S

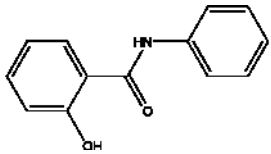
SALICYLANILIDE

Therapeutic Function: Antifungal

Chemical Name: 2-Hydroxy-N-phenylbenzamide

Common Name: N-Phenylsalicylamide

Structural Formula:



Chemical Abstracts Registry No.: 87-17-2

Trade Name	Manufacturer	Country	Year Introduced
Salinidol	Doak	US	1946
Ansadol	Rorer	US	1947
Hyanilid	Peau Seche	US	-

Raw Materials

Salicylic acid
Aniline

Manufacturing Process

Salicylanilide is ordinarily made by reacting salicylic acid with aniline in the presence of phosphorus trichloride at an elevated temperature. The theoretical proportions of reactants are usually employed for best results, that is, one mol each of aniline and salicylic acid to a third of a mol of phosphorus trichloride. An improved process employs an inert organic solvent as a reaction diluent.

References

Merck Index 8188
I.N. p. 861
Majewski, T.E., Parsey, E.S. and Skelly, N.E.; US Patent 3,221,051; November 30, 1965 Majewski, T.E., Stoesser, W.C. and Parsey, E.S.; US Patent 3,231,611;January 25, 1966; assigned to The Dow Chemical Company

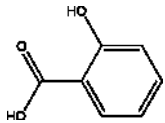
SALICYLIC ACID

Therapeutic Function: Keratolytic

Chemical Name: 2-Hydroxybenzoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 69-72-7

Trade Name	Manufacturer	Country	Year Introduced
Saligel	Stiefel	US	1978
Fomac	Dermik	US	1979
Aveenobar	Rydelle	US	-
Barseb	Barnes Hind	US	-
Cantharone	Seres	US	-
Compound W	Whitehall	US	-
Duofilm	Stiefel	US	-
Egocappol	Ego	Australia	-
Fostex	Westwood	US	-
Fungi-Nail	Kramer	US	-
Hydrisalic	Pedinol	US	-
Jabon Salicilico	Imba	Spain	-
Keralyt	Westwood	US	-
Komed	Barnes Hind	US	-
Night-Cast	Seres	US	-
Occlusal	Gen Derm	US	-
Pernox	Westwood	US	-
Sal Ac	Gen Derm	US	-
Salactic	Pedinol	US	-
Sebucare	Westwood	US	-
Sebulex	Westwood	US	-

Trade Name	Manufacturer	Country	Year Introduced
Tinver	Barnes Hind	US	-
Verrex	C and M	US	-
Verrusal	C and M	US	-
Viranol	Amer. Dermal	US	-
Wart-Off	Pfipharmecs	US	-
Whitfield's Ointment	Fougera	US	-

Raw Materials

Sodium phenolate
Nutrient medium
Naphthalene
Bacterium Pseudomonas
Carbon dioxide

Manufacturing Process

Made by reacting sodium phenolate and carbon dioxide. May also be made by microbiological oxidation of naphthalene by forming an aqueous nutrient medium for microorganisms capable of oxidizing naphthalene to salicylic acid of the genus Pseudomonas containing basal mineral salts, 0.5 to 4 wt % of finely divided naphthalene and 0.1 to 1 wt % of a boron compound, inoculating the nutrient medium with an inoculum containing a microorganism capable of oxidizing naphthalene to salicylic acid of the genus Pseudomonas, the inoculated nutrient medium having an initial pH value of about 4 to 9, incubating the inoculated nutrient medium at a temperature of about 25° to 50°C for a period of about 2 to 7 days and then recovering salicylic acid from the nutrient medium.

References

Merck Index 8190
PDR pp.580, 653, 777, 905, 985, 1397, 1417, 1575, 1696, 1779, 1890, 1898
I.N. p. 37
REM p. 785
Zaiic. J.E. and DunlaD. W.J.: US Patent 3274,074; SeDtember 20.1966; assisned to Kerr-McGee Oil Industhes, Inc.

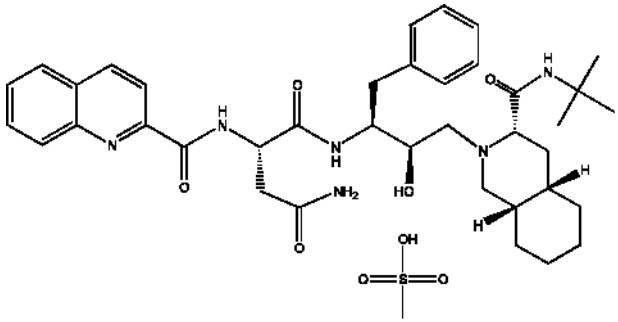
SAQUINAVIR MESYLATE

Therapeutic Function: Antiviral

Chemical Name: Butanediamide, N^1-(3-(3-(((1,1-dimethylethyl) amino)carbonyl)octahydro-2(1H)-isoquinolinyl)-2-hydroxy-1-(phenylmethyl)propyl)-2-((2-quinolinylcarbonyl)amino)-, (3S-(2(1R*(R*),2S*),3-α,4a-β,8a-β))-, monomethanesulfonate (salt)

Common Name: Saquinavir mesylate

Structural Formula:



Chemical Abstracts Registry No.: 149845-06-7; 127779-20-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Fortovase	Roche Laboratories	USA	-
Invirase	Hoffmann - La Roche Inc.	-	-
Invirase	Roche Laboratories	USA	-
Saquinavir	Roche Laboratories	USA	-

Raw Materials

Quinaldic acid
N-Ethylmorpholine
Rhodium on carbon
Citric acid
Hydroxybenzotriazole
Sodium hydroxide
N-(Benzyloxycarbonyl)-L-asparagine
Dicyclohexylcarbodiimide
Benzyl chloroformate
N-Hydroxysuccinimide
Palladium on carbon
1,2,3,4-Tetrahydro-3(S)-isoquinolinecarboxylic acid
3(S)-(Benzyloxyformamido)-1,2(S)-epoxy-4-phenylbutane

Manufacturing Process

A suspension of 12.676 g (71.6 mmol) of 1,2,3,4-tetrahydro-3(S)-isoquinolinecarboxylic acid (Chem. Pharm. Bull. 1983, 31, 312) in 200 ml of 90% acetic acid was hydrogenated at 80°C and under 140 atm pressure over 5% rhodium-on-carbon for 24 h. The mixture was left to cool to room temperature and the catalyst was then filtered off. The filtrate was evaporated to give a gum which was dissolved in 10 ml of ethyl acetate and added slowly to 100 ml of vigorously stirred diisopropyl ether. A resinous precipitate was produced. The supernatant liquors were removed by decantation and the precipitate was extracted with hot ethyl acetate. This hot solution was poured into a vigorously stirred mixture of 150 ml of diethyl ether/diisopropyl ether (1:1) to give a pale grey solid which was collected by filtration, washed with diethyl ether and dried. There were obtained 5.209 g of a mixture of decahydroisoquinoline-3(S)-carboxylic acids consisting of predominantly (about 65%) the 4aS,8aS isomer together with the 4aR,8aR isomer (about 25%) and about 10% of the trans isomers.

9.036 g (49.4 mmol) of the foregoing mixture of decahydroisoquinoline-3(S)-

carboxylic acids were dissolved in 50 ml (50 mmol) of 1 M sodium hydroxide solution and the resulting solution was cooled to 0°C. 7.40 ml (51.87 mmol) of benzyl chloroformate and 58.7 ml (58.7 mmol) of 1 M sodium hydroxide solution were added dropwise over a period of 1 h while maintaining a temperature of 0°-5°C by cooling. The mixture was then stirred for a further 2 h, during which time the mixture was allowed to warm to room temperature. 100 ml of diethyl ether were added and the mixture was filtered, whereby the insoluble R,R-isomer was removed. The aqueous layer of the filtrate was separated and adjusted to pH 1.5-2 by the addition of concentrated hydrochloric acid, whereby an oil precipitated. The mixture was extracted twice with 100 ml of ethyl acetate each time. The combined organic extracts were washed with water, dried over anhydrous sodium sulphate and evaporated to give an oil. This oil was dissolved in 35 ml of ethyl acetate and 2.85 ml (25 mmol) of cyclohexylamine were added. The white precipitate was collected by filtration to give, after several fractional recrystallizations from methanol/ethyl acetate, 2.38 g of the cyclohexylamine salt of 2-(benzyloxycarbonyl)-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxylic acid.

2.334 g of the cyclohexylamine salt of 2-benzyloxycarbonyl)-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxylic acid were partitioned between 50 ml of ethyl acetate and 50 ml of 10% citric acid solution. The organic phase was separated, washed with water, filtered and evaporated to give 1.87 g of 2-(benzyloxycarbonyl)-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxylic acid in the form of a colorless gum.

A solution of 0.634 g (2.0 mmol) of 2-(benzyloxycarbonyl)-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxylic acid in 6 ml of dimethoxyethane was treated with 0.23 g (2.0 mmol) of N-hydroxysuccinimide and 0.412 g (2.0 mmol) of dicyclohexylcarbodiimide. The mixture was stirred at room temperature for 18 hours. The mixture was filtered and the filtrate was evaporated to give 0.879 g of the N-hydroxysuccinimide ester of the foregoing acid in the form of a pale yellow oil. A solution of 0.828 g (2.0 mmol) of the foregoing N-hydroxysuccinimide ester in 5 ml of dichloromethane was stirred, cooled to 0°C and treated with 0.219 g (3.0 mmol) of tert.butylamine. The mixture was stirred at 0°C for 2 h and then at room temperature for 4.5 h. The mixture was then washed with 2 M hydrochloric acid, sodium carbonate solution and sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated. The residue was dissolved in 20 ml of diethyl ether and filtered. The filtrate was evaporated to give 0.712 g of 2-(benzyloxycarbonyl)-N-tert-butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide in the form of a white solid.

A solution of 0.689 g (1.85 mmol) of 2-benzyloxycarbonyl)-N-tert-butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide in 20 ml of ethanol was hydrogenated in the presence of 0.01 g of 10% palladium-on-carbon at room temperature and under atmospheric pressure for 18 h. The catalyst was removed by filtration and the solvent was removed by evaporation to give in quantitative yield N-tert-butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide as a clear oil.

A solution of 440 mg of N-tert-butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide and 549 mg of 3(S)-(benzyloxyformamido)-1,2(S)-epoxy-4-phenylbutane in 6 ml of ethanol was stirred at 60°C for 7 h. A further 54 mg of 3(S)-(benzyloxyformamido)-1,2(S)-epoxy-4-phenylbutane were added and

the solution was stirred at 20C for 16 h. The solvent was removed by evaporation and the residue was chromatographed on silica gel using diethyl ether/n-hexane/methanol (47.5:47.5:5) for the elution to give 771 mg of 2-[3(S)-(benzyloxyformamido)-2(R)-hydroxy-4-phenylbutyl-N-tert.butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide as a white solid.

A solution of 747 mg of 2-[3(S)-(benzyloxyformamido)-2(R)-hydroxy-4-phenylbutyl-N-tert.butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide in 40 ml of ethanol was hydrogenated over 10% palladium-on-carbon at 20°C and under atmospheric pressure for 5 h. The catalyst was removed by filtration and the filtrate was evaporated to give 561 mg of 2-[3(S)-amino-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-decahydro-(4aS,8aS) -isoquinoline-3(S)-carboxamide as a buff colored solid.

A solution of 561 mg of 2-[3(S)-amino-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl-decahydro-(4aS,8aS) -isoquinoline-3(S)-carboxamide and 372 mg of N-(benzyloxycarbonyl)-L-asparagine in 20 ml of dry tetrahydrofuran was cooled in an ice/salt mixture. 189 mg of hydroxybenzotriazole, 161 mg of N-ethylmorpholine and 317 mg of dicyclohexylcarbodiimide were added and the mixture was stirred for 16 h. The mixture was then diluted with ethyl acetate and filtered. The filtrate was washed with aqueous sodium bicarbonate solution and sodium chloride solution. The solvent was removed by evaporation and the residue was chromatographed on silica gel using dichloromethane/methanol (9:1) for the elution to give 434 mg of 2-[3(S)-[[N-(benzyloxycarbonyl)-L-asparaginyl]amino]-2(R)-hydroxy-4-phenyl butyl]-N-tert-butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide as a white solid from methanol/diethyl ether.

A solution of 195 mg of 2-[3(S)-[[N-(benzyloxycarbonyl)-L-asparaginyl]amino]-2(R)-hydroxy-4-phenyl butyl]-N-tert.butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide in 20 ml of ethanol was hydrogenated at room temperature and atmospheric pressure for 18 h over 10 mg of 10% palladium-on-charcoal. The catalyst was filtered off and the filtrate was evaporated under reduced pressure to give 154 mg of 2-[3(S)-[(L-asparaginyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert.butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide.

A solution of 154 mg of 2-[3(S)-[(L-asparaginyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-tert-butyl -decahydro(4aS,8aS)-isoquinoline-3(S)-carboxamide and 52 mg of quinaldic acid in 6 ml of dry tetrahydrofuran was cooled in an ice/salt mixture. 41 mg of hydroxybenzotriazole, 35 mg of N-ethylmorpholine and 68 mg of dicyclohexylcarbodiimide were added and the mixture was stirred for 64 h. The mixture was diluted with ethyl acetate and filtered. The filtrate was washed with aqueous sodium bicarbonate solution and with sodium chloride solution and then evaporated. The residue was chromatographed on silica gel using dichloromethane/methanol (9:1) for the elution to give 50 mg of N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide as a white solid.

The salt of saquinovir mesylate was obtained by the reaction of N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide with monomethanesulfonic acid.

References

Martin J.A., Redshaw S.; US Patent No. 5,196,438; March 23, 1993; Assigned: Hoffmann-La Roche Inc., Nutley, N.J.

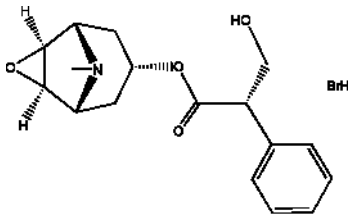
SCOPOLAMIN HYDROBROMIDE

Therapeutic Function: Sedative, Antiemetic

Chemical Name: Benzeneacetic acid, α-(hydroxymethyl)-, (1α,2β,4β,5α,7β)-9-methyl-3-oxa-9-azatricyclo(3.3.1.02,4)non-7-yl ester, (αS)-, hydrobromide

Common Name: Escopolamona hydrobromide; Hyoscine hydrobromide; Joscina hydrobromide; Oscine hydrobromide; Scopolamine hydrobromide; Skopolamin hydrobromide

Structural Formula:



Chemical Abstracts Registry No.: 114-49-8; 51-34-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hyoscine hydrobromide	GlaxoSmithKline Consumer Healthcare	UK	-
Hyoscine hydrobromide	Roche Consumer Health	Austria	-
Hyoscinhydrobromid	Boehringer Ingelheim Pharma KG	Germany	-
Isopto-Hyoscine	Alcon	-	-
Joy-rides	GlaxoSmithKline Consumer Healthcare	UK	-
Junior Kwells	Roche Consumer Health	Austria	-
Kwells	Roche Consumer Health	Austria	-
Scopace	Hope Pharmaceuticals	USA	-
Scopoderm TTS	Novartis Consumer Health	Switz.	-
Scopolamin Hydrobromide Inj.	Hospira Healthcare Corporation	Canada	-
Vorigeno	Anexo IV.c.	Spain	-

Raw Materials

Roots of Scopolia atropoides
Hydrochloric or acetic acid
Potassium carbonate

Manufacturing Process

Scopolamin was isolated from roots of Scopolia atropoides genus Solanaceae.

Alkaloids fraction was obtained from roots by extraction with benzene. First of all the atropine was isolated. Then after isolation of the atropine, the extract containing the scopolamin and other alkaloids was washed by slightly acidic solution (this solution was acidified with the hydrochloric or acetic acid). To the acidic solution the potassium carbonate was added, then scopolamin was extracted with chloroform, ether or their mixture. The organic extracts were combined and evaporated under reduce presser. Concentrated residue was washed with water, filtered and dried.

Scopolamin by obtaining of d-bromcamphar sulfoacid derivatives may be differented on d- and l-isomers.

Scopolamin may be isolated from seeds of Datura innoxia genus Solanaceae.

Scopolamin is used as salt of hydrobromic acid

References

"Pharmaceutical Chemistry" Leningrad, "Medicine", 1966

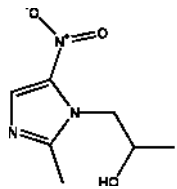
SECNIDAZOLE

Therapeutic Function: Antiamebic, Antiprotozoal

Chemical Name: α,2-Dimethyl-5-nitro-1H-imidazole-1-ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 3366-95-8

Trade Name	Manufacturer	Country	Year Introduced
Flagentyl	Rhone Poulenc	Switz.	1980

Raw Materials

Nitric acid
Hydrogen chloride
1-(2-Acetoxypropyl)-2-methylimidazole

Manufacturing Process

1-(2-Acetoxypropyl)-2-methylimidazole (18.2 g) is gradually dissolved in fuming nitric acid (d = 1.52; 25 cc) with stirring, the temperature being kept at about 2°C. Phosphorus pentoxide (20 g) is added, with caution, to the resulting solution and while maintaining the temperature at about 2°C. Afterwards, the reaction mixture is stirred for a further 3 hours 30 minutes at 2°C and poured onto ice (180 g).

The solution obtained is treated with ammonium hydroxide (d = 0.92; 105 cc), saturated with sodium chloride, and then extracted with ethyl acetate (total 650 cc). The combined organic extracts are washed with a saturated aqueous sodium chloride solution (50 cc) and then dried over sodium sulfate. The volatile products are evaporated under reduced pressure (20 mm Hg) and a mixture of 1-(2-acetoxypropyl)-2-methyl-4-nitroimidazole and 1-(2-acetoxypropyl)-2-methyl-5-nitroimidazole (18.6 g) is obtained in the form of a red oil.

A solution of a mixture of 1-(2-acetoxypropyl)-2-methyl-4-nitroimidazole and of 1-(2-acetoxypropyl)-2-methyl-5-nitroimidazole (18.6 g) (prepared as described above) in 4N hydrochloric acid (186 cc) is heated at 90°C for 90 minutes. The cooled solution is treated with ammonium hydroxide (d = 09; 100 cc), saturated with sodium chloride, and then extracted with ethyl acetate (total 550 cc). The combined organic extracts are washed with a saturated aqueous sodium chloride solution (50 cc) and then dried over sodium sulfate. The volatile products are evaporated under reduced pressure (25 mm Hg); the residual brown oil weighs 9.2 g.

This oil (5.8 g) is dissolved in methyl ethyl ketone (20 cc) and chromatographed over silica (232 g) contained in a column 45 cm in diameter. The column is eluted with methyl ethyl ketone; the first 600 cc of eluate are discarded and 500 cc of eluate are then collected and concentrated under reduced pressure (25 mm Hg);a partially crystalline product (2.4 g) is thus obtained. 1-(2-Hydroxypropyl)-2-methyl-5-nitroimidazole (0.96 g), melting point 72°C, is obtained on recrystallization from water (4 cc).

References

Merck Index 8267
DFU 4 (4)280 (1979)
Kleeman and Engel p. 817
DOT 17 (2) 62 (1981)
I.N. p. 867
Jeanmart, C. and Messer, M.N.; British Patent 1,278,757; June 21, 1972; assigned to Rhone-Poulenc S.A. (France)

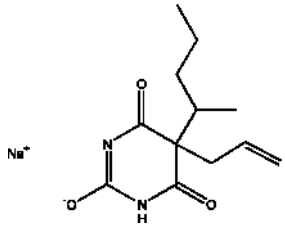
SECOBARBITAL SODIUM

Therapeutic Function: Hypnotic

Chemical Name: 5-(1-Methylbutyl)-5-(2-propenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione monosodium salt

Common Name: Meballymal sodium; Quinalbarbitone sodium

Structural Formula:



Chemical Abstracts Registry No.: 30943-3; 76-73-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Seconal	Lilly	US	1945
Dormatylan	Herz-Jew-Apotheke	Austria	-
Dormona	Wiedenmann	Switz.	-
Immenoctal	I.S.H.	France	-
Ional Sodium	Yoshitomi	Japan	-
Novosecobarb	Novopharm	Canada	-
Proquinal	Protea	Australia	-
Quinbar	Adams	Australia	-
Sebar	Vangard	US	-
Secaps	Saunders	Canada	-
Secocaps	M.T.C.	Canada	-
Secogen	Paul Maney	Canada	-
Seral	Medic	Canada	-
Tuinal	Lilly	US	-

Raw Materials

Allyl bromide
Propyl-methyl-carbinyl barbituric acid
Sodium hydroxide

Manufacturing Process

Propyl-methyl-carbinyl allyl barbituric acid (also called allyl 1-methyl-butyl barbituric acid) may be prepared as follows: 1 mol of propyl-methyl-carbinyl barbituric acid is dissolved in a suitable vessel in a 10 to 35% aqueous solution of 1 mol of potassium hydroxide. To this are added somewhat in excess of 1 mol of allyl bromide, and alcohol equal to about 10% of the total

volume of the solution. The vessel is agitated for 50 to 75 hours. At the end of this time, the solution, which may still exhibit two layers, is concentrated to about one-half its volume to remove the excess allyl bromide and the alcohol. On cooling, an oily layer, which is propyl-methyl-carbinylallyl barbituric acid, separates out as a sticky viscous mass. It is dried, washed with petroleum ether, and dissolved in the minimum amount of benzene. Any unreacted propyl-methyl-carbinyl barbituric acid, which does not dissolve, is filtered off. The addition of petroleum ether to the clear filtrate causes the propyl-methyl-carbinylallyl barbituric acid to precipitate as an oily mass.

This is separated, washed with petroleum ether, and dried in vacuo. After some time it hardens into a whitish solid, which if it was prepared from a 1-bromo-pentane which had some of its isomer 3-bromo-pentane copresent with it has a melting point of about 80°to 83°C. However, by using a pure 2-bromo-pentane, and/or by recrystallizing a number of times from dilute alcohol, the melting point may be raised to 98° to 100°C, corrected.

One part by weight of propyl-methyl-carbinyl allyl barbituric acid is added to enough alcohol to facilitate handling, in this case conveniently about six times its weight. To this is added a solution of sodium hydroxide, preferably carbonate-free or substantially so, containing 40/238 parts by weight of sodium hydroxide, which is the amount of sodium hydroxide necessary to combine in equal molecular proportions with the propyl-methyl-carbinyl allyl barbituric acid. This solution is filtered clear, and is then evaporated under vacuum until the sodium propyl-methyl-carbinyl allyl barbiturate (alternatively named sodium allyl 1-methyl-butyl barbiturate) separates out in solid form. The salt as thus obtained in solid form contains a varying amount of moisture.

If it is desired to have a stable salt substantially free from contaminants, the alcohol used for dissolving the barbituric acid is absolute alcohol, and the sodium hydroxide is added as a very concentrated aqueous solution so that the reaction which occurs to form the salt is in a substantially alcoholic solution. By having a substantially alcoholic solution, decomposition of the salt during the process of drying is effectively avoided; and the drying may be carried to a point where materially less than 1% of moisture remains, so that the salt is substantially anhydrous. In this way a stable salt substantially free from decomposition products formed during preparation or drying or on standing is obtained. This salt may be used safely for making aqueous solutions for intravenous injection; for such aqueous solutions, when freshly made, are clear solutions substantially free from haziness.

Sodium propyl-methyl-carbinyl allyl barbiturate is a white hygroscopic solid, readily soluble in water and alcohol, and insoluble in ether.

References

Merck Index 8268
Kleeman and Engel p. 816
PDR pp. 1067, 1989
OCDS Vol. 1 p.269 (1977)
I.N. p. 867
REM p. 1068
Shonle, H.A.; US Patent 1,954,429; April 10, 1934; assigned to Eli Lilly and Company

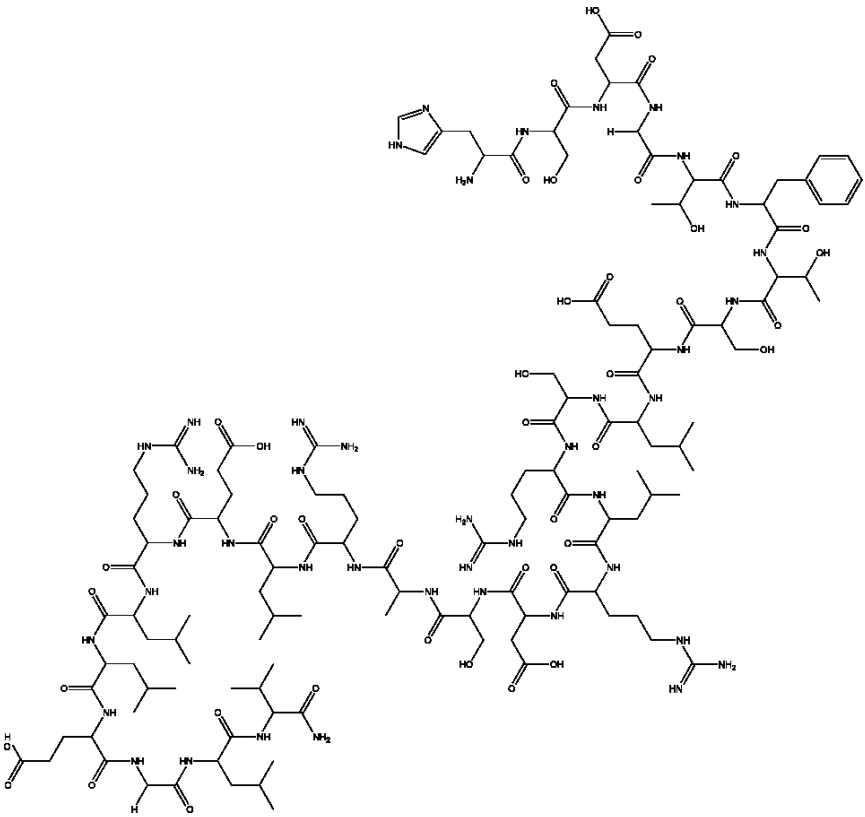
SECRETIN

Therapeutic Function: Diagnostic aid (organ function)

Chemical Name: Polypeptide peptide containing 27 amino acid residues containing the amino acids: L-His; L-Asp; L-Ser; Gly; L-Thr; L-Phe; L-Glu; L-Glu(NH2) ; L-Leu; L-Arg; L-Ala; and L-Val-NH2

Common Name:-

Structural Formula:



Chemical Abstracts Registry No.: 1393-25-5

Trade Name	Manufacturer	Country	Year Introduced
Secretin-Boots	Warren Teed	US	1970
Secretin-Kabi	Kabi	US	1981
Secrepan	Eisai	Japan	-
Secretine Sinbio	Fimex	France	-
Secretolin	Hoechst	-	-

Raw Materials

Tetrapeptide: L-Thr-L-Phe-L-Thr-L-Ser
Tetrapeptide: L-His-L-Ser-β-Benzyl-L-Asp-L-Gly

Manufacturing Process

The gastrointestinal hormone secretin is prepared by fragment condensation. The tetrapeptide L-Thr-L-Phe-L-Thr-L-Ser is coupled to the C-terminal nonadecapeptide of the hormone, and the tetrapeptide L-His-L-Ser-β-benzyl-L-Asp-Gly is coupled to the tricosapeptide resulting from the first coupling.

