to give an off white solid of (S)-N-[[3-(3-fluoro-4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl] methyl]acetamide, m.p. 181.5-182.5°C.

References

Barbachyn M.R. et al.; US Patent No. 5,688,792; Nov. 18, 1997; Assigned to Pharmacia and Upjohn Company (Kalamazoo, MI)

Pearlman B.A. et al.; US Patent No. 5,837,870; Nov.17, 1998; Assigned to Pharmacia and Upjohn Company (Kalamazoo, MI)

Lobray B.D. et al.; Tetrahedron Lett., 1999, 40(26), 4855

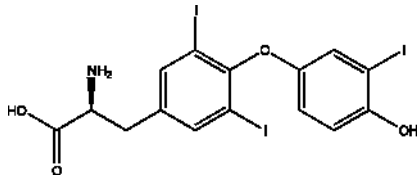
LIOTHYRONINE

Therapeutic Function: Thyroid hormone

Chemical Name: O-(4-Hydroxy-3-iodophenyl)-3,5-diiodo-L-tyrosine

Common Name: 3,5,3'-Triiodothyronine; L-3-[4-(4-Hydroxy-3-iodophenoxy)-3,5-diiodophenyl]alanine

Structural Formula:



Chemical Abstracts Registry No.: 6893-02-3; 55-06-1 (Sodium Salt)

Trade Name	Manufacturer	Country	Year Introduced
Cytomel	SKF	US	1956
Cynomel	Merrell	France	1961
Cytobin	Norden	US	-
Cytomine	Darby	US	-
Ro-Thyronine	Robinson	US	-
Tertroxin	Glaxo	UK	-
Thybon	Hoechst	W. Germany	-
Thyronamin	Takeda	Japan	-
Thyronine	Taisho	Japan	-
Tiromel	Abdi Ibrahim	Turkey	-
Ti-Tre	Glaxo	Italy	-
Trijodthyronin	Nyegaard	Norway	-
Trithyron	Millot	France	-

Raw Materials

L-Diiodothyronine
Iodine

Manufacturing Process

The 3,5-diiodo compound used as a starting material is a known material and may be prepared by the method in British Patents 643,089 and 671,070 and in the Journal of the Chemical Society, London, 1949, page 3424.

Synthesis: L-diiodo thyronine (1.05 g) is dissolved in ammonia (specific gravity 0.880) (40 ml) and methanol (40 ml) and iodinated slowly with shaking with N-iodine in KI solution at room temperature. After iodination,

most of the ammonia and methanol are removed by evaporation under diminished pressure, water is added to the original volume, the solution is heated to 60°C and brought to pH 4 with hydrochloric acid. A crystalline precipitate is obtained which after cooling to room temperature is collected and washed with water. At this stage, the crude triiodo thyronine is contaminated with thyroxine and a little unchanged diiodo thyronine.

Purification: The crude precipitate is dissolved in boiling 2N HCl (300 ml) and filtered from the relatively insoluble thyroxine hydrochloride. The hot filtrate is brought to pH 4 with 5N NaOH and triiodo thyronine again separates; after chilling at 0° to 4°C it is collected, washed with water and dried. The yield of triiodo thyronine is 70 to 75% of the theoretical. This triiodo thyronine still contains some thyroxine (about 10%).

The final purification consists of chromatographic separation of thyroxine and triiodo thyronine on a kieselguhr column using 20% chloroform in n-butanol equilibrated with 0.5N NaOH as the developing solvent. 80 to 100 mg triiodo thyronine is purified during each run on a 50 g kieselguhr column. Pure L-triiodo thyronine has MP 236° to 237°C (dec.) and $[\alpha]_D^{29.5^\circ}$ = +21.5 in a 4.75% solution in a mixture of 1 part of N HCl and 2 parts of ethanol. Liothyronine is commonly used as the sodium salt.

References

Merck Index 5337
Kleeman and Engel p. 527
PDR pp. 1606, 1709
OCDS Vol. 1 p. 97 (1977)
I.N. p. 562
REM p. 980
Pitt-Rivers, R. and Gross,J.; US Patent 2,823,164; February 11,1958; assigned to National Research Development Corporation, England
Platt, J.T. and Wenner, W.; US Patent 2,784,222; March 5, 1957; assigned to Hoffmann-La Roche Inc.
Razdan, R.K. and Wetherill, L.A.; US Patent 2,993,928; July 25, 1961;assigned to Glaxo Laboratories, Ltd.

LISINOPRIL

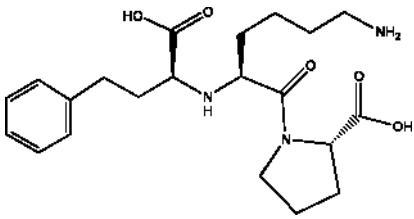
Therapeutic Function: Antihypertensive

Chemical Name: L-Proline, 1-(N^2)-(1-carboxy-3-phenylpropyl)-L-lysyl)-,(1S)-

Common Name: Lisinopril

Chemical Abstracts Registry No.: 76547-98-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Acebitor 5	Biddle Sawyer	India	-
Acemin	AstraZeneca	-	-
Acemin	ICI	-	-
Acetan	Merck Sharp and Dohme	-	-
Acetan	Kwizda	-	-
Acinopril	Nicholas Piramal India Ltd. (Npil)	India	-
Adicanil	Pharmathen	Greece	-
Biopril	Biochem Pharma Industries	India	-
Cipril	Cipla Limited	India	-
Cipril-H	Cipla Limited	India	-
Doxapril	Labs. Bago S. A.	Argentina	-
Ecalisin	Eurolabor	-	-
E.S.	Stadmed Private Limited	India	-
Hipril	Carsyon (Div. Of Microlabs)	India	-
Irumed	Belupo Ltd.	Croatia	-
Landolaxin	Faran Abee	Greece	-
L.P.L.	Concept Pharmaceuticals Ltd.	India	-
Lesopril	Themis Pharmaceuticals Ltd.	India	-
Linoril	Stadmed Private Limited	India	-
Linvas	Zydus Cadila	India	-
Lipril	Lupin Laboratories Ltd.	India	-
Lisinace	Alkem Laboratories Ltd.	India	-
Lisir	Kramer	India	-
Lislo	SPPL (Sarabhai Piramal Pharmaceuticals Ltd.)	India	-
Lisoril	IPCA laboratories Ltd.	India	-
Lisoril-5 Ht	IPCA laboratories Ltd.	India	-
Listril	Torrent Pharmaceuticals Ltd.	India	-
Listril Plus	Torrent Pharmaceuticals Ltd.	India	-
Nafodryl	Costas G. Xydias and Co.	Greece	-
Nivant	German Remedies Limited	Germany	-
Normopril	Otsira Genetica (A Div. Of Aristo Pharma Ltd.)	India	-
Odace	Zydus Medica	India	-

Trade Name	Manufacturer	Country	Year Introduced
Presokin	Chemopharma	Chile	-
Presokin	Sanitas	-	-
Prevace	RPG Life Sciences Ltd.	India	-
Sedotensil	Sanofi Winthrop	France	-
Sedotensil	Ramon	-	-
Tensopril	Syncro	-	-
Tensopril	IVAX Arg.	-	-
Tensopril	Teva	Israel	-
Veroxil	Anfarm	-	-
Zestril	AstraZeneca	Chile	-
Zestril	ICI India Limited	India	-

Raw Materials

Cyanoborohydride
XAD-2 resin
LH-20
2-Oxo-4-phenylbutyric acid
Sodium cyanoborohydride
t-BOC-L-lysyl-L-proline

Manufacturing Process

2-Oxo-4-phenylbutyric acid and t-BOC-L-lysyl-L-proline are condensed in the presence of sodium cyanoborohydride. Essentially all of the t-BOC protecting group is cleaved when the product is absorbed on strong acid ion exchange resin. The crude N-(1-carboxy-3-phenylpropyl)-L-lysyl-L-proline is eluted from the resin with 10% ammonia, freeze dried, and purified by gel filtration chromatography (LH-20). A minute peak for t-BOC protons in the NMR spectrum disappears when the product is treated with ethyl acetate that is 4 N in hydrogen chloride gas. The NMR spectrum of the resulting HCl salt of the product is consistent with structure. The mass spectrum shows a molecular ion at 693 m/e for the tetrasilylated species. Chromatography on XAD-2 resin using 3.5% acetonitrile in 0.1 molar ammonium hydroxide affords N-α-((1S)-1-carboxy-3-phenylpropyl)-L-lysyl-L-proline. The last peptide can be produced if 2-oxo-4-phenylbutyric acid and N-t-Boc-L-lysyl-L-proline are condensed in the presence of sodium cyanoborohydride. The product is absorbed on strong acid ion exchange resin, and eluted with 2% pyridine in water. Product-rich cuts are stripped to a glass and treated with 4 N HCl in ethylacetate to remove the t-Boc protecting group. The resulting hydrochloride salt is converted to the free base by absorbing on strong acid ion exchange resin and eluting with 2% pyridine in water. Freeze drying of product-rich cuts affords N-α-(1-carboxy-3-phenylpropyl)-L-lysyl-L-proline as a white fluffy solid. The NMR spectrum is consistent with structure. The mass spectrum shows a molecular ion at 549 for the disilylated species. Chromatography affords the desired isomer.

