G

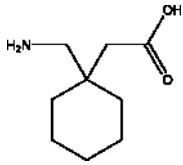
GABAPENTIN

Therapeutic Function: Anticonvulsant

Chemical Name: Cyclohexaneacetic acid, 1-(aminomethyl)-

Common Name: Gabapentin

Structural Formula:



Chemical Abstracts Registry No.: 60142-96-3

Trade Name	Manufacturer	Country	Year Introduced
Neurontin	Godecke	Germany	-
Neurontin	Parke-Davis	USA	-
Neurontin	Pfizer	USA	-

Raw Materials

Methanol
Triethylamine
Sodium azide
1,1-Cyclohexane-diacetic anhydride
Ethyl chloroformate

Manufacturing Process

32.8 g 1,1-cyclohexane-diacetic anhydride are mixed with 7 g anhydrous methanol and heated under reflux for 1 hour. After evaporation of the reaction mixture in a vacuum, was obtained 37.5 g monomethyl 1,1-cyclohexane-diacetate in the form of a yellowish oil.

5.6 ml triethylamine in 16 ml anhydrous acetone are added dropwise at 0°C

to a solution of 7.28 g monomethyl 1,1-cyclohexane-diacetate, then a solution of 3.6 ml ethyl chloroformate in 16 ml anhydrous acetone is added thereto. The reaction mixture is further stirred for 30 min at 0°C and and then a solution of 3.4 g sodium azide in 12 ml water added dropwise thereto. The reaction mixture is stirred for 1 hour at 0°C, then poured into ice water and extracted three times with 50 ml amounts of ice-cold toluene. The combined extracts are dried over anhydrous sodium sulphate at 0°C and subsequently introduced drop-wise into a flask pre-heated to 100°C. The mixture is then heated for a further hour under reflux and thereafter evaporated in a vacuum. The crude methyl 1-isocyanatomethyl-1-cyclohexane-acetate which remains behind is heated under reflux for 3 hours with 50 ml 20% hydrochloric acid. After cooling the solution, it is extracted three times with 100 ml amounts of chloroform to remove the 1-amino-methyl-1-cyclohexane-acetic acid lactam formed as a by-product product and the aqueous hydrochloric acid solution evaporated in a vacuum, whereby 1-aminomethyl-1-cyclohexane-acetic acid crystallises as the hydrochloride; m.p. 117-118°C, after recrystallisation from acetone/methanol/ether. After recrystallization from methanol/ether the melting point of the product is 129-133°C.

By treatment with a basic ion exchanger and crystallisation from ethanol/ether, there is obtained pure 1-amino-methyl-1-cyclohexane-acetic acid; melting point 162-166°C.

References

Tenconi F. et al.; US Patent No. 6,576,790; June 10, 2003; Assigned: Bioindustria Laboratorio Italiano Medicinali S.p.A. (Novi Ligure, IT)
Satzinger G. et al.; US Patent No. 4,024,175; May 17, 1977; Assigned: Warner-Lambert Company (Morris Plains, NJ)
Satzinger G. et al.; US Patent No. 4,087,544; May 2, 1978; Assigned: Warner-Lambert Company (Morris Plains, NJ)

GABEXATE MESYLATE

Therapeutic Function: Enzyme inhibitor

Chemical Name: Benzoic acid, 4-((6-((aminoiminomethyl)amino)-1-oxohexyl)oxy)-, ethyl ester, monomethanesulfonate

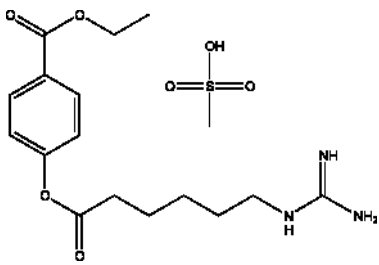
Common Name: Gabexate mesylate

Trade Name	Manufacturer	Country	Year Introduced
Gabexate Mesylate	Shangai Lansheng Corporation	-	-

Raw Materials

Pyridine
Thionyl chloride
Sodium hydroxide
Guanidinocaproic acid p-tosyl salt
Benzoic acid ethyl ester

Structural Formula:



Chemical Abstracts Registry No.: 39492-01-8 (Base)

Manufacturing Process

Guanidinocaproic acid p-tosyl salt and thionyl chloride were mixed together to react at the room temperature. An endothermic reaction occurred and the caproic acid gradually dissolved. Then the reaction mixture was left standing for 1 to 2 h and was extracted with ether. The lower oily layer and the ether layer were separated from each other and the lower layer was repeatedly washed with ether. Then the oily substance (caproic acid chloride) was added with benzoic acid ethyl ester in tetrahydrofuran, and the mixture was stirred. After the mixture became a uniform solution, of pyridine were gradually added. An exothermic reaction occurred and an oily substance came to be separated in the lower layer. After the completion of the reaction, the oily substance was washed with water and then recrystallized from hot water once or twice. Thus 4-(6-guanidino-hexanoyloxy)-benzoic acid ethyl ester salt was obtained as white crystals.

To obtained the base 4-(6-guanidino-hexanoyloxy)-benzoic acid ethyl ester the 4-(6-guanidino-hexanoyloxy)-benzoic acid ethyl ester salt must be treated by, for example, sodium hydroxide.

In practice it is usually used as mesylate.

References

Tokushima S.F., Nishinomiya T.W.; US Patent No. 3,751,447; Aug. 7, 1973; Assigned: Ono Pharmaceutical Co., Ltd., Osaka, Japan

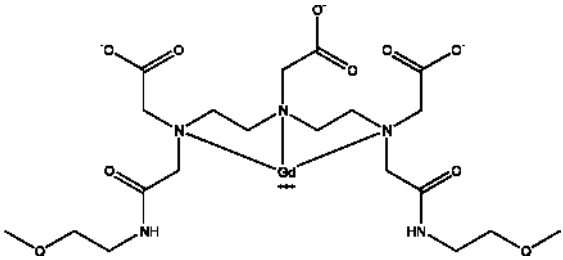
GADOVERSETAMIDE

Therapeutic Function: Diagnostic aid

Chemical Name: Gadoversetamide

Common Name: Gadoversetamide

Structural Formula:



Chemical Abstracts Registry No.: 131069-91-5

Trade Name	Manufacturer	Country	Year Introduced
Gadoversetamide	Mallinckrodt Inc.	-	-
OptiMARK	Mallinckrodt Inc.	-	-

Raw Materials

Diethylenetriaminepentaacetic acid dianhydride
2-Methoxyethylamine
Gadolinium (III) oxide

Manufacturing Process

A stirred suspension of diethylenetriaminepentaacetic acid dianhydride (10.8 g, 0.030 mole) in 100 ml of isopropanol was treated with 2-methoxyethylamine (5.0 g, 0.067 mole). The entire mixture was heated at 50°C for 4 hours in a water bath. The pale yellow solution was filtered through a medium porosity sintered glass funnel to remove undissolved impurities, and the filtrate was taken to dryness under reduced pressure. The resulting amorphous foam was dried (vacuum desiccator) at ambient temperature for 18 hours. The yield of the N,N"-bis[N-(2-methoxyethyl)-carbamoylmethyl]diethylenetriamine-N,N',N"-triacetic acid 14.4 g (93.5%).

A mixture of gadolinium (III) oxide (3.3 g, 0.0091 mole) and N,N"-bis[N-(2-methoxyethyl)-carbamoylmethyl]diethylenetriamine-N,N',N"-triacetic acid (10.2 g, 0.020 mole) in H_2O (100 ml) was heated at 60-65°C for 3 hours in a water bath. The pale yellow homogeneous solution was filtered through a fine porosity sintered glass funnel to remove undissolved impurities and the clear filtrate was poured into acetone (2 L). The heterogeneous mixture was stirred for 5 min and allowed to stand at ambient temperature for 30 min. Aqueous acetone was decanted off and the resulting gummy residue was dissolved with methanol (150 ml). The solution was concentrated under reduced pressure and the complex was precipitated from the solution by adding it to more acetone (1 L). The amorphous precipitate was collected, washed with acetone and dried. The yield of {N,N"-bis[N-(2-methoxyethyl)-carbamoylmethyl] diethylenetriamine-N,N',N"-triaceto}gadolinium (III) was 11.2 g (80.7%). The pale cream solid was crystallized from a mixture of methanol and tetrahydrofuran to give a colorless solid. It was 97.4% pure by HPLC. For

{N,N"-bis[N-(2-methoxyethyl)-carbamoylmethyl]diethylenetriamine-N,N',N"-triaceto}gadolinium (III) calculated: Gd, 22.88%, found: Gd, 22.52%.

References

Weber R.W.; US Patent No. 5,130,120; Jul.14, 1992; Assigned to Mallinckrodt Medical, Inc., St. Louis, Mo.

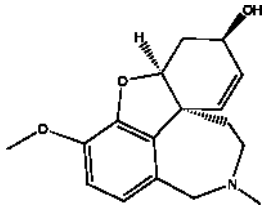
GALANTAMINE

Therapeutic Function: Cholinesterase inhibitor

Chemical Name: 6H-Benzofuro(3a,3,2-ef)(2)benzazepin-6-ol, 4a,5,9,10,11, 12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)-

Common Name: Galantamine; Galanthamine

Structural Formula:



Chemical Abstracts Registry No.: 357-70-0

Trade Name	Manufacturer	Country	Year Introduced
Reminyl	Janssen Pharmaceutica Inc.	-	-
Jilkon	Finadiet	-	-
Nivalin	Sopharma	-	-
Nivalin	Pharmachim Holding	-	-

Raw Materials

Ammonia	Bulbs of Narcissus pseudonarcissus
Sodium carbonate	Hydrogen bromide
Sulfuric acid	Bulbs of Galanthus nivalis or G. woronowi

Manufacturing Process

2 Methods of isolation of galantamine from Narcissus pseudonarcissus bulbs

1. 10 kg air-dried, comminuted bulbs of Narcissus pseudonarcissus "Carlton"

is carefully mixed with 400 g sodium carbonate. 23 L dichloroethane is added. The mixture is allowed to stand for 10 h; then the solvent is decanted. The bulbs are once again doused with 23 L dichloroethane which is decanted after 2 to 3 hs. After that, 17 L dichloroethane is added to the bulbs for the third time; however, this is decanted immediately. The mixed dichloroethane extracts are extracted by means of 10% sulfuric acid (2 times 600 ml each; 2 times 300 ml each).

The acidic extracts are mixed and purified from traces of dichloroethane by means of shaking out with diethyl ether. Under stirring and cooling to 15° to 20°C, about 200 ml of a 25% aqueous ammonia solution is then added up to alkaline litmus reaction (the pH is in the range of 7 to 8). Different from the indications in the art, the companion alkaloids do not precipitate. The alkaline solution is saturated with salt and extracted with diethyl ether.

After evaporation of the ether, a negligible residue remains, which is also different from the indications in the art. The pH-value of the aqueous phase is set to about 14 by saturating it with potash. The aqueous phase is repeatedly extracted with diethyl ether. The mixed ether extracts are evaporated to dryness, the remaining galanthamine-containing residue is dissolved in acetone (50 ml). In contrast to the art, there is no precipitate. 350 ml acetone is replenished, 200 g aluminum oxide is added, and stirring is effected for 45 min. The aluminum oxide is filtered off and washed twice with 100 ml acetone each time. The mixed acetone solutions are evaporated to dryness. 1.3 g of an oily residue is obtained which is examined by means of HPLC.

2. 100 kg air-dried, comminuted bulbs of Narcissus pseudonarcissus "Carlton" is carefully mixed with 4 kg of sodium carbonate. The mixture is divided into three equal parts, and each is doused with 15 L special boiling-point gasoline 80/110. The mixtures are allowed to stand for 24 hs. The solvents are each renewed twice, collected, and evaporated to dryness in low vacuum. The extracts are placed in 2% aqueous sulfuric acid and adjusted to a pH of 4 with concentrated aqueous ammonia solution. Five extractions with diethyl ether follow. The aqueous phase is set to a pH of 9 with concentrated ammonia and extracted five times with diethyl ether. These ether fractions are collected, dried with sodium sulfate, and evaporated. 20 g of a slightly yellow, oily residue is obtained, which is recrystallized from hot isopropanol. 10 g of white galanthamine base having a melting point of 129°-130°C is obtained.

Galantamine may be isolated from Galanthus nivalis or G. woronowi bulbs too.

References

Tiffin P.D.; US Patent No. 6,087,495; July 11, 2000; Assigned: Janssen Pharmaceutica, N.V., Belgium
Hille T. et al.; US Patent No. 5,877,172; March 2, 1999; Assigned: LTS Lohmann Theraple-Systeme GmbH, Neuwied, Germany
Proskurina N.F., Yakovleva A.P.; J. Org. Chem., 1955.V.25. P. 1036
Kalaschnicov I.D. The Chemistry of natural compounds, 1970. 3. P.380

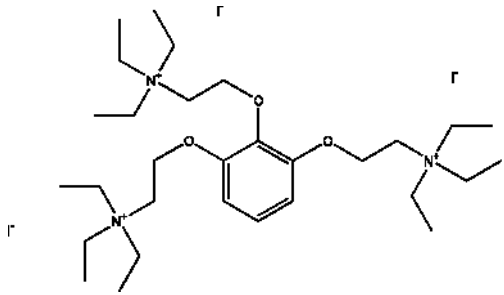
GALLAMINE TRIETHIODIDE

Therapeutic Function: Muscle relaxant

Chemical Name: 2,2',2"-[1,2,3-Benzenetriyltris(oxy)]tris[N,N,N-triethylethanaminium]triiodide

Common Name: Benzcurine iodide

Structural Formula:



Chemical Abstracts Registry No.: 65-29-2

Trade Name	Manufacturer	Country	Year Introduced
Flaxedil	Davis and Geck	US	1951
Flaxedil	May and Baker	UK	-
Flaxedil	Rhodia Iberica	Spain	-
Relaxan	Gea	Denmark	-
Sincurarina	Carlo Erba	Italy	-
Tricuran	Deutsches Hydrierwerk	E. Germany	-

Raw Materials

Pyrogallol
Diethylaminochloroethane
Sodium amide
Ethyl iodide

Manufacturing Process

12.6 grams of pyrogallol are dissolved in 100 cc of hot toluene. 14 grams of sodamide (85%)are added to the solution at about 100°C in 5 portions over a period of 15 minutes, with agitation. There are then added with agitation, over a period of 30 minutes, 100 cc of a toluene solution containing 474 grams of diethylaminochlorethane per liter of toluene.

The mixture is then heated for 1 hour, the toluene being refluxed, whereafter it is left to cool, 50 cc of water are added and, after decanting, the solution is

again washed with two quantities of 50 cc of water. The toluene solution is dried over potassium carbonate and distilled in vacuo. There is thus obtained 28 grams of 1.2.3-tri-(β-diethylaminoethoxy)benzene, boiling at 206°C under 1 mm pressure.

20 grams of 1.2.3-tri-(β-diethylaminoethoxy)-benzene is heated for 5 hours under reflux on the water bath with 30 grams of ethyl iodide. The hot mixture is dissolved in 50 cc of water, filtered after addition of 2 grams of decolorizing black, evaporated to dryness on the water bath and recrystallized from 120 cc of alcohol. The product can be further recrystallized in mixtures of acetone and water.

The triethiodide of 1.2.3-tri-(β-diethylaminoethoxy)-benzene is thus obtained as white crystals which, after drying, have a rather indefinite melting point at about 152° to 153°C, (Maquenne block).

References

Merck Index 4214
Kleeman and Engel p.437
I.N. p.454
REM p. 923
Fourneau, E.; US Patent 2,544,076; March 6, 1951; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

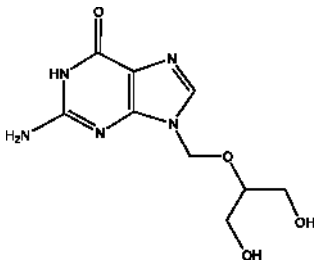
GANCICLOVIR

Therapeutic Function: Antiviral

Chemical Name: 6H-Purin-6-one, 2-amino-1,9-dihydro-9-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-

Common Name: Ganciclovir; Hydroxymethylaciclovir

Structural Formula:



Chemical Abstracts Registry No.: 82410-32-0

Trade Name	Manufacturer	Country	Year Introduced
Cymevene	Roche	Switz.	-
Cymevene	Roche Products Ltd.	UK	-
Cytovene	Hoffmann - LaRoche Inc.	USA	-
Ganciclovir	Ranbaxy	India	-
Ganciclovir eye gel	Chauvin	-	-
Vitrasert	Bausch and Lomb Surgical Inc	USA	-

Raw Materials

Benzyl alcohol
Sodium acetate
Acetic anhydride
Hydrogen
Palladium hydroxide on carbon
Sodium hydride
Epichlorohydrin
Hydrogen chloride
Paraformaldehyde

Manufacturing Process

Sodium hydride (100 g (50% dispersion in mineral oil), 2.08 mol) was washed twice with 1 L of hexane then dried under nitrogen. Dry DMF (1.5 L) was added. Benzyl alcohol (400 ml) was then added at for 2 hours such a rate to keep the temperature below 50°C. Epichlorohydrin (92.5 g, 1 mol) was then added dropwise over 0.5 hour with ice cooling in order to keep the temperature below 40°C. The solution was next stirred for 16 hours at 21°C then for 2.5 hours at 50°C. DMF was then removed by evaporation at reduced pressure. The oily residue was dissolved in 2.5 L diethyl ether. The organic solution was washed with 2 L of water, 2 L of 2% hydrochloric acid, 2 L of 1% sodium bicarbonate, and 1 L of brine, dried over sodium sulfate, and concentrated to a brown oil. Distillation gave 147.8 g of 1,3-di-O-benzylglycerol (boiling point 170-180°C/1 torr).

Dry hydrogen chloride gas was bubbled for 1.5 hours into a solution of 1,3-di-O-benzylglycerol (15 g, 55 mmole) and paraformaldehyde (3.3 g, 110 mmol) in 175 ml of 1,2-dichloroethane at 0°C. The solution was then stored in a stoppered flask for 21 hours at 4°C. Next, the solution was dried over magnesium sulfate with warming to 21°C and then filtered and concentrated to give 17.5 g of 1,3-di-O-benzyl-2-O-chloromethylglycerol.

To a solution of 1,3-di-O-benzyl-2-O-chloromethylglycerol (17.5 g, 55 mmol) in 400 ml of DMF at 0°C under a drying tube was added sodium acetate (6 g). The solution was then warmed to 21°C and magnetically stirred for 15 hours. The solvent was removed by evaporation at reduced pressure and the oily residue dissolved in 1 pound of diethylether. The ether solution was washed once with 750 ml of water, two times with 250 ml of water, and once with 250 ml of brine, dried over sodium sulfate and concentrated to give 19 g of 2-O-acetoxymethyl-1,3-di-O-benzylglycerol as an oil.