References

Merck Index 8269
Kleeman and Engel p.817
PDR p. 1428
DOT 10 (6) 210 (1974) and 16 (13) 87 (1980)
I.N. p. 868
REM p. 1277
Bodanszky, M., Ondetti, M.A., von Saltza, M.H., Narayanan, V.L. and Levine, S.D.; US Patent 3,767,639; October 23, 1973; assigned to E.R. Squibb and Sons, Inc.

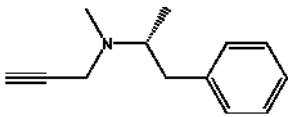
SELEGILINE

Therapeutic Function: Antidepressant

Chemical Name: N-(1-Phenylisopropyl)-N-methyl-prop-2-ynylamine

Common Name: Deprenil; Deprenaline

Structural Formula:



Chemical Abstracts Registry No.: 14611-51-9

Trade Name	Manufacturer	Country	Year Introduced
Eldepryl	Britannia	UK	1982
Deprenyl	EGYT	Hungary	-
Jumex	Medimpex	Hungary	-

Raw Materials

L-N-(2-phenylisopropyl)methylamine
Propargyl bromide

Manufacturing Process

50 g of L-N-(2-phenylisopropyl)methylamine are dissolved in 62.5 ml of toluene, whereupon 13 ml of propargyl bromide are added dropwise within about 20 minutes at a temperature in the range of 50°C to 60°C. The reaction mixture is stirred at 80°C for 3 hours, whereupon it is cooled and the toluene solution is extracted with 125 ml of a 5% hydrochloric acid solution. The acidic layer is separated and made alkaline. The precipitated oil is isolated, washed with benzene and evaporated. The residue is subjected to fractional distillation in vacuo. L-N-(2-phenylisopropyl)methylamine distills off at 65°C to 67°C (0.6 mm Hg, nD20= 1.5083). The L-N-(1-phenylisopropyl)-N-methyl-prop-2-ynylamine is obtained at 92°C to 93°C (0.8 mm Hg, nD20= 1.5180). The melting point of the hydrochloride is 141°C.

References

Merck Index 2876
DFU 4 (2) 128 (1979)
DOT 19 (1) 29 (1983)
I.N. p. 869
Chinoin Gyogyszer-es Vegyeszeti Termekek Gyara R.T.; British Patents 1,031,425; June 2, 1966; and 1,153,578; May 29, 1969

SELENIUM SULFIDE

Therapeutic Function: Dermatological

Chemical Name: Selenium sulfides

Common Name: -

Structural Formula: $Se_4S_4$and Se_2S_6

Chemical Abstracts Registry No.: 7488-56-4

Trade Name	Manufacturer	Country	Year Introduced
Selsun	Abbott	US	1951
Bioselenium	Uriach	Spain	-
Caspiselenio	Kin	Spain	-
Exsel	Herbert	US	-
Iosel	Owen	US	-
Sebusan	Laake	Finland	-
Selenol	N. D.and K.	Denmark	-
Sel-O-Rinse	U.S.V.	US	-

Trade Name	Manufacturer	Country	Year Introduced
Selsorin	Farmos	Finland	-
Selsun Blue	Ross	US	-
Selukos	Kabi	W. Germany	-

Raw Materials

Selenious acid
Hydrogen sulfide

Manufacturing Process

Selenium disulfide, SeS_2, may be made by the reaction of selenious acid, H_2SeO_3, and hydrogen sulfide. Its manufacture is described by B.W. Nordlander in US Patents 1,860,154 and 1,860,336. It is prepared in a detergent suspension for therapeutic use.

References

Merck Index 8283
PDR pp.552, 930, 1563
I.N. p.869
REM p. 1165
Baldwin, M.M. and Young, A.P. Jr.; US Patent 2,694,669; November 16, 1954; assigned to Abbott /Laboratories

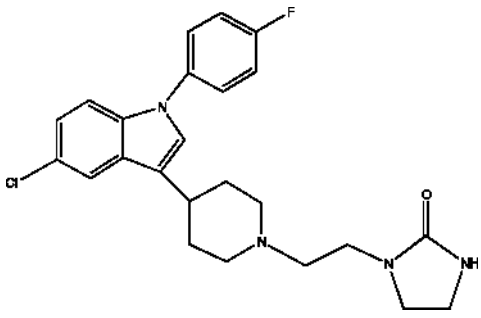
SERTINDOLE

Therapeutic Function: Neuroleptic, Antipsychotic

Chemical Name: 2-Imidazolidinone, 1-(2-(4-(5-chloro-1-(4-fluorophenyl)-1H-indole-3-yl)-1-piperidinyl)ethyl)-

Common Name: Sertindole

Structural Formula:



Chemical Abstracts Registry No.: 106516-24-9

Trade Name	Manufacturer	Country	Year Introduced
Serdolect	Lundbeck	Czech Republic	-
Serlect	Abbott Laboratories	UK	-
Sertindole	Lundbeck	-	-

Raw Materials

Copper bronze
Sodium acetate
Acetic anhydride
Acetic acid
Sodium carbonate
Platinum oxide
Tartaric acid, L-
1-(2-Chloroethyl)imidazolon
Potassium 2,5-dichlorobenzoate
Potassium N-(4-fluorophenyl)glycinate
Potassium carbonate
Sodium borohydride
Methyl isobutyl ketone
Hydrogen
Sodium hydroxide

Manufacturing Process

2 Methods of preparation of N-(4-fluorophenyl)-N-(2-carboxyphenyl)glycin

1. A suspension comprising potassium 2,5-dichlorobenzoate (100 g, 0.44 mol, 1 eq.), potassium N-(4-fluorophenyl)glycinate (190 g, 0.92 mol, 2.1 eq.), potassium carbonate (36.2 g, 0.26 mol, 0.6 eq. CO_3^-), copper bronze (2.8 g, 0.04 mol Cu, 0.1 eq.) and 250 ml demineralised water was heated at reflux under N_2 atmosphere for 20.5 h and then cooled to 50°C.

2.5 ml water and 5 g activated carbon were added to the reaction mixture which, except for the Cu-bronze, was homogeneous. The mixture was allowed to cool under stirring for 1 h and filtered. The filter cake was washed with 2 times 125 ml water. The filtrate was poured on a mixture of ice (2 L) and 37% aq. HCl (3-400 ml) under vigorous stirring, thereby crystallising the crude product as a fine, crystalline, yellow-brown material. The suspension was stirred at 75°-80°C for 30 min, cooled to 15°-20°C, and filtered, and the filter cake was washed with 500 ml water and dried under air stream over night at 50°C. Yield of N-(4-fluorophenyl)-N-(2-carboxyphenyl)glycin 113 g (80.3%). After recristalyzation of the product with toluene and reflux for 30 min the N-(4-fluorophenyl)-N-(2-carboxyphenyl)glycine of purity > 98%, have the melting point 190°-192°C.

2. 21.0 kg potassium 2,5-dichlorobenzoate was added to a 180 L reactor and 36.0 L water was added. This mixture was heated under stirring until substantially all solids were dissolved 60°-70°C and 25.0 kg potassium N-(4-fluorophenyl)glycinate was added slowly. The mixture was heated until all materials were dissolved, i.e. at about 80°C and added to a mixture of 7.67 kg K_2CO_3, 582 g Cu-bronze and 7 L water. The combined mixture was refluxed overnight (about 15 h) and cooled to 50°C. 1 kg activated carbon suspended in 5 L water was added followed by 40 L water. The mixture was stirred under cooling for 1 h, and filtered on a nutch covered with filter aid. The filter cake was washed with 10 L water and the green filtrate was slowly during about 2 h poured on a mixture of 22.5 L 37% HCl and 30 L water

under gentle heating (45°-50°C) and stirring. The mixture was heated to 72°C, cooled to 25°C and filtered. The filter cake was washed with water (2 times 10 L) and dried on trays overnight at 60°C. Yield 26.7 kg of a pale yellow crystalline crude product. The crude product, 26.7 kg, was transferred to a 200 L reactor and 150 L toluene added and the mixture was heated to the reflux temperature (90°C) under N_2 cover. Then the mixture was destilled until a temperature of 110°C was reached (5 L distillate). 5 L toluene was added, and the mixture was refluxed at 110°C for 2 h, cooled to about 60°C and left overnight at 27°C. The mixture was filtered and the filter cake was washed with toluene (3 times 15 L) and dried, thereby obtaining 21.0 kg of the pure N-(4-flourophenyl)-N-(2-carboxyphenyl)glycin.

The N-(4-flourophenyl)-N-(2-carboxyphenyl)glycin (717.1 g, 2.22 mol), sodium acetate (36.4 g, 0.44 mol, 0.2 eq.) and acetic anhydride were placed in a 4 L three necked flash equipped with mechanical stirrer and reflux condenser. The suspension was heated under stirring until reflux. The reaction mixture was refluxed for 1 h and was cooled to room temperature on ice/water bath. The homogenous suspension was under stirring poured onto ice (2 L) and was neutralised with concentrated NaOH (appr. 6 L) until a pH of 6-7. During the neutralisation the temperature was kept under appr. 30°C, which required the adding of a further 5-6 L of ice. Thereby the 1-(4-flourophenyl)-3-acetoxy-5-chloroindole precipitated and was isolated by filtration. The product was washed thoroughly with 3 L of water and 2 L of n-heptane and dried over night in vacuum at 60°C. Yield: 600.5 g (89.1%), melting point 109°-112°C.

1-(4-Flourophenyl)-3-acetoxy-5-chloroindole (100.0 g, 0.33 mol) was dissolved in 1000 ml EtOH. During the next hour sodium borohydride pellets (18.7 g, 1.5 eq.) were added batchwise at reflux. The reaction mixture was stirred over night at reflux and cooled to room temperature. Concentrated HCl (appr. 50 ml until pH 1) was added and the reaction mixture was stirred at room temperature for 1 h 200 ml demineralized water was added, and the resulting suspension was filtrated. The filter cake was washed with further 50 ml water and 10 ml EtOH. The obtained 1-(4-fluorophenyl)-5-chloroindole was dried over night in vacuum at 50°C. Yield: 68.4 g (84.7%), melting point 91°-93°C.

5-Chloro-1-(4-fluorophenyl)indole (6.70 kg) and 4-piperidone-monohydrate, hydrochloride (8.38 kg) were transferred to a 200 L reactor under N_2 cover. Acetic acid (67 L) was added and the reaction mixture was heated to 60°C. Concentrated HCl (37%, 33.5 L) was added during 0,5 h and then the mixture was heated to the reflux temperature (85°C) and refluxed for 1 h (final temperature 95°C). After cooling to 30°C, 33.5 L acetone was added followed by further cooling to 25°C. Filtration, wash (acetone 20 L) and drying in vacuum at 60°C gave the 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole as a white powder, yield 8.94 kg.

5-Chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole (6.0 kg, 16.5 mol), 1-(2-chloroethyl)imidazolon (3.19 kg, 1.3 eq.), sodium carbonate (anhydrous) and methyl isobutyl ketone (60 L) were mixed. The reaction mixture was heated under N_2-cover and stirring until 90°-95°C, and was stirred over night at this temperature. The next day the reaction mixture was filtered while still hot. The apparatus and filter cake were washed with further 2.5 L of methyl isobutyl ketone. The combined filtrates were left over night for

crystallisation. The 1-[2-[4-[5-chloro-1-(4-flourophenyl)-1H-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-imidazolidinone was isolated on a nutch, washed with 7.5 L n-heptane and dried over night in vacuum at 60°C. Yield: 5.39 kg (74.3%), melting point 146.4°C.

1-[2-[4-[5-Chloro-1-(4-flourophenyl)-1H-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-imidazolidinone(3.5 kg) was dissolved in acetic acid (98-100%, 29 L) while being heated until 40°C. Activated carbon was added and the suspension was stirred for 1 h, left over night and filtered. The filter cake was washed with 6 L acetic acid. The combined filtrates were added to a 50 L hydrogeneration reactor which was covered by N_2. 70 g PtO_2 was added, the apparatus was closed and N_2 blownthrough for 5 min. Hydrogeneration was carried out in an H_2-flow (2.5 L per min) for 8.25 H. The reaction mixture was blown through with nitrogen, activated carbon was added and the mixture was filtered on a closed nutch. The filtrate was combined with corresponding filtrates of three other hydrogenerations and evaporated in vacuum at appr. 50°C. The filtrate was flushed off with 3 times 10 L toluene at 50°-60°C. The remanence was dissolved in 146 L ethanol and to this suspension a 40°C suspnsion of 5.22 kg L-(+)-tartaric acid in 16 L demineralised water was added under stirring. The suspension was left over night with no cooling or stirring. The crystallised tartrate was filtered on a nutch and washed with 15 L ethanol.

The crude 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1-H-indol-3-yl]-1-piperidinyl]ethyl]-2 -imidazolidinone, tartrate was recrystallised from 190 L ethanol and 30 L demineralised water by heating until boiling (appr. 78°C). The suspension was left over night for crystallasation with no cooling or stirring. The next day the suspension was cooled to appr. 18°C and the tartrate was filtered off, washed with 60 L ethanol and dried over night under air stream at 60°C.

7.96 kg 1-[2-[4-[5-chloro-1-(4flourophenyl)-1H-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-imidazolodione, tartrate was suspended in 25 L demineralised water and 30 L dichloromethane was added. A total of 3 L 27% NaOH-solution, pH = 9, was added to the suspension under stirring. The mixture was stirred for 1 h (pH still = 9), whereafter the dichloromethane phase was separated.

The water phase was extracted with further 15 L dichloromethane. The combined dichloromethane phases were dried with Na_2SO_4 and were evaporated. The product was flushed off with 5 L acetone, 35 L acetone was added and the suspension was heated until reflux. The crystallised product did not dissolve completely. Heating was discontinued and the mixture was left over night with gentle cooling. The crystallised 1-[2-[4-[5-chloro-1-(4-flourophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]-2- imidazolidinone was isolated on a notch, washed with further 5 L acetone and dried over night under air stream at 60°C. Yield: 4.90 kg (83.2%), melting point 154.7°C.

References

Sommer M.B.; US Patent No. 6,335,463 B1; Jan. 1, 2002; Assigned: H. Lundbeck A/S, Valby-Copenhagen (DK)

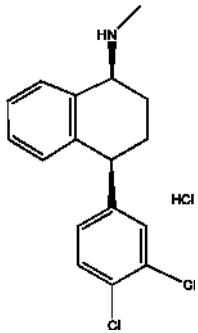
SERTRALINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 1-Naphthalenamine, 1,2,3,4-tetrahydro-4-(3,4-dichlorophenyl)-N-methyl-, (1S-cis)-, hydrochloride

Common Name: Sertraline hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 79559-97-0; 79617-96-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Lustral	Pfizer	UK	-
Riva-Sertraline	Riva	-	-
Serlift	Ranbaxy	India	-
Serlin	Zydus	-	-
Zoloft	Pfizer	USA	-

Raw Materials

Aluminum chloride
Potassium t-butoxide
Hydrogen bromide
Thionyl chloride
Titanium tetrachloride
Hydrogen chloride
3,4-Dichlorobenzoyl chloride
Diethyl succinate
Hydrogen
Methylamine
Mandelic acid, D-

Manufacturing Process

Anhydrous $AlCl_3$ (219 g, 1.64 moles) was added in portions over a 35 to 40 min period to a stirred solution of 3,4-dichlorobenzoyl chloride (313.5 g, 1.50 moles) in benzene (1.125 L) and dichloromethane (75 ml), with the mixture maintained at 3° to 5°C during the addition period. The reaction mixture was held at 0° to 5°C for another hour and then poured into 2.5 L of ice/water and stirred until the complex had decomposed. The organic and aqueous layers were then separated and the organic layer combined with one ethyl acetate

wash of the aqueous layer. The resulting organic solution was washed twice with water and once with saturated brine solution, dried (anhyd. $MgSO_4$), treated with decolorizing carbon and evaporated under vacuum to yield white solid of 3,4-dichlorobenzophenone, which was recystallized from 400 ml of hot ethyl acetate-pentane (156.8 g, 41% yield, melting point 100°-102°C.

A solution of 3,4-dichlorobenzophenone (398 g, 1.58 moles) in t-butyl alcohol (1500 ml) was treated sequentially with potassium t-butoxide (169 g, 1.5 moles) and diethyl succinate (402 ml, 2.4 moles). A mildly exothermic reaction ensued and the initially clear solution set up as a solid mass. The reaction mixture was slowly heated to reflux, at which it became a stirrable white suspension, and then stirred at reflux under nitrogen for about 16 h. The reaction mixture was then cooled and poured into 2 L of ice/water. The resulting mixture was acidified with 10% HCl and extracted with ethyl acetate (3 times 1 L). The combined ethyl acetate extract was extracted with 1 N NH_4OH (3 times 1 L) and the combined aqueous basic extract washed with ethyl acetate (2 L), cooled to 0° to 5°C, acidified slowly to a pH below 1.0 with concentrated HCl and extracted with ethyl acetate (4 times 2 L). The combined ethyl acetate extract was dried ($MgSO_4$) and evaporated under vacuum to a light yellow oil slightly contaminated with diethyl succinate (477 g, 80% yield). An analytical sample of 3-ethoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid was crystallized from petroleum ether (melting point 128°-130°C).

A suspension of 3-ethoxycarbonyl-4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid (227 g, 0.60 mole) in 48% aqueous HBr - glacial acetic acid (1:1, 1.80 L) was stirred at reflux for 36 h and then cooled to room temperature. A gum separated from the reaction mixture, which was isolated by decantation of the aqueous layer and then dissolved in ethyl acetate (2 L). The resulting organic solution was extracted with 10% aqueous NH_4OH (2 times 2 L). The combined extract was cooled to 0° to 5°C, acidified slowly to a pH below 1.0 with concentrated HCl and extracted with ethyl acetate (4 times 1 L). The combined ethyl acetate extract was washed with water, dried ($MgSO_4$) and evaporated under vacuum to a light brown oil (120 g), which was the 4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid and crystallized from hexane (91.4 g, 50% yield, melting point 115°-120°C).

A solution of 4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid (223 g, 0.73 mole) in ethyl acetate (2 L) was hydrogenated over 8 g of 5% Pd/C catalyst at atmospheric pressure and room temperature until hydrogen uptake ceased (24 h). The catalyst was separated by filtration and the filtrate evaporated under vacuum to a light brown oil containing traces of solvent (ca. 100% yield). An analytical sample of the 4-(3,4-dichlorophenyl)-4-phenylbutanoic acid was crystallized from hexane (melting point 118°-120°C).

A solution of 4-(3,4-dichlorophenyl)-4-phenylbutanoic acid (228 g, 0.74 mole) in toluene (1.2 L) was treated with thionyl chloride (66 ml, 0.90 mole) and the resulting solution heated at reflux for 75 min, with provision made for trapping HCl gas given off from the refluxing reaction solution. The reaction solution was then evaporated under vacuum to about 230 g of a light brown oil. The oil was dissolved in carbon disulfide (360 ml) and the resulting solution added to a well stirred suspension of $AlCl_3$ (1.5 kg, 12.5 moles) in carbon disulfide (1.20 L), with the mixture held below 8°C during the addition

period, forming a brown mass. After the addition was completed, the reaction mixture was stirred for about 16 h at room temperature and then slowly poured on ice (vigorous reaction). The resulting suspension was extracted with ethyl acetate (2 times 4 L). The combined extract was washed with water, washed with saturated aqueous sodium bicarbonate solution, dried and evaporated under vacuum to a residue, which was crystallized from hexane (500 ml) to yield the 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone (104.1 g, 48% yield, melting point 99°-101°C).

A solution of 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone (50 g, 0.17 mole) in tetrahydrofuran (800 ml.) was cooled to 0° to 5°C and treated with 52 ml (1.20 moles) of methylamine (condensed at 0°C). Titanium tetrachloride (10 ml, 0.087 mole) was added dropwise to the resulting solution (vigorous reaction), with the reaction mixture stirred at below 10°C during the addition period. After the addition was completed, the reaction mixture was stirred for 17 h at room temperature under nitrogen and then filtered. The solids were washed thoroughly with tetrahydrofuran and the combined filtrates were concentrated under vacuum to 600 ml. to remove excess methylamine. Further evaporation of an aliquot to dryness and trituration with hexane yielded the Schiff base (melting point 145°-146°C). The Schiff base-containing concentrate was hydrogenated for 2 h over 5.0 g of 10% Pd/C catalyst at atmospheric pressure and room temperature. Hydrogen uptake ceased within the 2 h reaction period. After removal of the catalyst by filtration, the reaction mixture was evaporated under vacuum to a residue. The residue was dissolved in anhydrous ether (1 L) and the resulting solution treated with gaseous hydrogen chloride to yield a white precipitate, containing about 70% cis-racemate and 30% tras-racemate of N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride.

The HCl salt cis-racemate and trans-racemate of N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride, was dissolved in hot methanol (2 L). Upon addition of ether (1200 ml) and cooling overnight, cis-(1S)(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride precipitated (47 g, melting point 290°-291°C). The supernatant was evaporated under vacuum to dryness and the residue triturated with acetone. The triturated residue (ca. 90% cis-racemate, 10% trans-racemate) was recrystallized from methanol:ether (1:1) to yield another 20 g of the same product. The total yield of cis-(1S)(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride was 67g, 68% yield; melting point 289°-290°C.

67.1 g of cis-(1S)(1R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride was partitioned between 20% aqueous NaOH and ethyl acetate to yield a solution of the cis-racemate free base (60.2 g, 0.197 mole) in ethyl acetate. This solution was dissolved in absolute ethanol (600 ml) and the resulting solution treated with D-(-)-mandelic acid (29.94 g, 0.197 mole). The resulting mixture was warmed on a steam bath to effect solution and then held overnight at room temperature to afford a white crystalline solid. This solid was separated by filtration, washed with ether and air dried (38.7 g, melting point 188°-189°C), and then cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine mandelate recrystallized from hot absolute ethanol (32.6 g, melting point 190°-191°C). An additional crop (4.4 g, melting point 190°-191°C) was obtained by evaporation of the mother liquors under vacuum to residues, followed by

crystallization of the residues from boiling ethanol (150 ml).

The mandelate salt were suspended in ethyl acetate (about 2 L). The ethyl acetate suspension was treated with 10% aqueous NaOH solution, thereby converting the amine to the free base. The resulting ethyl acetate solution was then dried, diluted with ether (2 L) and then treated with excess gaseous hydrogen chloride to give a gelatinous suspension which crystallized overnight. The crystalline HCl salt product was separated by filtration, washed with ether and air dried. The cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride 25.96 g, 39% yield, with melting point 243°-245°C.

References

Welch W.M. et al; US Patent No. 4,536,518; August 20, 1985; Assigned: Pfizer Inc., New York., N.Y.

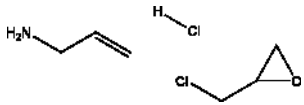
SEVELAMER HYDROCHLORIDE

Therapeutic Function: Antihyperphosphatemic

Chemical Name: poly(2-Propen-1-amine hydrochloride) cross-linked with epichlorohydrin

Common Name: Sevelamer hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 152751-57-0

Trade Name	Manufacturer	Country	Year Introduced
Renagel	Chugai Pharmaceutical Co., Ltd.	-	-
Renagel	GelTex Pharmaceuticals, Inc.	-	-
Renagel	Genzyme Corporation	USA	-

Raw Materials

Poly(allylamine hydrochloride)
Sodium hydroxide
Epichlorohydrin

Manufacturing Process

Poly(allylamine hydrochloride) (50% w/w, 426 kg) was charged to a 1000 L

reactor and water (200 L) was added. Sodium hydroxide solution (32% w/w, 208 kg) was added, followed by 85 L of water. The mixture was stirred for 1 h and filtered to a 2500 L reactor. The transfer line was rinsed with water (217 kg) and acetonitrile (1300 L) added. The temperature was adjusted to 40°C and epichlorohydrin (20 kg) added. The mixture was stirred at 40° to 50°C for 1.5 h and then heated to reflux for 16 h. The resulting product slurry may be isolated and washed in decanter centrifuge.

The crude gel suspension of epichlorohydrin cross-linked poly(allylamine hydrochloride) was fed to an Alfa Laval CHNX 318 at 9.5 to 12.3 L/min with bowl speeds of 2500 rpm to 3250 rpm and differential speeds between 1.3 and 10 rpm. The discharged gel had a moisture content of 75% to 82%.

References

McDonnell P.D. et al.; US Patent No. 6,600,011 B2; July 29, 2003; Assigned: Genzyme Corporation, Cambridge, MA (US)

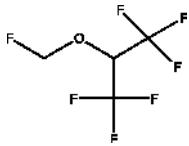
SEVOFLURANE

Therapeutic Function: Anesthetic

Chemical Name: Ether, fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl-

Common Name: Sevoflurane

Structural Formula:



Chemical Abstracts Registry No.: 28523-86-6

Trade Name	Manufacturer	Country	Year Introduced
Sevoflurane	Abbott Laboratories	UK	-
Ultane	Abbott Laboratories	USA	-

Raw Materials

Chlorine
Potassium carbonate
Potassium fluoride
Tetrahydrothiophene 1,1-dioxide
Chloromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether
Methyl 1,1,1,3,3,3-hexafluoroisopropyl ether

Manufacturing Process

164 g (2.31 mole) of chlorine is slowly bubbled into a flask containing 370 g (2.03 mole) of methyl 1,1,1,3,3,3-hexafluoroisopropyl ether illuminated with a 250 watt incandescent lamp, starting at room temperature. The product is washed with a potassium carbonate solution until neutral, dried over $MgSO_4$ and vacuum distilled to yield 304 g (1.5 mole) of chloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether (chloromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether), boiling point 78°C.

A solution of chloromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether (754 g, 3.49 moles) in dry tetrahydrothiophene 1,1-dioxide (203 g, 3,49 moles) were stirred and heated to 130°C in a creased flask fitted with a fractional distillation assembly. A distillate (200 ml), b_{748} 56.0° to 62°C, was collected during 5 h. Then the reaction mixture was cooled to room temperature, dry potassium fluoride (100 g, 1.74 moles) was added, and the cycle of operations was repeated 3 times at temperatures between 138° to 185°C to give distillates (100 ml, 100 ml and 50 ml), b_{746} 58° to 61°C, 55.5° to 57°C, and 54.2° to 55.9°C, respectively. From this portionwise addition of potassium fluoride (503 g, 8.7 moles) there was obtained distillates totalling 672 g, b_{746} 54.2° to 62.0°C, which by GLC analysis was about 92% fluoromethyl and 6.8% chloromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether.