References

Harris E.E. et al.; US Patent No. 4,374,829; Feb. 22, 1983; Assigned: Merck and Co., Inc. (Rahway, NJ)

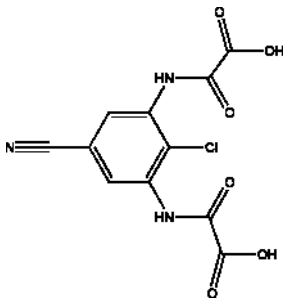
LODOXAMIDE

Therapeutic Function: Anti-asthmatic, Antiallergic

Chemical Name: 2,2'-((2-Chloro-5-cyano-1,3-phenylene)diimino)bis(2-oxo-acetic acid)

Common Name: Lodoxamide

Structural Formula:



Chemical Abstracts Registry No.: 53882-12-5

Trade Name	Manufacturer	Country	Year Introduced
Lodoxamide	Alcon	USA	-

Raw Materials

Stannous chloride dihydrate
4-Chloro-3,5-dinitrobenzonitrile
Ethyloxalyl chloride
Concentrated hydrochloric acid

Manufacturing Process

To a solution of 1.56 mole of stannous chloride dihydrate in 860 ml of concentrated hydrochloric acid is added 0.2195 mole of 4-chloro-3,5-dinitrobenzonitrile. The mixture is stirred at room temperature for 2 hours and cooled to 0°C in an ice-salt bath. A cold solution of 50% sodium hydroxide is added to the mixture until strongly basic. During the addition the temperature is kept below 30°C.The precipitate is removed by filtration and extracted three times with 400 ml of ethyl acetate. The extracts are combined and added to the aqueous filtrate. The phases are shaken well for ten minutes and separated. The organic phase is evaporated to dryness in vacuo. The solid residue is recrystallized from ethanol-water. There is obtained 25.0 g (68%) of 4-chloro-3,5-diaminobenzonitrile, melting point 169-170°C.

To a solution of 0.34 mole of 4-chloro-3,5-diaminobenzonitrile in 160 ml of dry DMF is added 0.82 mole of triethylamine. The solution is cooled to 5°C and

there is added 0.82 mole of ethyloxalyl chloride dropwise, keeping the temperature less than 15°C. The mixture is stirred for 1 hour and warmed to room temperature. The mixture is stirred at room temperature for 24 hours. The precipitate is removed by filtration and washed two times with ethyl acetate. The filtrate and washes are combined and the ethyl acetate distilled off in vacuo. The DMF solution is poured into 3 L of water. The semi-solid residue is removed by filtration. The residue is recrystallized from ethanol. There is obtained 72.4 g (58%) of diethyl N,N'-(2-chloro-5-cyano-m-phenylene)dioxamate, melting point 177-179°C.

A solution of 0.197 mole of diethyl (N,N'-(2-chloro-5-cyano-m-phenylene) dioxamate in 750 ml of methylene chloride is extracted with 465 ml of 1 N sodium hydroxide. The aqueous phase is separated and stirred for 20 min at room temperature. The solution is acidified with dilute hydrochloric acid. The precipitate is removed by filtration and washed with water. There is obtained 59.1 g (96%) of N,N'-(2-chloro-5-cyano-m-phenylene)dioxamic acid, melting point 212°C (dec.).

References

Hall Ch. M., Wright J.B.; US Patent No. 3,993,679; 11.23.1976; Assigned to The Upjohn Company

Aoki K.R. et al.; US Patent No. 5,457,126; Oct. 10, 1995; Assigned: Alcon Laboratories, Inc. (Fort Worth, TX)

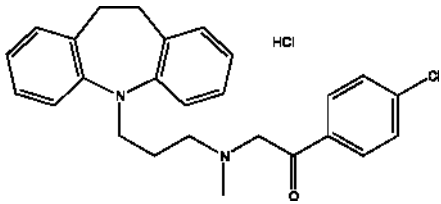
LOFEPRAMINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: Ethanone, 1-(4-chlorophenyl)-2-((3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyl)methylamino)-, hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26786-32-3; 23047-25-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Gamonil	E. Merck	-	-
Tymelyt	Leo	-	-

Trade Name	Manufacturer	Country	Year Introduced
Tymelyt	Lundbeck	-	-
Amplit	Daiichi	-	-
Gamanil	Merck KGaA	-	-
Timelit	UCB	-	-
Timelit	Montefarmaco	-	-
Lofepramine hydrochloride	Shanghai Lansheng Corporation	-	-
Deftan	Merck	-	-
Deprimyl	Merck Portuguesa	-	-
Emdalen	Merck	-	-
Lomont	Rosemont	-	-

Raw Materials

10,11-Dihydro-5H-dibenzo[b,f]azepine
1-(4-Chlorophenyl)-2-[(3-chloropropyl)methylamino]ethanone
Sodium amide

Manufacturing Process

9.8 parts of 10,11-dihydro-5H-dibenzo[b,f]azepine are dissolved in 10 parts of dry toluene and 3.1 parts of sodium amide are added and the mixture is refluxed and stirred for four hours. A solution of 13.5 parts of 1-(4-chlorophenyl)-2-[(3-chloropropyl)methylamino]ethanone in 20 parts of dry toluene is added dropwise and the mixture is stirred and refluxed for eight hours.

After cooling to room temperature water is carefully added to the reaction mixture and the toluene solution is extracted with water to which hydrochloric acid is added so that the aqueous phase obtains the pH-value of 5. The aqueous extract is discarded and the toluene phase is evaporated to dryness in vacuum. The residue is dissolved in 50 parts of methanol. Hydrogen gas is introduced to give the crystalline hydrochloride 1-(4-chlorophenyl)-2-((3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)propyl)methylamino)ethanone; MP: 154°-156°C. The hydrochloride may be removed by adding an equivalent of any base (triethyl amine, sodium hydroxide and so on).

References

Eriksoo E. et al.; US Patent No. 3,637,660; Jan. 25, 1972; Assigned to Aktiebolaget Leo, Halsingborg, Sweden

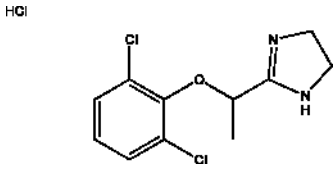
LOFEXIDINE HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 21498-08-8

Trade Name	Manufacturer	Country	Year Introduced
Lofetensin	Nattermann	W. Germany	1981

Raw Materials

α-2,6-Dichlorophenoxypropionitrile
Hydrogen chloride
Ethanol
Ethylenediamine

Manufacturing Process

10.4 ml of absolute ethanol are added to 57.5g of α-2,6-dichlorophenoxypropionitrile, followed by the introduction of 100 ml of chloroform dried over phosphorus pentoxide; 10.4 g of carefully dried hydrogen chloride being slowly introduced with stirring and cooling with ice/common salt. Most of the chloroform and excess hydrogen chloride is then removed by filtration in vacuo at room temperature, and dry ether added to the residue until the imido acid ester hydrochloride is quantitatively precipitated. The α-dichlorophenoxypropionimido acid ethyl ester hydrochloride can be obtained analytically pure in the form of white, strongly hygroscopic crystals by repeated dissolution in a little absolute ethanol in the absence of heat, and precipitation with ether.

The crude α-(2,6-dichlorophenoxy)propionamido acid ethyl ester hydrochloride is added in portions to a stirred, ice-cooled solution of 29.5 g of anhydrous ethylenediamine in 200 ml of absolute ethanol in such a way that the temperature does not exceed 0°C to 5°C. The cooling bath is then removed and the reaction mixture heated for 1 hour on a water bath to approximately 70°C.

After cooling, unreacted ethylenediamine is neutralized in a cooling mixture with the absolute ethanolic hydrochloric acid, filtered off from any components that are insoluble in ethanol and approximately two-thirds of the solvent filtered off under suction in a water jet pump vacuum. Residual quantities of

ethylenediamine dihydrochloride are precipitated in fractions by the careful addition of ethyl methyl ketone, after which the imidazoline hydrochloride is separated off by the addition of dry ether. Following repeated recrystallization from ethanol ether, 2-[α-(2,6-dichlorophenoxy)ethyl]-δ^2-imidazoline hydrochloride is obtained in the form of small white crystals melting at 221°C to 223°C.

References

Merck Index 5388
DFU 3 (8) 592 (1978)
DOT 19 (9) 496 (1983)
I.N. p. 566
Baganz, H. and May, H.J.; US Patent 3,966,757; June 29, 1976; assigned to A. Natterman and Cie GmbH

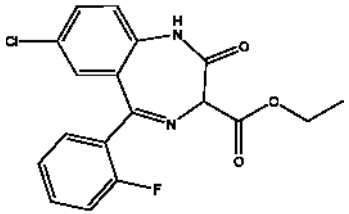
LOFLAZEPATE ETHYL

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepine-3-carboxylic acid ethyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 29177-84-2

Trade Name	Manufacturer	Country	Year Introduced
Victan	Clin Midy	France	1982

Raw Materials

2-Methylimidazole HCl
2-Amino-5-chloro-2'-fluoro-benzophenone
Ethyl aminomalonate hydrochloride

Manufacturing Process

(A) 1-(2-Amino-5-chlorophenyl)-1-(2-fluorophenyl)-2-aza-buty1-en-4-ol: A mixture of 40 g of 2-methylimidazole hydrochloride and of 90 g of 2-amino-5-chloro-2'-fluoro-benzophenone in 240 ml of ethanolamine is heated at 135°C for 2 hours. After cooling, the reaction mixture is poured into an aqueous sodium bicarbonate solution. The mixture is extracted with ether, the organic phase is washed repeatedly with water and is dried over sodium sulfate, and the solvent is evaporated to dryness. The residual oil is chromatographed on a silica column, elution being carried out with a 50/50 mixture of cyclohexane and ethyl acetate.

88 g of the expected amine are thus isolated. Melting point: 105°C to 110°C.

(B)1-(2-Amino-5-chlorophenyl)-1-(2-fluorophenyl)-3,3-bis-(ethoxycarbonyl)-2-aza-prop-1-ene: A mixture of 88 g of the product obtained above, 300 g of ethyl aminomalonate hydrochloride and 60 ml of acetic acid in 2.3 liters of absolute ethanol is heated to the reflux temperature for 6 hours. The alcohol and the acetic acid are evaporated in vacuo and the residue is taken up in ether. The solution is washed with a dilute sodium bicarbonate solution and then with water and is dried over sodium sulfate. The solvent is evaporated and the residue is then chromatographed on a silica column, using a 90/10 mixture of chloroform and ethyl acetate for the elution. An oil (64g) is thus obtained, and is used, without further treatment, for the cyclization.