Guanine (20 g, 0.132 mol) was combined with 300 ml of acetic anhydride and the mixture heated at reflux for 16 hours. The mixture was cooled and the excess acetic anhydride removed by evaporation at reduced pressure. The residue was recrystallized from dimethyl sulfoxide to give 25.6 g of N^2,9-diacetylguanine.

N^2,9-Diacetylguanine (15.61 g, 66 mmol), 2-O-acetoxymethyl-1,3-di-O-benzylglycerol (19 g, 55 mmol), and bis(p-nitrophenyl)phosphate (0.5 g) were stirred together with 150 ml of diethylether. The solvent was removed by evaporation and the residue heated in a 175°C oil bath for 1.5 hours under a stream of nitrogen. Column chromatography eluting with 1:9 methanol/methylene chloride followed by recrystallization from ethyl acetate afforded 4.76 g of N^2,9-acetyl-9-(1,3-dibenzyloxy-2-propoxymethyl)guanine, melting point 145-146°C.

To a solution of N^2,9-acetyl-9-(1,3-dibenzyloxy-2-propoxymethyl)guanine (4.62 g, 9.67 mmol) in 150 ml of methanol plus 40 ml of water was added 20% palladium hydroxide on carbon as a slurry in 10 ml of water. The mixture was hydrogenated on a Parr hydrogenator at 60 psi of hydrogen for 38 hours then filtered through celite and concentrated to a white solid. Recrystallization from methanol/ethyl acetate gave 1.4 g of N^2,9-acetyl-9-(1,3-dihydroxy-2-propoxymethyl)guanine,melting point 205-208°C.

The mother liquor was further reduced with 10% palladium on carbon (1 g) in 150 ml of methanol plus 50 ml of water at 60 psi for 47 hours. The total yield of N^2,9-acetyl-9-(1,3-dihydroxy-2-propoxymethyl)guanine was 2.11 g.

N^2,9 -Acetyl-9-(1,3-dihydroxy-2-propoxymethyl)guanine (721.9 mg, 2.4 mmol) was stirred with 50 ml of methanolic ammonia solution (methanol saturated with ammonia at 0°C) for 17 hours at 21°C. The solution was concentrated to a white solid and the residue recrystallized from methanol to give 582.3 mg of 9-(1,3-dihydroxy-2-propoxymethyl)-guanine, melting point 250°C (decomp.).

References

Verheyden J.P., Martin J.; US Patent No. 4,355,032; Oct. 19, 1982; Assigned: Syntex (U.S.A.) Inc. (Palo Alto, CA)

GANIRELIX ACETATE

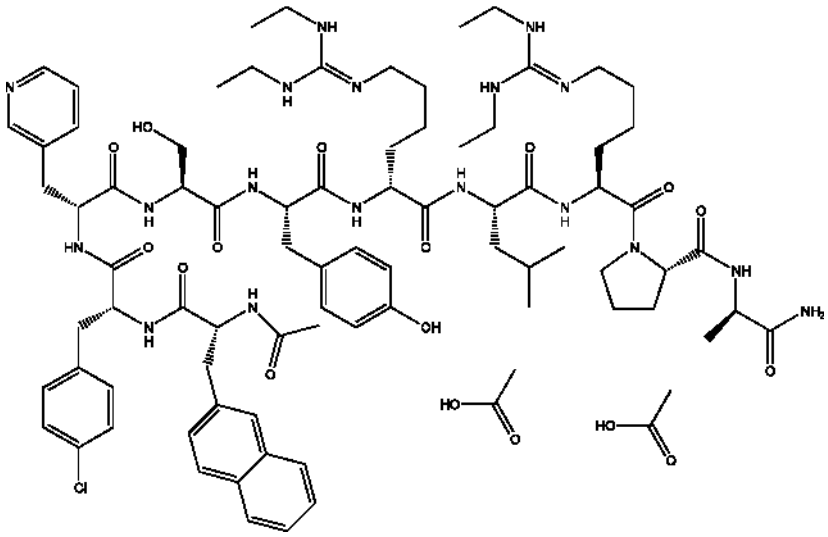
Therapeutic Function: LHRH antagonist

Chemical Name: D-Alaninamide, N-acetyl-3-(1-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N^6-(bis(ethylamino)methylene)-D-lysyl-L-leucyl-N^6-(bis(ethylamino)methylene)-L-lysyl-L-prolyl-, diacetate (salt)

Common Name: Ganirelix acetate

Chemical Abstracts Registry No.: 124904-93-4 (Base); 129311-55-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Antagon	Organon	-	-
Orgalutran	Organon	-	-
Ganirelix	Organon	-	-

Raw Materials

N(α)-Boc-Pro
N(α)-Boc-Leu H_2O
N(α)-Boc-Tyr
N(α)-Boc-D-Pal(3)
N(α)-Boc-D-Nal(2)
Acetic anhydride
Trifluoroacetic acid
N(α)-Boc-hArg(Et)$_2$ HCl
N(α)-Boc-D-hArg(Et)$_2$ HCl
N(α)-Boc-Ser(tBu)
N(α)-Boc-D-p-Cl-Phe
1-Hydroxybenzotriazole
N,N'-Diisopropyl carbodiimide

Manufacturing Process

The abbreviations for common aminoacids are those recommended by IUPAC-IUB Comission on Biochemical Nomenclature. Other abbreviations useful in describing the replacements of aminoacids in the natural LH-RH peptide are following:

Nal(2) - 3-(2-naphthyl)alanyl; p-Cl-Phe - 3-(p-chlorophenyl)alanyl; Pal(3) - 3-(3-pyridyl)alanyl; ; hArg(Et)$_2$ - N^G,N^G - bis(ethtyl)homoarginyl; Boc - t-butyloxycarbonyl.

Ganirelix (N-Ac-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-hArg(Et)$_2$-Leu-hArg(Et)$_2$-Pro-Ala-NH$_2$) was prepared using the following side chain protection protocol: salt protection for L- and D-hArg(Et)$_2$ (as the chloride) and t-butyl protection for serine.

Amino acids were added to the N$^\alpha$-Boc-D-Ala-O-Resin (1.0 mmol of resin was replaced in the reaction vessel of 5.0 L Vega 296 automated solid phase peptide synthesizer; in the following sequence:

N$^\alpha$-Boc-Pro	2.3 equiv.
N$^\alpha$-Boc-hArg(Et)$_2$ HCl	1 equiv./HBt
N$^\alpha$-Boc-Leu H_2O	2.3 equiv.
N$^\alpha$-Boc-D-hArg(Et)$_2$ HCl	1.6 equiv./HBt
N$^\alpha$-Boc-Tyr	2.1 equiv./HBt
N$^\alpha$-Boc-Ser(tBu)	2.0 equiv.
N$^\alpha$-Boc-D-Pal(3)	1.8 equiv./HBt
N$^\alpha$-Boc-D-p-Cl-Phe	2.0 equiv.
N$^\alpha$-Boc-D-Nal(2)	2.1 equiv./HBt

Acetic anhydride

An acetylation (capping of the resin) was done after Ala, Pro and Leu with N,N'-diisopropyl carbodiimide - 1-hydroxybenztriazole (HBt). Excess HBt (2 equiv.) was used for the coupling of the basic amino acids, hArg(Et)$_2$ and Pal(3).

The following protocols were used to remove the N$^\alpha$-protecting group following each addition.

Program A: The resin was first washed with CH_2Cl_2 1 times/1 min, TFA-CH_2Cl_2 (40/60) 1 times/1 min, TFA-CH_2Cl_2 (40/60) 1 times/30 min, CH_2Cl_2 2 5 times/1 min, Et_3N-CH_2Cl_2 (5/95) 3 times/1 min, CH_2Cl_2 4 times/1 min.

Program B: The resin was first washed with CH_2Cl_2 1 times/1 min, 4-4.5 N HCl in CH_2Cl_2/i-PrOH (1/1) 1 times/1 min, 4-4.5 N HCl in CH_2Cl_2/i-PrOH (1/1) 1 times/30 min, CH_2Cl_2 3 times/1 min, DMF 1 times/1 min, Et_3N-CH_2Cl_2 (5/95) 3 times/1 min, DMF 1 times/1 min, CH_2Cl_2 4 times/1 min.

After each deprotecting and washing step, following protocol A or B, the next amino acid in sequence was added and the resin washed with CH_2Cl_2 3 times/1 min, MeOH 4 times/1 min, DMF 2 times/1 min and CH_2Cl_2 4 times/1 min.

Program A was used for the removal of the protecting groups on Ala, Pro, L-hArg(Et)$_2$, Leu and D-Nal(2).

Program B was used for the removal of the protecting groups on D-hArg(Et)$_2$, Tyr, Ser, D-Pal(3) and p-Cl-Phe.

The crude peptide was first dissolved in 2 M acetic acid and converted to its

acetate salt by passage through a column of AG3-X4A resin (Bio-Rad). The acetate was subjected to chromatography on a silica gel column (CH_2Cl_2/i-PrOH/MeOH/H_2O/HOAc solvent); the acetate fractions dissolved in H_2O and loaded onto a reversed-phase column (Vydec C-18, 15-20 μ), and purified using acetonitrile/TEAP (pH 3). Fractions of the desired purity were combined and diluted with water and reloaded on a reversed-phase HPLC column, then washed with 1% acetic acid in water. The peptide was stripped with a mixture of MeOH/CH_3CN/HOAc/H_2O (44/50/1/5). The residue was dissolved in acetic acid and precipitated over ether, filtered, washed with ether and dried under vacuum. Amino acid analyses were performed on a Beckman 119CL amino acid analyzer. Samples for amino acid analyses were hydrolyzed with 6 N HCl at 110°C for 20 hrs. Analytical HPLC was performed on a Spectra Physics 8800 chromatograph. Synthesis of ganirelix was confirmed by the presence of a main peak at rt 18 min; no other peak over 1% was noted at rt 16 min.

References

Nestor J. et al.; US Patent No. 5,212,288; May 18; 1993; Assigned to Syntex (U.S.A.) Inc., Palo Alto, Calif.

GARDIMYCIN

Therapeutic Function: Antibiotic

Chemical Name: H-Ala-Leu-Abu-Ile-Glu-Abu-Ala-Val-Trp-Gly-Ser-Ala-Gly-Abu-Val-Ile-Ala-Ala-Ala-OH

Common Name: Actagardine; Gardimycin

Structural Formula: -

Chemical Abstracts Registry No.: 59165-34-3

Trade Name	Manufacturer	Country	Year Introduced
Actagardine	Lepetit S.p.A.	-	-

Raw Materials

Starch
Meat extract
Peptone
Glucose
Yeast extract
Soybean meal
Actinoplanes garbadinensis ATCC 31049
Calcium carbonate
Hydrochloric acid
Sodium chloride
Sodium-potassiumphosphate buffer

Manufacturing Process

The antibiotic actagardine is produced by aerobically pre-culturing of the strain *Actinoplanes garbadinensis* ATCC 31049 in a nutrient medium.

A shake flask culture may have the following composition in g/L: meat extract 3.0; yeast extract 10.0; calcium carbonate 4.0; Starch 25.0; tap water q.s. to 1000 ml. The flasks are shaken for about 24 h at about 28°-30°C an then the pre-cultures 1 L are used to inoculate jar fermentors each containing 10 L of the following nutrient medium, g: meat extract 40.0; peptone 40.0; yeast extract 10.0; sodium chloride 25.0; soybean meal 100.0; glucose 500.0; calcium carbonate 50.0; tap water q.s. to 10 L.

The fermentation batches are incubated aerobically under stirring at 28°-30°C. At intervals the antibiotic activity is assayed microbiologically by the agar diffusion method using Sarcina lutea as the test organism. The maximum activity is reached after 96-120 h of fermentation.

The fermentation broth is adjusted at pH 8.0 and then filtered using Hyflo super-cell as a filter aid. The mycelium is discarded and the filtrate is extracted with an amount of butanol corresponding to about 0.5 of its volume. The organic phase is separated from the aqueous one, and, after washing with acidic water (pH 4.0) is concentrated to about 1:10 of its original volume and allowed to stand for 10-12 h at a temperature of 3°-6°C. A crude precipitate forms, which is collected on filter, washed with butanol and dried under vacuum at room temperature: yield 3.0 g.

Chromatographic assays on Whatman paper N1 or on silica-gel of this crude precipitate, and subsequent microbiological development of the spots by using Staphylococcus aureus as the detecting system, indicate the presence of two components which are defined as metabolite A and metabolite B (gardimycin): they have different R values which depend on the nature of the employed eluting system. The crude mixture is further purified by dissolving in about 30 ml of water. The resulting solution is dialyzed for about 16 h against distilled water and then concentrated to small volume under vacuum. 1.5 g of rough antibiotic substance are obtained, which still is a mixture of metabolite A and gardimycin. The two antibiotic substances are separated and purified by several countercurrent extractions, by relying upon the different partition coefficients of component A and gardimycin in the predetermined solvent system. The employed solvent system consists of butanol:sodium-potassium phosphate buffer M/15 pH 7.2: hexane in the ratio 1:1:0.1; the partition coefficients in this medium of metabolite A and gardimycin are 0.3 and 0.8 respectively. After 100 extractions, 0.45 0 g of gardimycin as its monosodium salt, melting point 260°C (dec.) are obtained.

1.0 g of gardimycin monosodium salt is dissolved in 150 ml of water. The resulting solution is brought to pH 2.5 by adding aqueous 10% hydrochloric acid and is then extracted two times with 75 ml of butanol saturated with water. The butanol extracts are collected and concentrated in vacuum at 45°C to a volume corresponding to 1:20 of the initial volume. After standing at 4°C for 12 h a precipitate forms, which is collected, washed with light petroleum and dried in vacuo at 40°-45°C. 0.950 g of gardimycin (free acid), melting point 250°-300°C (dec.) are obtained.

References

Parenti F. al.; US Patent No. 4,022,884; May 10, 1977; Assigned: Gruppo Lepetit S.p.A., Milan, Italy

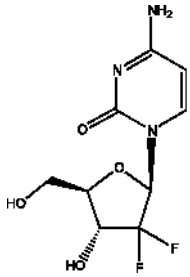
GEMCITABINE

Therapeutic Function: Antineoplastic, Antiviral

Chemical Name: Cytidine, 2'-deoxy-2',2'-difluoro

Common Name: Difluorodeoxycytidine; Gemcitabine

Structural Formula:



Chemical Abstracts Registry No.: 95058-81-4

Trade Name	Manufacturer	Country	Year Introduced
Gemzar	Lilly Co.	-	-
GEMCITE	Eli Lilly and Company India Pvt. Ltd.	-	-
Gemtro	Lilly Co.	-	-
LY 188011	Lilly Co.	-	-

Raw Materials

DAST (fluorinaiting agent)
Hydrogen chloride
Benzoyl chloride
Hydrogen
Phenylselenol
Pyridine
Ozone
Dimethyl sulfide
Methyl sulfate
N-Acetylcytosine
Boron trifluoride diethyl etherate
Sodium bicarbonate
Palladium on charcoal
Sodium periodate
Hydroperoxide, 1,1-dimethylethyl
Titanium tetraisopropoxide
Ethyl diisopropylamine
Triethylamine
Ammonium sulfate
Trimethylsilyl triflate
Benzyl 4,6-O-benzylidene-2-O-benzyl-3-oxo-α-D-gluco-pyranoside
Methyl 4,6-O-benzylidene-2-deoxy-3-oxo-α-D-erythro-hexopyranoside

Manufacturing Process

2 Methods of preparation of 3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-D-ribose:

1. Benzyl 4,6-O-benzylidene-2-O-benzyl-3-oxo-α-D-gluco-pyranoside was obtained by 4 steps from glucose.

0.53 ml (4.0 mmol) of DAST (fluorinaiting agent) was added to asolution of 300 mg (0.67 mmol) of benzyl 4,6-O-benzylidene-2-O-benzyl-3-oxo-α-D-gluco-pyranoside in anhydrous dichloromethane (4 ml). The solution was then stirred at room temperature for 2 h, and the excess of DAST was neutralized by careful addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2, and organic phase was dried and evaporated. The residue was purified by CC (Hexane/Ethyl acetate 7:1) to afford benzyl 4,6-O-benzylidene-2-O-benzyl-3-deoxy-3,3-difluoro-α-D-gluco-pyranoside (189 mg, 60%), melting point 118°-119°C.

Benzyl 4,6-O-benzylidene-2-O-benzyl-3-deoxy-3,3-difluoro-α-D-gluco-pyranoside (77 mg, 0.16 mmol) was dissolved in a 0.1 N solution of HCl in ethanol and stirred at room temperature for 40 h. The solution was then neutralized with solid $NaHCO_3$, filtered and evaporated to give an oily product that was dissolved in 2 ml of CH_2Cl_2 and 0.5 ml of pyridine. After cooling to 0°C, 0.40 ml (1.6 mmol) of benzoyl chloride was added and the solution was stirred for 1 h and poured into ice and water (200 ml) containing $NaHCO_3$, extracted several times with CH_2Cl_2, dried and evaporated to give 86 mg (0.14 mmol, 90%) of benzyl 4,6-di-O-benzoyl-2-O-benzyl-3-deoxy-3,3-difluoro-α-D-gluco-pyranoside.

Benzyl 4,6-di-O-benzoyl-2-O-benzyl-3-deoxy-3,3-difluoro-α-D-gluco-pyranoside (220 mg, 0.44 mmol) was dissolved in methanol in the presence of 200 mg of palladium on activated charcoal (10% Pd content). The suspension was stirred at room temperature under hydrogen pressure (10 bar) for 16 h. The suspension was then filtered through a thin silica gel pad, and evaporated. The residue was purified by CC to give 105 mg (59%) of 4,6-di-O-benzoyl-3-deoxy-3,3-difluoro-α/β-D-gluco-pyranoside as an inseparable anomeric mixture (ratio α/β = 5:1).

To a solution of 46 mg (0.11 mmol) of 4,6-di-O-benzoyl-3-deoxy-3,3-difluoro-α/β-D-gluco-pyranoside in water-dioxane 1:2 (2 ml) was added 120 mg (0.56 mmol) of sodium periodate. This resulting solution was stirred at room temperature for 20 h. Then, more sodium periodate (55 mg, 0.26 mmol) was added and stirring was continued for 6 h. After that, the solvents were evaporated and the solid was repeatedly extracted with ethyl acetate (total volume 70 ml). The solvent was then evaporated to give a solid that was treated for 15 min with a diluted (0.1%) methanolic solution of ammonia. THE solution was evaporated and the crude purified by preparative TLC (hexane/ethyl acetate 2:1) to yield 18 mg (0.04 mmol, 43%) of α-3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-D-ribose.

2. Methyl 4,6-O-benzylidene-2-deoxy-3-oxo-α-D-gluco-pyranoside was obtained by 3 steps from mannose accoding to Horton's procedure.