Fractional distillation of 659 g gave a forerun (46 g), b_{745} 53.5° to 57.0°C, and then 99.6% pure fluoromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether (505 g), b_{745} 57.0° to 57.7°C.

References

Regan B.M., Longstreet J.C.; US Patent No. 3,683,092; August 8, 1972; Assigned: Baxter Laboratories, Inc., Morton Grove
Croix L.S. et al; US Patent No. 3,476,860; Nov. 4, 1969; Assigned: Air Reduction Company, Incorpora, New York, N.Y.

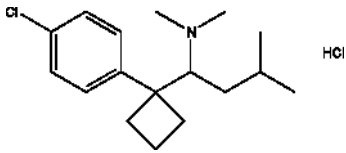
SIBUTRAMINE HYDROCHLORIDE

Therapeutic Function: Antidepressant, Anorexic

Chemical Name: Cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)-, hydrochloride

Common Name: Sibutramine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 84485-00-7; 106650-56-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Meridia	Abbott Laboratories	USA	-
Reductil	Abbott Laboratories	-	-
Reductil	Knoll AG	Germany	-
Reductil	Teva Pharmaceuticals	Israel	-

Raw Materials

4-Chlorobenzyl cyanide
1,3-Dibromopropane
Sodium hydride
Magnesium
Hydrochloric acid
Potassium hydroxide
Thionyl chloride
Ethyl bromide
Diethylene glycoldimethyl ether

Manufacturing Process

A solution of 4-chlorobenzyl cyanide and 1,3-dibromopropane in dry dimethylsulfoxide was added dropwise under nitrogen to a stirred mixture of sodium hydride dispersed in mineral oil and dimethylsulfoxide at a temperature in the range 30° to 35°C. The mixture was stirred at room temperature for 2 h and propan-2-ol and then water were added dropwise. The mixture was filtered through a diatomaceous earth sold under the Registered Trade Mark CELITE and the solid residue washed with ether. The ether layer was separated, washed with water, dried and evaporated. 1-(4-Chlorophenyl)-1-cyclobutanecarbonitrile was isolated by distillation.

1-(4-Chlorophenyl)-1-cyclobutanecarbonitrile (37.6 g) was added to a solution of potassium hydroxide (32.4 g) in diethyleneglycol (370 ml) and the mixture heated under reflux for three and a 0.5 h The reaction mixture was poured into an ice/water mixture and the resulting solution was washed with ether. The aqueous layer was added to a mixture of concentrated hydrochloric acid (100 ml) and ice and the resulting precipitate of 1-(4-chlorophenyl)-1-cyclobutanecarboxylic acid (melting point 86°-88°C) collected, washed with water and dried.

1-(4-Chlorophenyl)-1-cyclobutane carboxylic acid (10.5 g) was heated under reflux with thionyl chloride (20 ml) for 2.5 h. Excess thionyl chloride was evaporated off and the acid chloride of the above acid distilled (boiling point 82°-96°C /0.2 mm Hg). A solution of the acid chloride in dry tetrahydrofuran was added slowly to the product of the reaction of magnesium turnings and ethyl bromide in dry tetrahydrofuran. Water was added followed by 5 N hydrochloric acid with cooling. The reaction mixture was extracted with ether, washed with water, sodium bicarbonate solution, dried. The solvent was removed by evaporation and 1-isobutyl-1-(4-chlorophenyl)cyclobutane obtained by distillation. The 1-isobutyl-1-(4-chlorophenyl)cyclobutane, diethylene glycoldimethyl ether, water and concentrated hydrochloric acid were mixed and heated under reflux. The mixture was poured into water aqueous NaOH was added and the product extracted into ether. Evaporation gave a dark oil. A sample of this oil, water and formic acid were mixed and formaldehyde added. The mixture was heated under reflux and then concentrated hydrochloric acid and propan-2-ol were added. Evaporation to

dryness gave N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]isobutyl hydrochloride as a white solid.

References

Jeffery J.E. et al.; US Patent No. 4,746,680; May 24, 1988; Assigned: The Boots Company p.l.c., England

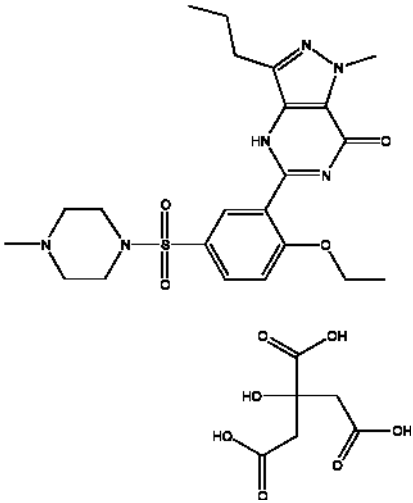
SILDENAFIL CITRATE

Therapeutic Function: Vasodilator

Chemical Name: Piperazine, 1-((3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo(4,3-d)pyrimidin-5-yl)-4-ethoxyphenyl)sulfonyl)-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

Common Name: Sildenafil citrate

Structural Formula:



Chemical Abstracts Registry No.: 171599-83-0; 139755-83-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alsigra	Alembic Ltd.	India	-
Androz	Torrent Pharmaceuticals Ltd.	India	-
Caverta	Ranbaxy Laboratories Limited	India	-
Edegra	Sun Pharmaceuticals Industries Ltd.	India	-
Erix	Unichem Laboratories Ltd.	India	-
Juan	IRM Pharma	India	-

Trade Name	Manufacturer	Country	Year Introduced
Mamforce	Mankind Pharma Pvt. Ltd.	India	-
Pefomax-50	Bestochem Formulations (I) Ltd.	India	-
Penegra	Zydus Alidac	India	-
Progra	Protech Biosystems	India	-
Silagra	Cipla Limited	India	-
Uplift-50	Wallace Pharmaceuticals Ltd.	India	-
Viagra	Pfizer	USA	-
Viagra	Allscripts	USA	-
Viagra	Ranbaxy	India	-
Vigreks	Medley Pharmaceuticals Pvt. Ltd.	India	-
Viraha	Micro Labs	India	-
Virecta	Seagull Labs (I) Pvt. Ltd.	India	-

Raw Materials

Dimethyl sulfate
Sodium hydroxide
Hydrochloric acid
Nitric acid
Thionyl chloride
Hydrochloric acid
Sodium carbonate
4-Methylpiperidine
Stannous chloride dihydrate
2-Ethoxybenzoyl chloride
4-Dimethylaminopyridine
Triethylamine
Hydrogen peroxide
Chlorosulfonic acid
3-n-Propylpyrazole-5-carboxylic acid ethyl ester

Manufacturing Process

A mixture of 3-n-propylpyrazole-5-carboxylic acid ethyl ester (24.1 g, 0.132 mol) (prepared by the method of Chem. Pharm. Bull., 1984, 32, 1568) and dimethyl sulfate (16.8 g, 0.133 mol) were heated to 90°C for 2.5 h. The mixture was dissolved in dichloromethane and the solution washed with sodium carbonate solution. The organic phase was separated, dried ($MgSO_4$) and evaporated under vacuum to give a solid. Chromatography on silica gel (300 g), eluting with dichloromethane gave the 1-methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester as a colourless oil (20.4 g, 79%).

1-Methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester (20.2 g, 0.10 mol) was suspended in 6 N aqueous sodium hydroxide solution (50 ml, 0.30 mol). The mixture was heated to 80°C for 2 h then diluted with water (50 ml) and acidified with concentrated hydrochloric acid (25 ml). Filtration gave the 1-methyl-3-n-propylpyrazole-5-carboxylic acid as pale brown crystals (12.3 g, 71%), melting point 150°-154°C.

1-Methyl-3-n-propylpyrazole-5-carboxylic acid (12.1 g, 0.072 mol) was added portionwise to a mixture of oleum (13 ml) and fuming nitric acid (11 ml), keeping the temperature below 60°C. After the addition, the mixture was heated at 60°C overnight and then cooled to room temperature before being poured onto ice. Filtration of the precipitate gave the 1-methyl-4-nitro-3-n-propylpyrazole-5-carboxylic acid as a white solid (11.5 g, 75%), melting point 124°-127°C.

1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxylic acid (11.3 g, 0.053 mol) was added to thionyl chloride (50 ml) and the resulting mixture heated under reflux for 3 h. The reaction mixture was then cooled and excess thionyl chloride removed by evaporation under vacuum. The oily residue was dissolved in acetone (50 ml) and the solution cautiously added to a mixture of ice (50 g) and concentrated aqueous ammonium hydroxide solution (50 ml). The precipitate was collected by filtration to provide the 1-methyl-4-nitro-3-n-propylpyrazole-5-carboxamide as a pale yellow solid (8.77 g, 78%), melting point 141°-143°C.

1-Methyl-4-nito-3-n-propylpyrazole-5-carboxamide (3.45 g, 16.2 mmol) and stannous chloride dihydrate (18.4 g, 81 mmol) were suspended in ethanol and the mixture heated under reflux for 2 h. The resulting solution was cooled to room temperature, basified to pH 9 by the addition of 2 N aqueous sodium hydroxide solution and extracted with dichloromethane (3 x 150 ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated under vacuum. Trituration of the residue with ether gave the 4-amino-1-methyl-3-n-propylpyrazole-5-carboxamide as an off-white solid (2.77 g, 94%), melting point 98°-101°C.

A solution of 2-ethoxybenzoyl chloride (6.1 g, 33.0 mmol) in dichloromethane (50 ml) was added to a stirred solution of 4-amino-1-methyl-3-n-propylpyrazole-5-carboxamide (3.0 g, 16.4 mmol), 4-dimethylaminopyridine (0.02 g, 0.1 64 mmol) and triethylamine (3.34 g, 33.0 mmol) in dichloromethane (50 ml) at 0°C. The resulting mixture was allowed to warm to room temperature and stirred for a further 2 h. The solvent was evaporated under vacuum, the residue dissolved in a 19:1 mixture of dichloromethane and methanol (250 ml), and then the solution washed with 1 N hydrochloric acid (100 ml), dried ($MgSO_4$) and evaporated under vacuum. The crude material was chromatographed on silica gel (200 g), eluting with a 97:3 mixture of dichloromethane and methanol, to give a pink solid; crystallisation from ethyl acetate-hexane gave the 4-(2-ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide as a pale pink solid (2.2 g, 40%), melting point 153°-155°C.

4-(2-Ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide (223 g, 0.676 mol) was added portionwise to a solution of sodium hydroxide (54 g, 1.35 mol) and 30% hydrogen peroxide solution (224 ml) in water (2000 ml). Ethanol (700 ml) was added and the resulting mixture heated under reflux for 2.5 h, cooled, then evaporated under vacuum. The resulting solid was treated with 2 N hydrochloric acid (380 ml), with external cooling, and the mixture was extracted with dichloromethane (1 x 700 ml, 3 x 200 ml). The combined organic extracts were washed successively with saturated aqueous sodium carbonate solution (3 x 400 ml) and brine (300 ml), then dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the residue on silica gel (1000 g), using a methanol in dichloromethane elution gradient (0-1%), followed by trituration of the crude product with ether (300 ml), gave the 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one as a colourless solid (152.2 g, 72%), melting point 143°-146°C.

5-(2-Ethoxyphenyl)-1-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (10.0 g, 32.1 mmol) was added portionwise to chlorosulfonic acid (20 ml) at 0°C under a nitrogen atmosphere. After being stirred overnight, the reaction solution was cautiously added to ice-water (150

ml) and the aqueous mixture extracted with a 9:1 mixture of dichloromethane and methanol (4 x 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated under vacuum to give the required 5-(5-chlorosulphonyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one as a white solid (12.8 g, 97%), melting point 179°-181°C.

4-Methylpiperidine was added to a stirred suspension of 5-(5-chlorosulphonyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one in ethanol at room temperature. The resulting mixture was stirred for 4 days before removing the solvent by evaporation under vacuum. The residue was dissolved in a 9:1 mixture of dichloromethane and methanol and the solution washed with saturated aqueous sodium carbonate solution. The aqueous phase was further extracted with dichloromethane-methanol mixtures (3 x 100 ml) and all the organic fractions were combined, dried ($MgSO_4$) and evaporated under vacuum to give a solid. Crystallisation from a mixture of methanol-dimethylformamide gave the 5-[2-ethoxy-5-(4-methylpiperidinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one as an off-white solid, melting point 187°-189°C.

After addition of citric acid to the 5-[2-ethoxy-5-(4-methylpiperidinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one (sildenafil) the it's salt is obtained, namely sildenafil citrate.

References

Bell A.S. et al.; EU Patent No. 0 463 756 A1; Jan. 2, 1992; Assigned: Pfizer Limited Ramsgate Road Sandwich

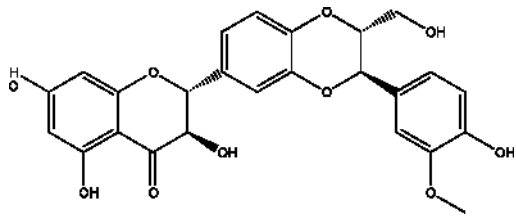
SILYMARIN

Therapeutic Function: Hepatoprotectant

Chemical Name: 2-[2,3-Dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one

Common Name: Silybin; Silibinine

Structural Formula:



Chemical Abstracts Registry No.: 27359-03-1

Trade Name	Manufacturer	Country	Year Introduced
Legalon	Madaus	W. Germany	1969
Legalon	I.B.I.	Italy	1971
Legalon	Roger Bellon	France	1974
Silliver	Abbott	Italy	1977
Apihepar	Panchemie Homburg	Austria	-
Cardornerin	Deiters	Spain	-
Cronol	Kappa	Spain	-
Dura Silymarin	Durachemie	W. Germany	-
Emil	Horus	Spain	-
Eparfit	Europa	Spain	-
Escarmine	Dreikehl	Spain	-
Flavobion	Spofa	Czechoslovakia	-
Halodren	Escaned	Spain	-
Hepadestal	Krugmann	W. Germany	-
Hepagerina	Kairon	Spain	-
Hepalar	Larma	Spain	-
Hepallolina	Callol	Spain	-
Hepato-Framan	Oftalmiso	Spain	-
Laragon	Roemmers	Argentina	-
Sematron	Madariaga	Spain	-
Silarine	Vir	Spain	-
Silepar	Ibirn	Italy	-
Silgen	Morgens	Spain	-
Silibancol	Durban	Spain	-
Silimazu	Mazuelos	Spain	-
Silirex	Lampugnani	Italy	-

Raw Materials

Silybum marianum fruit
Ethyl acetate

Manufacturing Process

Silymarin comprising polyhydroxyphenyl chromanones is recovered from the dried fruit of Silybum marianum Gaertn. by separating the fatty oils therefrom, extracting the remaining solid residue with ethyl acetate, evaporating the ethyl acetate and dissolving the dry residue in a solvent mixture comprising methanol, water and petroleum ether to form a two-phase system wherein the chromanones are contained in the lower phase, recovering the polyhydroxyphenyl chromanones from the lower phase after subjecting same to multiple counter-current contact with petroleum ether.

References

Merck Index 8372
Kleeman and Engel p. 818
DOT 7 (6) 216 (1971)

I.N. p. 873
Madaus, R.; US Patent 3,773,932; November 20, 1973; assigned to Dr. Madaus and Co. (Germany)

SIMETHICONE

Therapeutic Function: Antiflatulent

Chemical Name: alpha-(Trimethylsilyl)-omega-methylpoly(oxy (dimethylsilylene)), mixture with silicon dioxide

Common Name: -

Structural Formula: Dimethyl polysiloxane

Chemical Abstracts Registry No.: 8050-81-5

Trade Name	Manufacturer	Country	Year Introduced
Mylicon	Stuart	U.S.	1960
Silain	Robins	U.S.	1961
Celluzyme	Dalin	U.S.	-
Gelusil	Parke Davis	U.S.	-
Mylanta	Stuart	U.S.	-
Phazyme	Reed and Carnrick	U.S.	-
Riopan-Plus	Ayerst	U.S.	-
Simeco	Wyeth	U.S.	-
Tri-Cone	Glaxo	U.S.	-

Raw Materials

Dimethyl diethoxy silane
Trimethyl ethoxy silane
Sodium hydroxide

Manufacturing Process

In a 5 liter three-necked flask, fitted with a reflux condenser, agitator and thermometer, were placed 1,393 grams (9.41 mols) of redistilled $(CH_3)_2Si(OEt)_2$, and 1,110 grams (9.41 mols) of $(CH_3)_3SiOEt$. To this solution was added 254 grams (14.11 mols) of water containing 7.5 grams of NaOH, (approximately 1 NaOH per 100 silicon atoms). This insured the formation of only straight chain polymers. The mixture was heated to 40°C and the temperature continued to rise for nearly an hour. After adding 50 cc (20% excess) more water, the mixture was refluxed for two hours and then allowed to stand overnight.

Alcohol was then distilled off, until the temperature reached 100°C. 1,706.6 grams of distillate was collected (theory 1,430 grams). This alcohol was poured into four times its volume of water and an insoluble oil separated (457

grams). The insoluble fraction was added back to the copolymer residue from the distillation and 555 cc of 20% hydrochloric acid was added. The acid mixture was refluxed for two hours, and the silicon oils were carefully washed with distilled water until neutral. The yield was 1,420 grams (theory, 1,469 grams).

References

Merck Index 8374
PDR pp. 650, 829, 916, 1352, 1444, 1569, 1783, 1981
REM p. 814
Hyde, J.F.; U.S. Patent 2,441,098; May 4, 1948; assigned to Corning Glass Works

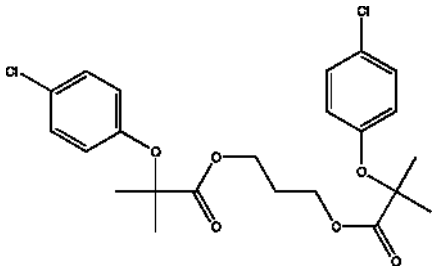
SIMFIBRATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2-(4-Chlorophenoxy)-2-methylpropanoic acid 1,3-propanediyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 14929-11-4

Trade Name	Manufacturer	Country	Year Introduced
Cholesorbin	Takeda	Japan	1971
Cholesolvin	Cyanamid	Italy	1977
Liposolvin	Tosi-Novara	Italy	-

Raw Materials

α-(p-Chlorophenoxy)isobutyric acid
1,3-Propanediol

Manufacturing Process

A mixture of 22 grams of α-(p-chlorophenoxy)isobutyric acid, 3.8 grams of 1,3-propanediol, 0.5 gram of p-toluenesulfonic acid and 150 ml of xylene was refluxed. When the theoretically calculated amount of water had been removed, the xylene solution was washed with dilute aqueous sodium bicarbonate and then the xylene was distilled off. The residue was distilled under reduced pressure to give 11 grams (47% yield) of 1,3-propanediol bis[α-(p-chlorophenoxy)isobutyrate] boiling at 197° to 200°C/0.03 mm Hg.

References

Merck Index 8377
Kleeman and Engel p.819
DOT 7 (6) 221 (1971)
I.N. p.874
Nakanishi, M., Kuriyama, T., Oe, T. and Kobayakawa, T.; US Patent 3,494,957; Feb. 10, 1970; assigned to Yoshitomi Pharmaceutical Industries, Ltd., Japan

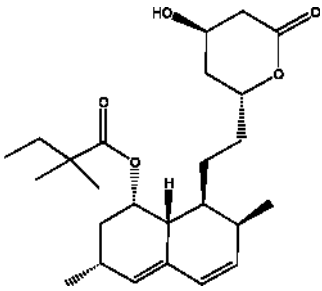
SIMVASTATIN

Therapeutic Function: Antihyperlipidemic

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

Common Name: Simvastatin; Sinvastatin; Synvinolin; Velastatin

Structural Formula:



Chemical Abstracts Registry No.: 79902-63-9

Trade Name	Manufacturer	Country	Year Introduced
Biosim	Biochem Pharma Industries	India	-
Clinfar	Merck	Netherlands	-
Detrovel	Pratapa	-	-

Trade Name	Manufacturer	Country	Year Introduced
Liponorm	Gentili	-	-
Lipovas	Banyu	-	-
Lovacor	Farmasa	-	-
Redusterol	Raffo	-	-
Simgal	Galena a.s.	Czech Republic	-
Simlo	IPCA laboratories Ltd.	India	-
Simvacard	Merck	Czech Republic	-
Sinvascor	Balducci/Hexal	-	-
Simvastatin	Biogal	Hungary	-
Simvor	Ranbaxy	India	-
Vasilip	Krka	Slovenia	-
Vero-Simvastatin	Okasa Pharma	India	-
Zocor	Merck	Netherlands	-

Raw Materials

Lovastatin
Phenylboronic acid
Methyl iodide
1,3-Propanediol

Manufacturing Process

A suspension of Lovastatin (350 g, 0.865 mmol), phenylboronic acid (110.8 g, 0.909 mmol) and toluene (1.75 L) was heated under a nitrogen atmosphere at 100-105°C for 55 min. The water was separated from the reaction mixture. The solution was cooled and 1.39 L of toluene was removed by vacuum distillation at 40-50°C. The concentrated solution was treated with hexanes (3.15 L) at 40-50°C. The resulting suspension was cooled to 0-5C for 2 hours and the product was filtered and washed with hexanes (350 mL). The product was dried at 35-40°C under vacuum to provide 427.9 g (37%) of lovastatin phenylboronate at >99% purity by HPLC.

A 2 L 3-necked flask was charged with pyrrolidine (56 mL, 0.67 mol) and dry THF (453 g) under a nitrogen atmosphere. n-Butyl lithium (419 mL, 1.6 M hexane solution, 0.67 mol) was added dropwise at -20°C over a period of 1 hour. The solution was maintained at this temperature for 30 min and then cooled to -55°C. A solution of lovastatin phenylboronate (101.7 g, 0.20 mol) in 274.7 g of THF was cooled to -50°C and then added to the cold lithium pyrrolidide solution at a rate such that the internal temperature was between -50°-55°C during the addition. The mixture was held at this temperature for 4 hours and then methyl iodide (116.4 g, 0.82 mol) was added at a temperature below -55°C. The reaction was stirred for 13 hours at -20°C and then quenched with 500 mL of 2 M HCl at a temperature below 0°C. After warming to 20°C, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 5% $NaHSO_3$ solution and deionized water. The solution was filtered through a Celite pad and concentrated to yield 102.8 g (98.4%) of crude Simvastatin phenylboronate at >95% purity by HPLC. A portion of the above material (50.0 g) was charged into a nitrogen purged flask with acetonitrile (100 mL). The suspension was heated at 110°C for 3 hours and then cooled to - 10°C

for 1 hour. The product was filtered and washed with 25 mL of acetonitrile and dried under vacuum to provide 43.7 g of Simvastatin phenylboronate at >99% purity by HPLC.

A suspension of simvastatin phenylboronate (30.0 g) and 1,3-propanediol (450 mL) was heated at 105-107°C at 0.2 mm Hg. After 1 hour, 182 mL of distillate was collected and the reaction was cooled to 20-25°C. Deionized water (270 mL) was added and toluene (3 times 75 mL) was used to extract the mixture. The combined toluene layers were washed with water (60 mL). The organic solution was heated at reflux for 1 hour and water was azeotropically removed. The solution was concentrated to a final volume of 24 mL under vacuum at 48-50°C. To the concentrated solution was added hexanes (215 mL) over 10 min. The resulting slurry was cooled to 0-5°C and filtered. The crude Simvastatin was washed at 0-5°C with hexanes and dried under vacuum to yield 21.0 g (88%) of Simvastatin.

References

Keshava K.S. et al.; US Patent No. 6,307,066; Oct. 23, 2001; Assigned to Brantford Chemicals Inc.

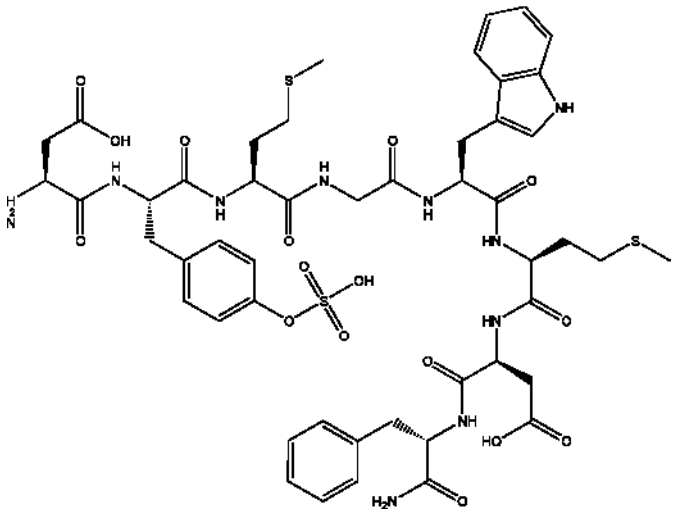
SINCALIDE

Therapeutic Function: Choleretic

Chemical Name: 1-De(5-oxo-L-proline)-2-de-L-glutamine-5-L-methioninecaerulein

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 25126-32-3

Trade Name	Manufacturer	Country	Year Introduced
Kinevac	Squibb	US	1976
Kinevac	Squibb	W. Germany	1977

Raw Materials

t-Butyloxycarbonyl-L-aspartyl-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide
Sulfuric acid

Manufacturing Process

The starting material in the following synthesis is: t-butyloxycarbonyl-L-aspartyl-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide designated (SM).

(A) A solution of (SM) (320 mg) in trifluoroacetic acid (7 ml) was kept under nitrogen at room temperature for 15 minutes. Ether (100 ml) was added and the precipitate filtered, washed thoroughly with ether and dried. This material (280 mg) was added to concentrated sulfuric acid (20 ml), cooled at -20°C. The solution was kept in the dry ice-acetone bath at -20°C for 75 minutes. The sulfuric acid solution was poured into ice water (80 ml). The precipitate was centrifuged, resuspended in ice water (30 ml) and 4N sodium hydroxide was added until a clear solution was obtained. After reacidification to pH 4 with dilute sulfuric acid, the precipitate formed was centrifuged, washed twice with ice water and dried. Yield 155 mg. Chromatograph of DEAE Sephadex (with ammonium carbonate buffer) yielded the desired octapeptide sulfate ester: 30 mg.