A sample recrystallized from isopropyl ether has a melting point of 119°C.

(C) Compound of Code No. CM 6912: 25 g of the imine obtained under (B), dissolved in 400 ml of acetic acid, are heated at the reflux temperature for 1 hour. After evaporating the solvent in vacuo, the residue is taken up in methylene chloride. The solution is washed with a dilute sodium bicarbonate solution and then with water. After evaporating the solvent, the residue is chromatographed on silica, elution being carried out with an 80/20 mixture of ether and ethyl acetate. 9 g of benzodiazepine are thus obtained. Melting point: 196°C.

References

Merck Index 3766
DFU 6 (12) 772 (1981)
DOT 19 (1) 24 (1983)
I.N. p. 566
Demarne, H. and Hallot, A.; British Patent 1,538,165; January 17, 1979; assigned to C.M. Industries (France)

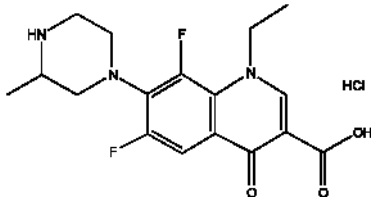
LOMEFLOXACIN HYDROCHLORIDE

Therapeutic Function: Antibacterial

Chemical Name: 3-Quinolinecarboxylic acid, 1,4-dihydro-6,8-difluoro-1-ethyl-7-(3-methyl-1-piperazinyl)-4-oxo-, hydrochloride

Common Name: Lomefloxacin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 98079-52-8; 98079-51-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Foxil	Sarabhai Chemicals	India	-
Liexina	Leti	-	-
Lomaday	Dr. Reddy's Laboratories Ltd.	India	-
Lomefloxacine hydrochloride	Searle Chemical Inc.	USA	-

Raw Materials

1-Ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid
2-Methylpiperazine
Pyridine
Sodium bicarbonate

Manufacturing Process

A mixture of 1.00 g of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 1.10 g of 2-methylpiperazine and 10 ml of pyridine was heated for 15 minutes under reflux. The reaction mixture was evaporated and methanol was added to the residue. The precipitate was filtered and recrystallized from ethanol to give 0.36 g of the 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid as colorless needles, melting point 239.0-240.5°C.

By the usual manner the hydrochloride was prepared and recrystallized from water as colorless needles, melting point 290-300°C (decomp.).

References

Yasuo Itoh et al.; US Patent No. 4,528,287; 07.09.1985; Assigned to Hokuriku Pharmaceutical Co., Ltd.

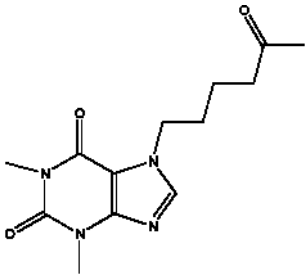
LOMIFYLLINE

Therapeutic Function: Vasodilator

Chemical Name: Purin-2,6-dione, 1,2,3,6-tetrahydro-1,3-dimethyl-7-(5-oxohexyl)-

Common Name: Lomifylline

Structural Formula:



Chemical Abstracts Registry No.: 10226-54-7

Trade Name	Manufacturer	Country	Year Introduced
Lomifylline	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-
Lomifylline	Shanghai Lansheng Corporation	-	-

Raw Materials

1,3-Dibromopropane
Ethyl acetoacetate
Hydrobromic acid
Theophylline sodium

Manufacturing Process

A mixture of 560 g of potassium carbonate, 700 ml of ethanol (96%), 404 g of 1,3-dibromopropane and 260 g of ethyl acetoacetate was heated with stirring to go 60°C. After the reaction had subsided, the reaction mixture was refluxed for 5 hours. Then the bulk of the alcohol was distilled off under ordinary pressure and the residue was mixed with 1.5 L of water. The resulting oily layer was separated, and the aqueous phase was extracted with benzene and the benzene layer was combined with the oil. After drying with sodium sulfate the benzene was distilled off and the residue was fractionally distilled 250 g (73% of theory) of 2-methyl-3-carbethoxy-5,6-dihydropyrane of boiling point 105°-108°C were obtained.

140 ml of 63% hydrobromic acid were slowly added at room temperature to 128 g of 2-methyl-3-carbethoxy-5,6-dihydropyrane, and much carbon dioxide

was evolved. After standing for 1 to 2 days at room temperature the mixture was diluted with an equal volume of iced water; the layer of dark colored oil formed was separated, the aqueous phase was extracted with chloroform, and the extract was combined with the oil and washed with a saturated solution of sodium bicarbonate. The solution was dried with sodium sulfate, the chloroform was distilled off under normal pressure, and the residue was fractionally distilled in vacuo. 109 g (81% of theory) of 1-bromohexanone-5 of boiling point 94°-98°C/12 mm Hg were obtained.

A solution of 10.0 g of 1-bromohexanone-5 in 100 ml of ethanol was gradually mixed at the boil with vigorous stirring with 11.3 g of the sodium salt of theophylline in 100 ml of water. After 3 hours refluxing the alcohol was distilled off, and the residual aqueous phase was cooled and made alkaline and extracted with chloroform. The chloroform solution was evaporated and the residue re-crystallized from a little isopropanol to yield 7-(5-oxohexyl) theophylline. MP: 75°-76°C; a yield of about 80% (calculated on the reacted theophylline).

References

Mohler W. et al.; US Patent No. 3,422,107; Jan. 14, 1969; Assigned to Chemische Werke Albert, Wiesbaden-Biebrich, Germany, a corporation of Germany

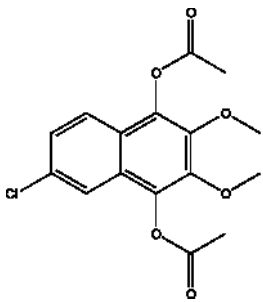
LONAPALENE

Therapeutic Function: Antipsoriatic

Chemical Name: 1,4-Naphthalenediol, 6-chloro-2,3-dimethoxy-, diacetate

Common Name: Lonapalene

Structural Formula:



Chemical Abstracts Registry No.: 91431-42-4

Trade Name	Manufacturer	Country	Year Introduced
Lonapalene	Syntex	-	-

Raw Materials

Sodium nitrate
6-Amino-2,3-dimethoxy-1,4-naphthoquinone
Hydrochloric acid
Copper chloride

Manufacturing Process

A solution of sodium nitrate (0.69 g, 10 mmol) in water (5 ml) was added at 0-5°C to a solution of 6-amino-2,3-dimethoxy-1,4-naphthoquinone (1.17 g, 5 mmol) in 5:1 acetic acid:water (25 ml) containing concentrated hydrochloric acid (1.7 ml). A further quantity of sodium nitrite (0.69 g) was then added to the reaction mixture after cooling to -5°C, followed by a solution of cuprous chloride (0.6 g) in concentrated hydrochloric acid (5 ml). The mixture was allowed to warm to room temperature and solid cuprous chloride was added portionwise until the mixture assumed a green color. Water was then added to the reaction mixture and the precipitated yellow solid filtered off, washed with water and recrystallized from methanol:water (2:1) giving 1.01 g of 6-chloro-2,3-dimethoxy-1,4-naphthoquinone, melting point 93-94°C (from ether-petrolium ether).

References

Jones Gordon H., Venuti Michael C., Young John M.; US Patent No. 4,466,981; August 21, 1984; Assigned to Syntex (U.S.A.) Inc. (Palo Alto, CA)
Jones G. H. et al.; Eur. pat. Appl. 107,512
Tetrahedron Letters 28, 4507 (1987)

LONAZOLAC

Therapeutic Function: Antiinflammatory

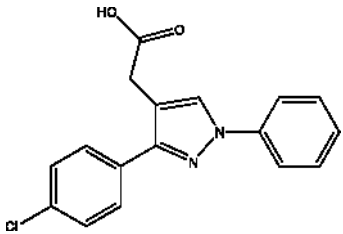
Chemical Name: 3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4-acetic acid

Common Name: -

Chemical Abstracts Registry No.: 53808-88-1

Trade Name	Manufacturer	Country	Year Introduced
Irriten	Tosse	W. Germany	1981
Irritren	Byk Gulden	Switz.	1982

Structural Formula:



Raw Materials

1-Phenyl-3-(p-chlorophenyl)-pyrazol-4-acetonitrile
Hydrogen chloride

Manufacturing Process

17.6 g 1-phenyl-3-(p-chlorophenyl)-pyrazol-4-acetonitrile and 180 ml 25% aqueous hydrochloric acid were mixed and heated to the boiling temperature under reflux for 6 hours. To the mixture was then added dropwise concentrated aqueous sodium hydroxide until the pH of the mixture reached a value in the range from 3 to 5. The free pyrazol-4-acetic acid precipitated thereby was filtered off, redissolved in dilute aqueous sodium hydroxide, the solution cleared by treatment with activated carbon, and the pyrazol-4-acetic acid precipitated by acidifying the solution by the addition of dilute mineral acid, sulfuric acid. The filtered acid was crystallized from a mixture of ethanol and water. 17.1 g 1-phenyl-3-(p-chlorophenyl)pyrazol-4-acetic acid, melting at 148°C to 150°C, were obtained, representing a yield of 91%.