DAST (0.60 ml, 4.6 mmol) was added to a solution of methyl 4,6-O-benzylidene-2-deoxy-3-oxo-α-D-erythro-hexopyranoside (0.315 g, 1.19 mmol) in dry dichloromethane (10 ml) under argon. The solution was stirred at room temperature for 2.5 h. The excess of DAST was neutralized by careful addition of saturated aqueous $NaHCO_3$. The combined layers were extracted (CH_2Cl_2),

and the extracts were dried ($MgSO_4$) and evaporated to give a syrup which was purified by column chromatography (hexane/ethyl acetate 2:1), to afford 0.24 g (0.84 mmol, 70%) of methyl 4,6-O-benzylidene-2,3-dideoxy-3,3-difluoro-α-D-erythro-hexopyranoside, melting point 92°-94°C.

Methyl 4,6-O-benzylidene-2,3-dideoxy-3,3-difluoro-α-D-erythro-hexopyranoside (0.70g, 2.5 mmol) was dissolved in a 0.1 N ethanolic solution of hydrochloric acid and stirred at room temperature for 1 day. The solution was then neutralized by addiing solid sodium bicarbonate. The solids were filtered, the solvent was then evaporated to dryness and residue dissolved in 5 ml of pyridine and 1.5 ml of benzoyl chloride. The solution was stirred for 10 h, poured into ice-water (300 ml), extracted with dichloromethane (3 x 100 ml), washed with a saturated solution of sodium bicarbonate, dried and evaporated, to give 0.86 g (2.1 mmol, 85%) of methyl 4,6-di-O-benzoyl-2,3-dideoxy-3,3-difluoro-α-D-erythro-hexopyranoside.

BF_3OEt_2 (0.060 ml, 0.48 mmol as a solution of 48% in BF_3) and phenylselenol (0.064 ml, 0.60 mmol) were added to a stirred solution of methyl 4,6-di-O-benzoyl-2,3-dideoxy-3,3-difluoro-α-D-erythro-hexopyranoside (100 mg, 0.24 mmol) in anhydrous dichlormethane (2 ml). The solution was heated to reflux for 3 h, neutralized by dropwise addition of pyridine and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate 10/1) to afford 92 mg (72%) of phenyl 4,6-di-O-benzoyl-2,3-dideoxy-3,3-difluoro-1-seleno-α-D-erythro-hexopyranoside as an anomeric mixture.

A 3 M solution of t-butylhydroperoxide in toluene (0.042 ml, 0.12 mmol), titanium tetraisopropoxide (0.008 ml, 0.02 mmol) and ethyl diisopropylamine (0.014 ml, 0.08 mmol) were added to a stirred solution of 40 mg (0.074 mmol) of phenyl 4,6-di-O-benzoyl-2,3-dideoxy-3,3-difluoro-1-seleno-α-D-erythro-hexopyranoside in 4 ml of anhydrous dichloromethane at room temperature. The reaction was complete within 6 h, and the solvent was then evaporated to dryness and the residue was quickly purified by preparative TLC to give 20 mg (72%) of 1,5-anhydro-4,6-di-O-benzoyl-2,3-dideoxy-3,3-difluoro-D-erythro-hex-1-enitol.

44 mg (0.12 mmol) of 1,5-anhydro-4,6-di-O-benzoyl-2,3-dideoxy-3,3-difluoro-D-erythro-hex-1-enitol were dissolved in dichloromethane and cooled in an acetone/carbon dioxide bath. Ozone was steadily bubbled through the solution until a light blue colour appeared (20 min). Then, bubbling oxygen for 10 more min, the solution was treated with an excess of dimethyl sulphide and stirred overnight at room temperature, washed with water (3 x3 ml), dried and evaporated to dryness to give a residue that was dissolved in methanolic ammonia (0.1% w/w, 1 ml) and stirred at 0°C for 43 min. The solvent was then evaporated to dryness and the residue was chromatographed (hexane/ethyl acetate 5:1) to give 14 mg of α-3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-D-ribose.

Preparation of gemcitabine:

Triethylamine and methylsulphonyl chloride were added to a solution of α-3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-D-ribose in dichloromethane cooled with an ice bath. The solution was stirred while warming to to room temperature. After 1 h triethylamine and methylsulphonyl were added. Stirring was continued for 3 more h, and then the solution was washed with diluted

aqueous HCl and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and evaporated to give a residue which was purified by flash chromatography (hexane/ethyl acetate 3:1), to yield α-3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-1-methylsulfonyl D-ribose.

N-Acetylcytosine was suspended in hexamethyldisilazane under an inert atmosphere. To this suspension of ammonium sulfate was added. The suspension was refluxed until a clear solution was obtained (1 h). The liquids were evaporated to dryness and the residue was dried under high vacuum before being used. This residue was redissolved in anhydrous 1,1,2,2-tetrachloroethane under argon, and a solution of α-3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-1-methylsulfonyl D-ribose in the same solvent was added. Then, trimethylsilyl triflate (catalyst) and freshly activated 4 a molecular sieve (50 mg) were added and the mixture was heated to reflux. After 3 h the solution was diluted in chloroform and filtered. The liquid was then washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous magnesium sulphate and evaporated to give a solid which was purified by flash chromatography (chloroform/methanol 20:1) to yield of α-N-acetyl-1-(3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-1-methylsulfonyl D-ribosyl)-cytosine.

α-N-Acetyl-1-(3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-1-methylsulfonyl D-ribosy)-cytosine was dissolved in methanolic ammonia solution and kept overnight in a closed flask. The solvent was then evaporated to dryness and the residue was purified by filtration through a thin silica gel pad using chloroform/methanol 10:1 as eluent to give 1-α-(2-deoxy-2,2-difluoro-D-ribosyl)-cytosine - gemcitabine.

References

Femandez R. et al.; Tetrahedron; vol. 54, p. 3523-3532, 1998
Femandez R., Castillon S.; Tetrahedron; vol. 55, p. 8497-8508, 1999
Gerecke M. et al.; US Patent No. 4,346,031; August 24, 1982; Assigned: Hoffmann-La Roche Inc., Nutley, N.J.

GEMEPROST

Therapeutic Function: Prostaglandin, Cervical softener

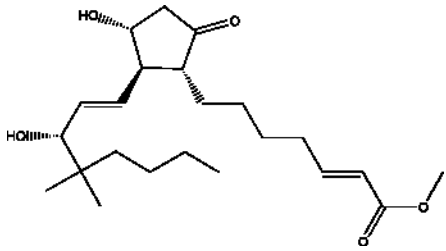
Chemical Name: 11,15-Dihydroxy-16,16-dimethyl-9-oxoprosta-2,13-dien-1-oic acid methyl ester

Common Name: -

Chemical Abstracts Registry No.: 64318-79-2

Trade Name	Manufacturer	Country	Year Introduced
Preglandin	Ono	Japan	1982

Structural Formula:



Raw Materials

Ethyl 9α-hydroxy-11α,15α-bis(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2,trans-13-dienoate
Potassium hydroxide
Manganese sulfate
Acetic acid

Manufacturing Process

Synthesis of 9-oxo-1α,15α-bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2, trans-13-dienoic acid: 4 g of ethyl 9α-hydroxy-11α15α-bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2,trans-13-dienoate were dissolved in 130 ml of a mixture of ethanol-water (3:1), mixed with 3.9 g of potassium hydroxide and stirred at 25°C for 2 hours. The reaction mixture was acidified with aqueous solution of oxalic acid to pH 5, and diluted with 100 ml of water, extracted with ethyl acetate. The extracts were washed with water, dried over sodium sulfate and concentrated under reduced pressure to obtain 3.88 g of 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2,trans-13dienoic acid.

The obtained compound 2.46 g were dissolved in 72 ml of diethyl ether and stirred at 3°C. To which a solution of manganese sulfate (15 g), 3.1 g of chromium trioxide, 72 ml of water and 3.5 ml of sulfuric acid was added. After stirring for 3.5 hours at 3°C, extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-benzene (1:1) as eluent to give 2.35 g of the title compound.

Synthesis of 16,16-dimethyl-trans-δ^2-PGE_1: 2.35 g of the bis-tetrahydropyranyl ether were dissolved in 6 ml of tetrahydrofuran and 60 ml of 65%-acetic acid aqueous solution and the solution stirred at 60°C to 70°C for 20 minutes. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-cyclohexane (2:3) as eluent to yield 270 mg of the title compound.

References

Merck Index 4245
DFU 4 (2) 911 (1979)
DOT 19 (7) 414 (1983)
I.N. p.456
Hayashi, M., Kori, S. and Wakasata, H.; US Patent 4,052,512; October 4, 1977; assigned to Ono Pharmaceutical Co. (Japan)

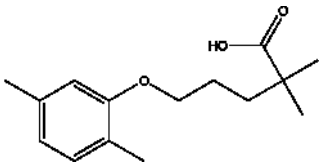
GEMFIBROZIL

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 25812-30-0

Trade Name	Manufacturer	Country	Year Introduced
Lopid	Warner Lambert	US	1982
Organolipid	Godecke	W. Germany	1982

Raw Materials

Isobutyric acid
3-(2,5-Xylyloxy)propyl bromide
Butyl lithium

Manufacturing Process

With stirring, 44.1 g of isobutyric acid is added to a mixture of 51.0 g of diisopropylamine, 23.2 g of a 57% sodium hydride dispersion in mineral oil, and 350 ml of tetrahydrofuran. When gas evolution subsides, the mixture is heated at reflux for 15 minutes, cooled to 0°C, and treated with 345 ml of a 1.45M solution of n-butyl lithium in heptane. After 5 hr, the mixture is warmed one-half hour at 30°C, cooled to 0°C, and treated with 122.0 g of 3-(2,5-xylyloxy)propyl bromide. After one more hour, it is stirred with 500 ml of water and the aqueous phase is separated and acidified with 150 ml of 6N

hydrochloric acid. The acidic mixture is extracted with ether and the ether extract is washed with saturated sodium chloride solution, dried over magnesium sulfate, concentrated almost to dryness, and distilled in vacuo. A distillate of 2,2-dimethyl-5-(2,5-xylyloxy)valeric acid is collected at boiling point 158°C to 159°C at 0.02 mm of Hg; melting point 61°C to 63°C following crystallization from hexane.

The same product is obtained by substituting 4.4 g of lithium hydride for the sodium hydride in the above procedure.

The same product is also obtained in the following manner. A mixture of 26.4 g of isobutyric acid, 6.0 g of magnesium oxide powder, and 250 ml of toluene is stirred and heated at reflux with continuous removal of the water formed in the reaction. When water formation ceases, the resulting mixture containing magnesium isobutyrate is concentrated to one-half its original volume, cooled in an ice bath, and treated with 31.0 g of diisopropylamine in 200 mi of dry tetrahydrofuran and then with 179 ml of 1.68M n-butyl lithium in heptane while the temperature is maintained below 10°C. After 15 more minutes, the mixture is warmed at 30°C for one-half hour, cooled to 0°C to 10°C, and treated with 75.0 g of 3-(2,5-xylyloxy)propyl bromide. The mixture is then stirred for 18 hr at room temperature and diluted with 125 ml of 6N hydrochloric acid and 250 ml of water. The organic phase is separated, concentrated, and the residue distilled in vacuo to give 2,2-dimethyl-5-(2,5-xylyloxy)valeric acid.

References

Merck Index 4246
DFU 1 (11) 520 (1976)
PDR p.1364
OCDS Vol.3 p.45 (1984)
DOT 18 (11) 582 (1982)
I.N. p.456
REM p.864
Creger, P.L.; US Patent 3,674,836; July 4, 1972; assigned to Parke, Davis and Co.

GENTAMICIN SULFATE

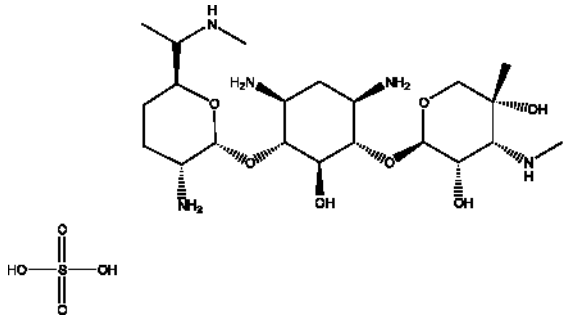
Therapeutic Function: Antibacterial

Chemical Name: Gentamicin, sulfate (salt)

Common Name: -

Chemical Abstracts Registry No.: 1405-41-0; 1403-66-3 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Garamycin	Schering	US	1966
Garramycin	Kirby-Warrick	UK	1966
Refobacin	Merck	W. Germany	1967
Gentalyn	Essex	Italy	1967
Gentalline	Unicet	France	1968
Genoptic	Allergan	US	1979
U-Gencin	Upjohn	US	1980
Bristagen	Bristol	US	1980
Apogen	Beecham	US	1980
Jenamicin	Hauck	US	1982
Gentafair	Pharmafair	US	1983
Biogen	Cusi	Spain	-
Biomargen	Biologia Marina	Spain	-
Cidomycin	Roussel	UK	-
Duramycin	Durachemie	W. Germany	-
Espectrosina	Centrum	Spain	-
Gensumycin	Roussel	-	-
Genta	I.E. Kimya Evi	Turkey	-
Genta-Gobens	Normon	Spain	-
Gentabac	Infan	Mexico	-
Gentacin	Schering-Shionogi	Japan	-
Gentadavur	Davur	Spain	-
Gentamedical	Medical	Spain	-
Gentamicin-Pos	Ursapharm	W. Germany	-
Gentamin	Medix	Spain	-
Gentamina	Essex	Argentina	-
Gentamival	Valles Mestre	Spain	-
Gentamorgens	Morgens	Spain	-
Gentamytrex	Mann	W. Germany	-
Gentaroger	Roger	Spain	-
Gentasillin	Nobel	Turkey	-
Gentibioptal	Farmila	Italy	-
Genticina	Antibioticos	Spain	-
Genticol	S.I.F.I.	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Gento	Bryan	Spain	-
Gentona	Asla	Spain	-
Gent-Ophtal	Winzer	W. Germany	-
Getamisin	Deva	Turkey	-
Gevramycin	Essex Espana	Spain	-
Glevomicina	Bago	Argentina	-
G-Mycin	Neofarma	Finland	-
Miramycin	Teva	Israel	-
Ophtagram	Chauvin-Blache	France	-
Plurisemina	Northia	Argentina	-
Ribomicin	Farmigea	Italy	-
Sulgemicin	Larma	Spain	-
Sulmycin	Byk-Essex	W. Germany	-

Raw Materials

Bacterium *Micromonospora purpurea*
Soybean meal

Manufacturing Process

Germination Stage: A lyophilized culture of *M. purpurea* is added to a 300 ml shake flask containing 100 ml of the following sterile medium: 3 grams bacto-beef extract; 5 grams tryptose; 1 gram dextrose; 24 grams starch (soluble); 5 grams yeast extract; and 1,000 ml tap water. The flask and its contents are incubated for 5 days at 37°C on a rotary shaker (280 rpm, 2 inch stroke).

Inoculum Preparation Stage: Two batches of inoculum of about 50 gallons each are prepared by the following method: A 25 ml inoculum (from the germination stage) is transferred to each of four 2-liter flasks, each containing 500 ml of the sterile medium utilized for germination. The flasks and contents are incubated for 5 days at 28°C on a rotary shaker (280 rpm, 2 inch stroke).

The contents of the flasks are pooled, a 25 ml inoculum (taken from the pool) is added to each of twenty 2-liter flasks, each containing 500 ml of the following sterile medium: 30 grams soybean meal; 40 grams dextrose (cerelose); 1 gram calcium carbonate; 1,000 milliliters tap water. The flasks and their contents are incubated for 3 to 5 days at 28°C on a rotary shaker (280 rpm, 2 inch stroke). The broth is pooled and aseptically transferred into a sterile inoculum flask having a side arm (total volume, about 10 liters).

The 10 liters of inoculum is aseptically transferred to a 65-gallon fermenter containing 50 gallons of the following sterile medium: 600 grams bacto-beef extract; 1,000 grams bacto-tryptose; 200 grams dextrose (cerelose); 4,800 grams starch (soluble); 1,000 grams yeast extract; 100 ml antifoamer GE 60 (General Electric Co. brand of silicone defoamer), or other defoamer; and tap water, qs to 50 gallons.

The pH is adjusted to 6.9 to 7.0 before sterilization and aerobic fermentation is effected for 24 hours (until the packed cell volume is about 10 to 15%)

under the following conditions: temperature, 37°C; sterile air input, 54 ft^3/min; pressure, 7 psi; and agitation, 180 rpm.

Fermentation Stage: One 50-gallon batch of inoculum is aseptically transferred to a 675-gallon fermenter (fermenter A) containing the following medium: 54.0 kg soybean meal; 72.0 kg cerelose; 9.0 kg calcium carbonate; 300 ml antifoamer GE 60; and 450 gallons soft water. The other 50-gallon batch of inoculum is aseptically transferred to a similar fermenter (fermenter B) containing the same medium as fermenter A with the addition of 200 mg of $CoCl_2 \cdot 6H_2O$. Fermentation is effected in each fermenter at 35°C while agitating at 120 rpm with air input at 7 psi and 15 ft^3/min. At various times, samples of the fermented broth are withdrawn and assayed for antibiotic production by the disc assay method. The following table shows the increase in yield effected by the presence of cobalt, (as described in US Patent 3,136,704).

Fermentation Time (hours)	**Yield of Gentamicin (units/ml)**	
	Fermenter A (no cobalt)	**Fermenter B (cobalt present)**
24	9.3	13
40	34	133
48	49	185
60	70	332
72	77	440
96	75	420

The conversion of the broth to gentamicin sulfate is described in US Patent 3,091,572.

References

Merck index 4251
Kleeman and Engel p.438
PDR pp.872, 888, 1397, 1429, 1606, 1621
DOT 2 (3) 99 (1966) and 17 (3) 106 (1981)
I.N. p.457
REM p.1180
Luedemann, G.M. and Weinstein, M.J.; US Patent 3,091,572; May 28, 1963; assigned to Schering Corporation
Charney, W.; US Patent 3,136,704; June 9, 1964; assigned to Schering Corporation

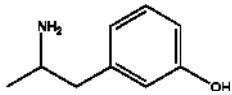
GEPEFRIN

Therapeutic Function: Antihypotensive

Chemical Name: 3-(2-Aminopropyl)phenol

Common Name: alpha-Methyltyramine

Structural Formula:



Chemical Abstracts Registry No.: 18840-47-6

Trade Name	Manufacturer	Country	Year Introduced
Pressionorm	Helopharm	W. Germany	1981

Raw Materials

D-(+)-1-(3-methoxyphenyl)-2-arninopropane
Hydrogen chloride

Manufacturing Process

Hydrolysis of D-(+)-1-(3-rnethoxyphenyl)-2-aminopropane: 2.42 mols (40 g) of the compound are dissolved in 6N hydrochloric acid in a bomb tube consisting of stainless steel and having a capacity of 500 ml. Hydrogen chloride gas is passed into the ice-cooled solution until this is saturated, The solution is then heated to 130°C for 2 hours in an air bath. After cooling and driving off the hydrochloric acid at a slightly elevated temperature, the hydrochloride of the 3-hydroxyphenyl derivative is present in the form of a yellowish syrup.