(B) A solution of (SM) (330 mg) in trifluoroacetic acid (7 ml) was kept under nitrogen at room temperature for 15 minutes. Ether (100 ml) was added and the precipitate was filtered, washed thoroughly with ether and dried. This material (300 mg) was added in portions to concentrated sulfuric acid (18 ml) cooled at -20°C with vigorous stirring. After 15 minutes a solution of potassium bisulfate in concentrated sulfuric acid (408 mg in 3 ml) was added. The reaction mixture was stirred for 75 minutes at -15°C and then stored at -7°C for 285 minutes. The sulfuric acid solution was poured into cold ether (400 ml); precipitate was filtered, washed with cold ether, and suspended in cold water. Complete solution was then achieved by careful addition of 2N sodium hydroxide. Acidification with N hydrochloric acid led to the precipitation of the desired octapeptide sulfate ester. Yield 200 mg.

References

Merck Index 8380
DOT 13 (9) 356 (1977)
I.N. p. 874
REM p. 1277
Ondetti, M.A., Pluscec, J., Sheehan, J.T., Jorpes, J.E. and Mott, V.; US Patent 3,723,406; March 27, 1973; assigned to E.R. Squibb and Sons, Inc.

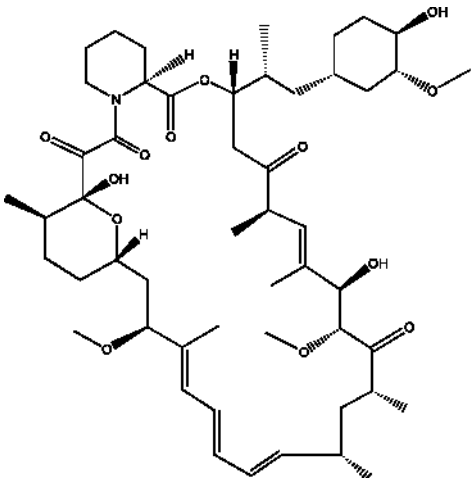
SIROLIMUS

Therapeutic Function: Immunosuppressive, Antifungal

Chemical Name: Rapamycin

Common Name: Rapamycin; Sirolimus

Structural Formula:



Chemical Abstracts Registry No.: 53123-88-9

Trade Name	Manufacturer	Country	Year Introduced
Rapamune	Wyeth Laboratories	UK	-
Rapamycin	Fujian Kerui Pharmaceutical Co., Ltd.	China	-
Rapamycin	Wyeth-Ayerst Canada Inc.	Canada	-

Raw Materials

Nutrient medium
Streptomyces hygroscopicus NRRL 5491

Manufacturing Process

Streptomyces hygroscopicus NRRL 5491 was grown and maintained on oatmeal-tomato paste agar slants (T. G. Pridham et al.; Antibiotic Annual 1956-1957, Medical Encyclopedia Inc., New York, p. 947) and in Roux bottles containing the same medium. Good growth was obtained after 7 days of incubation at 28°C. Spores from one Roux bottle were washed off and suspended into 50 ml of sterile distilled water. This suspension was used to inoculate the first stage inoculum.

The first-stage inoculum medium consisted of Emerson broth [R. L. Emerson et al., J. Bacteriol, 52, 357 (1946)] 0.4% peptone, 0.4% sodium chloride, 0.25% yeast extract and 1% glucose; pH 7.0; flasks containing the above medium were inoculated with 1 % of the spore suspension described above. The inoculated flasks were incubated for 30 hours at 28°C on a reciprocating shaker set at 65 r.p.m. (4 inch stroke).

Production stage

The production stage was run in 250-liter New Brunswick fermenters Model F-250, equipped with automatic antifoam addition system and pH recorder-controller. The fermenters were charged with 160 L of an aqueous production medium consisting of the following constituents: 1.0% soluble starch; 0.5% $(NH_4)_2SO_4$; 0.5% K_2HPO_4; 1.5% glucose (Cerelose); 0.025% $MgSO_4$; 0.005% $ZnSO_4$; 0.001% $MnSO_4$; 0.002% $FeSO_4 7H_2O$; 0.2% $CaCO_3$; 0.5% "Blackstrap" molasses; 0.5% hydrolyzed casein; 0.2% lard oil; pH 7.1 to 7.3 of first stage inoculum. Incubation temperature: 28°C; aeration: 0.5 vol/vol/min; agitation: 250 r.p.m. The fermenters were sterilized at 121°C for 45 min, cooled and inoculated with one flask inoculum).

A titre of ca. 20 μg/ml, determined by microbiological assay on agar plates seeded with Candida albicans, was reached in 5 days. The fermentation was stopped. The fermentation mixture was extracted twice with 1 v/v of n-butanol. The combined butanol extracts were washed with 1 v/v of water, dried with anhydrous sodium sulfate and evaporated to dryness under reduced pressure to yield a residue. The oily residue was extracted 3 times with 2 L of methanol. The combined methanol extracts were passed through diatomaceous earth (Celite) and evaporated to dryness to yield an oily residue containing crude Rapamycin.

References

Sehgal S.N. et al.; US Patent No. 3,929,992, Dec. 30; Assigned to Ayerst McKenna and Harrison Ltd., Montreal, Canada

SISOMICIN

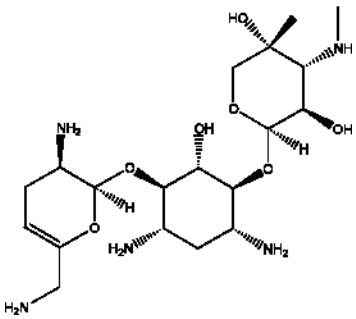
Therapeutic Function: Antibiotic

Chemical Name: O-2,6-Diamino-2,3,4,6-tetradeoxy-α-D-glycero-hex-4-enopyranosyl-(1-4)-O-(3-deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1-6)]-2-deoxy-D-streptamine

Common Name: Rickamicin

Chemical Abstracts Registry No.: 32385-11-8; 53179-09-2 (Sulfate salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Pathomyci n	Byk-Essex	W. Germany	1976
Extramycin	Bayer	W. Germany	1976
Extramycin	Bayer	Switz.	1978
Baymicina	Bayer	Italy	1978
Sisomin	Schering	Switz.	1978
Sisomicin	Essex	Italy	1978
Mensiso	Menarini	Italy	1979
Sissolline	Cetrane	France	1980
Siseptin	Essex	Japan	1981
Baymicine	Bayer	France	1981
Extramycin	Yoshitomi	Japan	1981

Raw Materials

Bacterium *Micromonspora inyoensis*
Dextrin
Soybean meal

Manufacturing Process

Tank fermentation of *Micromonospora inyoensis* - Germination stage 1: Under aseptic conditions, add a lyophilized culture (or cells obtained from a slant culture) of M. inyoensis to a 300 ml shake flask containing 100 ml of the following sterile medium:

Beef extract	3 g
Tryptone	5 g
Yeast extract	5 g
Dextrose	1 g
Starch	24 g
Calcium carbonate	2 g
Tap water	1,000 ml

Incubate the flask and its contents for 5 days at 35°C on a rotary shaker (280 rpm, 2'' stroke).

Germination stage 2: Aseptically transfer 25 ml of the fermentation medium of Germination stage 1 to a 2-l shake flask containing 500 ml of the above described sterile germination medium. Incubate the flask and its contents for 3 days at 28{]C on a rotary shaker (280 rpm, 2'' stroke).

Fermentation stage: Aseptically transfer 500 ml of the medium obtained from Germination stage 2 to a 14-l fermentation tank containing 9.5 l of the following sterile medium:

Dextrin	50 g
Dextrose	5 g
Soybean meal	35 g
Calcium carbonate	7 g
Cobalt chloride	10^{-6}M
Tap water	1,000 ml
Antifoam (GE 60)	10 ml

Prior to sterilizing the above described medium, adjust the pH to 8. Aerobically ferment for 66 to 90 hours while stirring at 250 rpm with air input at 4.5 l/l/min and 25 psi. The potency of the antibiotic produced at the end of this period reaches a peak of 150 to 225 mcm/ml and remains relatively constant. The pH of the fermentation medium changes slightly during the antibiotic production, varying in the range of 6.8 to 7.3.

Isolation of Antibiotic 66-40 - The whole broth is adjusted to pH 2 with 6N sulfuric acid. (For the purpose of this example, quantities are given in terms of 170 l of fermentation broth obtained by pooling acidified broth from 17 batches.) The acidified broth is stirred for about 15 minutes and then filtered. Wash the mycelium with water and combine the washings with the filtrate. Adjust the pH of the filtrate to 7 with 6N ammonium hydroxide.

To the neutralized filtrate, add sufficient oxalic acid to precipitate calcium and filter. Reneutralize the filtrate with ammonium hydroxide. Charge the filtrate onto a cationic exchange adsorption column containing 1,500 to 2,000 g of IRC-50 Amberlite in its ammonium form. Discard the eluate, wash the resin with water, and elute with 2N ammonium hydroxide. Collect 400 ml fractions and monitor by disc testing with S. aureus ATCC-6538P. Combine active fractions and evaporate to dryness under vacuum obtaining about 28 g of crude Antibiotic 6640 having an activity of about 500 mcm/g.

Purification of Antibiotic 66-40 - Dissolve 28 g of crude Antibiotic 6640 in 100 ml of distilled water and charge to an anion exchange adsorption column (Dowex 1 x 2) in the hydroxyl form. Slurry 2,000 g of the resin in water into a column 2,5" in diameter and 36" high. Elute the column with distilled water at a rate of about 23 ml/min collecting 100 ml fractions and monitor with a conductivity meter and by disc testing against Staphylococcus aureus.

The disc testing provides a gross separation of antibiotic-containing eluate fractions from those devoid of antibiotic. To insure that the fractions are properly combined, a portion of each fraction is paper chromatographed using the lower phase of a chloroform:methanol:17% ammonium hydroxide system (2:1:1). Each paper is sprayed with ninhydrin and the eluates containing like material are combined and lyophilized yielding about 5.7 g of Antibiotic 66-40 assaying about 900 mcm/mg.

References

Merck Index 8384
Kleeman and Engel p. 819
DOT 8 (8) 315 (1972) and 12 (10) 407 (1976)
I.N. p. 875
REM p. 1183
Weinstein, M.J., Luedemann, G.M. and Wagman, G.H.; US Patent 3,832,286; August 27, 1974; assigned to Schering Corp.

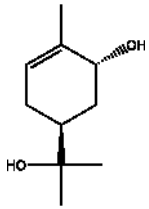
SOBREROL

Therapeutic Function: Mucolytic

Chemical Name: 5-Hydroxy-α,α,4-trimethyl-3-cyclohexene-1-methanol

Common Name: Pinol hydrate

Structural Formula:



Chemical Abstracts Registry No.: 498-71-5

Trade Name	Manufacturer	Country	Year Introduced
Sobrepin	Corvi	Italy	1970
Lysmucol	Schering	Switz.	1983

Raw Materials

α-Pinene oxide

Manufacturing Process

To 19 l of well-agitated distilled water plus 18 g of ditertiary-butyl-p-cresol was added 19.84 kg (130 mols) of pure α-pinene oxide that was about half racemic, half d-form. The temperature was maintained at 30°C to 50°C, first with ice bath cooling and then with tap water cooling. The addition of the pinene oxide required 1,5 hours. After the addition was complete and the exothermic reaction was about over, the mixture was stirred for 2,5 hours at about 30°C, and then centrifuged to separate the crude sobrerol from the liquid phase consisting of oil and water.

The crude sobrerol was washed with naphtha and then air dried to yield 14.81 kg (87.5 mols) of pure sobrerol, $[\alpha]_D^{25}$ -77.0°. It was found that 1 liter of the aqueous phase from the reaction contained 22 g of sobrerol, so, therefore, the entire aqueous phase contained 0.42 kg (2.5 mols) of sobrerol.

References

Merck Index 8395
I.N. p. 877
Klein, E.A.; US Patent 2,815,378; December 3, 1957; assigned to The Glidden Co.

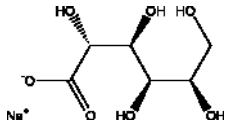
SODIUM GLUCONATE

Therapeutic Function: Electrolyte replenisher

Chemical Name: D-Gluconic acid, monosodium salt

Common Name: Natrium gluconicum; Natriumglukonat; Sodium gluconate

Structural Formula:



Chemical Abstracts Registry No.: 527-07-1

Trade Name	Manufacturer	Country	Year Introduced
Sodium gluconate	JUNGBUNZLAUER INC.	-	-
Sodium gluconate	GFS Chemicals	-	-
Sodium gluconate	Hudong Household Auxiliaries	-	-
Sodium gluconate	SINOTRANS HEBEI COMPANY	-	-
Sodium gluconate	Envitech, Inc.	-	-
Sodium gluconate	Global Calcium	-	-
Sodium gluconate	Hangzhou Linan Jinlong Chemical Co., Ltd.	-	-
Natriumglukonat	Scancem Chemicals AS	-	-

Raw Materials

Glucose
Aspergillus niger CCM 8004

Manufacturing Process

D-Gluconic acid was prepared by fermentation of glucose with Aspergillus niger CCM 8004 at 30°C. The fermentation medium contained 150 g/dm^{-3} glucose, 0.59 g/dm^{-3} ammonium sulfate, 0.25 g/dm^{-3} potassium chloride, 0.25 g/dm^{-3} potassium dihydrophosphate, 0.25 g/dm^{-3} $MgSO_4 \cdot 7H_2O$, 1.0 g/dm^{-3} $Ca(NO_3)_2 \cdot 4H_2O$, and 1.5 g/dm^{-3} of a 50% corn-steep liquor. The pH of the culture was maintained at the value of 6.5 during the growth phase and 5.5 (maximum glucose oxidase activity) during the production phase by addition of 11.7 M sodium hydroxide solution. Gluconic acid concentration was determined by HPLC analysis. By neutralization of D-gluconic acid with sodium hydroxide was obtained monosodium D-gluconate.

References

Znad H., Blazej M., Bales V., Markos J., Chem. Pap., 2004, 58, 1, 23

SOMATOTROPIN

Therapeutic Function: Growth stimulant

Chemical Name: See under Structural Formula

Common Name: Somatropin

Structural Formula: Proteins of molecular weights ranging from 22.124 for human growth hormone (HGH) to 47,400 for bovine growth hormone

Chemical Abstracts Registry No.: 9002-72-6

Trade Name	Manufacturer	Country	Year Introduced
Somatotrope	Choay	France	1951
Wachtungshormon	Kabi	W. Germany	1970
Crescormon	Sumitomo	UK	1973
Grorm	Serono	Italy	1975
Asellacrin	Calbiochem	US	1976
Crescormon	Kabi	US	1978
Nanormon	Hormonchemie	W. Germany	1978
Corpormon	Nikken	Japan	-
Somacton	Ferring	W. Germany	-
Somatormone	Byla	France	-

Raw Materials

Human pituitary glands
Acetone

Manufacturing Process

It has been found that the growth hormone can be obtained in crystalline

form from human pituitary glands by procedures comprising (1) extraction of the fresh glands with acetone, (2) extraction of the acetone residue with aqueous salt solutions, (3) precipitation from aqueous salt solutions by the addition of suitable miscible organic solvents of alkaline and acid pH, and finally crystallization from aqueous salt solutions by the addition of suitable miscible organic solvents.

References

Merck Index 8562
DOT 14 (9) 422 (1978)
I.N. p. 880
REM pp. 952, 955
Lewis, U.J. and Brink, N.G.; US Patent 2,974,088; March 7, 1961; assigned to Merck and Co., Inc.

SOMATREM

Therapeutic Function: Growth stimulant

Chemical Name: Somatotropin (human), N-L-methionyl-

Common Name: Somatrem

Structural Formula: Proteins of molecular weights ranging from 22.124 for human growth hormone (HGH) to 47,400 for bovine growth hormone, N-L-methionyl-

Chemical Abstracts Registry No.: 82030-87-3

Trade Name	Manufacturer	Country	Year Introduced
Protropin	Genentech	-	-

Raw Materials

Human growth hormone
Trypsin

Manufacturing Process

Highly purified human growth hormone was isolated from fresh glands by the procedure involving gel filtration of Sephadex. The hormone was oxidized by performing acid. Both the native and the oxidized product were submitted to digestion with trypsin as well as with chymotrypsin, while only native hormone was hydrolyzed with pepsin. These digests were fractionated on ion-exchange resin columns. Some of fraction required further purification by paper chromatography in a system consisting of 1-butanol/acetic acid/water (4:1:5) and by high-voltage electrophoresis on paper in a buffer of pH 2.3. Human growth hormone is contained 188 amino acids. From sedimentation equilibre

studies the molecular weight of the hormone was shown to be 21,500.

1000 ml of sterile intramuscular preparation containing 2.5 mg of chymotripsin hydrolyzed bovine growth hormone and 2.5 mg methylprednisolone is prepared from the following types and amounts of materials containing (per ml); 1) 2.5 mg chymotripsin hydrolyzed bovine growth hormone (powder), 2) 2.5 mg methylprednisolone (micronized), 3) 30 mg polyethylene glycol (40 000), 4) 9 mg sodium chloride, 5) 2 mg polysorbate 80, 1.8 mg methylparaben, 0.2 mg propylparaben and watef q.s. to 1000 ml.

The parabens are added to most of the water and dissolved with stirring and heating to 65-70°C. The mixture is cooled to room temperature and ingredient 3, 4 and 5 are added. The resulting solution was made up to 100 ml with water and sterilized by filtration. Ingredient 1 and 2 are sterilized with ethylene oxide and added aseptically. The final preparation is packaged in sterile containers with 1 ml of the final product. This is used advantageously in the treatment of arthritis and to avoid negative nitrogene balance.

References

Sprague J. M., D. Hill; US Patent No. 3,118,815; Sept. 17, 1946; Assigned to Sharp and DOHME, Incorporated, Philadelphia, Pa., a corporation of Maryland

Li Ch.H., Liu W.-K., Dixon J,S.; J. Am. Chem. Soc. 88, 2050 (1966)

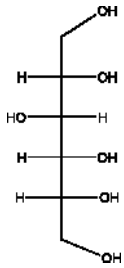
SORBITOL

Therapeutic Function: Cholecystokinetic, Diuretic, Pharmaceutic aid

Chemical Name: D-Glucitol

Common Name: d-Glucitol; Sorbit; Sorbitol

Structural Formula:



Chemical Abstracts Registry No.: 50-70-4

Trade Name	Manufacturer	Country	Year Introduced
Sorbitol	Memphis Co.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Sorbitol	Delalande Co.	-	-
Sorbitol	GreatVista Chemicals	-	-
Sorbit Sach	MUP Co.	-	-
Sorbostyl Amp.	Delalande Co.	-	-
Cystosol	Baxter	-	-
Resulax	Tika	-	-

Raw Materials

Polyethyleneimine	Cells of Zymomonas mobilis
Glutaraldehyde	Substrate solution (glucose, fructose, protein)

Manufacturing Process

20 ml of a suspension of CTAB-permeabilized cells of Zymomonas mobilis were mixed with 80 ml of a 4% carrageenan solution and the mixture was poured into shallow dishes and allowed to rigidify. The rigidified immobilizate was then divided into 3x3x3 mm cubes, exposed to a solution of 0.3 M KCl overnight and then divided into batches and exposed to one of the following treatments:

(A) Cubes stabilized with potassium ions were used without further treatment for production of sorbitol/gluconic acid.

(B) Cubes were incubated with a 1.0% solution of polyethyleneimine at room temperature for 30 min and then treated with glutaraldehyde at 4°C for 30 min.

Comparison of two rigidification methods:

A volume of 450 ml of cubes treated by the method described in (A) were reacted in a 1.5 liter fluidized bed fermenter with a substrate solution comprised of 100 g/L glucose, 100 g/L fructose and a protein concentration of 6.1 g/L, at a D of 0.053 h^{-1}, and titrated with 3 N KOH. After 48 hours, 68.8% of the substrate was converted with a resulting production of 3.65 g sorbitol/L*h and 0.6 g sorbitol/g protein*h. After approximately 50 days, the productivity of the fermenter was reduced by about one half.

Cubes treated as described (B) using glutaraldehyde at a concentration of 0.5%, were reacted in a 1.6 liter fermenter with a substrate solution comprised of 100 g/L glucose, 100 g/L fructose and a protein concentration of 8.6 g/L, at a D of 0.055 h^{-1}, and titrated with 3 N KOH. After 48 hours, 90.0% of the substrate was converted with a resulting production of 4.95 g sorbitol/L*h and 0 58 g sorbitol/g protein*h. After 75 days, the productivity of the fermenter was reduced by only 3.5%.

References

Merck Index, Monograph number: 8873, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

Rehr B., Sahm G.; US Patent No. Mar.2, 1993; Assigned to Forshungszentrum Juelich GmbH, Juelich, Fed. Rep. of Germany

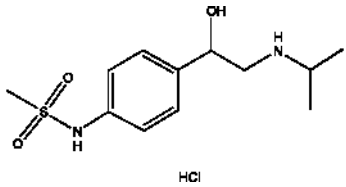
SOTALOL HYDROCHLORIDE

Therapeutic Function: Beta-adrenergic blocker, Antiarrhythmic

Chemical Name: Methanesulfonamide, N-(4-(1-hydroxy-2-((1-methylethyl)amino)ethyl)phenyl)-, monohydrochloride

Common Name: Sotalol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 959-24-0; 3930-20-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sotagard	Glaxo	-	-
Sotalol Hydrochloride	Teva	-	-
Sotalol Hydrochloride	Taizhou Dongdong Pharmachem Co., Ltd.	-	-
Betapace	Berlex	-	-

Raw Materials

Aniline
Bromacetyl bromide
Carbon disulfide
Palladium on carbon
Hydrochloric acid
Methansulfonyl chloride
Aluminum chloride
Isopropylamine
Sodium borohydride

Manufacturing Process

As a resulting of reaction of methansulfonylchloride reacted with aniline methansulfonanilide was obtained. The methansulfonanilide reacted with bromacetylbromide at the presence of $AlCl_3$ and CS_2 and 4-(bromacetyl)-methansulfonanilide was prepeared.

Then to the 4-(bromacetyl)-methansulfonanilide isopropylamine was added to give 4-(1-oxo-2-isopropylaminoethyl)methansulfonanilide.

The 4-(1-oxo-2-isopropylaminoethyl)methansulfonanilide was reduced by hydrogenesation in the presence of Pd-C catalyst and sodium borohydride. So 4-(1-hydroxy-2-isopropylaminoethyl)methansulfonanilide was obtained.

The 4-(1-hydroxy-2-isopropylaminoethyl)methansulfonanilide hydrochloride may be prepared by treatment of base with hydrochloric acid.

References

Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart. New York, 1982

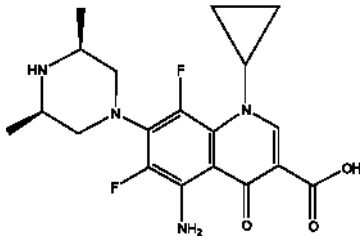
SPARFLOXACIN

Therapeutic Function: Antibacterial

Chemical Name: 3-Quinolinecarboxylic acid, 1,4-dihydro-5-amino-1-cyclopropyl-6,8-difluoro-7-(3,5-dimethyl-1-piperazinyl)-4-oxo-, cis-

Common Name: Esparfloxacino; Sparfloxacin

Structural Formula:



Chemical Abstracts Registry No.: 110871-86-8

Trade Name	Manufacturer	Country	Year Introduced
Acespar 200	Plethico Pharmaceuticals	India	-
Dinor	Nucron Pharma	India	-
Sparflo	Dr. Reddy's Laboratories Ltd.	India	-
Sparfloxacin	China Pharm Chemical Co., Ltd.	China	-
Sparfloxacin	Skymax Laboratories Pvt. Ltd.	India	-
Zagam	Aetna Inc.	USA	-
Zagam	Aventis Pharma	Ireland	-

Raw Materials

Ethyl orthoformate

Ethyl pentafluorobenzoylacetate

Acetic anhydride
Sodium hydride
Benzylamine
Acetic acid
Cyclopropylamine
Ethyl orthoformate Sulfuric acid
cis-2,6-Dimethylpiperazine
Potassium carbonate
Palladium on carbon

Manufacturing Process

A mixture of the known compound, ethyl pentafluorobenzoylacetate [J. Org. Chem., 35, 930 (1970)] (25 g), ethyl orthoformate (20 g), and acetic anhydride (23 g) was refluxed for 2 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in diethyl ether and allowed to react with cyclopropylamine (5.1 g) to give ethyl 2-pentafluorobenzoyl-3-cyclopropylaminoacrylate (28 g), melting point 89°C.

The ethyl 2-pentafluorobenzoyl-3-cyclopropylaminoacrylate (28 g) was dissolved in dry tetrahydrofuran and allowed to react with 60% sodium hydride (3.85 g) at room temperature to give ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (18.4 g), melting point 170°-171°C.

A mixture of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (28.2 g), benzylamine (9.8 ml), anhydrous potassium carbonate (23.6 g), and acetonitrile (140 ml) was heated at 100°-110°C for 1 h to give ethyl 5-benzylamino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (21.4 g), which was recrystallized from ethanol, melting point 134°-135°C.

The ethyl 5-benzylamino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (20 g) was dissolved in acetic acid (100 ml) and ethanol (150 ml), and hydrogenolyzed in the presence of 5% palladium-carbon (0.5 g) to give ethyl 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (14.1 g), which was recrystallized from chloroform-ethanol, melting point 236°-237°C.

A mixture of the ethyl 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (12.6 g), acetic acid (80 ml), water (50 ml), and concentrated sulfuric acid (9 ml) was heated at 100°-110°C for 40 min to give 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (11.1 g), which was recrystallized from chloroform-ethanol, melting point 294°-295°C.

A mixture of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (1.25 g), cis-2,6-dimethylpiperazine (2.0 g), and dimethylformamide was stirred at room tempersture for 24 h. The reaction mixture was evaporated to dryness under reduced pressure and water was added to the residue. The mixture was extracted with chloroform and the extract was dried. After evaporation of chloroform, ethanol was added to the residue. The resulting crystals were filtered and recrystallized from chloroform-ethanol to give 5-amino-1-cyclopropyl-6,8-difluoro-7-(cis-3,5-dimethyl-1-piperazinyl)-1,4-dihydro- 4-oxoquinoline-3-carboxylic acid (1.4 g), melting point: 258°-260°C.