References

Merck Index 5392
DFU 7 (2) 110 (1982)
DOT 18 (4) 184 (1982)
I.N. p. 567
Rainer, G.; US Patent 4,146,721; March 27, 1979; assgned to Byk Gulden Lomberg Chemische Fabrik G.m.b.H. (W. Germany)

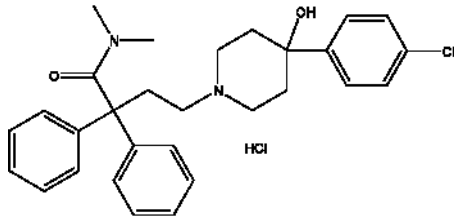
LOPERAMIDE HYDROCHLORIDE

Therapeutic Function: Antidiarrheal

Chemical Name: 4-(4-Chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutanamide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34552-83-5; 53179-11-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Imodium	Janssen	UK	1975
Imodium	Janssen-Le Brun	France	1976
Imodium	Janssen	W. Germany	1976
Imodium	Ortho	US	1977
Dissenten	S.P.A.	Italy	1978
Imodium	Janssen	Italy	1979
Lopemid	Gentili	Italy	1979
Imodium	Januen	Switz.	1981
Imodium	Dainippon	Japan	-
Blox	Biomedica Foscama	Italy	-
Brek	Irbi	Italy	-
Fortasec	Esteve	Spain	-
Lopermid	Drifen	Turkey	-
Loperyl	Zambeletti	Italy	-
Regulane	Finadiet	Argentina	-
Seldiar	Krka	Yugoslavia	-
Tebloc	Dukron	Italy	-

Raw Materials

Hydrogen bromide	2-Oxo-3,3-diphenyl-tetrahydrofuran
Thionyl chloride	4-(p-Chlorophenyl)-4-piperidinol
Dimethylamine	Hydrogen chloride

Manufacturing Process

23.6 parts of 2-oxo-3,3-diphenyl-tetrahydrofuranare melted at 100°C in an oil-bath and gaseous hydrogen bromide is introduced into it during 3 hours. The reaction mixture is cooled and triturated in benzene. The product is filtered off, washed with petroleum ether and dried in an exsiccator, yielding 4-bromo-2,2-diphenylbutyric acid; MP 127.5%.

To a stirred suspension of 16 parts of 4-bromo-2,2-diphenylbutyric acid in 150 parts of chloroform are added dropwise 16 parts of thionyl chloride and the whole is stirred and refluxed for 2 hours. The reaction mixture is evaporated,

yielding 4-bromo-2,2-diphenyl-butyrylchloride as a residue.

60 parts of 4-bromo-2,2-diphenylbutyrylchloride are dissolved in 400 parts of toluene and gaseous dimethylamine is introduced slowly into the solution while cooling (temperature is kept at about 0°C). The introduction is ceased when dimethylamine escapes from the cooler, and stirring is continued for 2 hours at ordinary temperature. The precipitated product is filtered off and dissolved in a minimum quantity of water. The product is extracted with chloroform. The extract is dried and evaporated. The residue solidifies on triturating in 4-methyl-2-pentanone. The solid is filtered off and dried, yielding dimethyl -(tetrahydro-3,3-diphenyl-2-furylidene)ammonium bromide; MP 169° to 171.5°C.

A mixture of 6.33 parts of 4-(p-chlorophenyl)-4-piperidinol, 8 parts of sodium carbonate, 0.2 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is distilled azeotropically. Then there are added 12.12 parts of dimethyl-(tetrahydro-3,3-diphenyl-2-furylidene)ammonium bromide (from the preceding step) and the whole is stirred and refluxed for about 15 hours. The reaction mixture is filtered hot and the filtrate is evaporated.

The oily residue is dissolved in 2-propanol and to this solution is added an excess of 2-propanol previously saturated with gaseous hydrogen chloride. The whole is evaporated and the oily residue is warmed in diluted hydrochloric acid solution. Upon the addition of toluene, the salt is precipitated. It is filtered off, boiled in acetone, and filtered off again after cooling, yielding 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenylpiperidine-1-butyramide hydrochloride; MP 222.1°C.

References

Merck Index 5396
Kleeman and Engel p. 530
PDR p. 953
OCDS Vol. 2 p. 334 (1980)
DOT 10 (6) 220 (1974)
I.N. p. 567
REM p. 814
Janssen, P.A.J., Niemegeers, C.J.E.J., Stokbroekx, R.A. and Vandenberk, J.; US Patent 3,714,159; January 30, 1973; and US Patent 3,884,916; May 20, 1975; both assigned to Janssen Pharmaceutica, NV, Belgium

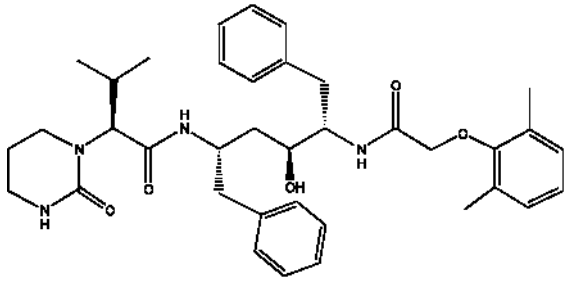
LOPINAVIR

Therapeutic Function: Antiviral

Chemical Name: 1(2H)-Pyrimidineacetamide, N-((1S,3S,4S)-4-(((2,6-dimethylphenoxy)acetyl)amino)-3-hydroxy-5-phenyl-1-(phenylmethyl) pentyl)tetrahyrdo-α-1-methylethyl)-2-oxo-, (αS)-

Common Name: Lopinavir

Structural Formula:



Chemical Abstracts Registry No.: 192725-17-0

Trade Name	Manufacturer	Country	Year Introduced
ABT 378	Abbott Laboratories	-	-
Aluviran	Abbott Laboratories	-	-
Kaletra	Abbott	-	-
Lopinavir	Abbott Laboratories	-	-

Raw Materials

Chloroacetic acid	2,6-Dimethylphenol
Oxalyl chloride	Sodium hydroxide
Trifluoroacetic acid	Valine methyl ester, (S)-, hydrochloride
Hydrogen chloride	Benzyl chloroformate
Nickel Raney	Palladium hydroxide
Lithium hydroxide	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
2-Amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexanesuccinate, (2S,3S,5S)-	

Manufacturing Process

2,6-Dimethylphenol (102.8 g, 0.842 mol) and chloroacetic acid (159.6 g, 1.68 mol) in 1000 ml of H_2O was added to a 3-L 3-necked round bottom flask with mechanical stirring and a water-cooled condenser. A solution of NaOH (134.9 g, 3.37 mol) dissolved in 500 ml of water was slowly added to the above mixture and heat to reflux. After 2 hours, additional chloroacetic acid (79.4 g, 0.84 mol) and NaOH solution (67.2 g, 1.68 mol in in 200 ml water) was added to the reaction mixture. After 19 hours, additional chloroacetic acid (39.8 g, 0.42 mol) and NaOH solution (33.6 g, 0.84 mol in in 100 ml water) was added to the reaction mixture and refluxing was continued until starting phenol was consumed. The reaction flask was cooled in and ice-water bath and acidified to pH 1 with conc. HCl, causing a precipitate to form. The resulting slurry was stirred in the ice bath for 1 hour then filtered. The solid was dissolved in hot water and cooled to crystallize 2,6-dimethylphenoxyacetic acid as white plates, m.p. 136-137°C, yield 78.8 g, 52%.

Oxalyl chloride (36.3 ml, 0.42 mol) was added to a slurry of 2,6-dimethylphenoxyacetic acid (50 g, 0.28 mol) in 500 ml toluene followed by addition of 5 drops of DMF and stirred at 20C for 30 min, then at 55°C for 1.5

hours. The toluene was removed in vacuum to afford 2,6-dimethylphenoxyacetyl chloride as an oil, yield 55 g, 100%.

(2S,3S,5S)-2-Amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexanesuccinate (111.9 g, 0.25 mol) was charged to a 2-L 3-necked flask with mechanical stirring. $NaHCO_3$ (106 g, 1.26 mol), 600 ml H_2O and 600 ml EtOAc were added and stirred until solids were dissolved (15 min). A solution of the 2,6-dimethyl-phenoxyacetyl chloride and EtOAc (100 ml) was added. After 30 min starting materials were consumed (HPLC analysis) and the layers were separated. The aqueous layer was extracted with EtOAc, the organic layers were combined and washed with 200 ml of 1 M NaOH, 200 ml of 10% HCl, 200 ml of brine, dried over $MgSO_4$, filtered and concentrated to provide (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane as a white solid.

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane(175.1 g, 0.32 mol) and 500 ml CH_2Cl_2 were mixed with CF_3CO_2H (249 ml, 3.2 mol) was added and stirred 20-25 min, then the reaction mixture was poured into a separatory funnel containing 1000 ml of water and 200 ml of CH_2Cl_2. The resulting mixture was shaken carefully and the layers were separated. The organic layer was washed again with 500 ml of water, then with $NaHCO_3$ andfinally with brine. The organic solution was dried over $MgSO_4$, filtered and concentrated to an oil. 300 ml of diethyl ether was added to the crude product and shaken to dissolve. Within minutes solid began to crystallize and the mixture became thick. Enough diethyl ether was added to make the mixture stirrable and the mixture was stirred at room temperature for 1 hour. The solid was filtered and dried to give (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-amino-1,6-diphenylhexane as a white needles, yield 115 g, 81%.

To a 12 L 3-neck round bottom flask was added isopropyl acetate (6.5 L). The solvent was cooled to 0°C in an ice-water bath and 3-amino-1-propanol (1.14 kg, 15.1 mol) was added in one portion. To this stirring solution, benzyl chloroformate (1.20 kg, 7.03 mol) was added dropwise over 2 hours while maintaining the internal temperature of the flask between 10-15°C. After the addition was complete, the reaction mixture was allowed to stir for an additional 0.3 hour after which time water (3.5 L) was added in one portion. The solution was then partitioned and washed with an additional 2 times 3.5 L of water. The organic layer was dried over potassium carbonate and concentrated to give a solid that was dissolved in excess isopropyl acetate and precipitated from solution by adding the compound to heptane. The solid was filtered under nitrogen to yield 1.20 kg (82%) of N-carbonylbenzyloxy-3-aminopropanol as a colorless solid.