The free base can be liberated from the hydrochloride by extracting a butanol solution of the hydrochloride several times with sodium bicarbonate solution. After recrystallization from isopropanol/ligroin, the yield of D-(+)-1-(3-hydroxyphenyl)-2-aminopropane amounts to 33.0 g, corresponding to 90.1% of theory relative to the D-form. Melting point = 152°C to 154°C.

References

Merck Index 4262
I.N. p. 458
Helopharm W. Petrik and Co., K.G.; British Patent 1,527,479; October 4, 1978

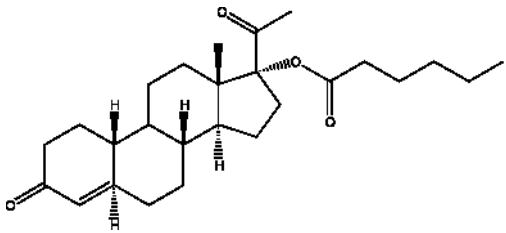
GESTONORONE CAPROATE

Therapeutic Function: Progestin

Chemical Name: 19-Norpregn-4-ene-3,20-dione, 17-hydroxy-, hexanoate

Common Name: Gestonorone caproate; Gestonorone hexanoate; Gestronol hexanoate; Hydroxynorprogesterone caproate

Structural Formula:



Chemical Abstracts Registry No.: 1253-28-7

Trade Name	Manufacturer	Country	Year Introduced
Depostat	Schering AG	-	-
Gestonorone Caproate	Shanghai Lansheng Corporation	-	-
Gestonorone Caproate	Hunan Steroid Chemicals Co., Ltd.	-	-
Primostat	Schering	-	-

Raw Materials

p-Toluensulfonate
Hydrochloric acid
Sodium bicarbonate
17-α-Hydroxy-19-norprogesteron
Capronic acid anhydride
3-Methoxy-17α-hydroxy-17β-acetyl-$\delta^{(2,5(10))}$-oestradien

Manufacturing Process

2 Methods of producing of 17-α-hydroxyl-19-norprogesteron-17-capronate:

1. To a solution of 1.0 g 17-α-hydroxy-19-norprogesteron in 32 ml capronic acid anhydride 1.32 g p-toluesulfonate (1 mole hydrate) were added, and allowed to stand for 3 h at 37°C. To the solution 1.43 ml conc. hydrochloric acid in 143 ml methanol were added and all this also for 1 h was left under N_2. Then mixture was washed with water and treated with ether. Ether extract was washed with water, and dried with Na_2SO_4. After that ether was distilled and residue was recrystallised with isopropyl ether. 1.1 g of 17-α-hydroxyl-19-norprogesteron-17-capronate was obtained, melting point 123°-124°C.

2. 2.0 g 3-methoxy-17α-hydroxy-17β-acetyl-$\delta^{2,5(10)}$-oestradien, 60 ml capronic acid anhydride, 2.6 g p-toluensulfonate and 18.0 g water were mixed and left for 6 h at room temperature. Then solution obtained was treated ether and sodium bicarbonate and washed with water. Etheral solution was dried over sodium sulfate. After distillation of ether 3.1 g 3,17α-dihydroxy-$\delta^{3,5}$-19-norpregnadien-3,17-dicapronate was produced.

To solution of 3.1 g 3,17α-dihydroxy-$\delta^{3,5}$-19-norpregnadien-3,17-dicapronate in 250 ml methanol 2.5 g conc. hydrochloric acid were added and mixture was left for 1 h. Then mixture was filtered and residue was washed. After recrystallisation with isopropyl ether 17-α-hydroxyl-19-norprogesteron-17-capronate was obtained, melting point 121°-123°C.

References

Popper A. et al.; D Patent No. 1,074,582; Sept. 24, 1958; Assigned: Schering Aktiengesellschaft, Berlin N65

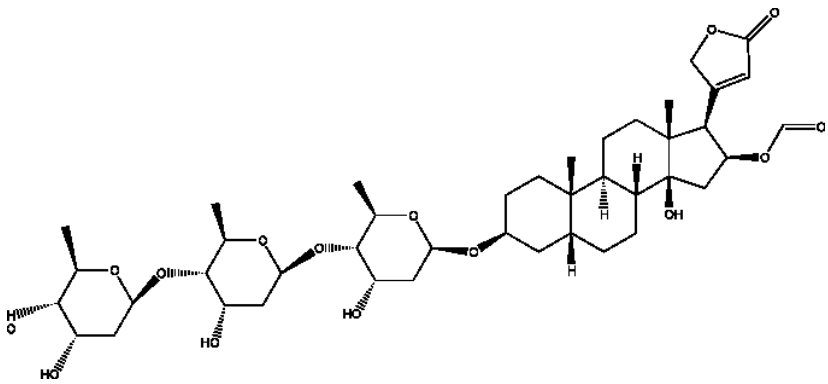
GITALOXIN

Therapeutic Function: Cardiotonic

Chemical Name: (3β,5β,16β)-3-((O-2,6-Dideoxy-β-D-ribo-hexopyranosyl-(1-4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1-4)-2,6-dideoxy-β-D-ribo-hexopyranosyl)oxy)-16-(formyloxy)-14-hydroxycard-20(22)-enolide

Common Name: 16-Formylgitoxin; Gitaloxin

Structural Formula:



Chemical Abstracts Registry No.: 3261-53-8

Trade Name	Manufacturer	Country	Year Introduced
Gitaloxin	Shanghai Lansheng Corporation	-	-

Raw Materials

Gitoxin
Acetanhydride
Formic acid
Triethylamine

Manufacturing Process

0.2 g gitoxin was dissolved in 15 ml of dimethylformamide and mixed with 2 ml of acetanhydride, 3 ml formic acid (98%) and 2 ml triethylamine or pyridine. The reaction mixture stood for 60 min. at room temperature, then it was diluted with water, a precipitated product was filtered off. A filtrate was shook with chloroform 2 times. Chloroform was distilled to dryness and the residue was added to the precipitate. 16-Formylgitoxin was isolated by fraction crystallization. MP: 250°-253°C, yield about 50%.

References

Kaiser F. et al.; DB Patent No. 1,026,312; Oct. 7, 1955; C.F.Boehringer and Soehne G. m. b. H., Mannheim-Waldorf

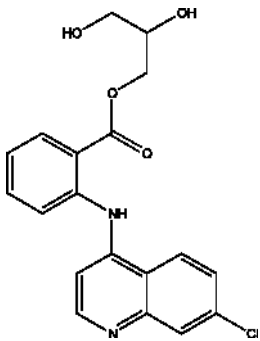
GLAFENINE

Therapeutic Function: Analgesic

Chemical Name: 2-[(7-Chloro-4-quinolinyl)amino]benzoic acid 2,3-dihydroxy-propyl ester

Common Name: Glycerylaminophenaquine

Structural Formula:



Chemical Abstracts Registry No.: 3820-67-5

Trade Name	Manufacturer	Country	Year Introduced
Glifanan	Roussel	France	1965
Glifanan	Albert Roussel	W. Germany	1968
Adalgur	Roussel	France	-
Glifan	Roussel Maestretti	Italy	-
Glifani	Nippon-Roussel-Chugai	Japan	-

Raw Materials

2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane
o-Nitrobenzoyl chloride
Hydrogen
4,7-Dichloroquinoline

Manufacturing Process

Step A: Preparation of (2,3-isopropylidenedioxy)-propyl o-nitrobenzoate - 59.6 g of 2,2-dimethyl-4hydroxymethyl-1,3-dioxolane were dissolved under agitation in 60 cc of anhydrous pyridine. The solution was cooled to +5°c and 86.5 g of o-nitrobenzoyl chloride (prepared by Leckermann et al., Ber. vol.80, p.488, 1947) were slowly introduced into it. The reaction mixture was agitated for a period of two hours at room temperature and then was poured into 500 cc of ether. The mixture was filtered and the filtrate was washed successively with 0.5 N sulfuric acid solution, with aqueous sodium bicarbonate solution and finally with water until the wash waters were neutral. The washed solution was dried over sodium sulfate and filtered again. The filtrate was distilled to dryness under vacuum to obtain 116.5 g (being a yield of 92%) of (2,3-isopropylidenedioxy)-propyl o-nitrobenzoate in the form of a yellow oil which distilled at 178°C to 180°C at a pressure of 1 mm.

Step B: Preparation of (2,3-isopropylidenedioxy)-propyl anthranilate - 80 g of (2,3-isopropyl-idenedioxy)propyl o-nitrobenzoate, obtained as described in Step A, were subjected to hydrogenation for a period of one hour in 800 cc of absolute alcohol in the presence of 2 g of palladized carbon black as catalyst. The reaction mixture was filtered and the filtrate was evaporated under vacuum to obtain 70.5 g (being a yield of 98.5%) of (2,3-isopropylidenedioxy)-propyl anthranilate in the form of a yellow oil which distilled at 159°C to 160°C under 0.5 mm of pressure.

Step C: Preparation of the (α-monoglyceride of 4-(2'-carboxyphenylamino)-7-chloro-quinoline - A mixture of 48 g of (2,3-isopropylidenedioxy)-propyl anthranilate, 36 g of 4.7-dichloro-quinoline, 36 cc of concentrated hydrochloric acid and 300 cc of water was agitated while heating to reflux for a period of two hours. The reaction mixture was filtered and the filtrate was allowed to stand at a temperature of 0°C for a period of three hours. The hydrochloride salt was then vacuum filtered and the salt was taken up in 600 cc 50% methanol at reflux. The solution was made alkaline by the addition of 120 cc of ammonia solution and iced for a period of one hour. The crystalline precipitate obtained was vacuum filtered, washed with water and dried to obtain 38.5 g (being a yield of 56%) of the α-monoglyceride of 4-(2'-carboxyphenylamino-7-chloro-quinoline having a melting point of 165°C.

The product occurred in the form of pale yellow prisms and was insoluble in water, ether, benzene, diluted alcohols, olive oil and chloroform, slightly soluble in absolute alcohol, dioxane, tetrahydrofuran and acetone, and soluble in dilute aqueous acids and alkalis.

References

Merck Index 4293
Kleeman and Engel p.441

OCDS Vol.1 p.342 (1977)
DOT 2 (4) 139 (1966)
I.N. p. 460
Allais, A. and Meier, J.; US Patent 3,232,944; February 1, 1966; assigned to Roussel-Uclaf S.A. (France)

GLATIRAMER ACETATE

Therapeutic Function: Immunomodulator

Chemical Name: See structure

Common Name: Copolymer-1; Glatiramer acetate

Structural Formula: L-Glutamic acid, polymers, polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt)

Chemical Abstracts Registry No.: 147245-92-9

Trade Name	Manufacturer	Country	Year Introduced
Copaxone	Teva Pharmaceuticals	Israel	-

Raw Materials

N-carboxyanhydrides of tyrosine, alanine, lysine, and glutamic acid
Diethylamine

Manufacturing Process

Glatiramer Acetate is water soluble copolypeptide with molecular weight 15,000-25,000.

Copolymer is prepared by copolymerization of the N-carboxyanhydrides of tyrosine, alanine, lysine, and glutamic acid. The polymerisation was carried out at ambient temperature in anhydrous dioxane with diethylamine as initiator. Glatiramer Acetate have the ratio alanin:glutamic acid:lysine:tyrosine = 1:6:4.54:2.

References

Steimon L. et al.; US Patent No. 6,531,130; March 11, 2003; Assigned to The Broad of Trustees of the Leland Stanford University
Teitelbaum D. et al.; US Patent No. 3,849,550; Nov. 19, 1974

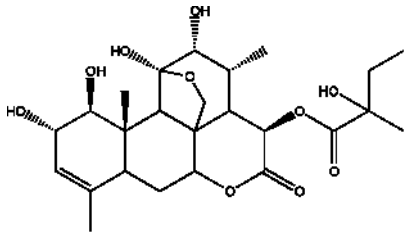
GLAUCARUBIN

Therapeutic Function: Amebicidal

Chemical Name: 11,20-Epoxy-1,2,11,12-tetrahydroxy-15-(2-hydroxy-2-methyl-1-oxobutoxy)picras-3-ene-16-one

Common Name: α-Kirondrin

Structural Formula:



Chemical Abstracts Registry No.: 1448-23-3

Trade Name	Manufacturer	Country	Year Introduced
Glarubin	Massengill	US	1959

Raw Materials

Aceituno meal
Water

Manufacturing Process

The preparation of pure glaucarubin from Aceituno meal is conveniently carried out by extracting the Aceituno meal with water, using about 100 gallons of the water per hundred pounds of meal. If the meal is in the form of a relatively solid cake, it should be soaked in the water for a time to cause disintegration. The temperature of the water is then raised to about 70°C for the actual extraction, and the mixture is moderately agitated, while maintaining a temperature of about 70°C for a period of about three hours, until extraction is substantially complete. If desired, the extraction may be conducted at lower temperatures down to about room temperature although at such lower temperatures, the extraction is much slower and less efficient at temperatures substantially higher than 70°C, there may be partial destruction or decomposition of the product being recovered.

The slurry or extraction mixture is filtered while hot, and the resulting filter cake is washed with about five to ten gallons of hot water; the primary filtrate and wash water are combined and held for further processing. In order to insure complete extraction of the desired material, the filter cake is again extracted with about 100 gallons of water at 70°C. Although not essential, it

is desirable to add to the second extraction a small quantity of acetic acid. The acetic acid appears to aid in obtaining a complete and thorough extraction. After extraction for about three hours with agitation at a temperature of about 70°C, the slurry is again filtered and the cake washed as before with about five to ten gallons of hot water. The resulting filtrate and wash are then combined with the primary filtrate and wash.

The combined filtrates or total aqueous extracts are cooled to about room temperature and filtered to remove any residual solids from solution. The clarified aqueous extract is then concentrated to about 70 gallons at a temperature below about 50°C, thus reducing the volume to about one-third the original volume. The resulting concentrate is cooled to room temperature or below and filtered to remove any tar or gum that may have separated. The presence of tar or gum at this stage of the process will vary depending upon the starting material and the manner in which the primary extraction has been carried out. It has been found, however, that unless any tar or gum present in the initial extract is removed by the procedure described, it will seriously interfere with the further concentration and crystallization steps hereinafter described.

After removal of such tar or gum, the concentrate is further evaporated at a temperature below about 50°C to about one-fourth the volume, i.e., 70 gallons is concentrated to about 15 to 20 gallons. This concentrate is cooled to a temperature of about 0°C to 5°C and allowed to stand for an extended period, such as overnight, whereupon there is a separation of crude crystalline glaucarubin therefrom. The crude crystals thus formed are removed by filtration and the mother liquors again concentrated to about one-half volume and cooled to permit separation of a second batch of crude glaucarubin crystals. The two batches of crude glaucarubin crystals are combined and dried preparatory to further purification.

The crude glaucarubin crystals obtained as above described from 100 pounds of Aceituno meal are slurried with about sevenandanehalf gallons of anhydrous methanol and refluxed until the crystals dissolve. The hot solution is then filtered and the resulting filter cake washed with methanol. The filter cake is then again extracted with an additional seven-and-one-half gallon quantity of anhydrous methanol in the manner described, and filtered. The methanol filtrates and washes are combined and concentrated at atmospheric pressure until crystals begin to appear, i.e., generally after concentration to about one-fifteenth volume. The solution is then cooled to about 0°C to 50°C and allowed to stand for crystallization to go substantially to completion. The resulting crystals are filtered off and the mother liquors are further concentrated and cooled to collect a second crop of crystals. The two crops of crystals are then combined and may be further purified by redissolving in methanol, filtering through activated charcoal, and recrystallizing after concentration of the methanol filtrate.

The purified crystalline glaucarubin thus obtained is colorless and odorless and is estimated to have a purity of about 96% to 97%. It has the formula $C_{25}H_{36}O_{10}$ and melts at 262°C to 263°C with decomposition (capillary tube).

References

Merck Index 4295

I.N. p. 460
Shafer, H.M.; US Patent 2,864,745; December 16, 1958; assigned to Merck and Co., Inc.

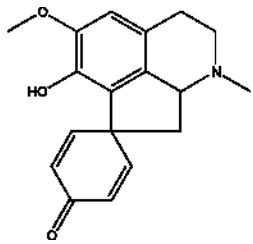
GLAZIOVINE

Therapeutic Function: Tranquilizer

Chemical Name: (+-)-[Hydroxy-6-methoxy-5-methyl-11H-cyclopenta[i,j]-isoquinoline]-7-spiro-1'-(2,5-cyclohexadiene-4-one)

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 17127-48-9

Trade Name	Manufacturer	Country	Year Introduced
Suavedol	Simes	Italy	1976

Raw Materials

Formaldehyde
Hydrogen
Sodium nitrite
Sulfuric acid
Nitric acid
p-Benzyloxyphenylacetic acid
3-Methoxy-4-hydroxyphenethyiamine
Phosphorus oxychloride
Sodium borohydride

Manufacturing Process

The thermal condensation of p-benzyloxyphenylacetic acid and of 3-methoxy-4-hydroxyphenethylamine occurs and gives, with a yield of 86% to 92%, the N-(3-methoxy-4-hydroxyphenethyl-p-benzyloxyphenyl)acetamide; from this latter, by cyclization according to Bischler-Napieralski with phosphorus oxychloride in acetonitrile, followed by reduction with sodium borohydride, there is obtained with a yield of 75% to 80% the 1-(p-benzyloxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline, which is methylated with

formaldehyde and formic acid giving 1(p-benzyloxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline with a yield of 90%.

This intermediate is then nitrated with 65% nitric acid. The nitro compound is then hydrogenated to give a hydroxybenzylamino compound.

A solution of 94.2 g of 1-(p-hydroxybenzyl)-2-methyl-6-methoxy-7-hydroxy-8-amino-1,2,3,4-tetrahydroisoquinoline in 3 liters of 1N sulfuric acid is supplemented, with stirring, between 0°C and 5°C, with 21 grams of sodium nitrite. The diazonium sulfate solution thus obtained is made alkaline with 2.5 liters of 2N sodium hydroxide: the diazo-oxide which is separated at the outset as a yellow precipitate is redissolved by the excess alkali, the solution is diluted to 10 liters with deaerated water and subjected, in a nitrogen atmosphere at 15°C in a Pyrex glass apparatus, to the radiations of a 2,000 W high-pressure mercury vapor lamp until the yellow hue is discharged (about 30 to 40 minutes). The solution is brought to a pH of 8.6 with hydrochloric acid and is stirred with 1.5 liters of chloroform. The two phases are filtered, the chloroform is separated and the aqueous phase is extracted four times with l .5 liters of chloroform. The extracts are evaporated under reduced pressure to a small volume and percolated through a chromatographic column containing 1.3 kilograms of neutral alumina (activity rating IV of the Brockmann scale). The column is then further eluted with chloroform. The eluates are evaporated under reduced pressure and the residue is recrystallized from ethyl acetate. There are thus obtained 40.2 grams (yield 45% of theory) of pure (+-)-glaziovine, having a melting point of 220°C to 222°C.