References

Conrath G.; US Patent No. 5,478,829; Dec. 26, 1995; Assigned: Rhone-DPC Europe, Antony, France

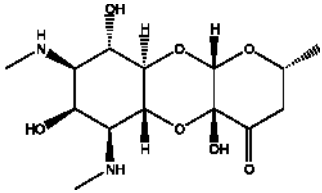
SPECTINOMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)-4H-pyrano-[2,3-b][1,4]benzodioxin-4-one

Common Name: Actinospectacin

Structural Formula:



Chemical Abstracts Registry No.: 1695-77-8; 22189-32-8 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Trobicin	Upjohn	US	1971
Trobicin	Upjohn	Italy	1973
Stanilo	Upjohn	W. Germany	1973
Trobicin	Upjohn	UK	1973
Trobicine	Upjohn	France	1974
Trobicin	Upjohn	Japan	1978
Kempi	Alter	Spain	-

Raw Materials

Nutrient medium
Bacterium *Streptomyces spectabilis*

Manufacturing Process

A lyophilized culture of *Streptomyces spectabilis*, NRRL 2792, was used to seed the following sterile agar medium on tubed slants:

	Grams
Maltose	10

Tryptone	5
K_2HPO_4	0.5
NaCl	0.5
$FeSO_4$	0.1
Agar	20

Deionized water to make 1 liter

The slants were incubated for 7 days at 30°C, after which time sporulation was complete. The spores from the agar slants were used, in an aqueous suspension, to inoculate 100 ml of preseed medium in a 500 ml Erlenmeyer flask. The sterile preseed medium consisted of:

	Grams
Dried whole yeast	10
Glucose	10
Pancreatic digest of casein (N-Z-Amine B)	5

Tap water to make 1 liter adjusted to pH 7.2 before sterilizing

The seed flash was incubated for 24 hours at 32°C on a reciprocating shaker after which it was used as an inoculum for a 20 liter seed fermenter in the amount of approximately 5%. the 20 liter seed fermenter contained a sterile medium consisting of:

	Grams
Glucose	15
Cornstarch	25
Distiller's solubles	15
Brewer's yeast	10
Corn steep liquor	20

Tap water to make 1 liter adjusted to pH 7.2 before sterilizing

The 20 liter seed fermenter was incubated for 24 hours at 32°C and aerated at the rate of 6 standard liters or about 0.2 standard cubic feet of air per minute and agitated with a sweep stirrer. The 20 liter seed fermenter was used to inoculate 250 liters of the same medium in a 100 gallon fermentation tank. 1,200 ml of lard oil were added during the fermentation to control foaming. The tank was agitated with a propeller and aerated at the rate of 75 standard liters of air per minute. After 96 hours of fermentation the beer assayed 500 mcg/ml (18.3 mcg/mg on a dry basis) of actinospectacin. Actinospectacin is assayed by its activity against *Klebsiella pneumoniae* by standard agar diffusion procedure and based on crystalline actinospectacin sulfate according to US Patent 3,234,092.

References

Merck Index 8584
Kleeman and Engel p. 821
PDR p. 1864
DOT 8 (3) 107 (1972)
I.N. p. 884
REM p. 1211

Jahnke, H.K.; US Patent 3,206,360; September 14, 1965; assigned to The Upjohn Co.
Bergy, M.E. and De Boer, C.; US Patent 3,234,092; February 8, 1966; assigned to The Upjohn Company
Peters, V.J.; US Patent 3,272,706; September 13, 1966; assigned to The Upjohn Company
Nara, T., Takasawa, S.,Okachi, R., Kawamoto, I., Kumakawa, M., Yamamoto, M. and Sato, S.; US Patent 3,819,485; June 25, 1974; assigned to Abbott Laboratories

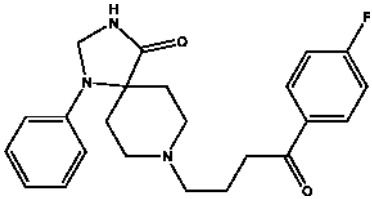
SPIPERONE

Therapeutic Function: Tranquilizer

Chemical Name: 8-[4-(4-Fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 749-02-0

Trade Name	Manufacturer	Country	Year Introduced
Spiropitan	Eisai	Japan	1969
Spiroperidol	Janssen	-	-

Raw Materials

Formamide
4-Carbamoyl-4-N-anilinopiperidine
4-Chloro-p-fluoro-butyrophenone

Manufacturing Process

A mixture of 4-carbamoyl-4-N-anilinopiperidine and formamide is heated for 12 hours at 170°C. After cooling, the reaction mixture is divided between 100parts water and 900 parts chloroform. The organic layer is separated, dried over $MgSO_4$ filtered and the filtrate is evaporated. The semisolid residue is stirred in ethyl acetate. The undissolved part is filtered off, washed with ethyl acetate, and dried, yielding 1-oxo-4-phenyl-2,4,8-triazaspiro[4.5]decane.

A mixture of 3.2 parts 4-chloro-p-fluoro-butyrophenone, 3.5 parts 1-oxo-4-phenyl-2,4,8-triazaspiro(4,5)decane, 2 parts Na_2CO_3 and 0.1 part KI in 200 parts hexone is refluxed with stirring for 50 hours. The mixture is cooled to room temperature, 200 parts water are added and the layers are separated. The organic layer is dried over 10 parts $MgSO_4$, filtered and the solvent removed under reduced pressure on the water bath. The residue is treated with 50 parts diisopropylether. The precipitate is filtered on a Buchner filter and recrystallized from 20 parts hexone at room temperature. The solid is filtered off and dried to yield 1-oxo-4-phenyl-8-[3-(4-fluorobenzoyl)-propyl] -2,4,8-triazaspiro(4.5)decane, melting point 190° to 193.6°C, as a light brown amorphous powder.

References

Merck Index 8596
Kleeman and Engel p. 821
I.N. p. 885
Janssen, P.A.J.; US Patent 3,155,669; November 3, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; US Patent 3,155,670; November 3, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium
Janssen, P.A.J.; US Patent 3,161,644; December 15, 1964; assigned to Research Laboratorium Dr. C. Janssen NV, Belgium

SPIRAMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Spiramycin

Common Name: -

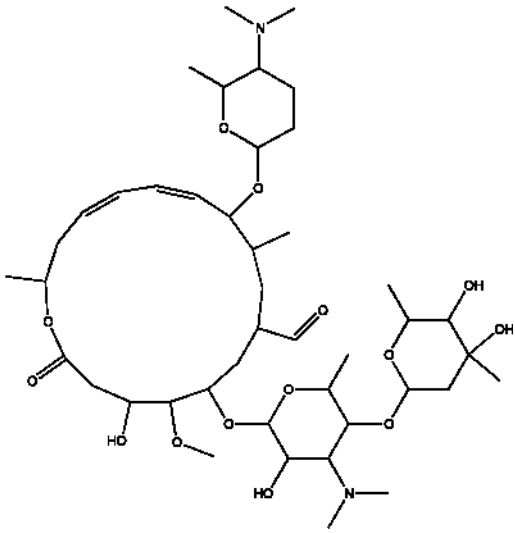
Chemical Abstracts Registry No.: 8025-81-8

Trade Name	Manufacturer	Country	Year Introduced
Rovamycine	Specia	France	1972
Rovamycina	Carlo Erba	Italy	1979
Apyrectol Spiramycine	Theranol	France	-
Bykomycetin	Byk Gulden	-	-
Selectomycin	Gruenenthal	W. Germany	-
Spiramycin	Kyowa	Japan	-

Raw Materials

Bacterium Streptomyces ambofaciens
Nutrient medium

Structural Formula:



Manufacturing Process

The process for producing spiramycin comprises inoculating an aqueous nutrient medium with a culture of the NRRL No. 2420, allowing aerobic fermentation to take place and separating from the culture medium the spiramycin thus formed. The culture medium also contains the antibiotic substance known as Congocidin which, however, does not possess the same useful properties as spiramycin and which can be isolated in crystalline form. The separation of the two antibiotic substances is readily achieved.

References

Merck Index 8597
Kleeman and Engel p. 822
I.N. p. 885
REM p. 1224
Ninet, L. and Verrier, J.; US Patent 2,943,023; June 28, 1960; assigned to Societe des Usines Chimiques Rhone-Poulenc
Ninet, L., Pinnert S.and Preud'homme, J.; US Patent 3,000,785; September 19, 1961;assigned to Societe des Usines Chimiques Rhone-Poulenc

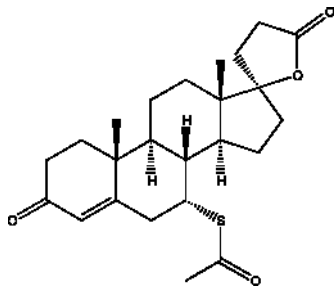
SPIRONOLACTONE

Therapeutic Function: Diuretic

Chemical Name: 7α-(Acetylthio)-17α-hydroxy-3-oxopregn-4-ene-21-carboxylic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 52-01-7

Trade Name	Manufacturer	Country	Year Introduced
Aldactone	Searle	US	1959
Aldactone	Searle	France	1960
Altex	Cenci	US	1980
Diatensec	Searle	UK	1981
Acelat	Endopharm	W. Germany	-
Airolactone	Horita	Japan	-
Aldactazide	Searle	US	-
Aldopur	Heumann	W. Germany	-
Aldospirone	Teva	Israel	-
Alexan	Sanwa	Japan	-
Almatol	Fujisawa	Japan	-
Alpamed	Sawai	Japan	-
Alpolasnon	Nihon Yakuhin	Japan	-
Aporasnon	NNichiiko	Japan	-
Dairopeal	Daito Koeki	Japan	-
Deverol	Waldheim	Austria	-
Dira	Kakenyaku Kako	Japan	-
Duraspiron	Durachemie	W. Germany	-
Euteberol	Merckle	W. Germany	-
Hokulaton	Hokuriku	Japan	-
Idrolattone	Zoja	Italy	-
Lacalmin	Tatsumi	Japan	-
Lacdene	Tsuruhara	Japan	-
Nefurofan	Maruko	Japan	-
Osyrol	Hoechst	W. Germany	-
Penantin	Teikoku	Japan	-
Practon	Genekod	France	-
Sagisal	Sagitta	W. Germany	-
Sincomen	Schering	W. Germany	-
Spiresis	Farmos	Finland	-
Spiretic	D.D.S.A.	UK	-
Spiridon	Orion	Finland	-

Trade Name	Manufacturer	Country	Year Introduced
Spirix	Benzon	Denmark	-
Spirolong	SKF	Italy	-
Spironazide	Schein	US	-
Spiropal	A.F.I.	Norway	-
Spiro-Tablinen	Sanorania	W. Germany	-
Spirotone	Protea	Australia	-
Suracton	Toho Iyaku	Japan	-
Uractone	SPA	Italy	-
Urosonin	Isei	Japan	-
Xenalone	Mepha	Switz.	-

Raw Materials

17α-(2-Carboxyethyl)-17β-hydroxyandrosta-4,6-dien-3-one lactone
Thioacetic acid

Manufacturing Process

A mixture of approximately 11 parts of 17α-(2-carboxyethyl)-17β-hydroxyandrosta-4,6-dien-3-one lactone and 10 parts of thioacetic acid is heated at 85° to 95°C for ½ hour. Excess thioacetic acid is removed by vacuum distillation at this point, and the residue is twice recrystallized from methanol, affording 7α-acetylthio-17α-(2-carboxyethyl)-17β-hydroxyandrost-4-en-3-one lactone, melting at approximately 134° to 135°C. Heated above this melting point, the product solidifies and melts again at approximately 201° to 202°C (with decomposition).

References

Merck Index 8610
Kleeman and Engel p. 822
PDR pp.830, 993, 1388, 1606, 1674, 1999
OCDS Vol.1 p.206 (1977)
2, 172 (1980) and 3, 91 (1984)
I.N. p. 886
REM p. 941
Cella, J.A. and Tweit, R.C.; US Patent 3,013,012; December 12, 1961; assigned to G.D.Searle and Co.

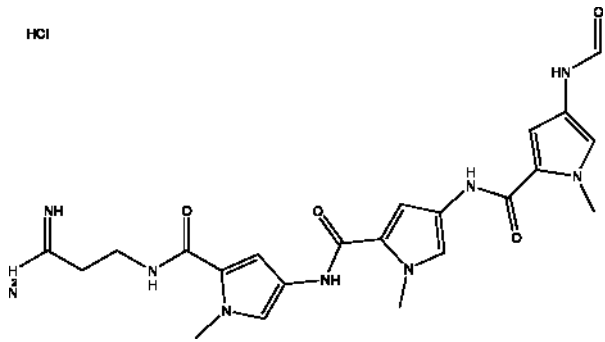
STALLIMYCIN HYDROCHLORIDE

Therapeutic Function: Antibiotic

Chemical Name: N''-(2-Amidinoethyl)-4-formamido-1,1',1''-trimethyl-N,4':N',4''-ter-(pyrrole-2-carboxamide) hydrochloride

Common Name: Distamycin A

Structural Formula:



Chemical Abstracts Registry No.: 6576-51-8; 636-47-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Herperal	Farmitalia	Italy	1978

Raw Materials

Bacterium *Streptomyces distallicus*
Dextrose
Corn steep liquor

Manufacturing Process

A spore suspension obtained upon washing a culture of *Streptomyces distallicus* is added to 3,000 ml of a sterile medium consisting of the following:

Dextrose	2%
Corn steep liquor extract	2%
$CaCO_3$	1%
$(NH_4)_2SO_4$	0.3%
NaCl	0.3%

Fermentation is continued at 28°C for 40 hours at a stirring rate of 150 to 250 rpm and a rate of air flow of 1 to 2 l/min/l of culture medium.

300 ml of a suspension of the vegetative mycelium of this culture are used for inoculating 6,000 ml of a similar sterile culture medium. At this production stage, the culture is kept fermenting for 85 to 100 hours (pH 7.6 at 28°C) at a stirring rate of 350 to 450 rpm and a rate of air flow of 1 to 1.5 l/min/l of culture medium.

To 17 l of a culture obtained by submerged fermentation as mentioned above, siliceous earth is added and the batch is filtered. The mixture of mycelium and the siliceous earth are agitated for 1 hour with 2.5 l of butanol. This treatment is repeated twice. The butanolic extracts are combined, washed with water, evaporated to dryness (about 10 g) and boiled with acetone (80 ml). The

residue (5.41 g of yellowish powder) is distamycin.

5 g of distamycin is extracted six times with ethanol. The ethanolic extracts are combined, concentrated and filtered through a column containing 70 g of alumina. Elution is carried out with the same solvent. The effluent (central fractions) is collected and evaporated to dryness to yield 0.43 g of pure distamycin A: decomposition point, 183°C to 185°C. The product can be further purified by crystallization from aqueous n-butanol.

References

Merck Index 8623
Kleeman and Engel p. 824
DOT 13 18) 322 (1977)
I.N. p. 887
Arcamone, F., Canevazzi, G., Grein, A. and Bizioli, F.; US Patent 3,190,801; June 22, 1965; assigned to Societa Farmaceutici Italia

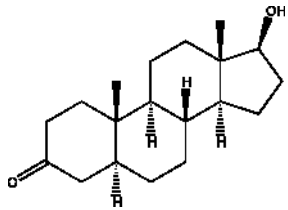
STANOLONE

Therapeutic Function: Androgen

Chemical Name: 17-Hydroxyandrostan-3-one

Common Name: Androstanolone

Structural Formula:



Chemical Abstracts Registry No.: 521-18-6

Trade Name	Manufacturer	Country	Year Introduced
Neodrol	Pfizer	US	1953
Anabolex	Lloyd	UK	-
Anaprotin	Cuxson	UK	-
Androlone	Orma	Italy	-
Ophthovitol	Winzer	W. Germany	-
Pesomax	Boniscontro	Italy	-
Protona	Gremy-Longuet	France	-
Stanaprol	Pfizer	-	-

Raw Materials

3,17-Androstandione
Selenium dioxide
Sodium borohydride

Manufacturing Process

A solution of 1.0 g of 3,17-androstandione in 50 ml of methanol and containing 1 g of selenium dioxide, was allowed to remain in an ice-chest overnight. The formed 3,3-dimethoxyandrostan-17-one was not separated. 1 g of solid potassium hydroxide and 2.5 g of sodium borohydride in 2.5 ml of water were added and the mixture allowed to react at room temperature for 24 hours. The solution was then poured into a large excess of water, extracted with methylene chloride, the organic layer dried and evaporated to a residue. The residue was dissolved in ether, and a small amount of selenium removed by filtration. The ether was boiled off and the organic material dissolved in 100 ml of boiling acetone. 25 ml of diluted hydrochloric acid were added, the solution boiled for 5 minutes and then allowed to cool. Upon crystallization, 0.85 g of androstan-17β-ol-3-one was obtained, melting point 175°C to 178°C.

References

Merck Index 8646
Kleeman and Engel p. 54
I.N. p. 88
Oliveto, E.P. and Hershberg, E.B.; US Patent 2,927,921; March 8, 1960; assigned to Schering Corp.

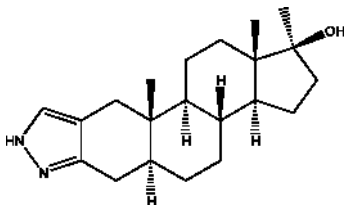
STANOZOLOL

Therapeutic Function: Anabolic

Chemical Name: 17-Methyl-2H-5α-androst-2-eno[3,2-c]pyrazol-17β-ol

Common Name: Androstanazole

Structural Formula:



Chemical Abstracts Registry No.: 10418-03-8

Trade Name	Manufacturer	Country	Year Introduced
Winstrol	Winthrop	US	1961
Strombaject	Winthrop	W. Germany	1961
Stromba	Sterling	UK	1961
Winstol	Zamba	Italy	1962
Stromba	Winthrop	France	1964
Anasynth	Causyth	Italy	-

Raw Materials

17β-Hydroxy-17α-methyl-4-androsteno[3,2-c]pyrazole
Lithium
Ammonia

Manufacturing Process

To a stirred solution of 1.00 gram of 17β-hydroxy-17α-methyl-4-androsteno[3,2-c]pyrazole in 200 ml of tetrahydrofuran and 400 ml of liquid ammonia was added 2.12 grams of lithium wire during 5 minutes. The dark blue mixture was stirred for 45 minutes. A solution of 40 ml of tertiary-butyl alcohol in 160 ml of diethyl ether was added with stirring.

After 15 minutes, 25 ml of ethanol was added with stirring. The mixture turned colorless after several hours, and the liquid ammonia was allowed to evaporate and the mixture was allowed to warm to room temperature over a period of about 15 hours.

The solvent was evaporated to yield a colorless solid residue, which was taken up in ethyl acetate-ice water. The two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, saturated sodium chloride solution and filtered through anhydrous sodium sulfate. The solvent was evaporated to yield 1.20 grams of light tan crystals, MP 151° to 155°C, ultraviolet maximum at 224 mμ (E = 4,095). Two recrystallizations from ethanol afforded: 1st crop, 0.619 grams (62%) of colorless crystals (dried at 120°C in vacuo for 17 hours), MP 232.8° to 238.0°C, ultraviolet maximum at 224 mμ (E = 4,840); 2nd crop, 0.142 gram (14%) of colorless crystals, MP 234° to 242°C.

References

Merck Index 8647
Kleeman and Engel p. 825
PDR p. 1935
DOT 15 (6) 278 (1979)
I.N. p. 888
REM p. 1000
Manson, A.J.; US Patent 3,030,358; April 17, 1962; assigned to Sterling Drug Inc.

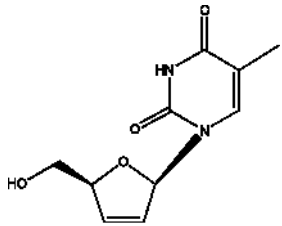
STAVUDINE

Therapeutic Function: Antiviral

Chemical Name: Thymidine, 2',3'-didehydro-3'-deoxy-

Common Name: Estavudina; Stavudine

Structural Formula:



Chemical Abstracts Registry No.: 3056-17-5

Trade Name	Manufacturer	Country	Year Introduced
d4T	Bristol-Myers Squibb	-	-
d4T	Cipla Limited	India	-
Stavir	Cipla Limited	India	-
Stavudine	Bristol-Myers Squibb	USA	-
Stavudine	Cipla Limited	India	-
Zerit	Bristol-Myers Squibb	USA	-

Raw Materials

Thymidine
Sodium hydroxide
KOtBu
Anhydronucleoside
Methanesulfonyl chloride
Oxetane
Tetrabutylammonium fluoride

Manufacturing Process

A 3 liter, 3 necked round-bottomed flask was equipped with an overhead stirrer and paddle, a 500 ml dropping funnel and a Claisen adapter containing a drying tube and a thermometer. Thymidine (200 g, 0.82 M) and pyridine (750 ml) were added to the flask. The mixture was stirred and warmed with a water bath (20 min) to give a clear solution. The solution was then cooled in an ice bath to 0°-3°C and the dropping funnel was charged with methanesulfonyl chloride (206.5 g, 1.08 M). The methanesulfonyl chloride was then added dropwise over 40 min with no noticeable exotherm. The solution was stirred at 0°C for 1 h and then stored at 5°C for 18 h. The light brown mixture was then poured onto rapidly stirred water (3 L) containing ice (approx. 500 g). The desired product crystallised immediately. After stirring for 0.5 h, the product was collected by filtration and washed several times with water (3 times 100 ml). The white solid was then dried under vacuum

overnight (322 g, 98% yield). The product was recrystallised from hot acetone to give 267 g of the 3',5'-di-O-(methanesulfonyl)thymidine as white solid (81% yield), melting point 169°-171°C (lit. 170°-171°C).

3',5'-Di-O-(methanesulfonyl)thymidine (248 g, 0.62 M) was added in portions to a stirred solution of sodium hydroxide (74.7 g, 1.87 M) in water (1.6 L). On addition the reaction mixture became a yellow-orange solution. This stirred solution was then heated to reflux for 2 h. Once the reaction mixture had cooled to room temperature, 6 N hydrochloric acid (100 ml) was added. The reaction mixture was concentrated in vacuo by removing 1.3 L of water. The resulting slurry was cooled in an ice bath for 2 h. The solid was then filtered and washed sparingly with ice water, and then vacuum dried to constant weight (103.7 g, 74%). The 1-(3,5-anhydro-2-deoxy-β-D-threo-pentofuranosyl)thymine, melting point 188°-190°C (lit. 190°-193°C) was used without further purification.

2 Methods of preparation of 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine

1. To a 3-necked, 1 L round-bottomed flask equipped with a mechanical stirrer, thermometer and nitrogen inlet was added dry DMSO (400 ml) and oxetane (90.0 g, 0.402 M). To this solution was added 97% KOtBu (74 g, 0.643M) in 1.5 g portions over 25 min. The temperature was maintained between 18° and 22°C by means of an external ice bath. After the addition was complete the reaction was stirred for a further 1 h and no further rise in temperature was observed and TLC indicated that the reaction was approximately 90% complete. The reaction was stirred at 21°C for 16 h, after which time TLC indicated that the reaction was complete. The viscous solution was poured onto cold (4°C) toluene (3 L), resulting in a beige colored precipitate. The temperature of the mixture rose to 7°C upon addition of the DMSO solution. The mixture was occasionally swirled over 20 min, then filtered on a 18.5 cm Buchner funnel. The collected yellowish solid was washed twice with cold toluene and allowed to dry under suction for 1 h. The solid was dissolved in 300 ml of water, whereupon two layers formed. The mixture was placed in a separatory funnel and the upper layer (containing residual toluene) was discarded. The aqueous layer was placed in a 1 L beaker equipped with a pH probe, magnetic stirring bar and thermometer. The temperature was cooled to 10°C by the use of an external ice bath. Concentrated HCl was added dropwise to the stirred solution at a rate in which the temperature was kept below 15°C. After the addition of HCl (50.5 ml, 0.61 M) the pH = 70.1 and a precipitate began to form. To this thick mixture was added potassium chloride (70 g) and stirring was continued at 5°C for 1 h. The precipitate was collected and sucked dry for 2 h, then air dried for 16 h. The solid was crushed up and slurried in hot acetone (500 m) and filtered. The residue in the filter paper was rinsed with hot acetone (2 times 200 ml), then slurried again with hot acetone (300 ml), filtered, and washed once more with hot acetone (2 times 100 ml). The combined filtrate was concentrated to dryness to give 51.3 g (57%) of the 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (d4T) as an off-white solid, melting point 165°-166°C.

2. Tetrabutylammonium fluoride (0.22 mL, 0.22 mM, 1.0 M) was added to a suspension of the 1-(3,5-anhydro-2-deoxy-beta;-D-threo-pentofuranosyl)thymine (25 mg, 0.11 mM) in dry THF (3 ml). The mixture

was heated to reflux for 18 h, at which time the reaction appeared to be complete. After cooling, the solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2/MeOH/NH_4OH (90:10:1). Purification was performed on a 20 mm flash chromatography column, eluting with CH_2Cl_2/MeOH/NH_4OH (90:10:1). Concentration of the fractions containing the product afforded 18 mg (72%) of the dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (d4T).

References

Starrett J.E. et al.; US Patent No. 4,904,770; Feb. 27, 1990; Assigned: Bristol-Myers Company, New York, N.Y.

STREPTOKINASE

Therapeutic Function: Enzyme

Chemical Name: Streptococcal fibrinolysin

Common Name: -

Structural Formula: Complex enzyme mixture

Trade Name	Manufacturer	Country	Year Introduced
Streptase	Hoechst	France	1970
Streptase	Hoechst	US	1977
Kabikinase	Kabi	US	1980
Awelysin	Arzneimittelwerk Dresden	E. Germany	-
Varidase	Lederle	UK	-

Chemical Abstracts Registry No.: 9002-01-1

Raw Materials

Bacterium *Streptococcus haemolyticus*
Nutrient medium

Manufacturing Process

The following description is from US Patent 2,701,227: To 50 liters of distilled water there was added 10.17 kg of enzyme hydrolyzed casein (N-Z-Amine). The temperature was raised to 100°C and held until the casein digest solution was clear. The container was then cooled rapidly to 15°C and the cooled solution filtered through a coarse grade of filter paper. A small amount of toluene was added as a preservative and the solution stored at 2°C for 4 days, at the end of which time it was again filtered to remove any insoluble material.

The following ingredients were then added to the casein digest solution:

1,165.0 grams of KH_2PO_4 dissolved in 8 liters of distilled water; 35.0 grams of cysteine in approximately 800 cc of 10% HCl (the least amount of 10% HCl required to obtain a clear solution); 35 grams of glycine dissolved in 100 cc of distilled water; 300 grams dextrose in 2 liters of distilled water; 3.5 grams of uracil in 1 liter of distilled water; 3.5 grams of adenine sulfate in 1 liter of distilled water; 0.35 gram of nicotinic acid in 35 cc of distilled water; 0.59 gram of pyridoxine dissolved in 59 cc of distilled water; 7.0 grams of tryptophane in 1 liter of distilled water; 1.75 grams of calcium pantothenate in 70 cc of distilled water; 0.875 gram of thiamin hydrochloride dissolved in 87.5 cc of distilled water; 0.175 gram of riboflavin dissolved in 1,000 cc of distilled water; 55.65 cc of thioglycollic acid in 100 cc of distilled water; 700 grams of $KHCO_3$ in 500 cc of distilled water and 700 cc of a trace element salt solution containing 11.5 kg of $MgSO_4$; 50 g of $CuSO_4 \cdot 5H_2O$; 50 g of $ZnSO_4 \cdot 7H_2O$; 20 g $MnCl_2 \cdot 4H_2O$; 50 g of $FeSO_4 \cdot 7H_2O$; 1 liter of HCl per 100 liters of solution. The medium was then adjusted to pH 7.2 and sterilized by filtration.