A mixture of 335 mL of DMSO and 9 L of methylene chloride were chilled to -48°C. 313 mL of oxalyl chloride was added over 25 min at temperature below -40°C. At -48°C added 500 g of N-carbonylbenzyloxy-3-amino-1-propanol dissolved in 1 L of methylene chloride. 1325 mL of triethylamine was added at such a rate that the temperature remained below -40°C. After stirring an additional 15 min, the mixture was allowed to warm to -30°C, then added 2.5 L of 20% aqueous potassium dihydrogen phosphate. Stirred for one hour, then separated the layers, washed the organic layer with brine, and dried with magnesium sulfate. The resulting N-carbonylbenzyloxy-3-aminopropanal was

kept in solution at -20°C.

To a 5 L 3-neck round bottom flask was added the crude carbonylbenzyloxy-3-aminopropanal (115 g, 0.555 mol) followed by addition of water (400 mL) and methanol (1600 mL). The reaction mixture was maintained at 25°C throughout the course of the reaction. After the solution became homogeneous. (S)-Valine methyl ester hydrochloride (90.2 g, 0.538 mol) was added in one portion followed by rapid addition of sodium acetate trihydrate (151 g, 1.11 mol) and sodium cycanoborohydride (73.2 g, 1.17 mol). The reaction mixture was allowed to stir at room temperature for 0.5 hour and was concentrated in vacuo. To this solution, saturated aq sodium bicarbonate (400 mL) was added and the mixture was extracted with isopropyl acetate (1 L). The organic layer was washed with water, dried over sodium sulfate, and concentrated to yield 150 g of crude product, which was dissolved in isopropyl acetate (300 mL) and heptane (2400 mL). Dry HCl was bubbled in and an oily solid precipitated out of solution. The liquid was decanted away from and the solid was dissolved in dichloromethane (3 L). The solution was washed with water (600 mL) and saturated aq sodium bicarbonate (600 mL) and dried over sodium sulfate. It was concentrated in vacuo to yield 105 g (59%) of N-(N-(benzyloxycarbonyl-3-amino)-propyl)valine methyl ester as a light yellow oil.

To a 3 L flask was added N-(N-(benzyloxycarbonyl-3-amino)-propyl)valine methyl ester (120 g, 0.372 mol) and methanol (1 L). This solution was allowed to stir in the presence of Raney Nickel (180 g) for 1 h. After removal of Raney Nickel by filtration, $Pd(OH)_2$ (24 g) was added and the solution was allowed to stir under 60 psi of a hydrogen atmosphere for 12 h. The solution was purged with nitrogen and repressurized with 60 psi of hydrogen for an additional 1 h. The solution was filtered and concentrated to give 63 g of N-(3-amino)-propyl)valine methyl ester as an an oil (90%). To this oil toluene (120 mL) was added and the solution was again concentrated in vacuo to give the desired product.

To a 5 L 3-neck round bottom flask with stir bar was added the crude N-(3-amino)-propyl)valine methyl ester (150 g, 0.8 mol) and dichloromethane (3.2 L). Carbonyldiimidazole (232 g, 1.44 mol) was added slowly in portions over 25 min. The solution was allowed to stir at ambient temperature for 40 hours. Water (200 mL) was added over 1 h with stirring until no more gas evolution occurred. A solution of 35% HCl was slowly added to the stirring solution until the solution became acidic. The solution was then partitioned and was washed with water. The organic layer was dried over sodium sulfate and was concentrated to yield 126 g (74%) of 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid methyl ester as a colorless solid.

To a 12 L 3-neck round bottom flask with stir bar was added 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid methyl ester (126 g, 0.588 mol), water (1.3 L), and THF (3.9 L). The solution was cooled to 0°C in an ice-water bath and lithium hydroxide monohydrate (74 g, 1.76 mol) was added in one portion with rapid stirring. The solution was allowed to stir at 0°C for 14 hours. It was then acidified to pH 11 by slow addition of 50% aq. phosphoric acid and the THF was removed in vacuo. The aqueous phase was washed with isopropyl acetate (2 L) and was subsequently acidified to pH by slow addition of 35% aq. HCl. The aqueous layer was then extracted with ethyl acetate. The combined organic layers were concentrated to give the desired product (105 g) as a white solid. The compound was then purified by

addition of isopropyl acetate (500 mL) and ethanol (15 mL) and bringing the solution to a boil with rapid stirring until 50 mL of solvent had evaporated. The solution was cooled to 0°C and filtered to give 92 g (75%) of pure 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid methyl ester.

The mixture of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-amino-1,6-diphenylhexane (100 g, 0.22 mol), 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid methyl ester (44.8 g, 0.22 mol) and 750 ml DMF was cooled in an ice/water bath. N-Hydroxybenzotriazole (90.9 g, 0.67 mol), 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide (86 g, 0.45 mol) and triethylamine (62.5 ml, 0.45 mol) were added and the ice bath was removed, allowing the reaction mixture to stir with warming to room temperature for 5 hours. The mixture was diluted with 1000 ml of IPAC and quenched with 1000 ml of water. The mixture was shaken and separated, the aq. layer was extracted IPAC, the organics were washed with 10% HCl, solution of $NaHCO_3$ with 100 ml hexanes, then washed 500 ml water, and brine, dried over $MgSO_4$, filtered and concentrated to provide. (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl)amino-1,6-diphenylhexane as a white foam.

References

Chemburkar S.R. et al.; US Patent No. 6,372,905; Apr.16, 2002; Assigned to Abbott Laboratories, Abbot Park,IL (US)
Sham H.L.; US Patent No. 5,914,332; Jun.22, 1999; Assigned: Abbott Laboratories (Abbott Park, IL)

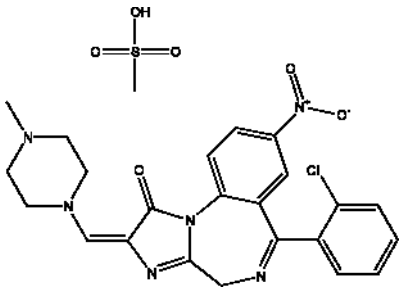
LOPRAZOLAM

Therapeutic Function: Tranquilizer

Chemical Name: 8-Nitro-1,2-dihydro-2-(N-methyl-piperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo-[1,2-a][1,4]-benzodiazepin-1-one methanesulfonate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 61197-93-1

Trade Name	Manufacturer	Country	Year Introduced
Avlane	J.A.S.M.	France	1981
Dormonoct	Roussel	UK	1983

Raw Materials

8-Nitro-1,2-dihydro-2-(N-methylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo[1,2-a][1,4]benzodiazepin-1-one
Methanesulfonic acid

Manufacturing Process

1.1 g of methanesulfonic acid were added dropwise to a mixture of 4.6 g of 8-nitro-1,2-dihydro-2-(N-methylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo-[1,2-a][1,4]benzodiazepin-1-one in 100 ml of anhydrous methylene chloride and 5 ml of methanol. Dry ether was slowly added until crystals formed on scratching and the solution was allowed to crystallize with further ether being added to complete the crystallization. The pale yellow solid was filtered off, washed with ether and crystallized from methylene chloride-methanol to obtain 5.4 g of 8-nitro-1,2-dihydro-2-(N-methylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-1H,4H-imidazo-[1,2-a][1,4]-benzodiazepin-1-one methanesulfonate melting at 205°C to 210°C.

References

Merck Index 5399
DFU 5 (3) 144 (1980) (As Ru-31, 158) and 5 (12) 635 (1980)
Taylor, F.B. and Harrison, D.R.; US Patent 4,044,142; August 23, 1977; assigned to Roussel Uclaf.

LORACARBEF

Therapeutic Function: Antibiotic

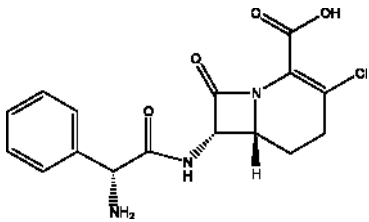
Chemical Name: 1-Azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-(((2R)-aminophenylacetyl)amino)-3-chloro-8-oxo-, (6R,7S)-

Common Name: Loracarbef

Chemical Abstracts Registry No.: 76470-66-1

Trade Name	Manufacturer	Country	Year Introduced
Lorabid	Eli Lilly and Company	-	-
Lorabid	Monarch. Pharm.	-	-
Lorax	Lilly	-	-

Structural Formula:



Raw Materials

(+/-)-cis-7-Amino-3-chloro-1-azabicyclo[4,2,0]oct-2-en-8-on-2-carboxylic acid trifluoroacetate
D-Phenylglycine methylester hydrochloride
Potassium phosphate buffer

Manufacturing Process

Loracarbef was obtained by biochemical method.

a) Cultivation of a microorganism having an ability of optically selective acylation

As a seed strain, Pseudomonas melanogenum ATCC 17808 [Biological properties are described in Journal of the Agricultural Chemical Society of Japan 37, 71 (1963)] is used.