References

Kleeman and Engel p.442
DOT 13 (1) 24 (1977)
I.N. p.460
Casagrande, C. and Canonica, L.; US Patent 3,886,166; May 27, 1975; assigned to Siphar S.A. (Switz.)

GLIBORNURIDE

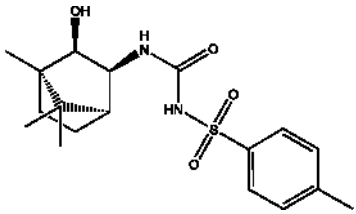
Therapeutic Function: Oral hypoglycemic

Chemical Name: [1S-(endo,endo)]-N-[[(3-Hydroxy-4,7,7-trimethylbicyclo [2.2.1]hept-2-yl)amino]carbonyl]-4-methylbenzenesulfonamide

Common Name: 1-(p-Toluenesulfonyl)-3-(2-endo-hydroxy-3-endo-D-bornyl)urea

Chemical Abstracts Registry No.: 26944-48-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Glutril	Roche	W. Germany	1972
Glutril	Roche	France	1973
Glutril	Roche	UK	1975
Glitrim	Roche	-	-
Gluborid	Gruenenthal	W. Germany	-
Glytril	Roche	-	-
Logiston	Laake	Finland	-

Raw Materials

3-Endo-aminoborneol HCl
o-Methyl-N-p-toluene sulfonyl urea

Manufacturing Process

2.1 grams of 3-endo-aminoborneol hydrochloride and 2.4 grams of O-methyl-N-p-toluene-sulfonyl-urea are heated at 125°C for 3 hours with 2 ml of dimethylformamide. After cooling, the reaction mixture is stirred with 100 ml of water for 10 minutes, while a pH of 3.5 is maintained by the addition of a few drops of dilute hydrochloric acid. The precipitate is removed by filtration, washed with water and suspended in 100 ml of water. The suspension is dissolved by the addition of 20 ml of 1 N caustic soda. The alkaline solution is extracted with ether, acidified with dilute hydrochloric acid and filtered. The precipitate is washed with water and recrystallized from alcohol/water to yield 1-(p-toluene-sulfonyl)-3-(2-endo-hydroxy-3-endo-bornyl)-urea having a melting point of 193° to 195°C.

References

Merck Index 4299
Kleeman and Engel p.443
OCDS Vol.2 p.117 (1980)
DOT 8 (3) 88 (1972)
I.N.p.461
Bretschneider, H., Grassmayr, K., Hohenlohe-Oehringen, K. and Grussner, A.; US Patent 3,654,357; April 4, 1972;assigned to Hoffmann-La Roche Inc.

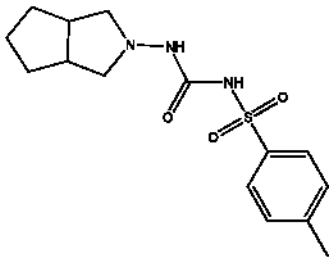
GLICLAZIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: 1-(Hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-(p-tolylsulfonyl)urea

Common Name: N-(4-Methylbenzenesulfonyl)-N'-(3-azabicyclo[3.3.0]-3-octyl)urea

Structural Formula:



Chemical Abstracts Registry No.: 21187-98-4

Trade Name	Manufacturer	Country	Year Introduced
Diamicron	Servier	France	1972
Diamicron	Servier	Italy	1977
Diamicron	Servier	Switz.	1979
Diamicron	Pharmacodex	W. Germany	1980
Diamicron	Servier	UK	1980
Dramion	Maggioni	Italy	-

Raw Materials

4-Methylbenzenesulfonylurethane
N-Amino-3-azabicyclo(3.3.0)octane

Manufacturing Process

To a suspension containing 4.86 parts of 4-methylbenzenesulfonyl urethane (MP 80° to 82°C) and 36 parts of anhydrous toluene there are rapidly added 2.5 parts of N-amino-3-azabicyclo(3.3.0)octane (BP/18 mm = 86°C). The reaction mixture is heated under reflux for 1 hour. The resulting clear solution crystallizes on cooling. The crystals are filtered, washed with 2 parts of toluene, then recrystallized from anhydrous ethanol. There are obtained 3.8 parts of the desired product, MP 180° to 182°C.

References

Merck Index 4300
Kleeman and Engel p.444
DOT 8 (4) 136 (1972)
I.N. p.461
Beregi, L., Hugon, P. and Duhault, J.; US Patent 3,501,495; March 17, 1970; assigned to Science Union et Cie, Societe Francaisede Recherche Medicale, France

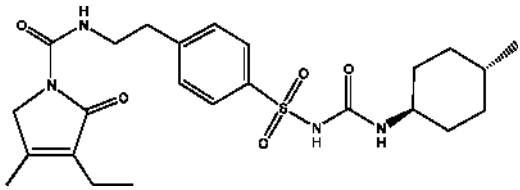
GLIMEPIRIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: 1H-Pyrrole-1-carboxamide, 2,5-dihydro-3-ethyl-4-methyl-N-(2-(4-(((((4-methylcyclohexyl)amino)carbonyl)amino)sulfonyl)phenyl) ethyl)-2-oxo-, trans-

Common Name: Glimepiride

Structural Formula:



Chemical Abstracts Registry No.: 93479-97-1

Trade Name	Manufacturer	Country	Year Introduced
Amaryl	Hoechst	Germany	-
Amaryl	Aventis Pasteur	India	-
Betaglim	Panacea Biotec Ltd.	India	-
Emperide	Emcure Pharmaceuticals Ltd.	India	-
Glifix	Argus	India	-
Glimepiride	Aventis Pharmaceuticals	France	-
Glimetop	RPG Life Sciences Ltd.	India	-
Glimulin	Healtheon (A Div. of Glenmark)	India	-
Karmelitos	Cadila Pharmaceuticals Ltd.	India	-
Prichek	Indoco Remedies Ltd.	India	-
Supride	Life Medicare and Biotech Pvt. Ltd.	India	-
Zoryl	Intas Pharmaceuticals Pvt. Ltd.	India	-

Raw Materials

Ammonium hydroxide
Cyclohexyl isocyanate
3-Ethyl-4-methyl-2-pyrrolone
Chlorosulfonic acid
2-Phenylethylisocyanate

Manufacturing Process

By heating of a mixture of 3-ethyl-4-methyl-2-pyrrolone and 2-phenylethylisocyanate at 150°C is obtained 3-ethyl-4-methyl-2-oxo-3-pyrroline-1-(N-2-phenylethyl)-carboxamide, melting point 106°-108°C. Then the carboxamide are introduced in portions at 30°C into chlorosulfonic acid, and agitated for 1 hour at 40°C. The sulfochloride (melting point 172-175°C), introduced into concentrated ammonia, and heated for 30 min on a steam bath. The mixture of sulfonamide obtained (melting point 180°-182°C), of acetone and K_2CO_3 are refluxed with agitation for 6 hours. Subsequently the cyclohexyl isocyanate are added dropwise, and agitation is continued for 6 hours at boiling temperature. After standing overnight, the product is filtered, the crystals obtained are treated with dilute hydrochloric acid, and again filtered. It is prepared N-(4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]benzenesulfonyl)-N'-cyclohexyl urea; melting point 185°-187°C (from acetone) (Glimepiride).

References

Weyer R. et al.; US Patent No. 4,379,785; April 12, 1983; Assigned to Hoechst Aktiengesellschaft (Frankfurt am Main, DE)

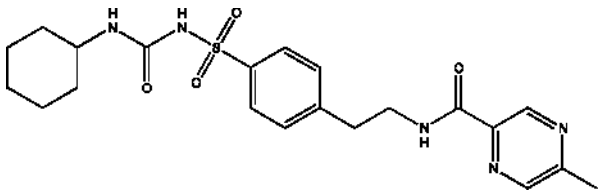
GLIPIZIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: 1-Cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl] phenyl]-sulfonyl] urea

Common Name: Glydiazinamide

Structural Formula:



Chemical Abstracts Registry No.: 29094-61-9

Trade Name	Manufacturer	Country	Year Introduced
Minidiab	Carlo Erba	Italy	1973
Glibenese	Pfizer	France	1974
Glibenese	Pfizer	UK	1975
Minodiab	Farmitalia	UK	1975
Glibenese	Pfizer	W. Germany	1977
Glucotrol	Roerig	US	-
Melizid	Medica	Finland	-
Mindiab	Aesca	Austria	-
Minibetic	Ikapharm	Israel	-

Raw Materials

Thionyl chloride
Cyclohexyl isocyanate
5-Methylpyrazinedcarboxylic acid
p-(β-Aminoethyl)benzenesulfonamide

Manufacturing Process

5-Methyl pyrazine-2-carboxylic acid is refluxed with thionyl chloride in anhydrous benzene for approximately 12 hours. Benzene and thionyl chloride excess is removed by distillation. Then some anhydrous dioxane is added and this acid chloride solution is allowed to drop into p-(β-aminoethyl)-benzenesulfonamide suspension in dioxane and anhydrous pyridine. The resulting mixture is then refluxed for 3 hours. Dioxane is removed by distillation and then the residue is washed with water and acetic acid. The raw acylated sulfonamide is then filtered and crystallized from 95% ethanol, thus obtaining a product of MP 200° to 203°C.

This product is then reacted with cyclohexyl isocyanate to give glipizide.

References

Merck Index 4302
Kleeman and Engel p.444
PDR p.1525
OCDS Vol.2 p.117 (1980)
DOT 8 (11) 435 (1972) and 9 (11) 463 (1973)
I.N. p.462
REM p.977
Ambrogi, V. and Logemann, W.; US Patent 3,669,966; June 13, 1972; assigned to Carlo Erba SPA, Italy

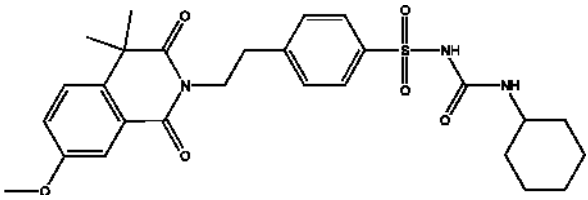
GLIQUIDONE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[(Cyclohexylamino)carbonyl]-4-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1H)-isoquinolinyl)ethyl] benzenesulfonamide

Common Name: Gliquidor

Structural Formula:



Chemical Abstracts Registry No.: 33342-05-1

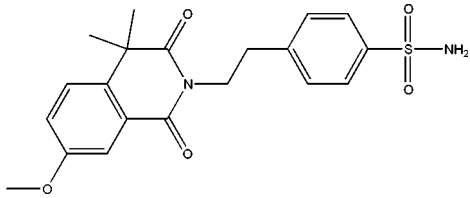
Trade Name	Manufacturer	Country	Year Introduced
Glurenorm	Thornae	W. Germany	1975
Glurenorm	Winthrop	UK	1979
Glurenor	Boehringer Ingelheim	-	-

Raw Materials

1,2,3,4-Tetrahydro-4,4-dimethyl-7-methoxy-isochrornane-1,3-dione
4-Aminosulfonyl-phenyl-(2)-ethylamine
Potassium t-butylate
Cyclohexyl isocyanate

Manufacturing Process

A mixture consisting of 4 grams of 1,2,3,4-tetrahydro-4,4-dimethyl-7-methoxy-isochromanedione-(1,3) (MP 95° to 97°C), 2.53 grams of 4-aminosulfonyl-phenyl-(2)-ethylamine and 150 ml of xylene was heated for 2 hours at its boiling point in an apparatus provided with a water separator. Thereafter, the reaction mixture was allowed to cool and was then vacuum-filtered, and the filter cake was recrystallized from n-propanol in the presence of activated charcoal. 2.9 grams (58% of theory) of 1,2,3,4-tetrahydro-4,4-dimethyl-2-[p-aminosulfonylphenyl-(2)-ethyl]-7-methoxy-isoquinolinedione-(1,3), MP 203° to 205°C, of the formula below were obtained.



32.2 grams of 1,2,3,4-tetrahydro-4,4-dimethyl-2-[p-aminosulfonylphenyl-(2)-

ethyl]-7-methoxy-isoquinolinedione-(1,3) were dissolved in 700 ml of dimethylformamide, 9.1 grams of potassium tert-butylate were added to the solution, and, while cooling the mixture with ice, 14.9 grams of cyclohexyl isocyanate were added dropwise thereto.

Subsequently, the reaction mixture was stirred for 5 hours on an ice bath and was then allowed to stand overnight at -2°C. Thereafter, the reaction solution was admixed with water, the precipitate formed thereby was separated by vacuum-filtration, the filtrate was admixed with more water, and the aqueous solution was acidified with 2N hydrochloric acid. A greasy substance precipitated out which crystallized after a brief period of contact with boiling methanol. 2.6 grams (85% of theory) of 1,2,3,4-tetrahydro-2-[p-(N'-cyclohexyl-ureido-N-sulfonyl)-phenethyl]-4,4-dimethyl-7-methoxy-isoquinolinedione-(1,3), MP 180° to 182°C, were obtained.

References

Merck Index 4303
Kleeman and Engel p.445
DOT 11 (7) 281 (1975) and 16 (2) 47 (1980)
I.N. p.462
Kutter, E., Griss, G., Grell, W. and Kleemann, M.; US Patent 3,708,486; January 2, 1973; assigned to Boehringer Ingelheim GmbH, Germany

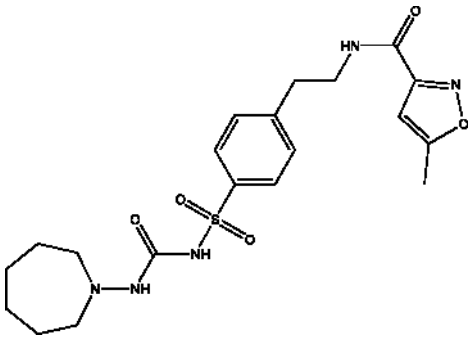
GLISOXEPID

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[2-[4-[[[[(Hexahydro-1H-azepin-1-yl)aminolcarbonyl] amino]sulfonyl]-phenyl]ethyl]-5-methyl-3-isoxazolecarboxamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 25046-79-1

Trade Name	Manufacturer	Country	Year Introduced
Pro-Diaban	Bayer	W. Germany	1974
Pro-Diaban	Schering	W. Germany	1974
Glysepin	Bayer	Italy	1978
Glucoben	Farmades	Italy	1979

Raw Materials

5-Methylisoxazole-3-carboxylic acid chloride
4-(β-Aminoethyl)benzene sulfonamide hydrochloride
Chloroformic acid methyl ester
N-Amino-hexamethyleneimine

Manufacturing Process

There is obtained from 4-[β-[5-methyl-isoxazolyl-(3)-carboxamido]-ethyl]-benzene-sulfonamide (prepared from 5-methyl-isoxazole-(3)-carboxylic acid chloride and 4-(β-aminoethyl)benzene-sulfonamide hydrochloride, MP 213° to 214°C in pyridine) and chloroformic acid methyl ester, in a yield of 69%, the compound N-[[-4-[β-[5-methyl-isoxazolyl-(3)-carboxamido]-ethyl]]-benzene-sulfonyl]]-methyl-urethane in the form of colorless crystals of MP 173°C.

From the sulfonyl-urethane described above and N-amino-hexamethylene-imine, there is obtained, in a yield of 70%. the compound 4-[[4-[β-[5-methyl-isoxazolyl-(3)-carboxamido]-ethyl]-benzene-sulfonyl]]-1,1-hexamethylene-semicarbazide in the form of colorless crystals of MP 189°C.

References

Merck Index 4304
Kleeman and Engel p.445
DOT 10 (10) 257 (1974) and 16 (1) 15 (1980)
I.N. p.462
Plumpe, H. and Puls,W.; US Patent 3,668,215; June 6, 1972; assigned to Farbenfabriken Bayer AG, Germany

GLUCAGON

Therapeutic Function: Antidiabetic

Chemical Name: Polypeptide of molecular weight approximately 3,550

Common Name: Hg-Factor; HGF

Structural Formula: His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Tyr-Leu-Met-Asn-Thr

Chemical Abstracts Registry No.: 9007-92-5

Trade Name	Manufacturer	Country	Year Introduced
Glucagon	Lilly	US	1960
Glukagon	Lilly	W. Germany	1962
Glucagon	Novo	Italy	1964
Glucagon	Novo	France	1966
Glucagon Novo	Kodama	Japan	1977

Raw Materials

Pancreatic gland material
Acetone

Manufacturing Process

The process comprises treating pancreatic gland material having hyperglycemic activity in aqueous solution at pH 3-4 with 3-4 volumes of acetone to precipitate the hyperglycemic activity material, separating the precipitate and dializing the precipitate to remove inorganic salts and dialyzable low molecular weight impurities, and crystallizing the undialyzed hyperglycemic activity material from aqueous glycine buffer.

References

Merck Index 4307
PDR p.1050
I.N. p.463
REM p. 974
Eli Lilly and Co.; British Patent 762,885; December 5, 1956

GLUCAMETACIN

Therapeutic Function: Antiinflammatory, Analgesic, Antipyretic

Chemical Name: D-Glucose, 2-(((1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl)amino)-2-deoxy-

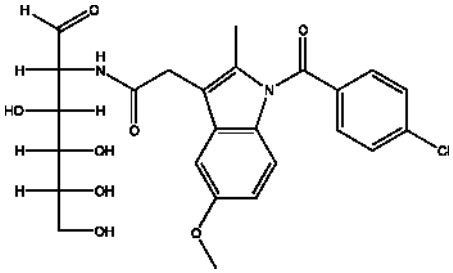
Common Name: Glucametacin; Glumetacin; Indometacin glucosamide; Indosamide

Chemical Abstracts Registry No.: 52443-21-7

Raw Materials

Thionyl chloride
1-(p-Chlorobenzoyl)-2-methyl-5-methoxy-indolyl-3-acetic acid (indometacine)
d(+)-Glucosamine hydrochloride

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Glucametacin	Shanghai Lansheng Corporation	-	-
Teoremac	Sanfer	-	-

Manufacturing Process

125 g (75 ml) thionyl chloride were added to 30 g 1-(p-chlorobenzoyl)-2-methyl-5-methoxy-indolyl-3-acetic acid (indometacine) in 200 ml of dry chloroform and heated to reflux for 15 min. The solvent was distilled off and the residue was recrystallized from benzene to give 23 g 1-(p-chlorobenzoyl)-2-methyl-5-methoxy-indolyl-3-acetyl chloride. MP: 126°-129°C.

43 g d-(+)-glucosamine hydrochloride in 140 ml of cold water, 20 g above prepared acetyl chloride in any inert solvent (chloroform, ethyl acetate, dioxane) and 35 ml 12% NaOH was mixed and stirred for 1hour at a room temperature. Then it was diluted with water and a solid was filtered off, washed and dried in vacuum. 10 volumes (by weight) methanol was added to the obtained dry product, filtered off and dried in vacuum. Yield of 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid monohydrate glucosamide 20 g. Glucametacine was obtained as a powder. MP: about 218°C (with decomposition).