The above sterilized medium was inoculated with 11 liters of seed inoculum having a bacterial count of approximately 20 billion per cc. The tank was fermented at 37°C without pH adjustment, aeration, or other modification for 14 hours at the end of which time 320 cc of 50% dextrose was added. After this the pH was adjusted to 7.0 at 15 minute intervals with 5.0 N sodium hydroxide. The volume of sodium hydroxide required for neutralization was noted and 115% of this volume of 50% dextrose solution added after each pH adjustment. At the end of about 8 hours the bacterial count had ceased to increase and the fermentation was terminated. At this time the fermentation medium contained approximately 1,000 units of streptokinase per cc.

References

Merck Index 8683
Kleeman and Engel p. 826
PDR pp.944, 963, 1428
I.N. p. 891
REM p. 1037
Ablondi, F.B. and Adam, J.N. Jr.; US Patent 2,701,227; February 1, 1955; assigned to American Cyanamid Company
Mowat, J.H., Krupka, G.C. and Nalesnyk, S.; US Patent 2,753,291; July 3, 1956; assigned to American Cyanamid Company
Singher, H.O. and Zuckerman, L.; US Patent 3,016,337; January 9, 1962; assigned to Ortho Pharmaceutical Corporation
Siegel, M., Palombo, G. and Beumgarten, W.; US Patent 3,042,586; July 3, 1962; assigned to Merck and Co., Inc.
von Polnitz, W., Schwick, H.G. and Bickhard, J.H.; US Patent 3,063,913; November 13, 1962; assigned to Behringwerke AG, Germany
von Polnitz, W., Schwick, H.G. and Bickhard, J.H.; US Patent 3,063,914; November 13, 1962; assigned to Behringwerke AG, Germany
Baumgarten, W. and Cole, R.B.; US Patent 3,107,203; October 15, 1963; assigned to Merck and Co., Inc.
von Polnitz, W., Schwick, H.G. and Bickhard, J.H.; US Patent 3,138,542; June 23, 1964; assigned to Behringwerke AG, Germany

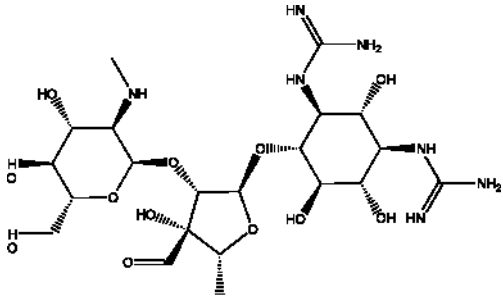
STREPTOMYCIN

Therapeutic Function: Antitubercular

Chemical Name: O-2-Deoxy-2-(methylamino)-α-L-glucopyranosyl-(1-2)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(1-4)-N,N'-bis(aminoiminomethyl)-D-streptamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57-92-1

Trade Name	Manufacturer	Country	Year Introduced
Streptomycin	MSD	US	1945
Streptomycine	Diamant	France	1961
Cidan-Est	Cidan	Spain	-
Darostrep	SCS Pharmalab	S. Africa	-
Estrepto E	Wassermann	Spain	-
Estrepto Level	Level	Spain	-
Estreptomicina	Cepa	Spain	-
Estreptomicina Normon	Normon	Spain	-
Estrepto Wolner	Wolner	Spain	-
Estreptomade	Made	Spain	-
Neodiestostreptobap	Martin Santos	Spain	-
Orastrep	Dista	UK	-
Servistrep	Servipharm	Switz.	-
Solvo-Strep	Heyl	W. Germany	-
Streptaguaine	Dista	UK	-
Streptobretin	Norbrook	UK	-
Streptosol	Therapex	Canada	-
Strycin	Squibb	US	-

Raw Materials

Nutrient medium
Bacterium Streptomyces griseus

Manufacturing Process

A medium is prepared having the following composition in tap water: 1.0% glucose; 0.5% peptone; 0.3% meat extract; and 0.5% NaCl. This medium is distributed in appropriate vessels to a depth of 1 to 2 inches, sterilized at 10 pounds steam pressure for 45 to 50 minutes, and then cooled.

The medium in each vessel is then inoculated with a heavy aqueous suspension of spores of a strain of Actinomyces griseus, and the inoculated media are maintained at an incubation temperature of 22° to 28°C for 10 days. The growth is then filtered off and the filtrates are combined for further treatment.

To a batch of approximately 10 liters of filtered broth is added 150 grams of activated charcoal. The mixture is stirred continuously for about 5 minutes and is then filtered. The slightly yellowish (almost colorless) filtrate is discarded and the charcoal residue is washed several times with distilled water and finally with 95% ethanol. The washed material is then suspended in 1.5 liters of 95% ethanol, made 0.15 normal with hydrochloric acid. The suspension is stirred for about an hour and allowed to stand in the cold for about 10 hours more with occasional stirring. The suspension is then filtered, the charcoal residue discarded, and the yellowish clear filtrate thus obtained is poured into 10 liters of ether, with stirring. A brown-colored aqueous layer separates and is drawn off.

The alcohol-ether solution is washed with 100 cc of water and the brown aqueous layer is drawn off and added to the first aqueous layer. The aqueous solution is neutralized to pH 6 to 7 with dilute sodium hydroxide and any precipitate that forms is filtered off and discarded. A faintly colored aqueous solution containing streptomycin is thus obtained.

References

Merck Index 8685
Kleeman and Engel p. 827
PDR p. 1410
I.N. p. 892
REM p. 1260
Waksman, S.A. and Schatz, A.: US Patent 2,449,866; September 21, 1948; assigned to Rutgers Research and Endowment Foundation
Bartels, C.R., Bryan, W.L. and Berk, B.; US Patent 2,868,779; January 13, 1959; assigned to Olin Mathieson Chemical Corporation

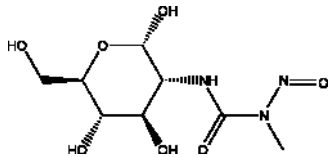
STREPTOZOCIN

Therapeutic Function: Antineoplastic

Chemical Name: 2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 18883-66-4

Trade Name	Manufacturer	Country	Year Introduced
Zanosar	Upjohn	US	1982

Raw Materials

Bacterium Streptomyces achromogenes
Nutrient medium

Manufacturing Process

On a sterile maltose-tryptone agar slant of the following composition: 1 g maltose; 0.5 g tryptone; 0.05 g K_2HPO_4; 0.01 g $FeSO_4 \cdot 7H_2O$; 1.5 g agar; and sufficient distilled water to make 100 ml, Streptomyces achromogenes var. streptozoticus was grown for 7 days at 28°C.

The culture thus produced was used as an inoculum for the following sterile medium: 1 g glucose; 1 g beef extract; 0.5 g Bacto peptone (Difco); 0.5 g NaCl; and sufficient distilled water to make 100 ml. The pH was adjusted to 7.0 before sterilization. The inoculated medium was incubated in shake flasks for 3 days at 28°C on a reciprocating shaker and 75 ml of the resulting growth was used to inoculate 12 l of sterile medium of the same formulation. The medium was incubated in a 20 l stainless steel bottle, at 28°C for 2 days, the contents being stirred continuously with sparged air at the rate of 6 l of free air per minute. The resulting growth was used to inoculate 250 l of the following sterile medium. 2 g Bacto peptone (Difco); 2.5 g blackstrap molasses; 2 g glucose; 0.25 g NaCl; and sufficient distilled water to make 100 ml. The pH was adjusted to 7.0 before sterilization.

This medium was incubated in a 100 gallon stainless steel fermentor, at 24°C with sparged air being introduced at the rate of 50 l/min and with agitation by an impeller. After 66 hours of fermentation the beer was harvested. To 100 gallons of harvested beer was added 17 pounds of diatomite, and 35 pounds of activated carbon. The mixture was stirred well and then filtered, the cake was water-washed with 10 gallons of tap water, and then washed with 25 gallons of acetone followed by 30 gallons of 1:1 aqueous acetone. The acetone solutions of streptozotocin were pooled and dried in vacuo to 3.88 pounds.

References

Merck Index 8695

DFU 4 (2) 137 (1979)
DOT 19 (5) 242 (1983)
I.N. p. 892
REM p. 1156
Bergy, M.E., De Boer, C., Dietz, A., Eble, T.E., Herr, R.R. and Johnson, L.E.; US Patent 3,027,300; March 27, 1962; assigned to The Upjohn Co.

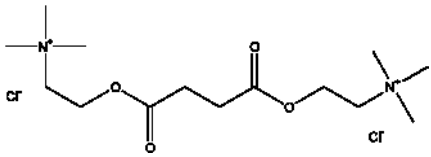
SUCCINYLCHOLINE DICHLORIDE

Therapeutic Function: Muscle relaxant

Chemical Name: Choline, chloride, succinate (2:1)

Common Name: Choline succinate dichloride; Diacetylcholine dichloride; Suxamethonium chloride

Structural Formula:



Chemical Abstracts Registry No.: 71-27-2; 306-40-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Anectine	Glaxo Wellcome	-	-
Anectine Flo-Pak	Glaxo Wellcome	-	-
Esculin	Embil	-	-
Myolaxin	Star	-	-
Nicolin	Asta	-	-
Quelicin	Abbott Laboratories	-	-
Relaxin	Kyorin	-	-
Scoline	Evans	-	-
Scoline	Glaxo Wellcome	-	-
Succinylcholine Chloride	Organon	USA	-

Raw Materials

Sodium hydroxide
Succinic acid chloroanhydride
Methyl chloride
Dimethylaminoethanol hydrochloride

Manufacturing Process

For the first time Fusko with coworkers synthesied the succinylcholine in 1949 year.

By the etherification of succinic acid chloroanhydride with dimethylaminoethanol hydrochloride in the presence of sodium hydroxide succinylcholine was prepared. Then the obtained succinylcholine was purified. To the succinylcholine the methylchloride was added (1:2 mols) and the succinylcholine dichloride was obtained as white powder.

The succinylcholine is used as succinylcholine diiodide. This salt may be prepeared identicaly.

References

Haletsky A.M.; Pharmaceutical Chemistry, "Medicina". Leningrad, 1966, 762 p.

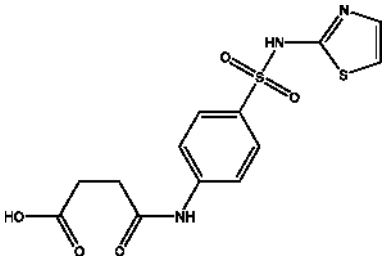
SUCCINYLSULFATHIAZOLE

Therapeutic Function: Antibacterial (intestinal)

Chemical Name: 4-Oxo-4-[[4-[(2-thiazolylamino)-sulfonyl]phenyl]amino] butanoic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 116-43-8

Trade Name	Manufacturer	Country	Year Introduced
Sulfasuxidine	MSD	US	1942
Thiacyl	Theraplix	France	1946
Colistatin	Smith and Nephew	UK	-
Cremosu xidine	MSD	UK	-

Raw Materials

2-Sulfanilamidothiazole
Succinic anhydride

Manufacturing Process

3.92 g of succinic anhydride was added to a boiling suspension of 10 g of 2-sulfanilamidothiazole in 100 cc of alcohol. The mixture was then refluxed for five minutes after the addition was complete at which time all of the solids were in solution. The solution was then cooled and diluted with an equal volume of water. The white solid precipitate which formed was filtered and recrystallized from dilute alcohol, yielding 2-N4-succinylsulfanilamidothiazole, melting at 184°C to 186°C.

References

Merck Index 8753
Kleeman and Engel p. 831
OCDSVol. 1 p. 132 (1977)
I.N. p. 894
Moore, M.L.; US Patents 2,324,013 and 2,324,014; both dated July 13, 1943; assigned to Sharp and Dohme, Inc.

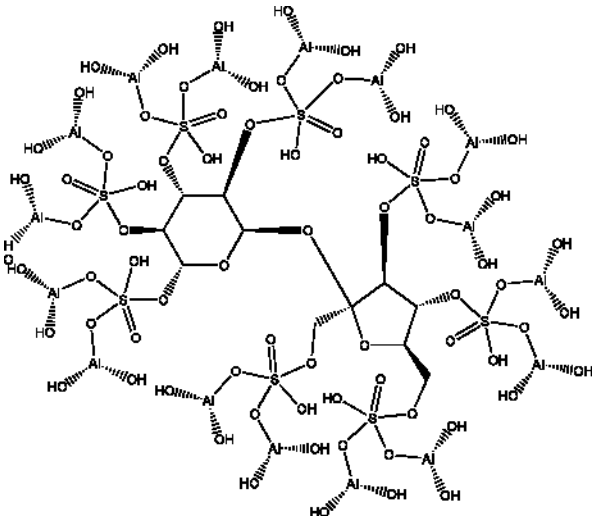
SUCRALFATE

Therapeutic Function: Antiulcer

Chemical Name: Hexadeca-μ-hydroxytetracosahydroxy[μ_8-[1,3,4,6-tetra-O-sulfo-β-D-fructofuranosyl-α-D-glucopyranosidetetrakis(hydrogen sulfato)(8-)]]hexadecaaluminum

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54182-58-0

Trade Name	Manufacturer	Country	Year Introduced
Antepsin	Baldacci	Italy	1975
Ulcogant	Cascan	W. Germany	1980
Carafate	Marion	US	1981
Ulogant	Merck	Switz.	1982
Antepsin	Ayerst	UK	1982
Ulsanic	DuPont	Australia	1983
Andapsin	Farmos	Sweden	1983
Sulcrate	Nordic	Canada	-
UlcerImin	Chugai	Japan	-

Raw Materials

Sulfur trioxide
Sodium hydroxide
Sucrose
Aluminum dihydroxychloride
Pyridine

Manufacturing Process

A disaccharide is added to a pyridine SO_3 complex solution, which is prepared by reacting 5 to 6 times the molar amount of liquid SO_3 as much as that of disaccharide with 5 to 10 times the amount of pyridine as that of the disaccharide at 0°C to 5°C, for sulfation at 50°C to 70°C for 3 to 7 hours. After the completion of sulfation, the greater part of pyridine is removed by decantation. The obtained solution exhibits an acidity that is so strong that it is improper to apply the reaction with aluminum ion and, therefore, sodium hydroxide is added for neutralization. After the remaining pyridine is removed by concentration, 100 unit volumes of water per unit volume of the residue is added thereto. To the solution is then added aluminum ion solution mainly containing aluminum dihydroxychloride, the pH of which is 1.0 to 1.2, in such an amount that the aluminum ion is present in an amount of 4 to 6 molar parts of the amount of disaccharide to provide a pH of 4 to 4.5. The mixture is reacted under stirring at room temperature and the formed disaccharide polysulfate-aluminum compound is allowed to precipitate. After filtration, the residue is washed with water and dried.

References

Merck Index 8755
PDR p. 1074
I.N. p. 894
REM p. 815
Nitta, Y., Namekata, M., Tomita, E. and Hirota, Y.; US Patent 3,432,489; March 11, 1969; assigned to Chugai Seiyaku K.K. (Japan)

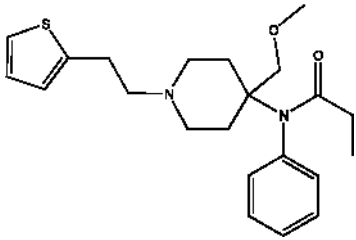
SUFENTANIL

Therapeutic Function: Analgesic

Chemical Name: N-[4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56030-54-7

Trade Name	Manufacturer	Country	Year Introduced
Sufenta	Janssen	Netherlands	1983
Sufenta	Janssen	US	-

Raw Materials

N-[4-(Methoxymethyl)-4-piperidinyl]-N-phenylpropanamide
2-Thiopheneethanol

Manufacturing Process

A mixture of 4.1 parts of N-[4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide, 5.3 parts of sodium carbonate and 120 parts of 4-methyl-2-pentanone is stirred and refluxed with water-separator. Then there are added 4.1 parts of 2-thiopheneethanol methanesulfonate ester and stirring at reflux is continued for 18 hours. The reaction mixture is cooled, washed twice with water and evaporated. The oily residue is purified by column-chromatography over silica gel, using a mixture of trichloromethane and 5% of methanol as eluent. The first fraction is collected and the eluent is evaporated. The oily residue is converted into the hydrochloride salt in 2,2'-oxybispropane. The free base is liberated again in the conventional manner. After extraction with 2,2'-oxybispropane, the latter is dried, filtered and evaporated. The oily residue solidifies on triturating in petroleum-ether. The solid product is filtered off and crystallized from petroleum-ether at -20°C, yielding, after drying, N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide; melting point 98.6°C.

References

Merck Index A-12

DFU 2 (5) 334 (1977)
PDR p. 959
I.N. p. 895
Janssen, P.A.J. and Daele, H.P.V.; US Patent 3,998,834; December 21, 1976; assigned to Janssen Pharmaceutica N.V. (Belgium)

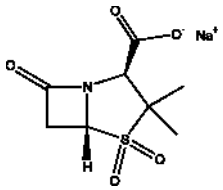
SULBACTAM SODIUM

Therapeutic Function: Beta-lactamase inhibitor

Chemical Name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-, 4,4-dioxide, (2S-cis), sodium salt

Common Name: Sulbactam sodium

Structural Formula:



Chemical Abstracts Registry No.: 69388-84-7; 68373-14-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sulbactam-Sodium	Antibiotic Co.	Bulgaria	-

Raw Materials

Bromine
$NaNO_2$
Iron
Sodium 2-ethylhexanoate
6-Aminopenicillanic acid
Hydrochloric acid
Potassium permanganate

Manufacturing Process

Sulbactam sodium is semi-synthetic antibiotic of penicillinic group. Start material for it's synthesis is 6-aminopenicillanic acid. First 6-aminopenicillanic acid was isolated in 1957 year from benzylpenicilline as resalt of treating of it by penicillinaze. Benzylpenicilline is produced by microorganism of genus Streptomyces.

Further, 6-aminopenicillanic acid reacted with bromine, hydrochloric acid and $NaNO_2$. As a result the 6,6-dibromopenicillanic acid was obtained.

6,6-Dibromopenicillanic acid was oxidized by $KMnO_4$, to give 6,6-dibromo-1,1-

dioxopenicillanic acid.

The 6,6-dibromo-1,1-dioxopenicillanic acid in presence of Fe was converted to the 1,1-dioxopenicillanic acid (sulbactam acid). The sulbactam acid was treated by sodium 2-ethylhexanoate and crude sulbactam sodium was obtained.

References

Gomis D.B. et al.; Fast high performance liquid chromatography method for in-process control of sulbactam. Analytica Chimica Acta, 498, (2003), 1-8

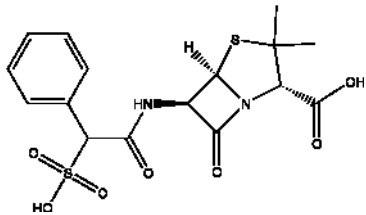
SULBENICILLIN

Therapeutic Function: Antibacterial

Chemical Name: 3,3-Dimethyl-7-oxo-6-[(phenylsulfoacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Common Name: Sulfocillin

Structural Formula:



Chemical Abstracts Registry No.: 41744-40-5; 28002-18-8 (Sodium salt)

Trade Name	Manufacturer	Country	Year Introduced
Lillacillin	Takeda	Japan	1973
Kedacillina	Bracco	Italy	1982

Raw Materials

α-Sulfophenacetyl chloride
6-Aminopenicillanic acid

Manufacturing Process

To a suspension of 1.08 parts by weight of 6-aminopenicillanic acid in 8 parts by volume of water is added 1.48 parts by weight of sodium bicarbonate. After the mixture is dissolved, a solution of 1.18 parts by weight of α-

sulfophenylacetyl chloride in 10 parts by volume of diethylether is gradually added thereto. The mixture is stirred at a temperature in the neighborhood of 0°C for 1 hour. The aqueous layer is washed twice with 10 parts by volume of portions of ether and adjusted to pH 1.2 with cation exchange resin of polystyrene sulfonic acid type under constant cooling. Then the solution is washed twice with 15 parts by volume of portions of ethyl acetate, followed by extraction twice with 15 parts by volume of portions of n-butanol. The extracts are combined and washed twice with 15 parts by volume of portions of water and, then, extracted with an aqueous solution of sodium bicarbonate. The extract is adjusted to pH 6.5, washed with ether and lyophilized to give the sodium salt of α-sulfobenzylpenicillin. Yield is 1.2 parts by weight.

References

Merck Index 8762
DOT 8 (5) 199 (1972) and 9 (4) 149 (1973)
I.N. p. 895
REM p. 1201
Morimoto, S., Nomura, H., Fugono, T., Maeda, K. and Ishiguro, T.; US Patent 3,600,379; May 2, 1972; assigned to Takeda Chemical Industries, Ltd. (Japan)

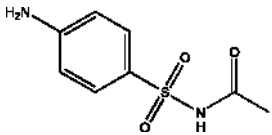
SULFACETAMIDE

Therapeutic Function: Antimicrobial

Chemical Name: N-[(4-Aminophenyl)sulfonyl]acetamide

Common Name: N'-Acetylsulfanilamide

Structural Formula:



Chemical Abstracts Registry No.: 144-80-9

Trade Name	Manufacturer	Country	Year Introduced
Sulamyd	Schering	US	1941
Urosulfon	Consol. Midland	US	1955
Sulfacidin	Crookes	UK	-
Sultrin	Ortho	US	-
Triple Sulfa	Fougera	US	-
Trysul	Savage	US	-

Raw Materials

4-Aminobenzenesulfonamide
Acetic anhydride
Sodium hydroxide

Manufacturing Process

17.2 grams of 4-aminobenzene-sulfonamide are heated to boiling with 75 cc of acetic anhydride for 1 hour and thereupon the diacetyl product caused to separate by stirring into ice water. After recrystallization from alcohol the 4-acetylaminobenzene-sulfonacetyl-amide forms colorless prisms of melting point 253°C with decomposition. The product is easily soluble in alkalies and forms neutral salts. The acetylation can also take place with acetyl chloride. Instead of the 4-aminobenzene-sulfonamide also 4-acetylaminobenzene-sulfonamide can be employed. The action of 4-acetylaminobenzene-sulfonic acid chloride on acetamide yields the same product.

By heating the diacetyl compound with sodium hydroxide solution partial saponification of the acetyl groups takes place. 25.6 grams of diacetyl compound are heated to boiling for some hours with 100 cc of 2N sodium hydroxide solution. The precipitate produced by acidification of the solution with acetic acid is filtered off and treated with dilute sodium carbonate solution. The 4-aminobenzene-sulfonacetylamide passes into solution while the simultaneously formed 4-acetylaminobenzene-sulfonamide remains undissolved. It is filtered with suction and the filtrate again acidified with acetic acid. The 4-aminobenzene-sulfon-acetamide separates out and is recrystallized from water. It forms colorless lustrous rhombic crystals of MP 181°C.

References

Merck Index 100
Kleeman and Engel p. 833
PDR pp. 888, 1306, 1606
OCDS Vol. 1 p. 123 (1977)
I.N. p. 897
REM p. 1176
Dohrn, M. and Diedrich, P.; US Patent 2,411,495; November 19, 1946; assigned to Schering Corporation

SULFACHLORPYRIDAZINE

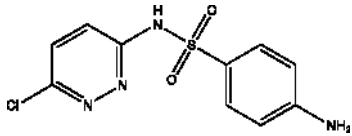
Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(6-chloro-3-pyridazinyl)benzenesulfonamide

Common Name: -

Chemical Abstracts Registry No.: 80-32-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sonilyn	Mallinckrodt Inc.	US	1962
Nefrosul	Riker	US	1974
Consulid	Ciba Geigy	US	-
Cosulfa	Elliott-Marion	Canada	-
Durasulf	Dessy	Italy	-
Sulfaclorazina	Ellem	Italy	-

Raw Materials

3,6-Dichloropyridazine
Sulfanilamide

Manufacturing Process

1.9 parts of 3,6-dichloropyridazine, 3.4 parts of sulfanilamide, 2.7 parts of potassium carbonate and 1 part of sodium chloride were ground together. The solid mixture was heated with stirring and as the dichloropyridazine and sulfanilamide melted, the mixture became a slurry. When the bath temperature had reached 140°C a sudden evolution of carbon dioxide occurred which lasted about 5 minutes, after which the mixture set in fine granules. When no more carbon dioxide was evolved, heating was stopped and the reaction mixture was heated with sufficient water to dissolve it and the solution allowed to cool. Unreacted sulfanilamide was collected by filtration. Excess dichloropyridazine was removed from the filtrate by extraction with a water immiscible organic solvent such as ether.

The basic solution was chilled and poured into one-half volume of 1:3 acetic acid. Sufficient hydrochloric acid was added to bring the mixture to pH 4. The crude 3-sulfanilamido-6-chloropyridazine which precipitated was purified by solution in 6 parts of 1:100 ammonium hydroxide, charcoal treatment and precipitation by pouring of the filtrate into dilute acetic acid.

References

Merck Index 8770
Kleeman and Engel p. 833
OCDS Vol. 1 pp. 124, 131 (1977)
I.N. p. 897
Lester, M.M. and English, J.P.; US Patent 2,790,798; April 30, 1957; assigned to American Cyanamid Company

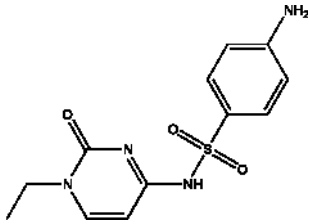
SULFACYTINE

Therapeutic Function: Antibacterial

Chemical Name: 4-(Amino-N-(1-ethyl-1,2-dihydro-2-oxo-4-pyrimidinyl) benzenesulfonamide

Common Name: N-Sulfanilyl-1-ethylcytosine; Sulfacitine

Structural Formula:



Chemical Abstracts Registry No.: 17784-12-2

Trade Name	Manufacturer	Country	Year Introduced
Renoquid	Glenwood	US	1975
Renoquid	Parke Davis	US	1983

Raw Materials

Sodium	3-(Ethylamino)propionitrile
Hydrogen bromide	N-Acetylsulfanilyl chloride
Potassium cyanate	Methanol
Bromine	Sodium hydroxide

Manufacturing Process

The N-(N-acetylsulfanilyl)-1-ethylcytosine used as a starting material is prepared as follows: To a solution of 333 grams of 3-(ethylamino)propionitrile in 1,697.3 ml of 2 N hydrochloric acid is added 275 grams of potassium cyanate, the resulting solution is concentrated under reduced pressure to a syrup, and the syrup is heated at 90° to 100°C for 6 hours and then evaporated to dryness at 90° to 100°C under reduced pressure. The residue is extracted with 1,600 ml of hot absolute ethanol, and the extract is concentrated to 500 ml and chilled. The crystalline 1-(2-cyanoethyl)-1-ethylurea obtained is isolated, washed with cold absolute ethanol, and dried, melting point 88° to 91°C. This intermediate (58.7 grams) is added to a solution of 11.5 grams of sodium in 500 ml of methanol and the resulting solution is heated under reflux for 30 minutes. After cooling, the mixture, containing 1-ethyl-5,6-dihydrocytosine, is treated with a slight excess of gaseous hydrogen bromide and evaporated to dryness. The residue is extracted, first with 500 ml, then with 100 ml of hot isopropyl alcohol, the extracts are combined and chilled, and the crystalline 1-ethyl-5,6-

dihydrocytosine hydrobromide obtained is isolated and dried, MP 167.5° to 169.5°C. This salt (88.8 grams) is dissolved in 200 ml of nitrobenzene at 174°C, 22.6 ml of bromine is added over a period of 8 minutes, and the mixture is kept at 170° to 175°C until hydrogen bromide evolution ceases (about 15 minutes). Upon cooling, there is obtained crude 1-ethylcytosine hydrobromide, which is isolated, washed with ether, and dried, MP 170° to 187°C.