As the seed medium, an aqueous solution containing 1% polypepton, 1% yeast extract, 0.5% meat extract, 0.5% sodium glutamate and 0.25% sodium chloride and adjusted to a pH of 7.0 with 5 N NaOH is used. One loopful of the seed strain is inoculated into 10 ml the seed medium and culturing is carried out at of 30°C for 24 hours. The whole amount of the seed medium is put into 300 ml of the culture medium in a 2 L Erlenmeyer flask and culturing is carried out at a temperature of 30°C. The composition of the culture medium is the same as that of the seed medium.

b) Preparation of cell suspension

After culturing for 24 hours, cell bodies are recovered from the culture broth by centrifugation and washed 2 times with 50 ml of 0.9% saline solution. The cells are suspended in a concentration of 20 mg/ml by dry weight in 1/30 M phosphate buffer (pH 6.5).

c) Preparation of a substrate solution

200 mg of the trifluoroacetate of ()-cis-7-amino-3-chloro-1-azabicyclo[4,2,0] oct-2-en-8-on-2-carboxylic acid (obtained by the method described in JPUPA No. 87791/80) and 800 mg of the hydrochloride of D-phenylglycine methylester are added in 9 ml of 1/30 M potassium phosphate buffer (pH

6.5). 5 N KOH is added in a small portion and the mixture is again adjusted to a pH of 6.5 to dissolve two starting compounds. Finally, deionized water is added to make 10 ml of a solution.

d) Enzyme reaction

In this step, 10 ml of the disrupted cell suspension is added to 10 ml of the substrate solution and enzyme reaction is carried out at a temperature of 30°C for 2 hours. The reaction is monitored by high speed liquid chromatography. Elution is carried out with 7% methanol - 0.2 M KH_2PO_4 solution. Reaction reaches maximum in a yield of 90% to the starting compound in 2 hours.

After the completion of reaction, cell bodies are removed from the reaction solution by centrifugation. The supernatant is concentrated under reduced pressure and charged on a column with 100 ml of Diaion HP-10. After adding 200 ml of deionized water, elution is carried out with 25% aqueous methanol solution. Then, the fractions containing the desired compound are concentrated under reduced pressure to make a 5 ml of concentrate. The concentrate is charged on a column packed with 130 ml of Sephadex-LH20 and elution is carried out with a solvent of water and methanol (50:50). The desired product is eluted in 55 ml to 75 ml of fractions. The fractions are concentrated under reduced pressure and lyophilized to obtain 78 mg (6R,7S)-7-(R)-phenylglycinamido-3-chloro-1-azabicyclo[4,2,0]oct-2-en-8-on-2-carboxylic acid of a white powder $[\alpha]_D^{21}$ = -75.8° (c = 0.4, H_2O), melting point 300°C or more (browning).

References

Hashimoto Yu. et al.; US Patent No. 4,335,211; 06.15.1982, Assigned to Kyowa Hakko Kogyo Co.

LORATADINE

Therapeutic Function: Antihistaminic, Antiallergic

Chemical Name: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-, ethyl ester

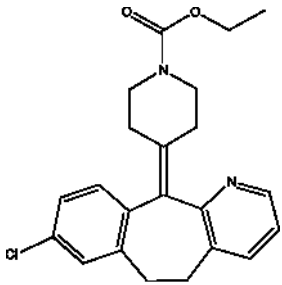
Common Name: Loratadine

Chemical Abstracts Registry No.: 79794-75-5

Raw Materials

Pyridine	Titanium tetrachloride
Zinc	Ethyl 4-oxopiperidine-1-carboxylate
Tetrahydrofuran	8-Chloro-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b] pyridin-11-one

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alledryl	Prater	-	-
Alergaliv	Sigma/Neo Quimica	-	-
Claratyne	Schering-Plough Pty	-	-
Claritin	Schering-Plough	-	-
Claritin 24 hour	Schering Canada Inc.	-	-
Difmedol	Faran	-	-
Histadin	Nodel	-	-
Loranil	Libbs	-	-
Lorin	Stadmed Private Limited	India	-
Lorinol	Micro Labs	India	-
Loronet	Klar Sehen Pvt. Ltd.	India	-
Noxin	Bussie	-	-
Ponderal	Biogen	-	-
Versal	Nycomed	-	-

Manufacturing Process

Preparation of Loratadine

In a two-liter vessel provided with a thermometer, a reflux condenser and nitrogen atmosphere, dry tetrahydrofuran (343 ml) was placed, and cooled between 0 and -5°C. Titanium tetrachloride (28.5 ml, 49.5 g, 0.255 mol) was slowly added with stirring (17 min.), keeping the temperature in the above indicated range, a yellow suspension being formed. After the addition was finished, stirring was continued for 10 min. Then, zinc dust (34.5 g, 0.524 mol) was added with stirring in approximately 15 min. keeping the temperature in the above cited range, and after addition was finished, stirring was continued at this temperature for 20 min., a blue suspension being formed. Then, pyridine (17 ml, 0.21 mol) was added with stirring, keeping the temperature in the above range, and then, a solution of 8-chloro-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-one (30.0 g, 0.123 mol) and ethyl 4-oxopiperidine-1-carboxylate (25.2 g, 0.147 mol) in anhydrous tetrahydrofuran (96 ml) was added in about 20 min., with stirring and keeping the temperature in the above cited range. The, thus obtained, dark brown mixture was stirred for 3 h keeping the temperature in the above cited range, then was allowed to heat to room temperature and kept at this temperature

for 2 h and then heated to 40°C for 17 h. The tetrahydrofuran was distilled off from the reaction mixture to give a black resin that was dissolved in dichloromethane (300 ml) and acidified by addition of isopropanol/HCl 7.2 N (97 ml). The mixture was stirred for 10 min, and the phases were separated, being the aqueous one extracted with dichloromethane (150 ml). The combined organic phases were washed 6 times with a mixture of water (125 ml) and 35% aqueous HCl (7.5 ml). Then, the organic phase was basified to pH 7.5-8.0 by addition of 30% aqueous NH_3. The mixture was stirred for 10 min and the phases were separated, and then washed 3 times with water (250 ml). The organic phase was dried with anhydrous sodium sulfate, filtered and the solvent eliminated in vacuo to give a residue (47.47 g) that was treated with acetonitrile (97 ml). The solid was filtered and crystallized from the same solvent to give pure Loratadine, m.p. 132-133°C (18.8 g, 40% yield).

References

Stampa A. et al.; US Patent No. 6,084,100; 007.04.2000; Assigned to Medichem, S.A.

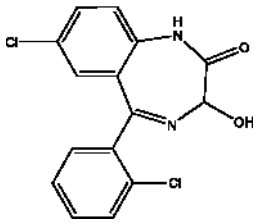
LORAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 846-49-1

Trade Name	Manufacturer	Country	Year Introduced
Tavor	Wyeth	Italy	1972
Tavor	Wyeth	W. Germany	1972
Ativan	Wyeth	UK	1973
Temesta	Wyeth Byla	France	1973
Ativan	Wyeth	US	1977
Wwax	Wellcome	Japan	1978

Trade Name	Manufacturer	Country	Year Introduced
Bonton	Unipharm	Israel	-
Control	Sigurta	Italy	-
Emotion	Alpes	Argentina	-
Emotival	Armstrong	Argentina	-
Idalprem	Prem	Spain	-
Lorans	Schiapparelli	Italy	-
Lorivan	Disco	Israel	-
Lorsilan	Belupo Ltd.	Yugoslavia	-
Orfidal	Orfi	Spain	-
Piralone	Ferrer	Spain	-
Placidia	Fedal	Spain	-
Pro Dorm	Schurholz	W. Germany	-
Ouait	Jamco	Italy	-
Securit	Marxer	Italy	-
Sedarkey	Cuatrecasas-Darkey	Spain	-
Sedatival	Raffo	Argentina	-
Sedicepan	Septa	Spain	-
Sidenar	Syncro	Argentina	-

Raw Materials

Chloroacetyl chloride
Acetic anhydride
Methyl amine
2-Amino-2',5-dichlorobenzophenone
Hydroxylamine
Sodium hydroxide

Manufacturing Process

The starting material was 2-amino-2',5-dichlorobenzophenone which was reacted with hydroxylamine and then with chloroacetyl chloride. The intermediate thus obtained is reacted with methylamine and then with acetic anhydride.

To a slightly warm suspension of 3-acetoxy-7-chloro-5-(o-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one thus obtained was added 4N sodium hydroxide solution with stirring. All the solid dissolved and soon a thick white solid precipitated out. The solid was filtered, washed well with water and recrystallized from ethanol. The product was isolated as a solvate with 1 mol of ethanol. When heated it loses the ethanol of solvation and melts at 166°C to 168°C.

References

Merck Index 5400
Kleeman and Engel p. 530
PDR p. 1938
OCDS Vol. 1 p. 368 (1977)
DOT 7 (6) 210 (1971) and 9 (6) 238 (1973)
I.N. p.568
REM p. 1063

Bell, S.C. British Patent 1,057,492; February 1, 1967; assigned to American Home Products Corporation
Bell, S.C. US Patent 3,176,009; March 30, 1965; assigned to American Home Products Corp.
Bell, S.C.; US Patent 3,296,249; January 3, 1967; assigned to American Home Products Corp.

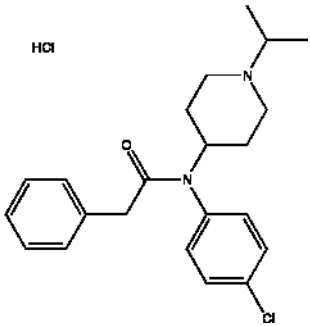
LORCAINIDE HYDROCHLORIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: N-(p-Chlorophenyl)-N-(1-isopropylpiperidin-4-yl) phenylacetamide hydrochloride

Common Name: Isocainide hydrochloride; Socalnide hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 59729-31-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Remivox	Janssen	W. Germany	1980

Raw Materials

N-(4-Chlorophenyl)-N-(piperidinyl)benzeneacetamide
2-Bromopropane
Hydrogen chloride

Manufacturing Process

To a stirred suspension of 5 parts of N-(4-chlorophenyl)-N-(4-piperidinyl) benzeneacetamide, 5 parts of sodium carbonate, a few crystals of potassium iodide in 200 parts of butanol is added dropwise 4 parts of 2-bromopropane at room temperature. After the addition is complete, the whole is stirred and

refluxed for 20 hours. Then the second portion of 4 parts of 2-bromopropane is added and stirring and refluxing is continued for another 19 hours. The reaction mixture is cooled, filtered and the filtrate is evaporated. From the oily free base, the hydrochloride salt is prepared in the conventional manner in 1,1'-oxybisethane and 2-propanone. The precipitated solid salt is filtered off and crystallized from a mixture of 2-propanone and 2-propanol, yielding 2 parts of N-(4-chlorophenyl)-N-[1-(1-methylethyl)-4-piperidinyl] benzeneacetamide hydrochloride; melting point 263°C.