References

Dimetrio A. et al.; DB Patent No. 2,223,051; May 12, 1972

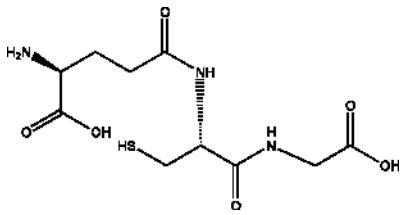
GLUTATHION

Therapeutic Function: Anabolic, Antidote

Chemical Name: Glycine, N-(N-L-γ-glutamyl-L-cysteinyl)-

Common Name: Glutathione

Structural Formula:



Chemical Abstracts Registry No.: 70-18-8

Trade Name	Manufacturer	Country	Year Introduced
L-Glutathione	Solgar	USA	-
L-Glutathione	Twinlab	-	-

Raw Materials

Yeast
Copper oxide
Hydrogen sulfide
Ascorbic acid

Manufacturing Process

The tripeptide thiol glutathione (L-γ-glutamyl-L-cysteinyl-glycine (GSH)) found in virtually all cells functions in metabolism, transport and cellular protection.

Glutathione may be obtained from an yeast or synthetically.

A yeast containing 600 parts of yeast solids is heated just to the boiling point of water. The yeast solids are removed by centrifuging or filtration. Sulphuric acid is added to the filtrate to give 0.5 N strength as sulphuric acid 6 parts of ascorbic acid are added. Then 2 parts of cuprous oxide are added with stirring. The reaction mixture is then centrifuged and washed until the precipitate is free from sulphates. The precipitate is suspended in 100 parts of water and hydrogen sulfide is bubbled through the water until all of the copper is precipitated as copper sulphide. The filtrate is evaporated and the glutathione is purified by recrystallization from 50% ethanol. All parts are by weight.

The preparation of glutathion by methods of peptide synthesis is expansive and gives 20-30% yield of GHS. For the first time synthetic glutathion was prepared by M. Bergmann et al.

References

Dalby G.; US Patent No. 3,281,407; Oct. 25, 1966; Assignor of one-half to B. T. Rauber, New York, N.Y.
Bergmann M. et al., J. Biol. Chem. 109, 325, 1935

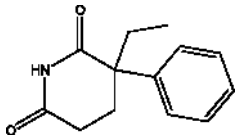
GLUTETHIMIDE

Therapeutic Function: Sedative, Hypnotic

Chemical Name: 3-Ethyl-3-phenyl-2,6-piperidinedione

Common Name: 3-Ethyl-3-phenyl-2,6-dioxopiperidine

Structural Formula:



Chemical Abstracts Registry No.: 77-21-4

Trade Name	Manufacturer	Country	Year Introduced
Doriden	U.S.V.	US	1955
Doridene	Ciba Geigy	France	1956
Alfimid	Pliva	Yugoslavia	-
Elrodorm	Deutsches Hydrierwerk	E. Germany	-
Glimid	Polfa	Poland	-
Glutethimide	Danbury	US	-
Rigenox	Gedeon Richter	-	-

Raw Materials

Acetic acid
Sulfuric acid
Sodium hydroxide
α-Phenylbutyric acid nitrile
Methyl acrylate

Manufacturing Process

The 2-phenyl-2-ethyl-pentane-1,5-diacid-mononitrile-(1) of melting point 72° to 76°C, used as starting material in this process, can be produced for example from α-phenyl-butyric acid nitrile by condensation with acrylic acid methyl ester and subsequent hydrolysis of the thus-obtained 2-phenyl-2-ethyl-pentane-1,5-diacid-monomethyl ester-mononitrile-(1) of boiling point 176° to 185°C under 12 mm pressure.

140 parts by weight of 2-phenyl-2-ethyl-pentane-1,5-diacid-mononitrile-(1) are dissolved in 200 parts by volume of glacial acetic acid and, at an initial temperature of 60°C, 100 parts by volume of concentrated sulfuric acid added in portions. In this operation the temperature of the reaction mixture rises to 100°C. The whole is finally maintained for a short time on the boiling water bath, then cooled and poured on ice and neutralized with alkali to a pH of 6. Extraction with chloroform is then effected and the chloroform extract washed

with dilute caustic soda solution, dried over calcium chloride, the chloroform evaporated and the residue crystallized from ethyl acetate with addition of ligroin. The obtained 3-phenyl-3-ethyl-2,6-dioxo-piperidine melts at 78° to 81°C.

References

Merck Index 4338
Kleeman and Engel p.446
PDR pp. 830, 1606, 1812
OCDS Vol.1 p.257 (1977)
I.N. p.466
REM p.1071
Hoffmann, K. and Tagmann, E.; US Patent 2,673,205; March 23, 1954; assigned to Ciba Pharmaceutical Products, Inc.

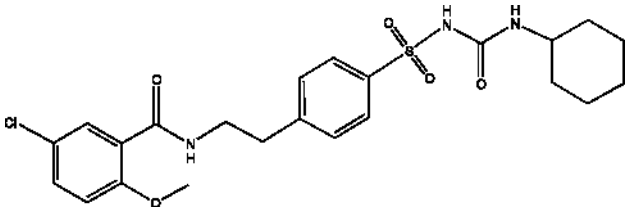
GLYBURIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: Benzamide, 5-chloro-N-(2-(4-((((cyclohexylamino)carbonyl) amino)sulfonyl)phenyl)ethyl)-2-methoxy-

Common Name: Glibenclamide; Glibenklamid; Glybenzylclamide; Glyburide

Structural Formula:



Chemical Abstracts Registry No.: 10238-21-8

Trade Name	Manufacturer	Country	Year Introduced
Daonil	Hoechst	Germany	-
Diabeta	Aventis	-	-
Euglucon	Asta	-	-
Gliben	Pacific	-	-
Glyburide	Upjohn	-	-
Glyburide	Apotex Inc.	-	-
Glyburide	Greenstone Ltd.	-	-
Micronase	Upjohn	-	-

Raw Materials

4-(β-(2-Ethoxy-5-chlorobenzamido)ethyl)-benzenesulfonamide
Sodium hydroxide
Cyclohexyl isocyanate

Manufacturing Process

To a solution of 10.2 g of 4-(β-(2-ethoxy-5-chlorobenzamido)ethyl)-benzenesulfonamide in 12.5 ml of 2 N sodium hydroxide solution and 30 ml acetone are added dropwise, at 0-5°C, 3.3 g of cyclohexyl isocyanate. The whole is stirred for 3 hours, diluted with water and methanol, undissolved matter is separeted by filtration. The filtrate is acidified with dilute hydrochloric acid. The 4-(β-(2-ethoxy-5-chlorobenzamido)ethyl)-benzenesulfonyl)-N'-cyclohexylurea which precipitates in the form of crystals melts after recrystallization from methanol at 168-170°C.

References

Weber H. et al.; US Patent No. 3,507,954; Apr. 21, 1970; Assigned to Farbwerke Hoechst Aktiengesellschaft vormals Meister Lucius and Bruning, Frankfurt am Main, Germany

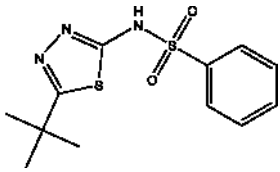
GLYBUZOLE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide

Common Name: Desaglybuzole

Structural Formula:



Chemical Abstracts Registry No.: 1492-02-0

Trade Name	Manufacturer	Country	Year Introduced
Gludease	Kyowa Hakko	Japan	1972

Raw Materials

Benzene sulfonyl chloride

2-Amino-5-t-butyl-1,3,4-thiadiazole

Manufacturing Process

15.7 g of 2-amino-5-tert-butyl-1,3,4-thiadiazole (0.1 mol) and 17.6 g of benzene sulfonyl chloride (0.1 mol) were dissolved in 150 ml dry pyridine and heated over steam for 4 hr. The pyridine was removed by distillation under reduced pressure and the residue treated with 50 ml 2N HCl. The solid product, MP 162° to 163°C. was filtered off and recrystallized once from benzene and twice from 50% aqueous EtOH.

References

Merck Index 4341
Kleeman and Engel p.447
I.N. p.466
MacRae, F.J. and Drain, D.J.; British Patent 822,947; November 4, 1959; assigned to T.J Smith and Nephew Limited

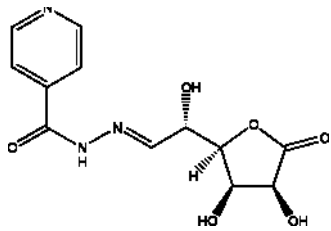
GLYCONIAZIDE

Therapeutic Function: Antitubercular

Chemical Name: Glucuronic acid, γ-lactone, 1-((4-pyridinylcarbonyl) hydrazone)

Common Name: Gluconiazide; Gluconiazone; Glyconiazide; Glyconiazonum

Structural Formula:



Chemical Abstracts Registry No.: 3691-74-5

Trade Name	Manufacturer	Country	Year Introduced
Gatalone	Barnes-Hind	-	-

Raw Materials

D-Glucuronolactone

Isonicotinic acid hydrazide
D-Glucuronic acid
Hydrochloric acid

Manufacturing Process

2 Methods of producing of d-glucuronolactone isonicotinyl hydrazone:

1. To 88.0 g of D-glucuronolactone, in the bottom of a 3 L round bottom flask, was added 1.5 liters of methyl alcohol (acetone-free). The mixture was boiled gently on a steam bath for 10 min, producing a clear solution. To this hot solution, 70.0 g of isonicotinic acid hydrazide was added all at once. The mixture was then boiled vigorously for 10 min and the clear solution filtered without suction through a piece of lens paper into a two liter Erlenmeyer flask. After the flask had been allowed to stand 24 h at room temperature, crystals in the form of beautiful white rods and narrow plates were observed. These crystals were filtered with suction, washed with a small amount of methyl alcohol, and sucked to complete dryness. The resulting product was dried in a vacuum desiccator for 3 days. Actual yield was 148.0 g, (yield of better than 99%). On heating the d-glucuronolactone isonicotinyl hydrazone thus formed, the crystals charred and decomposed with foaming between 150° and 160°C without any sharp melting point. The new compound was already very pure, and upon recrystallization from a large amount of methyl or ethyl alcohol (absolute) showed no appreciable change in physical properties from the unrecrystallized product.

2. D-Glucuronic acid was liberated from a solution of its sodium salt (12.0 g) in water (25 ml) by the addition of concentrated hydrochloric acid (5 ml). To the mixture, sodium acetate (5.0 g) was added to remove the excess of the mineral acid. Isonicotinic acid hydrazide (7.0 g) was then introduced into the clear solution and mixing accomplished by thorough shaking. Methyl alcohol (250 ml) was added and the mixture boiled on a steam bath for 10 min. A white crystalline precipitate started to separate from the solution after a few minutes heating and was allowed to stand overnight at room temperature before filtering. The crystals (white small rods) were sucked to dryness, washed with a small amount of absolute methanol and again sucked to dryness. The product was further dried in a vacuum desiccator for 24 h. Yield: 25-50%. The hydrazone melted at 150°-160°C (dec.).

References

Sah P.P., Calif D.; US Patent No. 2,940,899; June 14, 1960; Assigned: The Regents of the University of California, Berkeley, Calif.

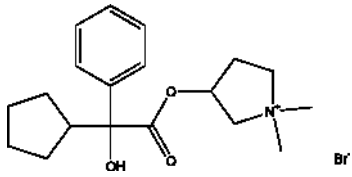
GLYCOPYRROLATE

Therapeutic Function: Spasmolytic

Chemical Name: 3-[(Cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide

Common Name: Glycopyrronium bromide

Structural Formula:



Chemical Abstracts Registry No.: 596-51-0

Trade Name	Manufacturer	Country	Year Introduced
Robinul	Robins	US	1961
Robinul	Robins	UK	1962
Robinul	Kaken	Japan	1975
Robinul	Brenner	W. Germany	1975
Asecryl	Martinet	France	-
Gastrodyn	Medica	Finland	-
Nodapton	Geistlich	Switz.	-
Robanul	Lasa	Spain	-
Tarodyl	Lundbeck	-	-

Raw Materials

Methyl bromide
Sodium
Hydrogen chloride
Methyl-α-cyclopentyl mandelate
1-Methyl-3-pyrrolidinol

Manufacturing Process

A mixture of 42.5 grams (0.17 mol) of methyl α-cyclopentyl mandelate and 18 grams (0.175 mol) of 1-methyl-3-pyrrolidinol in 500 ml of heptane was refluxed under a Dean and Stark moisture trap, with the addition of four 0.1 gram pieces of sodium at 1-hour intervals. After 5 hours' refluxing the solution was concentrated to one-half volume, and extracted with cold 3N HCl. The acid extract was made alkaline with aqueous sodium hydroxide and extracted with ether which was washed, dried over sodium sulfate, filtered and concentrated. The residue was fractionated at reduced pressure. Yield 33 grams (64%); BP 151° to 154°C/0.2 mm, n_D^{23}= 1.5265.

The hydrochloride salt was precipitated as an oil from an ethereal solution of the base with ethereal hydrogen chloride. It was crystallized from butanone; MP 170° to 171.5°C.

The methyl bromide quaternary was prepared by saturating a solution of the base in dry ethyl acetate with methyl bromide. After standing for 9 days the

resulting crystalline solid was filtered and recrystallized from butanone and from ethyl acetate; MP 193° to 194.5°C.

References

Merck Index 4365
Kleeman and Engel p.448
PDR pp.830, 1466
DOT 18 (3) 128 (1982)
I.N. p.467
REM p.915
Lunsford, C.D.; US Patent 2,956,062; October 11, 1960; assigned to A.H. Robins Co., Inc.

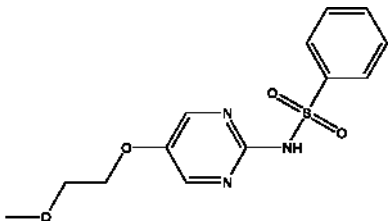
GLYMIDINE

Therapeutic Function: Antidiabetic

Chemical Name: N-[5-(2-Methoxyethoxy)-2-pyrimidinyl]benzenesulfonamide

Common Name: Glycodiazine

Structural Formula:



Chemical Abstracts Registry No.: 339-44-6

Trade Name	Manufacturer	Country	Year Introduced
Redul	Bayer/Schering	W. Germany	1964
Gondafon	Schering	UK	1966
Gondafon	Schering	Italy	1968
Glycanol	Bayer	Italy	-
Glyconormal	Bayer	France	-
Lycanol	Bayer	Japan	-

Raw Materials

Dimethylformamide
Sodium hydroxide
Guanidine nitrate
Phosphorus pentachloride

Benzene sulfonyl chloride
Methoxyethoxyacetaldehyde-di-methoxyethyl acetal

Manufacturing Process

210 g phosphorus pentachloride are gradually added to 252 g methoxyethoxyacetaldehyde-di-methoxyethylacetal with agitation. The mixture is externally cooled with ice to hold the reaction temperature below 25°C. Moisture is carefully excluded. After addition of the condensation agent is completed, the reaction mixture is further agitated at room temperature for 30 minutes. 225 ml dimethylformamide are then added drop by drop while the reaction temperature is held at 20°C to 25°C by external cooling of the reaction vessel with ice. When the dimethylformamide has been added, the temperature is raised to 60°C, and this temperature is maintained for 70 minutes.

The temperature is again lowered to 20°C to 25°C and maintained at this value by cooling with ice while 500 ml methanol are added drop by drop. The resulting solution is admixed drop by drop to a suspension of 240 g powdered caustic soda in 800 ml methanol at 20°C to 25°C. After mixing is completed, stirring is continued for 30 minutes at room temperature. The solution now contains inorganic salts and β-dimethylamino-α-methoxyethoxyacrolein.

200 g guanidine nitrate and thereafter 70 g sodium hydroxide are added to the solution. The methanol is evaporated with agitation. The residue is dissolved in 1.5 liters water and is repeatedly extracted with chloroform. The combined chloroform extracts are evaporated to dryness, and the residue is recrystallized from carbon tetrachloride. 80 g of 2-amino-5-methoxyethoxypyrimidine of MP 80°C to 81°C are obtained.

This material is then dissolved in pyridine. Benzenesulfonylchloride is added and the resulting mixture is heated two hours to 60°C. It is then poured into 300 ml water. The precipitate formed thereby is filtered off and dissolved in dilute ammonium hydroxide. The solution is purified with charcoal, and filtered. The filtrate is acidifed with acetic acid to give glymidine.

62 g 2-benzenesulfonamido-5-methoxyethoxypyrimidine are dissolved jointly with 8 g sodium hydroxide in 250 ml ethanol. The solution is evaporated to dryness, and the residue is suspended in 300 ml acetone. The sodium salt of 2-benzenesulfonamido-5-methoxyethoxypyrimidine may be filtered off, washed with acetone, and dried. The yield of glymidine sodium is about 60 g, the MP 220°C to 223°C.