This salt is heated at 90° to 100°C with 70 ml of N,N-dimethylformamide and 60 ml of piperidine, and the resulting solution is chilled to give 1-ethylcytosine, MP 238° to 243°C. A mixture of 10.5 grams of 1-ethylcytosine, 18.6 grams of N-acetylsulfanilyl chloride, and 50 ml of pyridine is stirred at room temperature for 2 days. The precipitated solid is removed by filtration, and the filtrate is evaporated at 60°C under reduced pressure to a syrup. The syrup is triturated with 0.25N hydrochloric acid, and the solid N-(N-acetyl-sulfanilyl)-1-ethylcytosine obtained is isolated and dried. This solid is suitable for use without further purification.

A solution of 65 grams of N-(N-acetylsulfanilyl)-1-ethylcytosine in 380 ml of 2 N aqueous sodium hydroxide is heated under reflux for 1 hour. Upon cooling, the solution is treated with charcoal, purified by filtration, and acidified with acetic acid. The solid N-sulfanilyl-1-ethylcytosine that precipitates is isolated, washed with water, and dried, MP 166.5° to 168°C following successive crystallizations from butyl alcohol and from methanol.

References

Merck Index 8771
Kleeman and Engel p. 834
PDR p. 926
OCDS Vol. 2 p. 113 (1980);
DOT 12 (9) 370 (1976)
I.N. p. 898
REM p. 1172
Doub, L.and Krolls, U.; US Patent 3,375,247; March 26,1968; assigned to Parke, Davis and Company

SULFADIAZINE

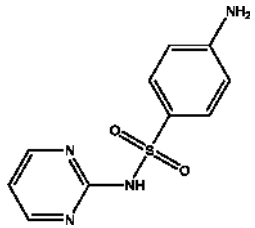
Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-2-pyrimidinylbenzenesulfonamide

Common Name: Sulfanilylaminopyrimidine; Sulfapyrimidine

Chemical Abstracts Registry No.: 68-35-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sulfadiazine	Lederle	US	1941
Adiazin	Star	Finland	-
Adiazine	Theraplix	France	-
Coco-Diazine	Lilly	US	-
Di-Azu-Mul	First Texas	US	-
Flamazine	Smith and Nephew	UK	-
Lipo-Diazine	Donley Evans	US	-
Magmoid Sulfadiazine	Pitman-Moore	US	-
Sulfadets	Dymond	Canada	-
Sulfolex	Medica	Finland	-
Theradia	Daiichi	Japan	-
Theradiazine	Daiichi	Japan	-
Ultradiazin	Atabay	Turkey	-

Raw Materials

2-Aminopyrimidine
p-Nitrobenzenesulfonyl chloride
Iron
Hydrogen chloride

Manufacturing Process

5.4 parts of 2-amino-pyrimidine were covered with 15 parts of anhydrous pyridine. The reaction mixture was treated with 14 parts of p-nitrobenzenesulfonyl chloride and the whole heated briefly on the steam bath and let stand 45 minutes at room temperature. To the reaction mixture were added 80 parts of hot alcohol and the precipitate was filtered off and washed with water. The solid was dissolved in dilute caustic solution and the solution was filtered, cooled and acidified. The 2-(p-nitrobenzenesulfonamido)-pyrimidine precipitated and was collected.

The crude 2-(p-nitrobenzenesulfonamido)-pyrimidine from the preceding step was suspended in 130 parts alcohol and 1.5 parts of concentrated hydrochloric acid were added. The suspension was then heated to reflux and 30 parts of iron powder were added with mechanical stirring. The mixture was refluxed and stirred for 24 hours with occasional addition of concentrated hydrochloric acid. The reaction mixture was then made slightly basic and filtered hot and the residues were extracted with several portions of boiling alcohol. The

filtrate and wash solutions were combined and evaporated. The 2-(sulfanilamido)-pyrimidine was recrystallized from boiling water with decolorizing charcoal added, according to US Patent 2,410,793.

References

Merck Index 8772
Kleeman and Engel p. 834
OCDS Vol. 1 p. 124 (1977)
DOT 16 (8) 261 (1980)
I.N. p. 898
REM p. 1173
Sprague, J.M.; US Patent 2,407,966; September 17, 1946; assigned to Sharp and Dohme, Inc.
Winnek, P.S. and Roblin, R.O. Jr.; US Patent 2,410,793; November 5, 1946; assigned to American Cyanamid Company

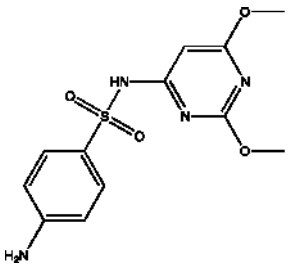
SULFADIMETHOXINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(2,6-dimethoxy-4-pyrimidinyl) benzenesulfonamide

Common Name: Sulforthomidine; Sulphormethoxine

Structural Formula:



Chemical Abstracts Registry No.: 122-11-2

Trade Name	Manufacturer	Country	Year Introduced
Madribon	Roche	US	1958
Madrigid	Roche	US	1959
Abcid	Daiichi	Japan	-
Albon	Roche	US	-
Ancosul	Anchor	US	-
Asthoxin	Kobayashi	Japan	-
Bensulfa	Caber	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Chemiosalfa	Salfa	Italy	-
Crozinal	Borromeo	Italy	-
Deltin	Wassermann	Italy	-
Deposol	Pliva	Yugoslavia	-
Diasulfa	Crosara	Italy	-
Diazinol	Washington	Italy	-
Dimetossilina	Lister	Italy	-
Dimetossin	Caber	Italy	-
Dimetoxan	Nessa	Spain	-
Dimetoxin	Nissin	Japan	-
Dimexin	Fuso	Japan	-
Duramid	Deva	Turkey	-
Emerazina	Croce Bianca	Italy	-
Fultamid	Fulton	Italy	-
Hachimetoxin	Toyo	Japan	-
Ipersulfa	Ion	Italy	-
Jatsulph	Clinimed	S. Africa	-
Lensulpha	Lennon	S. Africa	-
Levisul	A.F.I.	Italy	-
Madribon	Roche	Italy	-
Madroxin	Polfa	Poland	-
Melfa	Tanabe	Japan	-
Micromega	Sidus	Italy	-
Mition D	Taisho	Japan	-
Neostreptal	Locatelli	Italy	-
Neosulfamyd	Libra	Italy	-
Omnibon	Yamanouchi	Japan	-
Oxazina	Made	Spain	-
Redifal	A.M.S.A.	Italy	-
Risulpir	Lisapharma	Italy	-
Ritarsulfa	Benvegna	Italy	-
Scandisil	Firma	Italy	-
Sulfabon	Vaillant	Italy	-
Sulfadomus	Medici Domus	Italy	-
Sulfaduran	Janus	Italy	-
Sulfalon	Sumitomo	Japan	-
Sulfastop	Vis	Italy	-
Sulfathox	SCS Pharmalab	S. Africa	-
Sulfoplan	Gea	Denmark	-
Sulf -Reten	Pons	Spain	-
Sulmethon	Mohan	Japan	-
Sulmetoxyn	Nichiiko	Japan	-
Sulxin	Chugai	Japan	-
Sumetamin	Samva	Japan	-
Tempodiazina	C.I.F.	Italy	-

Raw Materials

Sodium sulfanilamide
4-Phenylsulfonyl-2,6-dimethoxypyrimidine

Manufacturing Process

1.4 g of 4-phenylsulfonyl-2,6-dimethoxypyrimidine and 4 g of sodium sulfanilamide (both dried over potassium hydroxide) were very finely ground and heated in an oil bath for 10 hours at 120°C (inside temperature). The reaction mixture was taken up in 30 ml of water and treated with 3 ml of 2 N sodium hydroxide solution. After standing for one hour at 0°C, the turbid solution was filtered and the filtrate was made alkaline with sodium carbonate. After again standing for one hour at 0°C, the precipitate was filtered off (1.9 g of regenerated sulfanilamide) and the filtrate was neutralized with acetic acid, whereupon crystallization resulted. The isolated crystals of 4-sulfanilamido-2,6-dimethoxypyrimidine weighed 1.3 g (84% of theory), melting point 190°C to 196°C.

References

Merck Index 8775
Kleeman and Engel p. 835
OCDS Vol. 1 pp. 125, 129 (1977)
I.N. p. 899
Bretschneider, H. and Klotzer, W.; US Patent 2,703,800; March 8,1955; assigned to Oesterreichische Stickstoffwerke AG
Bretschneider, H. and Klotzer, W.; US Patent 3,127,398; March 31, 1964; assigned to Hoffmann-LaRoche, Inc.

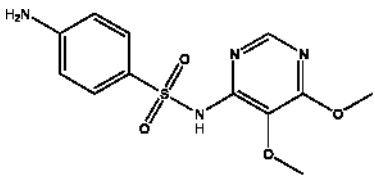
SULFADOXINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(5,6-dimethoxy-4-pyrimidinyl) benzenesulfonamide

Common Name: Sulforthomidine; Sulformethoxine

Structural Formula:



Chemical Abstracts Registry No.: 2447-57-6

Trade Name	Manufacturer	Country	Year Introduced
Fanasil	Roche	Italy	1973
Fansidar	Roche	US	1982

Raw Materials

Thiourea
Sodium
Methanol
Methyl iodide
α-Methoxycyanoacetic acid methyl ester
Phenyltrimethylammonium toluene sulfonate
p-Acetylaminobenzenesulfonyl chloride

Manufacturing Process

(a) α-methoxy-cyanoacetic acid methyl ester is condensed with thiourea, in the presence of sodium methylate, to form 2-thio-4-amino-5-methoxy-6-hydroxy-pyrimidine.

(b) The product thus obtained is methylated in a sodium methylate solution with methyl iodide to form 2-methylthio-4-amino-5-methoxy-6-hydroxy-pyrimidine of MP 203°C, from water.

(c) The latter product is methylated with phenyltrimethylammonium-toluenesulfonate to form 2-methylthio-4-amino-5,6-dimethoxy-pyrimidine of MP 112° to 115°C, from 20% methanol.

(d) 0.9 gram of 2-methylthio-4-amino-5,6-dimethoxy-pyrimidine are dissolved in 3 ml of absolute pyridine. At 0°C, 1.2 grams of p-acetylaminobenzenesulfonyl chloride are added thereto and the mixture is shaken until all the material is dissolved. The solution is allowed to stand for 22 hours at 0°C and the pyridine eliminated in vacuo at 20°C. To the resulting product are added 20 ml of water and 3 ml of glacial acetic acid, whereupon the whole mixture is heated to the boil, thus causing crystallization. The crude product obtained is dissolved in 40 ml of 2.5% soda solution, and the solution obtained is filtered and supersaturated with gaseous carbon dioxide. There is thus obtained 1.5 grams (85%) of 2-methylthio-4-(N_4-acetyl-sulfanilamido)-5,6-dimethoxy-pyrimidine of MP 220° to 221°C, from 50% ethanol.

(e) 1.3 grams of 2-methylthio-4-(N_4-acetyl-sulfanilamido)-5,6-dimethoxy-pyrimidineare dissolved in 25 ml of water and 0.4 gram of anhydrous sodium carbonate, then refluxed for 3 ½ hours in the presence of 6 to 7 grams of Raney nickel. Then, a solution of 1 gram of sodium hydroxide in 3 ml of water is added thereto and heating continued for another hour. The catalyst is filtered off and the filtrate acidified to Congo red with hydrochloric acid. The pH is then brought to 5 by means of ammonia, thus causing crystallization. There is thus obtained 0.51 gram of 4-sulfanilamido-5,6-dimethoxy-pyrimidine of MP 190° to 194°C, from 50% ethanol.

References

Merck Index 8776
PDR p. 1484
I.N. p. 899
REM p. 1176

Bretschneider, H., Klotzer, W. and Schantl, J.; US Patent 3,132,139; May 5, 1964; assigned to Hoffmann-La Roche Inc.

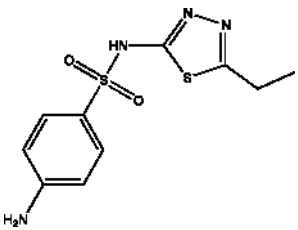
SULFAETHIDOLE

Therapeutic Function: Antibacterial

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

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 94-19-9

Trade Name	Manufacturer	Country	Year Introduced
Sul-Spansion	SKF	US	1956
Globucid	Schering	-	-
Spasmo-Urosulf	T.A.D.	W. Germany	-
Sulfa-Perlongit	Boehringer Ingelheim	W. Germany	-
Urosulf	T.A.D.	W. Germany	-

Raw Materials

2-Amino-5-ethyl-1,3,4-thiadiazole
p-Acetylaminobenzenesulfonyl chloride

Manufacturing Process

0.163 mol of 2-amino-5-ethyl-1,3,4-thiadiazole was covered with 43 parts of anhydrous pyridine. To the mixture was added 50 parts (0.214 mol) of p-acetylaminobenzenesulfonyl chloride with vigorous shaking at 50°C to 60°C. The reaction mixture was then heated to 125°C. When the mixture had cooled somewhat it was placed in a Claisen flask and 27.6 parts (0.69 mol) of sodium hydroxide dissolved in 110 parts of water was added through a dropping funnel while distilling off a mixture of pyridine and water. The distillation was stopped when the temperature reached 100°C and the residual liquor in the flask heated at 95°C for 30 minutes.

The reaction mixture was then poured into 1,650 parts of hot water, the pH adjusted to 8 to 9, decolorizing charcoal was added and the whole was heated on the steam for 15 minutes. The charcoal was filtered off and the hot filtrate neutralized and cooled. The 2-(sulfanilamido)-5-ethyl-1,3,4-thiadiazole was purified by repeated crystallization from boiling water.

References

Merck Index 8777
Kleeman and Engel p. 836
OCDS Vol. 1 p. 125 (1977)
I.N. p. 900;
Roblin, R.O. Jr. and Winner, P.S.; US Patent 2,358,031; September 12, 1944; assigned to American Cyanamid Co.

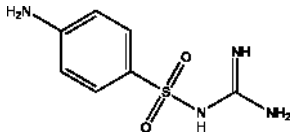
SULFAGUANIDINE

Therapeutic Function: Antimicrobial

Chemical Name: 4-Amino-N-(aminoiminomethyl)benzenesulfonamide

Common Name: Sulfanilylguanidine

Structural Formula:



Chemical Abstracts Registry No.: 57-67-0

Trade Name	Manufacturer	Country	Year Introduced
Sulfaguanidine	Lederle	US	1941
Aseptil-Guanadina	Wassermann	Italy	-
Aterian	Takeda	Japan	-
Devaguanil	Deva	Turkey	-
Ganidan	Specia	France	-
Guabeta	O.T.W.	W. Germany	-
Guasept	Ferrosan	Denmark	-
Resulfon	Nordmark	W. Germany	-

Raw Materials

Iron
Guanidine hydrochloride
Hydrogen chloride
p-Nitrobenzenesulfonyl chloride

Manufacturing Process

10 parts of guanidine hydrochloride (0.1 mol) was dissolved in 75 parts of water and the pH adjusted to 8 to 9. The solution was warmed to 50°C to 60°C and kept at this temperature while a slurry of 25 parts (0.113 mol) of p-nitrobenzenesulfonyl chloride was added slowly with mechanical stirring. The pH was kept at 8 to 9 by the addition of 40% sodium hydroxide solution. At the end of the reaction the solution was cooled and filtered from the separated solid. The p-nitrobenzene sulfonyl guanidine was recrystallized from hot water.

5 parts (0.024 mol) of p-nitrobenzene sulfonyl guanidine was dissolved in 50 parts of boiling 95% alcohol and to the solution was added 0.5 part of concentrated hydrochloric acid. The solution was heated to reflux and 6 parts of iron dust was added. The suspension was refluxed for 3 hours, made basic with potassium carbonate, and filtered hot. The alcohol was evaporated off and the p-aminobenzene sulfonyl guanidine recrystallized from boiling water with the addition of decolorizing charcoal.

References

Merck Index 8779
Kleeman and Engel p. 837
OCDS Vol. 1 p. 123 (1977)
I.N. p. 900
Winnek, P.S.; US Patent 2,218,490; October 15, 1940; assigned to American Cyanamid Co.
Winnek, P.S.; US Patent 2,229,784; January 28, 1941; assigned to American Cyanamid Co.
Winnek, P.S.; US Patent 2,233,569; March 4, 1941; assigned to American Cyanamid Co.

SULFAGUANOL

Therapeutic Function: Antibacterial

Chemical Name: N^1-[(4,5-Dimethyl-2-oxazolyl)amidino]sulfanilamide

Common Name: Sulfadimethyloxazolylguanidine

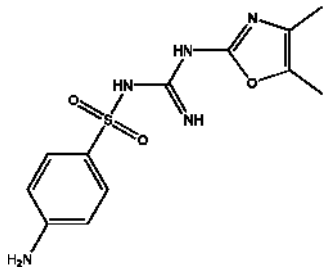
Chemical Abstracts Registry No.: 27031-08-9

Trade Name	Manufacturer	Country	Year Introduced
Enterocura	Nordmark	W. Germany	1973
Enterocura	De Angeli	Italy	1981

Raw Materials

Acetoin
Hydrogen chloride
$N(^1)$-[p-Aminobenzenesulfonyl]-$N(^3)$-cyanoguanidine

Structural Formula:



Manufacturing Process

23.9 grams (0.1 mol) of N^1-[p-amino benzene sulfonyl]-N^3-cyanoguanidine and 13.2 grams (0.15 mol) of acetoin are thoroughly stirred in a mixture of 120 cc of water and 120 cc of methanol. 25 cc of concentrated hydrochloric acid are added dropwise with stirring to this suspension at 40°C. A clear solution is obtained after 30 minutes which solution is kept at 40°C for another hour. Thereafter, the methanol is distilled off in a vacuum, the remaining solution is treated with charcoal and the pH of the filtered solution is quickly brought to 11 by addition of 10% soda lye with quick stirring.

The compound at first precipitated is redissolved at a pH of 11. The solution is treated another time with charcoal and is filtered. Thereafter, a mixture of anhydrous acetic acid and water in a proportion of 1:1 is added with stirring and cooling until a pH of 7 is reached. Thus, the reaction product separates with crystallization.

For purification, the product is recrystallized from 15 times the amount of a 9:1 mixture of acetone and water. The resulting N^1-[p-amino benzene sulfonyl] -N^3-(4,5-dimethyl-oxazolyl-(2)]-guanidine is obtained as colorless crystals having a MP of 233° to 236°C.

References

Merck Index 8780
Kleeman and Engel p. 838
DOT 9 (5) 185 (1973)
I.N. p. 900
Loop, W., Baganz, H., Kohlmann, F.-W. and Schultze, H.; US Patent 3,562,258; Feb. 9, 1971; assigned to Nordmark-Werke GmbH, Germany

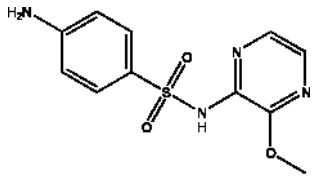
SULFALENE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(3-methoxypyrazinyl)benzenesulfonamide

Common Name: Sulfamethopyrazine

Structural Formula:



Chemical Abstracts Registry No.: 152-47-6

Trade Name	Manufacturer	Country	Year Introduced
Longum	Farmitalia	W. Germany	1962
Kelfizina	Farmitalia	Italy	1962
Kelfizine	Farmitalia	UK	1969
Kelfizine	Bellon	France	1969

Raw Materials

2-Aminopyrazine
Sodium
Bromine
Sodium hydroxide
p-Acetylaminobenzenesulfonyl chloride
Hydrogen
Methanol

Manufacturing Process

2-Amino-3,5-Dibromo-Pyrazine: 112.7 ml of bromine in 375 ml of acetic acid are slowly added at 0° to +2°C, while stirring, to a solution of 95.11 grams of 2-amino-pyrazine and 326.5 grams of acetic acid trihydrate ($CH_3COONa \cdot 3H_2O$) in 1,480 ml of acetic acid. This addition requires about 2 to 3 hours and it is carried out in the dark. The mixture is then allowed to stand at room temperature (25° to 30°C) for 15 to 16 hours. About 1.5 liters of acetic acid are distilled off under vacuum (12 to 14 mm Hg) at 35°C and the brown and viscous residue is poured into 500 grams of ice-water under stirring.

Aqueous 20% sodium hydroxide is added in order to obtain a pH = 8 and then the product is filtered and air-dried. The air-dried product is extracted 6 times with 150 ml of ether; the filtered ethereal solutions are evaporated to dryness and the residue (50 to 52 grams) is crystallized from hot water. The yield is 34.36 grams, melting at 114°C.

2-Amino-3-Methoxy-5-Bromo-Pyrazine: 7 grams of 2-amino-3,5-dibromo-pyrazine are boiled for 9 hours in a methanolic solution of sodium methylate (obtained from 0.65 gram of Na and 18.5 ml of methanol). By cooling a crystalline product is obtained, filtered and washed once with methanol and 2 to 3 times with water. The yield is 5.4 grams, melting at 138°C.

2-Amino-3-Methoxy-Pyrazine: 3 grams of 2-amino-3-methoxy-5-bromo-pyrazine are hydrogenated, in methanolic solution at room temperature and at atmospheric pressure, in the presence of 1 gram of palladium over charcoal

(10%) and 0.9 gram of potassium hydroxide. When the stoichiometric amount of hydrogen is absorbed, the suspension is filtered and the filtrate is evaporated to dryness. The residue is extracted with acetone, the acetonic solution is evaporated and the residue (1.8 grams, melting at 75° to 82°C) is crystallized from cyclohexane. The yield is 1.5 grams, melting at 85°C.

2-(p-Acetylaminobenzene-sulfonamido)-3-Methoxy-Pyrazine: 1.5 grams of 2-amino-3-methoxy-pyrazine dissolved in 15 ml of anhydrous pyridine are treated, under cooling and stirring, with 2.81 grams of p-acetylaminobenzenesulfonyl chloride, at small portions in about 30 minutes. The mixture is allowed to stand for 20 hours at room temperature and then is heated to 50°C for 4 hours.

The solution is concentrated to one-third of its volume, under vacuum, and poured into ice-water under stirring. The precipitate is filtered and washed with water. 2.21 grams melting at 218° to 220°C are obtained. The MP (crystallized from alcohol) is 224°C.

2-Sulfanilamido-3-Methoxy-Pyrazine: 1.5 grams of the product from the preceding step and 7 to 8 ml of aqueous 10% sodium hydroxide are boiled for 1 hour. The cooled solution is slightly acidified to pH 6 with aqueous 2 N hydrochloric acid and the product is filtered. The yield is 1.25 grams, melting at 175°C.

References

Merck Index 8781
Kleeman and Engel p. 838
OCDS Vol. 1 p. 125 (1977)
I.N. p. 901
Camerino, B. and Palamidessi, G.; US Patent 3,098,069; July 16, 1963; assigned to Societa Farmaceutici Italia, Italy

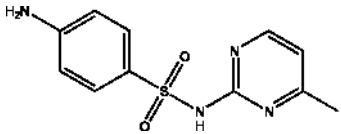
SULFAMERAZINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(4-methyl-2-pyrimidinyl)benzenesulfonamide

Common Name: Sulfamethyldiazine; Methylsulfadiazine

Structural Formula:



Chemical Abstracts Registry No.: 127-79-7

Trade Name	Manufacturer	Country	Year Introduced
Sulfamerazine	Lederle	US	1943
Dosulfin	Geigy	W. Germany	-
Mebacid	VEB Berlin Chemie	E. Germany	-
Polagin	De Angeli	Italy	-
Percoccide	A.C.F.	Netherlands	-
Romezin	Tanabe	Japan	-
Septosil	EGYT	Hungary	-
Solumedine	Specia	France	-
Spanbolet	Norden	US	-

Raw Materials

2-Amino-6-methyl pyrimidine
p-Acetylaminobenzenesulfonyl chloride
Hydrogen chloride

Manufacturing Process

To a well agitated solution of 6.95 grams of 2-amino-6-methyl pyrimidine in 40 cc of pyridine, 15 grams of p-acetylaminobenzenesulfonyl chloride are added in small portions over a 30 minute period. The reaction mixture is then heated on a steam bath for 30 minutes, the free pyridine being then removed under reduced pressure and the residue mixed with cold water, and the latter mixture is vigorously stirred. The solid reaction product is removed by filtration and washed with cold water.

There is obtained a yield of 14 grams of crude 2-(p-acetylaminobenzenesulfonamido)-6-methyl pyrimidine, which on recrystallization from alcohol and water melts at 238° to 239°C. The crude product is hydrolyzed by suspending it in 400 cc of 2 N hydrochloric acid and warming until solution is complete. The solution is neutralized with sodium carbonate and the precipitated 2-(sulfanilamido)-6-methyl pyrimidine is removed by filtration. The latter on recrystallization from alcohol and water shows a melting point of 225° to 226°C.

References

Merck Index 8783
Kleeman and Engel p. 839
OCDS Vol. 1 pp. 124, 128 (1977)
I.N. p. 901
REM p. 1173
Sprague, J.M.; US Patent 2,407,966; September 17, 1946; assigned to Sharp and Dohme, Inc.