References

Merck Index 5401
DFU 3 (7) 518 (1978)
OCDS Vol. 3 p. 40 (1984)
DOT 18 (1) 17 and (10) 548 (1982)
I.N. p. 568
Sanczuk, S. and Hermans, H.K.F.; US Patent 4,196,210; April 1, 1980; assigned to Janssen Pharmaceutica NV

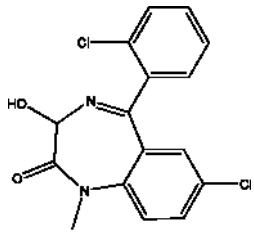
LORMETAZEPAM

Therapeutic Function: Hypnotic

Chemical Name: 7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-1-methyl-2H-1,4-benzodiazepin-2-one

Common Name: N-Methyllorazepam

Structural Formula:



Chemical Abstracts Registry No.: 848-75-9

Trade Name	Manufacturer	Country	Year Introduced
Loramet	Wyeth	W. Germany	1980
Noctamid	Schering	W. Germany	1980
Loramet	Wyeth	Switz.	1981
Noctamid	Schering	UK	1981
Noctamid	Schering	France	1981

Trade Name	Manufacturer	Country	Year Introduced
Loramet	Wyeth	UK	1983
Loramid	Wyeth	W. Germany	-
Minias	Farmades	Italy	-
Pronoctan	Schering	-	-

Raw Materials

3-Acetoxy-7-chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepin-2-one
Sodium hydroxide

Manufacturing Process

To a suspension of 3.4 g of 3-acetoxy-7-chloro-1,3-dihydro-5-(o-chlorophenyl)-2H-1,4-benzodiazepin-2-one in 80 ml of alcohol was added 6 ml of 4 N sodium hydroxide. After complete solution had taken place a solid precipitated that redissolved upon the addition of 80 ml of water. The solution was acidified with acetic acid to give white crystals. After recrystallization from alcohol the compound melted at 192°C to 194°C.

References

Merck Index 5403
DFU 5 (10) 495 (1980)
Kleeman and Engel p. 531
OCDS Vol. 3 p. 196 (1984)
DOT 17 (4) 137 (1981)
I.N. p. 569
American Home Products Co.; British Patent 1,022,642; March 16, 1966

LOSARTAN POTASSIUM

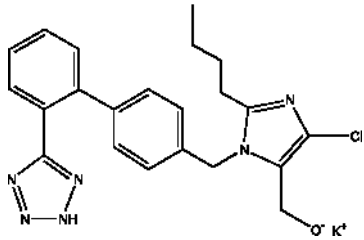
Therapeutic Function: Antihypertensive

Chemical Name: 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-, monopotassium salt

Common Name: Losartan potassium

Trade Name	Manufacturer	Country	Year Introduced
Alsartan	Aristo Pharmaceutical Ltd.	India	-
Cozaar	Merck Frosst	Canada	-
Czar	Argus	India	-
Losacar	Cadila	India	-
Losartan Potassium	Merck Sharp and Dohme	UK	-
Paxon	Gador	-	-
Redupress	Ache	-	-

Structural Formula:



Chemical Abstracts Registry No.: 124750-99-8; 114798-26-4 (Base)

Raw Materials

Potassium hydroxide	Concentrated hydrochloric acid
Thionyl chloride	Ammonium hydroxide
Bromine	2-n-Butyl-4-chloro-5-(hydroxymethyl)-imidazole
Sodium azide	Methyl 4'-methylbiphenyl-2-carboxylate

Manufacturing Process

2-Butyl-4-chloro-1-(2'-(tetrazol-5-yl)biphenyl-4-ylmethyl)-1H-imidazole-5-methanolpotassium was synthesized in 5 stages.

1. Methyl 4'-methylbiphenyl-2-carboxylate (44.2 mmol), 0.5 N KOH in methanol (133 mmol), and water (50 mL) were mixed and refluxed under nitrogen. After 5 hours, the solvent was removed in vacuo and water (200 mL) and ethyl acetate (200 mL) added. The aqueous layer was acidified with concentrated hydrochloric acid to a pH of 3 and the layers were separated. The aqueous phase was extracted with ethyl acetate, the organic layers collected, dried ($MgSO_4$) and the solvent removed in vacuo to yield 8.71 g of a 4'-methylbiphenyl-2-carboxylic acid, melting point 140.0-145.0°C.

2. 4'-Methylbiphenyl-2-carboxylic acid (41 mmol) and thionyl chloride (411 mmol) were mixed and refluxed for 2 hours. The excess thionyl chloride was removed in vacuo and the residue was taken up in toluene. The toluene was removed by rotary evaporation. The crude acid chloride was then added slowly to cold (0°C) concentrated NH_4OH (50 mL) so that the temperature was kept below 15°C. After 15 minutes of stirring, water (100 mL) was added and solids precipitated. These were collected, washed with water and dried under high vacuum over P_2O_5 to yield 7.45 g of a white solid, melting point 126.0-128.5°C. The above product amide (35 mmol) and thionyl chloride (353 mmol) were mixed and refluxed for 3 hours. The thionyl chloride was removed using the same procedure as described above. The residue was washed with a little hexane to yield 6.64 g of 4'-methyl-2-cyanobiphenyl, melting point 44.0-47.0°C.

3. 4'-Methyl-2-cyanobiphenyl (5.59 g) was brominated using benzoyl peroxide as an initiator. The product was recrystallized from ether to yield 4.7 g of 4'-bromomethyl-2-cyanobiphenyl, melting point 114.5-120.0°C.

4. 4'-Bromomethyl-2-cyanobiphenyl (4.6 g) was alkylated onto 2-n-butyl-4-chloro-5-(hydroxymethyl)-imidazole. For separation of the product was used a flash chromatography in 1:1 hexane/ethyl acetate over silica gel. The regioisomeric products yielded 2.53 g of the faster eluting isomer. Recrystallization from acetonitrile yielded 1.57 g of analytically pure 2-n-butyl-4-chloro-1-[2'-cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole, melting point 153.5 -155.5°C.

5. 2-n-Butyl-4-chloro-1-[(2'-cyanobiphenyl-4-yl)-methyl]-5-(hydroxymethyl)-imidazole (10 mmole), sodium azide (10 mmol), and ammonium chloride (30 mmol) were mixed in DMF (150 mL) under N_2 at 100°C for 2 days, after which the temperature was raised to 120°C for 6 days. The reaction was cooled and 3 more equivalents each of ammonium chloride and sodium azide were added. The reaction was again heated for 5 days at 120°C. The reaction was cooled, the inorganic salts filtered, and the filtrate solvent removed in vacuo. Water (200 mL) and ethyl acetate (200 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with ethyl acetate, the organic layers were collected, dried ($MgSO_4$) and the solvent removed in vacuo, to yield a dark yellow oil. The product was purified by flash chromatography in 100% ethyl acetate to 100% ethanol over silica gel to yield 5.60 g of a light yellow 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole. Recrystallization from acetonitrile yielded 4.36 g of light yellow crystals which still melted broadly. The crystals were taken up in 100 mL of hot acetonitrile. The solid that did not dissolve was filtered off to yield 1.04 g of product as a light yellow solid, melting point of 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole 183.5-184.5°C.

2-n-Butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole may be converted to potassium salt.

References

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LOTEPREDNOL ETABONATE

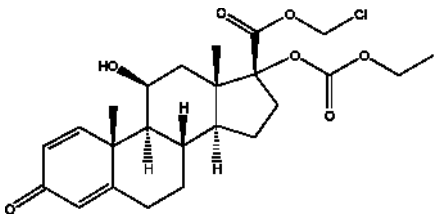
Therapeutic Function: Glucocorticoid

Chemical Name: Androsta-1,4-diene-17-carboxylic acid, 17-((ethoxycarbonyl)oxy)-11-hydroxy-3-oxo-, chloromethyl ester, (11β,17α)-

Common Name: Loteprednol etabonate

Trade Name	Manufacturer	Country	Year Introduced
Alrex	Bausch and Lomb	USA	-
Alrex	Pharmos	-	-
Lotemax	Bausch and Lomb	USA	-
Lenoxin	Pharmos	-	-

Structural Formula:



Chemical Abstracts Registry No.: 82034-46-6

Raw Materials

Hydrocortisone	Sodium metaperiodate
Ethyl chloroformate	Sodium hydroxide

Manufacturing Process

To a solution of hydrocortisone (15 g, 0.04 mol) in 120 ml of THF and 30 ml of methanol at room temperature is added a warm solution of sodium metaperiodate (25.7 g, 0.12 mol) in 100 ml of water. The reaction mixture is stirred at room temperature for 2 hours, then is concentrated under reduced pressure to remove the tetrahydrofuran and methanol. The solid is triturated with 50 ml of water, separated by filtration, washed with water and dried in vacuo at 50°C for 3 hours. The product, 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid (i.e., cortienic acid), is obtained in approximately 96% yield (13.76 g); melting point 231-234°C.

To a cold solution of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid (5% weight/volume; 1 mol) and triethylamine (4 mol) in dichloromethane is added a 50% (weight/volume) solution of ethyl chloroformate (3.9 mol) in dichloromethane. The reaction mixture is allowed to warm to room temperature over a 2 hour period. The triethylamine hydrochloride precipitate which forms is removed by filtration and the filtration is washed successively with 3% sodium bicarbonate, 1% hydrochloric acid and water. The organic layer is separated, dried with magnesium sulfate, and filtered. The filtrate is concentrated in vacuo to a foam.