References

Merck Index 4371
Kleeman and Engel p.448
OCDS Vol.1 p.125 (1977)
DOT 1 (2) 72 (1965) and 2 (3) 104 (1966)
I.N. p.468
Priewe, H. and Gutsche, K.; US Patent 3,275,635; September 27, 1966; assigned to Schering A.G. (W. Germany)

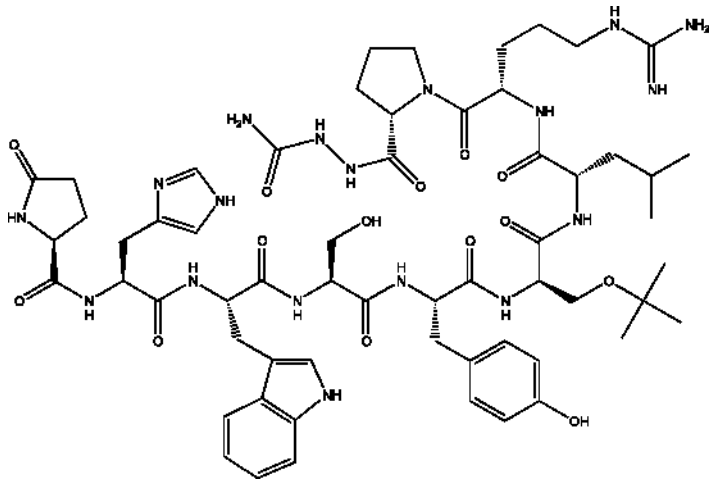
GOSERELIN

Therapeutic Function: Antineoplastic, Antitumor

Chemical Name: Luteinizing hormone-releasing factor (pig), 6-(O-1,1-dimethylethyl)-D-serine)-10-deglycinamide-, 2-(aminocarbonyl)hydrazide

Common Name: Goserelin

Structural Formula:



Chemical Abstracts Registry No.: 65807-02-5

Trade Name	Manufacturer	Country	Year Introduced
Goserelin	AstraZeneca	UK	-
Zoladex	AstraZeneca	UK	-

Raw Materials

Diethyl amine
Fmoc-Ser-OH
Boc-Leu-OH
Fmoc-Trp-OH
Hydrazine
Piperidine
Triflouroacetic acid
Potassium cyanate
1-Hydroxybenzotriasole
Boc-Arg(HCl)-OH
Diisopropylcarbodiimide
Fmoc-D-Ser(But)-OH
Fmoc-Tyr(BrZ)-OH
Fmoc-His(Fmoc)-OH
Pyr-OH (pyroglutamic acid)
Boc-Pro-OBzl-polystyrene resin 1% cross-linked with divinylbenzene

Manufacturing Process

(a) Solid Phase Preparation of Nonapeptide

The solid phase synthesis was carried out in automatic mode on an Applied Biosystems 430A Peptide Synthesizer using Boc-Pro-OBzl-polystyrene resin 1% cross-linked with divinylbenzene (Peninsula Laboratories), 1.25 g, 0.38 meq/g though nominally 0.7 meq/g). The following protected amino acids were converted to benzotriazolyl esters by reaction with HOBt (1-hydroxybenzotriasole) and DIPC (di-isopropylcarbodiimide) in DMF immediately before use. The protected amino acids were coupled in the following sequence: Boc-Arg(HCl)-OH; Boc-Leu-OH; Fmoc-D-Ser(But)-OH; Fmoc-Tyr(BrZ)-OH; Fmoc-Ser-OH; Fmoc-Trp-OH; Fmoc-His(Fmoc)-OH; Pyr-OH. The sequence of operations for the first two stages (using Boc-protected-amino acids) was: removal of Boc with 45% triflouroacetic acid in dichloromethane;10% DIEA (diethyl amine)/DMF wash; coupling (2 equivalents of protected amino acid HOBt ester); removal of Boc as above. The sequence of operations for the last six stages (using Fmoc-protected-amino acids) was: removal of Fmoc with 20% piperidine/DMF; 0.5 molar HOBt/DMF wash; coupling (1 equivalent of protected amino acid HOBt ester). All coupling reactions except that using Boc-Arg(HCl)-OH were of 1 hour duration; the Boc-Arg(HCl)-OH one was of 2 hours duration. There was thus obtained the nonapeptide-resin (1.7 g; 0.29 mmole peptide per g) with the Tyr still protected by BrZ.

(b) Cleavage of Peptide From Resin

The peptide resin prepared above was treated with a 20-fold excess of anhydrous hydrazine in DMF (20 ml) at laboratory temperature for 24 hours, and the mixture was filtered and evaporated to dryness. This procedure also removed the BrZ protecting group from the Tyr moeity. The residue was purified by gel filtration on a column (LH 20 Sephadex) using a 20:1 v/v mixture of water and acetic acid as eluant. There was thus obtained Pyr-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg(H^+)-Pro-NH-NH_2. The structure of which was confirmed by amino acid analysis and mass spectroscopy.

(c) Preparation of Goserelin

A solution of potassium cyanate (11 mg) in water (1.36 ml) was added portionwise during 1 hour to a solution of the above hydrazide (118 mg) in a 20:1 v/v mixture of water and acetic acid (10 ml). The mixture was freeze-dried and the residue was purified by reverse-phase column chromatography (Dynamax 60 ANG, C18, 1 inch diameter) using a gradient of 10% to 40% by volume of acetonitrile in water containing 0.1% trifluoroacetic acid. There was thus obtained goserelin (100 mg, 25% yield overall), the structure of which was confirmed by mass spectroscopy.

References

Hayward C.F.; US Patent No. 5,510,460, April 23, 1996; Assigned to Zeneca Limited (London, GB)

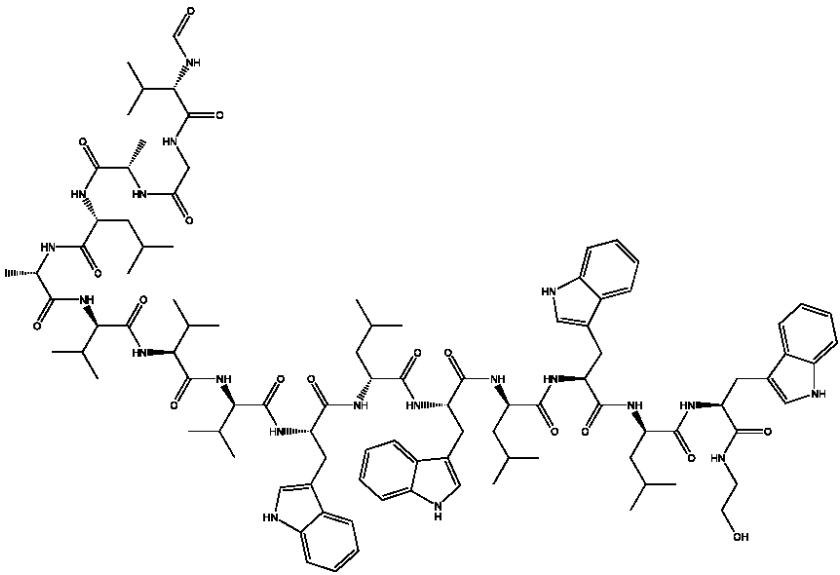
GRAMICIDIN

Therapeutic Function: Antibacterial

Chemical Name: Gramicidin D

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 113-73-5

Trade Name	Manufacturer	Country	Year Introduced
Gramoderm	Schering	US	1949
Mytrex	Savage	US	-
Neosporin	Burroughs-Wellcome	US	-
Nyst-Olone	Schein	US	-
Tri-Thalmic	Schein	US	-

Raw Materials

Pentane
Acetone
Benzene
Tyrothricin fermentation liquor
Ethanol

Manufacturing Process

5 lb of acid precipitated solid (Hotchkiss, Advances in Enzymology, pages 157-158) from 30 gal of tyrothricin fermentation liquor containing about 40 g (2%)of tyrothricin were extracted with 12 liters of absolute ethyl alcohol and filtered. The filtrate was evaporated in vacuo to 1 liter, and the concentrate extracted twice with 1 liter of pentane. The pentane layers were discarded.

40 g of decolorizing charcoal were added to the pentane-extracted filtrate and filtered off.

To 500 ml of the charcoal-treated filtrate were added 200 ml benzene and 300 ml water, the whole shaken thoroughly, centrifuged, and the benzene layer separated. This treatment of the charcoal-treated filtrate was repeated twice, all benzene fractions were combined and evaporated in vacuo.

200 ml of absolute acetone were added to the residue and concentrated by boiling to 150 ml. The concentrate was refrigerated overnight. The crystals which had formed in the concentrate were filtered off, and the mother liquor concentrated first to 50 ml and then to 25 ml, the two concentrates refrigerated overnight, and the formed crystals filtered off. Total yield of crystalline gramicidin was 3.85 g = 19.2% of estimated tyrothricin in the initial material.

The combined crystal crops were redissolved in 50 ml absolute acetone, and the solution refrigerated overnight. After filtering, the formed crystals were dried in vacuo. The total yield of crystalline gramicidin thus obtained was 2.5 g.

References

Merck Index 4405
PDR pp.758, 1604, 1606
I.N. p.470
REM p.1203
Baron, A.L.; US Patent 2,534,541; December 19, 1950; assigned to S.B. Penick and Co.

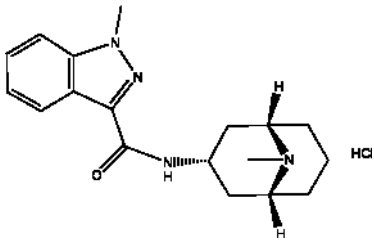
GRANISETRON HYDROCHLORIDE

Therapeutic Function: Serotonin antagonist

Chemical Name: 1H-Indazole-3-carboxamide, 1-methyl-N-(9-methyl-9-azabicyclo(3.3.1)non-3-yl)-, monohydrochloride, 3-endo-

Common Name: Granisetron hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 107007-99-8

Trade Name	Manufacturer	Country	Year Introduced
Granicip	Cipla Limited	India	-
Graniset	Sun Pharmaceuticals Industries Ltd.	India	-
Kevatril	SmithKline Beecham Pharmaceuticals	UK	-
Kytril	SmithKline Beecham Pharmaceuticals	UK	-
Kytril	Hoffmann - La Roche Inc.	USA	-

Raw Materials

Methyl iodide
1-(Penylmethyleneamino)isatin
Sodium hydride
Hydrochloric acid
endo-3-Amino-9-methyl-9-azabicyclo[3.3.1]nonane

Manufacturing Process

A solution of 1-(phenylmethyleneamino)isatin (1.354 g, 0.0054 mol) and endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane (0.832 g, 0.0054 mol) in dry THF (25 ml) under argon was heated to reflux for 5 hours. The solution was cooled and evaporated and the residual traces of THF were azeotropically removed with dichloromethane. The residue was triturated with ether to give the intermediate 2-(benzylidenehydrazino)-α-oxophenyl-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)carboxamide as an orange powder (1.583 g, 73%).

Sodium hydride (50 mg, 60% dispersion in oil) was added to a solution of the 2-(benzylidenehydrazino)-α-oxophenyl-(9-methyl-9-azabicyclo[3.3.1]non-3-yl) carboxamide in dry THF (2.3 ml) under argon at -50°C. The resultant solution was warmed to 0°C over 20 min then cooled to -30°C and treated with methyl iodide (0.020 ml). The solution was allowed to warm to room temperature and stirred for 24 hours then filtered. The filtrate was evaporated to dryness, and triturated with chloroform to give the 2-(N-methylbenzylidenehydrazo)-α-oxophenyl-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)carboxamide as a light coloured powder (50 mg, 38%). Further trituration of the mother liquor gave a further crop, (37 mg, 28%, after recrystallisation from chloroform).

A solution of 2-(N-methylbenzylidenehydrazo)-α-oxophenyl-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)carboxamide (37 mg) in methanol (1 ml) was treated with 2 N hydrochloric acid (0.1 ml) and left at room temperature for several hours. Evaporation of the solvent gave the crude product as a brown oil (36 mg). HPLC and MS analysis confirmed the structure and indicated a quantitative yield of endo-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methylindazole-3-carboxamide (Ganisetron).

In practice it is usually used as hydrochloride.

References

Ward N. et al.; US Patent No. 6,268,498; July 31, 2001; Assigned to Hoffmann-La Roche Inc. (Nutley, NJ)

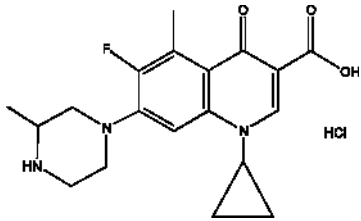
GREPAFLOXACIN HYDROCHLORIDE

Therapeutic Function: Antibacterial

Chemical Name: 3-Quinolinecarboxylic acid, 1,4-dihydro-1-cyclopropyl-6-fluoro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-, monohydrochloride

Common Name: Grepafloxacin hydrochloride; Tomefloxacin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 161967-81-3

Trade Name	Manufacturer	Country	Year Introduced
Raxar	Glaxo Wellcome	UK	-
Raxar	Otsuka Pharmaceutical Company, Ltd.	Japan	-

Raw Materials

3-(3-Methyl-1-piperazinyl)-4-fluoro-5-methyl-6-nitro-N-cyclopropylaniline
Diethyl ethoxymethylenemalonate
Acetic anhydride
Sulfuric acid

Manufacturing Process

To 3-(3-methyl-1-piperazinyl)-4-fluoro-5-methyl-6-nitro-N-cyclopropylaniline is added diethyl ethoxymethylenemalonate and the mixture is heated at 150°C for 25 hours. After cooling, the reaction product is purified by silica-gel column-chromatography (dichloromethane:methanol = 100:1) to give diethyl[N-cyclopropyl-N-[3-(3-methyl-1-piperazinyl)-4-fluoro-5-methyl-6-

nitrophenyl] aminomethylene]malonate. The product is dissolved in acetic anhydride and thereto conc. sulfuric acid is added dropwise at 50-60°C, followed by stirring for 30 min. The mixture is poured into ice-water, neutralized, extracted with dichloromethane and the extract is dried. The solvent is distilled off under reduced pressure. Purification by silica-gel column-chromatography (dichloromethane:methanol = 10:1) to give ethyl 7-(3-methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylate. To these compound is 10% aqueous solution of sodium hydroxide and ethanol, and the mixture is refluxed for 1 hour. After cooling, the reaction mixture is diluted with water and washed with dichloromethane. The aqueous layer is made acidic with acetic acid and then made weakly alkaline with an aqueous sodium hydrogen carbonate. The product is extracted with dichloromethane and the extract is dried. The solvent is distilled off under reduced pressure and to the residue is added ethanol. The precipitated crystals are filtered and recrystallized from DMFA to give 7-(3-methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (12 mg), as white powder, m.p. 206-208°C.

7-(3-methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-5-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylicacid may be transformed to hydrochloride.

References

Ueda H. et al.; US Patent No. 5,563,138; Oct. 8, 1996; Assigned: Otsuka Pharmaceutical Company, Limited (Tokyo, JP)

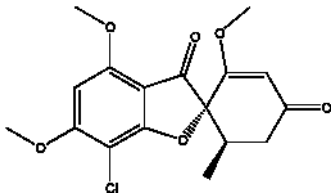
GRISEOFULVIN

Therapeutic Function: Antifungal

Chemical Name: (2S-trans)-7-Chloro-2',4,6-trimethoxy-6'-methylspiro [benzofuran-2(3H),1'-[2]cyclohexene]-3,4'-dione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 126-07-8

Trade Name	Manufacturer	Country	Year Introduced
Grifulvin	McNeil	US	1959
Fulvicin	Schering	US	1959
Grisactin	Ayerst	US	1959
Fulcine Forte	I.C.I.	France	1972
Gris-Peg	Dorsey	US	1975
Delmofulvina	Coli	Italy	-
Fulcin	Cepharma	Italy	-
Fungivin	Nyegaard	Norway	-
Gricin	Arzneimittelwerk Dresden	E. Germany	-
Grifulin	Teva	Israel	-
Grifulvin	Yamanouchi	Japan	-
Grisefuline	Clin-Comar-Byla	France	-
Grisetin	Nippon Kayaku, Co.	Japan	-
Grisovin	Fujisawa	Japan	-
Guservin	Chugai	Japan	-
Lamoryl	Lovens	Denmark	-
Likuden	Hoechst	W. Germany	-

Raw Materials

Bacterium Penicillium petulum
Corn steep liquor

Manufacturing Process

Corn steep liquor nitrogen	0.40% w/v
KH_2PO_4	0.40% w/v
$CaCO_3$	0.40% w/v
KCl	0.20% w/v
Mobilpar S	0.0275% v/v
White mineral oil	0.0275% v/v
H_2SO_4	0.0125% v/v
Preinoculation volume	800 gal
Fermentation temperature	25°C
Inoculum volume	10%

The experiment was carried out on the 1,000 gallon scale. Three impellers 1'8" diameter at 220 rpm were employed. The air rates were 0 to 5 hours, 40 cfm, 5 to 10 hours, 80 cfm and after 10 hours, 125 cfm. The inoculum rate was 10% v/v. It was prepared by the standard inoculum development technique on the following medium:

Corn steep liquor nitrogen	0.30% w/v
Brown sugar	2.0% w/v
Chalk	1.0% w/v
Maize oil	1.0% v/v
Hodag MF	0.033% v/v

This was inoculated with a spore suspension of P. patulurn (1 liter containing 3-5 x 10^7 spores/ml) and grown at 25°C in 100 gallon tank. The inoculum is transferred at 40 hours or when the mycelial volume (after spinning 10 minutes at 3,000 rpm) exceeds 25%. The fermentation is conducted as near to the ideal pH curve as possible by addition of crude glucose, according to US Patent 3,069,328.

References

Merck Index 4420
Kleeman and Engel p.449
PDR pp.621, 931, 1307, 1620
OCDS Vol.1 p.314 (1977)
I.N. p.471
REM p.1228
Hockenhull, D.J.D.; US Patent 3,069,328; December 18, 1962; assigned to Glaxo Laboratories Limited, England
Dorey, M.J., Mitchell, I.L.S., Rule, D.W. and Walker, C.; US Patent 3,069,329; Dec. 18, 1962; assigned to Glaxo Laboratories Limited, England

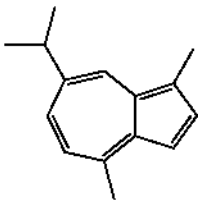
GUAIAZULENE

Therapeutic Function: Antiinflammatory

Chemical Name: Azulene, 1,4-dimethyl-7-(1-methylethyl)-

Common Name: Guaiazulene; Guajazulen; Matricin

Structural Formula:



Chemical Abstracts Registry No.: 489-84-9

Trade Name	Manufacturer	Country	Year Introduced
AZ 8	Millet Roux	-	-
AZ 8 Beris	Weimer	-	-
AZ 8 Beris	Gernerpharma	-	-
Azulenol	Biogal	-	-
Guaiazulene	Shanghai Lansheng Corporation	-	-
Azulene Cryst.	Dragoco Inc.	-	-

Raw Materials

Guacum officinale
Sulfur

Manufacturing Process

10 kg a gum of Guacum officinale was heated with 3-4 kg of sulfur to 130°C. The heating was slowly continued for 220°C under the nitrogen. The formed water steam was removed with the nitrogen current. The temperature should be higher 100°C in order to the water didnt fall into reaction mixture. H_2S was obtained simultaneously the dehydrogenation and removed with water steam. Hydrogen sulfide was connected in an alkaline trap.

When a H_2S discharge stopped, the temperature was decreased to 120°C and the reaction mixture was distilled in vacuum 1-20 mm. The distillate had deep blue color and contained 6-7 kg oil with 20% of 7-isopropyl-1,4-dimethylazulene. It was dissolved in the 5-10 volumes of light petroleum, shook with sodium hydroxide for removing the sulfur containing substaneces, washed to neutral. Then petrolem layer was mixed with 10-15 L 62% H_2SO_4 for removing the by-products, the petroleum layer lost the blue color and the desired substance was in sulphuric acid layer. The last one was shook with ice and NaOH. As a result about 7% $NaSO_4$ solution in sulfuric acid was obtained. It was diluted and azulene gave an emulsion, which was extracted with 10 L of petrolem and distilled. The 7-isopropyl-1,4-dimethylazulene is distilled at 167°-168°C/12 mm. Yield 10-15%.