The foam is used in the next step below or chromatographed and crystallized for analysis. The product 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, melting at 192-195°C C after chromatography and crystallization.

17α-Ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid is combined with an equivalent amount of 1 N sodium hydroxide in methanol and that solution is diluted to 100 times the original volume with ethyl ether. The suspension which results is refrigerated for 1 hour. Then, the crystals which form are removed by filtration, dried in an evacuated desiccator, and dissolved in hexamethylphosphoramide (10% weight/volume). A portion of the resultant solution containing 1 mole of the acid salt, i.e. of sodium 17α-

ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, is combined with 4 moles of chloromethyl iodide. The reaction mixture is maintained at room temperature for 3 hours, then is diluted to 10 times the original volume with ethyl acetate. The diluted reaction mixture is washed successively with 5% sodium thiosulfate, 3% sodium bicarbonate, and water. The organic layer is separated, dried with magnesium sulfate and filtered. The filtrate is concentrated in vacuo to a foam. The foam is purified by crystallization from ethyl ether or tetrahydrofuran/hexane. There is thus obtained chloromethyl-17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 197-200°C after crystallization.

References

Bodor N.S.; US Patent No. 4,996,335; Feb. 26, 1991; Assigned to Bodor; Nicholas S. (Gainesville, FL)

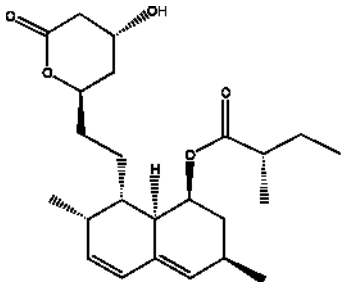
LOVASTATIN

Therapeutic Function: Antihyperlipidemic

Chemical Name: Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-((2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-1-naphthalenyl ester, (2S)-

Common Name: Lovastatin; Mevinolin; Monacolin K

Structural Formula:



Chemical Abstracts Registry No.: 75330-75-5; 71949-96-7; 74133-25-8

Trade Name	Manufacturer	Country	Year Introduced
Aztatin	Sun Pharmaceuticals Industries Ltd.	India	-
Choletar	Krka	Slovenia	-
Favolip	SPPL (Sarabhai Piramal Pharmaceuticals Ltd.)	India	-

Trade Name	Manufacturer	Country	Year Introduced
Lovastatin	Ranbaxy	India	-
Lovasterol	Polpharma	Poland	-
Mevacor	Aetna Inc.	-	-
Mevacor	Merck and Company, Inc.	Germany	-
Medostatin	Medochemie Ltd.	Cyprus	-
Rovacor	Ranbaxy	India	-

Raw Materials

Coniothyrium fuckelii ATCC 74227
Nutrient medium

Manufacturing Process

1) *Coniothyrium fuckelii* ATCC 74227 was grown in a sterilizable fermentation apparatus with a volume of 15 L. The apparatus was equipped with an agitator, aerator, pH control system, dissolved oxygen control system, and a pump and feed system designed to allow the sterile addition of glucose solutions. The pH was controlled by the automatic addition of ammonium hydroxide or phosphoric acid to maintain the pH of the culture medium constant at 5.0. Periodically, the fermentation broth was sampled, measured for glucose concentration and an addition of glucose was made manually to maintain a concentration of glucose at approximately 2-5 g/L. After 192 hours of growth under these conditions, the concentration of biomass reached 65 g/L and the concentration of Lovastatin reached 102 mg/L.

2) A further medium for the growth of *Coniothyrium fuckelii* ATCC 74227, has the following composition: Glucose 12%, Peptone 1%, $(NH_4)_2SO_4$ 0.4%, $MgSO_4 \cdot 7H_2O$ 0.05%, P 2000 0.1% (Antifoam agent), L-isoleucine 0.2-1.5%, L-aspartic acid 0.2-1.5%. The fermentation was carried out as before.

With this medium, the lovastatin concentration was 430 mg/L.

References

Gerson D.F., Xiao X.; US Patent No. 5,409,820; Apr.,25, 1995; Assigned to Apoptex, Inc.

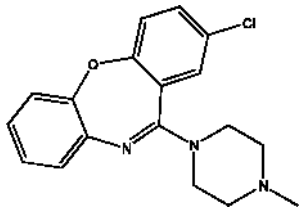
LOXAPINE

Therapeutic Function: Tranquilizer

Chemical Name: 2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4] oxazepine

Common Name: Oxilapine

Structural Formula:



Chemical Abstracts Registry No.: 1977-10-2

Trade Name	Manufacturer	Country	Year Introduced
Loxitane	Lederle	US	1976
Loxapac	Lederle	France	1980
Loxapac	Cyanamid	Italy	1981
Daxolin	Dome	US	-

Raw Materials

o-(p-Chlorophenoxy)aniline
1-Methylpiperazine
Ethyl chloroformate
Phosphorus oxychloride

Manufacturing Process

One route is described in US Patent 3,412,193 as follows. To a mixture of o-(p-chlorophenoxy)aniline hydrochloride (prepared from 32 g of the base) in 50 ml of pyridine is added gradually while heating under reflux, 25 ml of ethyl chloroformate. After the addition is completed, the mixture is heated under reflux for one hour longer, and then evaporated under reduced pressure to an oily residue. The residue is taken up in 300 ml of water, and extracted with ether (approximately 200 ml).

The ether extract is separated, dried over sodium sulfate, and evaporated to an oily residue (40 g) which contains ethyl o-(p-chlorophenoxy)carbanilate and is used without further purification. The crude ethyl o-(p-chlorophenoxy) carbanilate is dissolved in 20 ml of benzene, and 20 ml of 1l-methylpiperazine and a small amount of sodium methylate (approximately 25 to 50 mg) are added. Benzene is then removed by slow distillation; and the mixture is heated overnight under reflux (approximately 16 hours).

Evaporation under reduced pressure then gives a solid residue which is dissolved in 400 ml of ether with heating. Concentration to half-volume under reduced pressure produces a precipitate which is collected, washed with petroleum ether and dried (36 g). A second crop of product is isolated from the filtrate. This product is dissolved in 200 ml of chloroform and treated with an excess of anhydrous hydrogen chloride. The resulting precipitate is collected and dried at 50°C (in vacuo), and 4-methyl-2'-(p-chlorophenoxy)-1-

piperazinecarboxanilide hydrochloride, MP 210° to 213°C, is thereby obtained.

A mixture of 4-methyl-2'-(p-chlorophenoxy)-1-piperazinecarboxanilide hydrochloride (6 g), 50 ml of phosphorus oxychloride and 10 g of phosphorus pentoxide is heated under reflux for about 24 hours, and then concentrated to a gummy residue by evaporation under reduced pressure. This residue is taken up in 150 ml of ether, 200 g of ice is added, and the mixture is made basic with concentrated aqueous ammonium hydroxide. The ether layer is separated, dried over potassium hydroxide pellets and evaporated to a solid residue (approximately 4 g).

This crude product is dissolved in 100 ml of dilute hydrochloric acid, the acid solution is extracted with ether, and the aqueous layer is made basic with sodium hydroxide solution (3N) in the presence of ether (approximately 250 ml). The ether layer is separated, dried over potassium hydroxide and evaporated to a white solid. Additional purification by repeating the formation of the hydrochloric acid salt and reprecipitation of the base is carried out. When purified in this manner, followed by drying at 80°C in vacuo over phosphorus pentoxide, 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f] [1,4]oxazepine, MP 109° to 111°C, is obtained.

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Coppola, J.A.; US Patent 3,412,193; November 19, 1968;assigned to American Cyanamid Company
Schmutz, J., Hunziker, F. and Kunzle, F.M.; US Patent 3,546,226; December 8, 1970

LYMECYCLINE

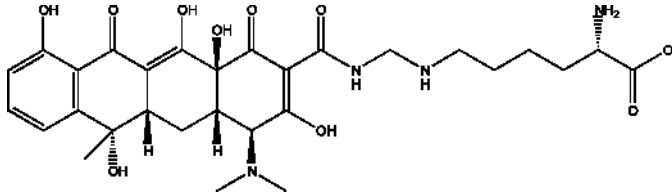
Therapeutic Function: Antibiotic

Chemical Name: Lysine, N^6-((4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamido)methyl)-, (+)-

Common Name: Limeciclina; Lymecycline

Trade Name	Manufacturer	Country	Year Introduced
Armyl	Armour Pharm.	-	-
Tetralysal	Farmitalia	-	-
Tetralysal	Galderma International	-	-
Tetradin	Granelli	-	-

Structural Formula:



Chemical Abstracts Registry No.: 992-21-2

Raw Materials

L-Lysine hydrochloride
Formaldehyde
Tetracycline

Manufacturing Process

Amido-N-(lysinomethyl)tetracycline hydrochloride:

To 18.3 g of L-lysine hydrochloride dissolved in 100 ml of water is added 10 ml of 37% aqueous solution of formaldehyde. To the resultant mixture is added 44.0 g of anhydrous tetracycline dissolved in 500 ml of tetrahydrofuran. After thorough mixing the product forms over a period of about 15 min as an oily layer which after separation from the aqueous phase is added dropwise to 3 L of stirred isopropyl alcohol. The product after recovery by filtration, is reslurried with acetone, filtered and dried at 65°C at reduced pressure.

The product thus obtained has a bioassay of 500 mcg/mg (K. pneumonlae oxytetracyoline assay).

References

Blackwood R.K. et al.; US Patent No. 3,042,716; July 3, 1962; Assigned: Chas. Pfizer and Co., Inc., New York, N.Y., a corporation of Delaware