References

Joos B.; C.H. Patent No. 314,487; July 31, 1956, Zurich

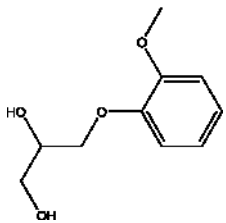
GUAIFENESIN

Therapeutic Function: Expectorant

Chemical Name: 3-(2-Methoxyphenoxy)-1,2-propanediol

Common Name: Guaiacol glyceryl ether

Structural Formula:



Chemical Abstracts Registry No.: 93-14-1

Trade Name	Manufacturer	Country	Year Introduced
GG Cen	Central	US	1975
Breonesin	Breon	US	1980
Cremacoat	Vicks	US	1983
Ambenyl	Marion	US	-
Asbron G	Sandoz	US	-
Balminil	Rougier	Canada	-
Bromphen	Schein	US	-
Bronchol	Streuli	Switz.	-
Broncovanil	Scharper	Italy	-
Brondecon	Parke Davis	US	-
Bronkolixir	Winthrop-Breon	US	-
Bronkotuss	Hyrex	US	-
Congess	Fleming	US	-
Cortussin	Xttrium	US	-
Corutrol	Dow	US	-
Coryban	Pfipharmecs	US	-
Deconsal	Adams	US	-
Detussin	Schein	US	-
Dilaudid	Knoll	US	-
Dilur-G	Savage	US	-
Donatussin	Laser	US	-
Dorcol	Dorsey	US	-
Dura-Vent	Dura	US	-
Entex	Norwich Eaton	US	-
Entuss	Hauck	US	-
Fedahist	Rorer	US	-
Gaiapect	Eri	Canada	-
Guajacuran	Spofa	Czechoslovakia	-
Guajasyl	Mepha	Switz.	-
Guiatuss	Schein	US	-
Gvaja	Lek	Yugoslavia	-
Head and Chest	Procter and Gamble	US	-
Histalet	Reid-Rowell	US	-
Humibid	Adams	US	-
Hustosil	Kyoto	Japan	-
Hycotuss	Du Pont	US	-
Hytuss	Hyrex	US	-
Lufyllin	Wallace	US	-
Mucostop	Verla	W. Germany	-
Mudrane	Poythess	US	-
Naldecon	Bristol	US	-
Neo-Spec	Neo	Canada	-
Novahistine	Lakeside	US	-
Nucofed	Beecham	US	-
Quibron	Mead Johnson	US	-

Trade Name	Manufacturer	Country	Year Introduced
Reorganin	Brunnengraber	US	-
Resyl	Ciba	Italy	-
Robitussin	Robins	US	-
Ru-Tuss	Boots	US	-
Scot-Tussin	Scot-Tussin	US	-
Sinufed	Hauck	US	-
Sorbutuss	Dalin	US	-
Triaminic	Dorsey	US	-
Tussar	U.S.V.	US	-
Tussend	Merrell Dow	US	-
Zephrex	Bock	US	-

Raw Materials

o-Methoxyphenol (guaiacol)
Glycidol

Manufacturing Process

A mixture of o-methoxyphenol (57 g), glycidol (32 g) and pyridine (1 g) is warmed to 95°C at which temperature a vigorous reaction takes place. The reaction mixture is cooled to prevent the temperature rising above 110°C. When the exothermic reaction has subsided the reactants are heated at 95°C for one hour longer and then distilled under low pressure. The main fraction boils in the range 176°C to 180°C/0.5 mm. It crystallizes on cooling. Recrystallization from benzene gives the pure product, MP 78.5°C to 79.0°C.

References

Merck Index 4432
Kleeman and Engel p.449
OCDS Vol.1 p.118 (1977)
I.N. p.472
REM p. 868
Bradley, W. and Forrest, J.; British Patent 628,497; August 30, 1949; assigned to British Drug Houses, Ltd.

GUANABENZ

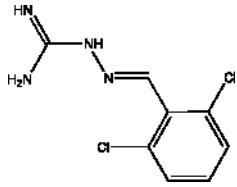
Therapeutic Function: Antihypertensive

Chemical Name: 2-[(2,6-Dichlorophenyl)methylene] hydrazinecarboximidamide

Common Name: -

Chemical Abstracts Registry No.: 5051-62-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Wytensin	Wyeth	US	1982
Rexitene	L.P.B.	Italy	-

Raw Materials

2,6-Dichlorobenzaldehyde
Aminoguanidine bicarbonate

Manufacturing Process

A mixture of 14.0 g of 2,6-dichlorobenzaldehyde, 10.8 g of aminoguanidine bicarbonate and 100 ml of pyridine was refluxed for 3 hours. The reaction mixture was poured into water and the crystalline precipitate filtered off; MP 225°C to 227°C.

References

Merck Index 4436
DFU 1 (11) 523 (1976)
Kleeman and Engel p.451
PDR p.1997
OCDS Vol.2 p.123 (1980)
DOT 15 (11) 481 (1979)
I.N. p.473
REM p.846
Yates, J. and Haddock, E.; British Patent 1,019,120; February 2, 1966; assigned to Shell International Research Maatschappij N.V. (Netherlands)

GUANADREL SULFATE

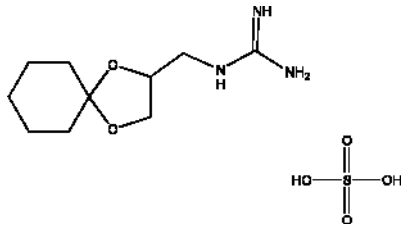
Therapeutic Function: Antihypertensive

Chemical Name: (1,4-Dioxaspiro[4.5]decan-2-ylmethyl)guanidine sulfate

Common Name: -

Chemical Abstracts Registry No.: 40580-59-4 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Hylorel	Pennwalt	US	1983
Hycoral	Pennwalt	W. Germany	1983
Anarel	Cutter	US	-

Raw Materials

1,4-Dioxaspiro[4.5]decane-2-methylamine
2-Methyl-2-thiopseudourea sulfate

Manufacturing Process

A mixture of 10.5 g of 1,4-dioxaspiro[4.5]decane-2-methylamine and 8.6 g of 2-methyl-2-thiopseudourea sulfate in 40 ml of water was heated on the steam bath for 4 hours during which 2.0 g of methylmercaptan was collected in a dry ice bath connected to the reaction flask through a water cooled reflux condenser. The reaction mixture was then evaporated at 15 mm pressure to a solid residue which was then dissolved in 80 ml of 50/50 methanol-ethanol. The solution was filtered and evaporated to approximately 50 ml volume and allowed to cool and crystallize, giving a crop melting at 213.5°C to 215°C of 1,4-dioxaspiro[4.5]decan-2-ylmethyl)-guanidine sulfate.

References

Merck Index 4438
Kleeman and Engel p.451
PDR p.1398
OCDS Vol.1 p.400 (1977)
DOT 16 (4) 140 (1980)
I.N. p.473
REM p.907
Hardie, W.R. and Aaron, J.E.; US Patent 3,547,951; December 15, 1970

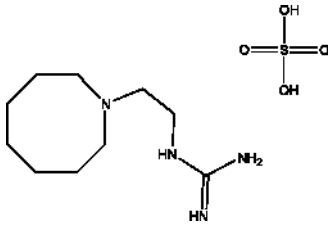
GUANETHIDINE SULFATE

Therapeutic Function: Antihypertensive

Chemical Name: [2-(Hexahydro-1(2H)-azocinyl)ethyl]guanidine sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 60-02-6; 55-65-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ismelin	Ciba	US	1960
Ismelin	Ciba	W. Germany	1960
Ismelin	Ciba	UK	1960
Ismelin	Ciba	Italy	1961
Ismeline	Ciba Geigy	France	1963
Abapresin	Polfa	Poland	-
Antipres	Protea	Australia	-
Dopom	Galter	Italy	-
Ganda	Smith and Nephew	UK	-
Iporal	Euro-Labor.	Portugal	-
Ipotidina	Francia	Italy	-
Izobarin	Pliva	Yugoslavia	-
Normalin	Taro	Israel	-
Pressedin	Chiesi	Italy	-
Santotensin	EGYT	Hungary	-
Visutensil	I.S.F.	Italy	-

Raw Materials

Chloroacetyl guanide
Lithium aluminum hydride
Heptamethyleneimine
Sulfuric acid

Manufacturing Process

13.6 grams of chloroacetyl guanide is added while stirring to a solution of 22.6 grams of heptamethylene imine in 200 ml of benzene. After warming for 1 hour, and then cooling, the solution is filtered and the filtrate concentrated under reduced pressure. The residue, containing the 2-(1-N,N-

heptamethylene-imino)-aceticacid guanide, is suspended in tetrahydrofuran and added to a refluxing solution of 6 grams of lithium aluminum hydride in tetrahydrofuran. After completion of the reaction, the excess of lithium aluminum hydride is decomposed by adding water, then aqueous sodium hydroxide. The solid material is filtered off, the filtrate is acidified with sulfuric acid and the 2-(1-N,N-heptamethylene-imino)-ethyl-guanidine sulfate can be recovered and recrystallized from aqueous ethanol, MP 276° to 281°C (with decomposition).

References

Merck Index 4441
Kleeman and Engel p.452
PDR p.797
OCDS Vol.1 p.282 (1977) and 2, 100 (1980)
DOT 16 (4) 137 (1980)
I.N. p.474
Mull, R.P.; US Patent 2,928,829; March 15, 1960; assigned to Ciba Pharmaceutical Products, Inc.
Mull, R.P.; US Patent 3,006,913; October 31, 1961; assigned to Ciba Pharmaceutical Products, Inc.
Mull, R.P.; US Patent 3,055,882; September 25, 1962; assigned to Ciba Corporation

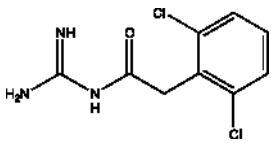
GUANFACINE

Therapeutic Function: Antihypertensive

Chemical Name: N-(Aminoiminomethyl)-2,6-dichlorobenzeneacetamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 29110-47-2; 29110-48-3 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Estulic	Sandoz	Switz.	1980
Estulic	Sandoz	UK	1980
Estulic	Sandoz	W. Germany	1980
Estulic	Wander	France	1981
Estulic	Sandoz	France	1981
Hipertensal	Finadiet	Argentina	-

Raw Materials

2,6-Dichlorophenylacetic acid chloride
Guanidine
Hydrogen chloride

Manufacturing Process

2,6-Dichlorophenyl-acetyl-guanidine: A solution of 3.245 g (0.055 mol) of guanidine in isopropanol is added to a solution of 11.7 g (0.05 mol) of 2,6-dichlorophenyl-acetic acid ethyl ester (BP 142°C to 143°C/12 mm of Hg) in 20cc of isopropanol. The reaction mixture is allowed to stand overnight and is subsequently concentrated by evaporation. After recrystallizing the residue from methanol/ether 2,6-dichlorophenyl-acetyl-guanidine is obtained in the form of white grains having a MP of 225°C to 227°C.

2,6-Dichlorophenyl-acetyl-guanidine hydrochloride: A solution of 5.6 g (0.025 mol) of 2,-dichlorophenylacetic acid chloride (BP 137°C to 138°C/12 mm of Hg) in 10 cc of toluene is added dropwise to a mixture of 4.5 g (0.076 mol) of guanidine and 60 cc of toluene. The reaction mixture is allowed to stand at room temperature for 20 minutes, is then heated on a steam bath for 2 hours and is subsequently cooled. The resulting precipitate is filtered off and washed twice with 25 cc amounts of water in order to separate the guanidine hydrochloride. The residue (2,6-dichlorophenyl-acetyl-guanidine) is washed with chloroform for further purification and is then dissolved in 50 cc of isopropanol. The pH-value of the solution is adjusted to 6 with ethanolic hydrochloric acid and the solution is cooled. The resulting white needles are again washed with chloroform. The resulting 2.6-dichlorophenyl-acetyl-guanidine hydrochloride has a MP of 213°C to 216°C.

References

Merck Index 4442
DFU 2 (4) 278 (1977)
OCDS Vol.3 p.40 (1984)
DOT 16 (12) 416 (1980)
I.N. p.474
REM p.846
Bream, J.B. and Picard, C.W.; US Patent 3,632,645; January 4, 1972; assigned to Dr. A.Wander S.A. (Switz.)

GUANOCLOR SULFATE

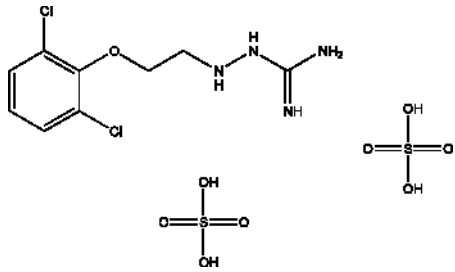
Therapeutic Function: Antihypertensive

Chemical Name: 2-(2,6-Dichlorophenoxy)ethylaminoguanidine, sulfate

Common Name: Guanoclor sulfate

Chemical Abstracts Registry No.: 551-48-4; 5001-32-1 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Vatensol	Pfizer	-	-

Raw Materials

2-(2,6-Dichlorophenoxy)ethyl bromide
Hydrazine hydrate
Sodium hydroxide
S-Methylisothiouronium sulfate

Manufacturing Process

20 parts by weight of 2-(2,6-dichlorophenoxy)ethyl bromide dissolved in 75 parts by volume of ethanol are slowly added with stirring to 37 parts by weight of hydrazine hydrate in 25 parts by volume of ethanol. The mixture is boiled under reflux conditions for 16 h. The solvent and excess hydrazine are removed by distillation under reduced pressure. Water and excess solid sodium hydroxide are added to make the mixture alkaline. The mixture is extracted with chloroform, dried over anhydrous potassium carbonate, filtered and freed from solvent by distillation. The residual oil is distilled at 1 mm of mercury pressure. The fraction boiling at 132° to 140°C and consists of 2-(2,6-dichlorophenoxy)ethyl hydrazine.

23 parts by weight of 2-(2,6-dichlorophenoxy)ethyl hydrazine and 14.46 parts by weight of S-methylisothiouronium sulfate in 150 parts by volume of water are boiled together under reflux conditions for 4 h. The solid which precipitates on cooling is recrystallized from water and consists of 14.5 parts by weight of N-[2-(2,6-dichlorophenoxy)ethylamino]guanidine hydrogen sulfate having a melting point of 214°C.

References

Canterbury J. A. et al.; US Patent No. 3,271,448; Sept. 6, 1966; Assigned: Chas. Pfizer and Co., Inc., New York, N.Y.

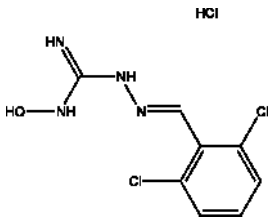
GUANOXABENZ HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 1-(2,6-Dichlorobenzylideneamino)-3-hydroxyguanidine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 24047-25-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Benezrial	Houde	France	1978

Raw Materials

S-Methylisothiosemicarbazide hydroiodide
Hydroxylamine hydrochloride
2,6-Dichlorobenzaldehyde

Manufacturing Process

2N sodium hydroxide solution (5 ml) is added to a stirred suspension of S-methylisothiosemicarbazide hydroiodide (2.33 g) and hydroxylamine hydrochloride (0.70 g) in water (6 ml) and stirred for 48 hours. The solution is evaporated in vacuo to provide 1-amino-3-hydroxyguanidine. One-third of the residue is dissolved in 16 ml of ethanol and 2,6-dichlorobenzaldehyde (0.6 g) is added to this solution. The reaction mixture is then stirred for 48 hours. The solution is then evaporated in vacuo and the residue dissolved in ether (30 ml) and in hydrochloric acid (30 ml). The aqueous phase is rendered alkaline with 2N sodium carbonate solution and extracted with ether. The ether layer is dried with sodium sulfate and evaporated. The residue is dissolved in ether and excess dry hydrogen chloride is passed into the solution.

The resultant mixture is evaporated in vacuo and the residue triturated with methylene chloride to afford a crude product. Recrystallization from ethanol-ether (1:3) provides 1-(2,6-dichlorobenzylideneamino)-3-hydroxyguanidine hydrochloride; MP 173°C to 175°C. When the above process is carried out and S-benzylisothiosemicarbazide hydroiodide is used in place of S-

methylisothiosemicarbazide hydroiodide, the identical product is again obtained.

References

Merck Index 4449
Kleeman and Engel p.453
OCDS Vol.2 p.123 (1980)
DOT 14 (6) 244 (1978)
I.N. p.474
Houlihan, W.G. and Manning, R.E.; US Patent 3,591,636; July 6, 1971; assigned to Sandoz-Wander, Inc.

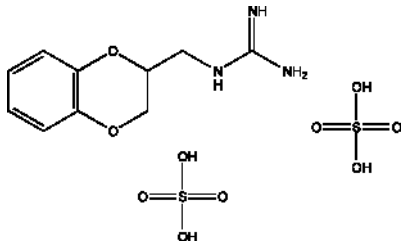
GUANOXAN SULFATE

Therapeutic Function: Antihypertensive

Chemical Name: Guanidine, ((2,3-dihydro-1,4-benzodioxin-2-yl)methyl)-, sulfate

Common Name: Guanoxan sulfate

Structural Formula:



Chemical Abstracts Registry No.: 5714-04-5; 2165-19-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Envacar	Pfizer	-	-
Guanoxan Sulfate	Shanghai Lansheng Corporation	-	-

Raw Materials

Benzylamine
Hydrogen
Epichlorohydrin
Thionyl chloride
2-Aminomethyl-1,4-benzodioxane
S-Methylisothiouronium sulfate
Sodium hydroxide
o-Dihydroxybenzene

Palladium on carbon
S-Methylisothiouronium sulfate

Manufacturing Process

2 Methods of producing of 2-guanidinemethyl-2,3-dihydro-1,4-benzodioxine:

1. 3.3 parts by weight of 2-aminomethyl-1,4-benzodioxane and 2.78 parts by weight of S-methylisothiouronium sulfate were dissolved in 20 parts by volume of water, and the resulting aqueous solution was heated under reflux for 3 h. At the end of this time, the solvent was removed by means of evaporation under reduced pressure and the residue so obtained dissolved in a minimum amount of fresh water and treated with charcoal. Upon filtration, there was obtained a clear filtrate which, on standing, soon afforded pure crystals of di(2-guanidinomethyl-1,4-benzodioxane)sulfate, melting point 204°-205°C.

The base 2-guanidinemethyl-2,3-dihydro-1,4-benzodioxine may be obtained by reaction of di(2-guanidinomethyl-1,4-benzodioxane)sulfate with, for example, sodium hydroxide.

2. o-Dihydroxybenzene reacted with epichlorhydrine in the presence sodium hydroxide and 2-hydroxymethyl-2,3-dihydro-1,4-benzodioxine was obtained.

To solution of 2-hydroxymethyl-2,3-dihydro-1,4-benzodioxine thionylchloride was added to give 2-chlormethyl-2,3-dihydro-1,4-benzodioxine.

2-Chloromethyl-2,3-dihydro-1,4-benzodioxine reacted with benzylamine to produced 2-benzylaminomethyl-2,3-dihydro-1,4-benzodioxine, which was reduced at the presence of hydrogen and Pd-C (catalyst) to 2-aminomethyl-2,3-dihydro-1,4-benzodioxine.

2-Aminomethyl-2,3-dihydro-1,4-benzodioxine was treated by S-methylisothiouronium sulfate and there was produced 2-guanidinemethyl-2,3-dihydro-1,4-benzodioxine.

References

Augstein J, et al.; US Patent No. 3,247,221; April 19, 1966; Assigned: Chas. Pfizer and Co., Inc., New York, N.Y.
Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982