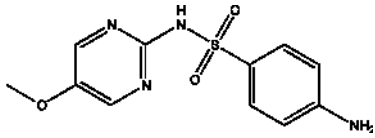
SULFAMETER

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(5-methoxy-2-pyrimidinyl)benzenesulfonamide

Common Name: Sulfamethoxydiazine

Structural Formula:



Chemical Abstracts Registry No.: 651-06-9

Trade Name	Manufacturer	Country	Year Introduced
Sulla	Robins	US	1968
Bayrena	Bayer Pharma	France	-
Durenat	Bayer/Schering	W. Germany	-
Durenate	Bayer	UK	-
Fortesul	Pliva	Yugoslavia	-
Kirocid	Schering	W. Germany	-
Kiron	Schering	W. Germany	-
Ultrax	Chemie Linz	Austria	-

Raw Materials

Phosphorus oxychloride
Guanidine carbonate
Zinc
Methoxymalonic acid ester
Carbethoxy-sulfanilic acid chloride
Sodium hydroxide

Manufacturing Process

2-Amino-5-methoxy pyrimidine is obtained having a melting point of about 300°C by condensation of methoxymalonic acid ester with guanidine carbonate in the presence of sodium ethylate. The resultant reaction product is then converted to 2-amino-5-methoxy-4,6-dichloropyrimidine (melting point 216°C to 217°C) by heating this reaction product with phosphorus oxychloride. The dichloro compound is then suspended in water with zinc dust and is tested in the presence of caustic alkaline or carbonates to produce the 2-aminod-methoxy pyrimidine compound, melting point 80°C to 82°C, (benzene).

12.6 g of 2-amino-5-methoxy pyrimidine, 26.4 g of carbethoxy-sulfanilic acid chloride and 50 cc of dry pyridine are heated for 30 minutes with frequent shaking to a temperature of 80°C. The reaction product is then mixed with 200 cc of water and with dilute hydrochloric acid (0.1 N) until the reaction is acid to Congo Red indicator. A precipitate is formed which is then filtered under suction, washed with distilled water, and dried at 150°C. A practically quantitative yield is recovered of 2-(p-carbethoxyaminobenzene-sulfonamido)-5-methoxypyrimidine, melting point 248°C to 250°C.

To hydrolyze the sulfapyrimidine compound, the same is heated at 90°C with 200 cc of 2 N potassium hydroxide solution for about one hour until complete solution is obtained. The resultant solution is then cooled to room temperature (25°C) and acidified with acetic acid to precipitate the hydrolyzed product, which is then recrystallized from dilute acetone admixed with animal charcoal.

References

Merck Index 8785
Kleeman and Engel p. 841
OCDS Vol. 1 pp. 125, 129 (1977)
I.N. p. 902
Diedrich, P.; US Patent 3,214,335; October 26, 1965; assigned to Schering A.G. (Germany)

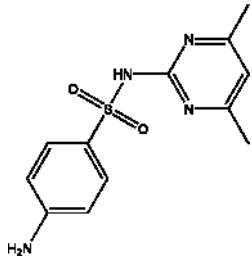
SULFAMETHAZINE

Therapeutic Function: Antimicrobial

Chemical Name: 4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide

Common Name: Sulfamezathine; Sulfadimerazine; Sulfamidine; Sulfadimethylpyrimidine; Sulfadimidine (UK Name)

Structural Formula:



Chemical Abstracts Registry No.: 57-68-1

Trade Name	Manufacturer	Country	Year Introduced
Cremomethazine	MSD	US	1947
Deladine	Delmaak	S. Africa	-
Intradine	Norbrook	UK	-
Rigesol	Ferrosan	Denmark	-
Rivodine	Rivopharm	Switz.	-
S-Dimidine	Protea	Australia	-
Sulphix	Protina	W. Germany	-

Raw Materials

p-Aminobenzenesulfonamidoguanidine
Sodium acetylacetonate

Manufacturing Process

A flask heated in an oil bath is filled with 600 ml water and 60 g (1 mol) glacial acetic acid (or an equivalent quantity of diluted acetic acid). While stirring 235 g (1.1 mols) anhydrous p-aminobenzenesulfonamidoguanidine (or an equivalent quantity of a nonanhydrous product) and 122 g (1 mol) sodium acetylacetonate 100% purity (or an equivalent quantity of product of a lower purity) are introduced into the flask while stirring.

The temperature of the reaction mixture is brought to 102°C to 103°C, the mixture is further stirred at this temperature during 24 hours. The pH value of the mixture, which should range between 5 and 6 is checked during the reaction.

On expiry of the reaction period heating is cut off, the mass being cooled or allowed to cool down to 60°C.

Filtering under suction is effected, the solids on the filter being washed with 100 ml water at 80°C.

After drying of the product on the filter 256 g of 2-p-aminobenzenesulfonamido-4,6-dimethylpyrimidine, melting point 196°C to 197°C, purity 99.5% are obtained. The output is 92% of the theory calculated with respect to the sodium acetylacetonate employed.

References

Merck Index 8786
I.N. p. 839
REM p. 1173
Sprague, J.M.; US Patent 2,407,966; September 17, 1946; assigned to Sharp and Dohme, Inc.
Garzia, A.; US Patent 3,119,818; January 28, 1964; assigned to Istituto Chemioterapico Italiano SpA

SULFAMETHIZOLE

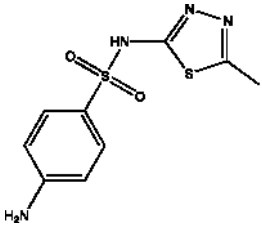
Therapeutic Function: Antibacterial

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

Common Name: Sulfamethylthiadiazole

Chemical Abstracts Registry No.: 144-82-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Thiosulfil	Ayerst	US	1953
Sulfurine	Table Rock	US	1963
Ultrasul	Webcon	US	1963
Sulfasol	Hyrex	US	1963
Renasul	Century	US	1966
Famet	Calmic	Australia	-
Harnway	Nichiiko	Japan	-
Rufol	Debat	France	-
Salimol	Maruishi	Japan	-
S-Methizole	Protea	Australia	-
Starisil	Star	Finland	-
Sulfa Gram	Beach	US	-
Sulfametin	Pharmacia	Sweden	-
Urobiotic	Roerig	US	-
Urokinon	Chugai	Japan	-
Urokizol	Chugai	Japan	-
Urolex	Ohio Medical	US	-
Urosol	Kanto	Japan	-
Urosul	Mohan	Japan	-
Utrasul	Chicago Pharmacal	US	-

Raw Materials

Acetaldehyde thiosemicarbazone
p-Acetaminobenzolsulfonyl chloride
Calcium ferricyanide

Manufacturing Process

To 10 grams acetaldehyde-thiosemicarbazone in 80 grams pyridine gradually 20 grams p-acetaminobenzolsulfonyl chloride is added. The reaction mixture is heated about 1 hour on a water bath and is then charged in 1 liter water, to which some acetic acid is added. The bottom sediment is sucked off and washed with water, after which it is crystallized by alcohol. 20 grams of the condensation product thus obtained is cleared in 100 cc water at about 30°C, after which 45 grams calcium ferricyanide dissolved in about 100 cc water is added. The reaction mixture is made slightly alkaline and held at a temperature of about 80°C for 2 to 3 hours. It is important that the reaction

mixture during the whole period of 2 to 3 hours is steadily held alkaline.

After the said 2 to 3 hours the liquid is cooled and the bottom sediment, which has a greenish color, is filtered off. The liquid sucked off eventually is treated with active carbon, filtered and made slightly acid by means of acetic acid, at which 2-amino-benzolsulfonamido-5-methyl-1,3,4-thiodiazol (melting point 204° to 206°C) is precipitated.

References

Merck Index 8787
Kleeman and Engel p. 839
PDR pp. 650, 1533
OCDS Vol. 1 p. 125 (1977)
I.N. p. 901
REM p. 1174
Hubner, O.; US Patent 2,447,702; August 24, 1948; assigned to H. Lundbeck & Co., Kemisk Pharmaceutisk Laboratorium A/S, Denmark

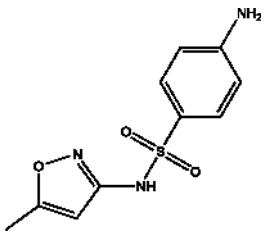
SULFAMETHOXAZOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(5-methyl-3-isoxazolyl)benzenesulfonamide

Common Name: Sulfisomezole

Structural Formula:



Chemical Abstracts Registry No.: 723-46-6

Trade Name	Manufacturer	Country	Year Introduced
Gantanol	Roche	US	1961
Urobax	Shionogi	US	1980
Azo Gantanol	Roche	US	-
Bactrim	Roche	US	-
Comoxol	Squibb	US	-
Cotrim	Lemmon	US	-
Gantaprim	Ausonia	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Metoxal	Farmos	Finland	-
Septra	Burroughs-Wellcome	US	-
Sinomin	Shionogi	Japan	-
Sulfatrim	Schein	US	-
Urobak	Shionogi	Japan	-

Raw Materials

Ethyl 5-methylisoxazole-3-carbamate
Sodium hydroxide
Acetylsulfanil chloride

Manufacturing Process

Preparation of 3-Amino-5-Methylisoxazole: 1.7 grams of ethyl 5-methylisoxazole-3-carbamate was heated on a boiling water-bath with 5 cc of a 10% aqueous sodium hydroxide solution for 8 hours, then the reaction mixture was extracted several times with ether or benzene and the extract was cooled followed by the removal of the solvent and drying. The residue was solidified after a while and gave prismatic crystals, melting point 61° to 62°C, of 3-amino-5-methylisoxazole by recrystallization from benzene.

Preparation of 3-Acetylsulfanilamido-5-Methylisoxazole: 0.9 gram of 3-amino-5-methylisoxazole in 5 cc of pyridine was allowed to react with 2.0 grams of acetylsulfanil chloride accompanied by the generation of heat. After about one hour, water was added to the reaction mixture and the crystal precipitated out was recrystallized from alcohol to give 2.5 grams of 3-acetylsulfanilamido-5-methylisoxazole, melting point (decomposition) 220° to 221°C.

Preparation of 3-Sulfanilamido-5-Methylisoxazole: 2 grams of 3-acetylsulfanilamido-5-methylisoxazole was heated with 10 cc of an aqueous sodium hydroxide solution on a water-bath for one hour and after cooling the reactant was acidified by addition of acetic acid. The precipitate thus formed was recrystallized from dilute alcohol to give 15 grams of colorless prisms of 3-sulfanilamido-5-methylisoxazole, melting point 167°C.

References

Merck Index 8789
Kleeman and Engel p. 840
PDR pp. 673, 763, 830, 993, 1034, 1473, 1606, 1738; DOT 7 (5) 189 (1971)
I.N. p. 901
REM p. 1174
Kano, H., Nishimura, H., Nakajima, K. and Ogata, K.; US Patent 2,888,455; May 26, 1959; assigned to Shionogi & Co., Ltd., Japan

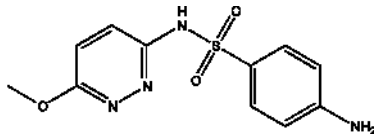
SULFAMETHOXYPYRIDAZINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(6-methoxy-3-pyridazinyl)benzenesulfonamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 80-35-3

Trade Name	Manufacturer	Country	Year Introduced
Kynex	Lederle	US	1957
Midicel	Parke Davis	US	1957
Aseptilex	Wassermann	Spain	-
Asey-Sulfa	Quimia	Spain	-
B-Sulfamethoxy	Biokema	Switz.	-
Davosin	Parke Davis	W. Germany	-
Durasul	Estedi	Spain	-
Exazol	Andreu	Spain	-
Fercasulf	Arco	Switz.	-
Lederkyn	Lederle	UK	-
Lentosulfa	I.S.F.	Italy	-
Longamid	A.L.	Norway	-
Longisul Jarabe	Landerlan	Spain	-
Metazina	Piam	Italy	-
Microcid	Borromeo	Italy	-
Novosulfin	Galenika	Yugoslavia	-
Oroxin	Otsuka	Japan	-
Paramid Supra	Kwizda	Austria	-
Pirasulfon	Neo	Canada	-
S.D.M.	Barlow Cote	Canada	-
Sulfabon	Biokema	Switz.	-
Sulamin	Pliva	Yugoslavia	-
Sulfadazina	Guidi	Italy	-
Sulfadepot	Almirall	Spain	-
Sulfadin	C.I.F.	Italy	-
Sulfaintensa	Robert	Spain	-
Sulfalex	De Angeli	Italy	-
Sulfamizina	Wells	Italy	-
Sulfamyd	Libra	Italy	-
Sulfapyrazin	Bosnalijek	Yugoslavia	-
Sulfatar	Arnaldi	Italy	-
Sulfocidan	Cidan	Spain	-
Sulforetent	Cifa	Italy	-
Sulfo-Rit	Aristochimica	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Sultirene	Specia	France	-
Unisulfa	Angelini	Italy	-

Raw Materials

3-Sulfanilamido-6-chloropyridazine
Sodium
Methanol

Manufacturing Process

The following description is taken from US Patent 2,712,012: 2.3 parts of clean sodium metal is dissolved in 50 parts of anhydrous methyl alcohol. 11.4 parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture heated in a sealed tube 13 hours at 130° to 140°C. After the tube has cooled it is opened and the reaction mixture filtered, acidified with dilute acetic acid, then evaporated to dryness on the steam bath. The residue is dissolved in 80 parts of 5% sodium hydroxide, chilled and acidified with dilute acetic acid. The crude product is filtered and then recrystallized from water to give 3-sulfanilamido-6-methoxypyridazine of melting point 182° to 183°C.

References

Merck Index 8790
Kleeman and Engel p. 842
OCDS Vol. 1 pp. 124, 131 (1977)
I.N. p. 902
Clark, J.H.; US Patent 2,712,012; June 28, 1956; assigned to American Cyanamid Co.
Murphy, D.M. and Shepherd, R.G.; US Patent 2,833,761; May 6, 1958; assigned to American Cyanamid Co.

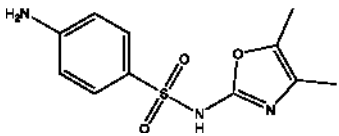
SULFAMOXOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(4,5-dimethyl-2-oxazolyl)benzenesulfonamide

Common Name: Sulfadimethyloxazole

Structural Formula:



Chemical Abstracts Registry No.: 729-99-7

Trade Name	Manufacturer	Country	Year Introduced
Sulfuno	Nordmark	W. Germany	1960
Justamil	Anphar-Rolland	France	1961
Justamil	Anphar-Rolland	Italy	1964
Naprin	Upjohn	US	-
Oxasulfa	Trinum	Italy	-
Tardamide	Gruenenthal	W. Germany	-

Raw Materials

2-Amino-4,5-dimethyloxazole
p-Acetaminobenzenesulfonyl chloride
Hydrogen chloride

Manufacturing Process

11.2 g of 2-amino-4,5-dimethyloxazole (0.1 mol), 46.8 g of anhydrous p-acetaminobenzenesulfonyl chloride (0.2 mol) and 60 cc of methylene chloride are mixed and then treated while stirring and with exclusion of water with 12.0 g (0.2 mol) of anhydrous trimethylamine, dissolved in 60 cc of benzene. After adding the trimethylamine, the mixture is heated for 30 minutes to 40°C, left to stand for 12 hours and then the solvent is distilled off. The distillation residue is heated with 300 cc of water until the residual organic solvents are driven off. The residue is filtered and thoroughly washed with water. Yield of condensation product: 46.4 g. The mass is triturated with 80 cc of cold 2.5% caustic soda solution, filtered and thoroughly washed with water. The residue which is insoluble in caustic soda solution consists of bis-(p-acetaminobenzenesulfonyl)-2-amino-4,5-dimethyloxazole. It melts indefinitely between 201°C and 206°C with decomposition (browning). Yield: 42.3 g corresponding to 83.6%.

The 42.3 g of the bis-compound are heated under reflux in 210 cc of 96% ethanol containing 10% of hydrogen chloride, to the boiling point of the alcohol. After dissolution, the substance is boiled for 20 minutes under reflux. It is cooled, filtered and washed with alcohol. By concentrating the mother liquor and the washing liquid by evaporation, further amounts of substance are obtained.

The total amount of the hydrochloride obtained is stirred with 50 cc of water and the mixture is mixed with 15 cc of 45% caustic soda solution. After complete dissolution, the mixture is treated with decolorizing carbon and the filtrate is brought to a pH value of 5.5 by means of hydrochloric acid. 17.6 g of p-aminobenzenesulfonyl-2-amino-4,5-dimethyloxazole are obtained as colorless crystals with a melting point of 193°C to 194°C (corrected), corresponding to a yield of 65.9% calculated on the basis of the 2-amino-4,5-dimethyloxazole used.

References

Merck Index 8797
Kleeman and Engel p. 843
OCDS Vol. 1 p. 124 (1977)
DOT 12 (9) 377 (1976)

I.N. p. 903
Loop, W., Luhrs, E. and Hauschildt, P.; US Patent 2,809,966; October 15, 1957; assigned to Nordmark-Werke G.m.b.H. (Germany)

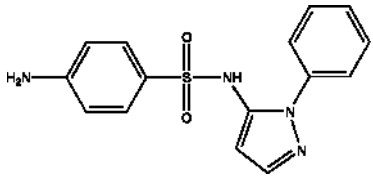
SULFAPHENAZOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 526-08-9

Trade Name	Manufacturer	Country	Year Introduced
Sulfabid	Purdue Frederick	US	1962
Fenazolo	S.A.M.	Italy	-
Merian	Dainippon	Japan	-
Microsulf	Novafarnova	Italy	-
Orisul	Ciba	W. Germany	-
Orisulf	Ciba	UK	-
Plisulfan	Pliva	Yugoslavia	-
Sulfapadil	Padil	Italy	-
Sulfazol	Barlocco	Italy	-
Sulfenal	Kanto	Japan	-
Sulforal	Farber-R.E.F.	Italy	-
Sulfostat	Bieffe	Italy	-
Sulphena	Nisshin	Japan	-

Raw Materials

3-Amino-2-phenylpyrazole
Sodium hydroxide
p-Carbethoxyamino-benzenesulfonyl chloride

Manufacturing Process

Into a solution of 15.9 grams of 3-amino-2-phenyl-pyrazole in 60 cc of anhydrous pyridine, 29 grams of p-carbethoxyamino-benzenesulfonyl chloride are introduced within about 25 minutes. When the reaction subsides, heating

is carried out for a further hour to 90° to 95°C internal temperature. The reaction solution is then poured into 300 cc of 2 N hydrochloric acid. The precipitate is filtered with suction and recrystallized from dilute alcohol. The 3-(p-carbethoxyaminobenzene sulfonamido)-2-phenyl-pyrazole is obtained thus in white crystals of MP 175° to 176°C.

These are taken up in 250 cc of 2 N caustic soda solution and heated for 1 hour on a boiling water bath. With hydrochloric acid, the pH is then adjusted to 6 to 7 and the precipitate is filtered with suction and crystallized from 75% ethyl alcohol. The resulting 3-(p-aminobenzenesulfonamido)-2-phenyl-pyrazole crystallizes in white crystals and has a melting point of 177° to 178°C.

References

Merck Index 8810
Kleeman and Engel p. 844
OCDS Vol. 1 p. 124 (1977)
I.N. p. 904
Druey, J. and Schmidt, P.; US Patent 2,858,309; October 28, 1958: assigned to Ciba Pharmaceutical Products Inc.

SULFASALAZINE

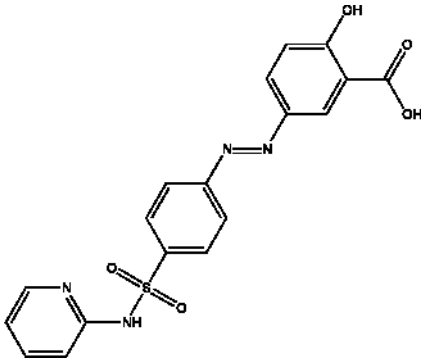
Therapeutic Function: Antibacterial

Chemical Name: 2-Hydroxy-5-[[4-[(2-pyridinylamino)sulfonyl]phenyl]azo]-benzoic acid

Common Name: Salicylazosulfapyridine; Salazosulfapyridine

Structural Formula:

Chemical Abstracts Registry No.: 599-79-1



Trade Name	Manufacturer	Country	Year Introduced
Azulfidine	Pharmacia	US	1952
Salazopyrine	Pharmacia	France	1958
Salazopyrin	Pharmacia	UK	1968
Salazopyrin	Green Cross	Japan	1969
S.A.S-500	Rowell	US	1972
Sulcolon	Lederle	US	1974
Rorasul	Rorer	US	1975
Colo-Pleon	Henning	W. Germany	-
Salisulf	Giuliani	Italy	-

Raw Materials

α-(p-Aminobenzenesulfonamido)pyridine
Sodium nitrite
Hydrogen chloride
Salicylic acid

Manufacturing Process

50 g of α-(p-aminobenzenesulfonylamido)pyridine are dissolved in a mixture of 50 cc of concentrated hydrochloric acid and 25 cc of water and diazotized with a solution of 13.8 g sodium nitrite. In the meantime 28 g of salicylic acid, 24 g of potassium hydroxide and 12 g of sodium carbonate are dissolved in water. The diazo suspension is added in portions to the alkaline solution of salicylic acid and the alkalinity maintained at a sufficiently high level during the whole reaction by means of addition of further quantities of potassium hydroxide solution. After 2 days the reaction mixture is heated for ½ hour at 50°C. After cooling the azo compound formed is precipitated by means of hydrochloric acid and filtered off.

References

Merck Index 8818
Kleeman and Engel p. 812
PDR pp. 830, 993, 1426, 1606
OCDS Vol. 2 p. 114 (1980)
I.N. p. 860
REM p. 1175
Askelof, E.E.A., Svartz, N. and Willstaedt, H.C.; US Patent 2,396,145; March 5, 1946; assigned to A.B. Pharmacia (Sweden)

SULFATHIAZOLE

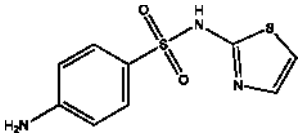
Therapeutic Function: Antibacterial

Chemical Name: Benzenesulfonamide, 4-amino-N-2-thiazolyl-

Common Name: Norsulfazol(um); Solfatiazolo; Sulfamida-Tiazol;

Sulfanilamidothiazole; Sulfathiazole; Sulfatiazole; Sulfonazolum; Sulfothiazole; Sulphathiazole; Tiazin; Thiazylsulfonamide

Structural Formula:



Chemical Abstracts Registry No.: 72-14-0

Trade Name	Manufacturer	Country	Year Introduced
Tiazol	C. and C.	-	-
Sulfathiazole	Carolina Animal Chemicals Co.	-	-
Sulfathiazole	Ofichem B.V.	-	-
Sulfathiazole	Shanghai Sunve Pharmaceutical Corporation	-	-

Raw Materials

4-Acetamidobenzolsufonyl chloride
2-Aminothiasole

Manufacturing Process

116 parts 4-acetamidobenzolsufonyl chloride (prepared from acetanilide and chlorosulfonic acid) was mixed with 100 parts 2-aminothiasole in 1000 parts water by cooling and stirred for some hours. The bis-amide obtained was filtered off and re-crystallized from 50% ethanol to give bis-(p-acetylaminobenzolsulfo)-2-aminothiazol with MP: 129°C.

10 parts above bis-amide was heated with 10% sodium hydroxide solution for 0.5 hour on water bath. On cooling and filtration the alkaline solution was acidified with glacial acetic acid. The amide obtained was cleared by re-crystallized from water to give N^1-2-thiazolylsulfanilamide; MP: 202°-203°C.

References

Hartmann M., Merz E.; D.R. Patent No. 742,753; Dec. 18, 1938; Gesellshaft fur Chemishe Industrie in Basel, Schweiz.

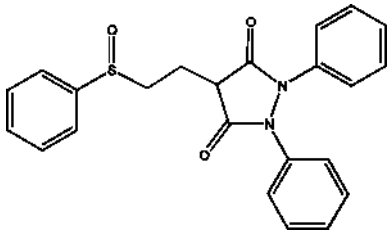
SULFINPYRAZONE

Therapeutic Function: Antiarthritic (uricosuric)

Chemical Name: 1,2-Diphenyl-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57-96-5

Trade Name	Manufacturer	Country	Year Introduced
Anturane	Geigy	US	1959
Anturan	Ciga Geigy	France	1960
Antazone	I.C.N.	Canada	-
Enturen	Geigy	Italy	-
Novopyrazone	Novopharm	Canada	-
Pyrocard	Trima	Israel	-
Zynol	Horner	Canada	-

Raw Materials

Sodium
Hydrazobenzene
Ethanol
(β-Phenylmercaptoethyl)-malonic acid diethyl ester

Manufacturing Process

296 parts of (β-phenylmercapto-ethyl)-malonic acid diethyl ester and then 203 parts of hydrazobenzene are added while stirring to a warm sodium ethylate solution obtained from 23 parts of sodium and 400 parts by volume of absolute alcohol. About half the alcohol is then distilled off, after which 200 parts by volume of absolute xylene are gradually added without removing the inclined condenser. The temperature of the oil bath is kept at about 130°C for 12 hours while continuously stirring so that the alcohol still present and that which is liberated distills off but the xylene remains as solvent.

After cooling, 400 parts by volume of water are stirred in. The aqueous layer is separated from the xylene, shaken out twice with 40 parts by volume of chloroform and then made acid to Congo red paper with concentrated hydrochloric acid. The oil which separates is taken up in ethyl acetate and the solution obtained is washed with water. After drying over sodium sulfate the solvent is distilled off under reduced pressure and the residue is recrystallized from alcohol. 1,2-diphenyl-3,5-dioxo-4-(β-phenylmercapto-ethyl)-pyrazolidine melts at 106° to 108°C.

References

Merck Index 8828
Kleeman and Engel p. 845
PDR pp. 788, 830, 1606, 1999
OCDS Vol. 1 p. 238 (1977)
DOT 15 (2) 61 (1979)
I.N. p. 907
REM p. 1115
Hafliger, F.; US Patent 2,700,671; January 25, 1955; assigned to J.R. Geigy AG, Switzerland

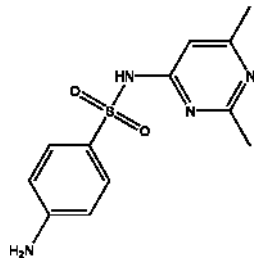
SULFISOMIDINE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(2,6-dimethyl-4-pyrimidinyl)benzenesulfonamide

Common Name: Sulfadimetine; Sulfaisodimidine; Sulfasomidine

Structural Formula:



Chemical Abstracts Registry No.: 515-64-0

Trade Name	Manufacturer	Country	Year Introduced
Elkosin	Ciba	US	1951
Elosine	Ciba Geigy	France	1953
Aristamid	Nordmark	W. Germany	-
Domion	Dainippon	Japan	-
Entamidine	Nippon Shoji	Japan	-
Isosulf	A.L.	Norway	-
Sulfamethin	Chemiek. Bitterfeld	E. Germany	-

Raw Materials

Iron
p-Nitrobenzenesulfonyl chloride
Hydrogen chloride
6-Amino-2,4-dimethylpyrimidine

Manufacturing Process

This starting material can be prepared as follows. 123 parts of finely powdered 6-amino-2,4-dimethylpyrimidine are suspended in 250 parts of dry pyridine and 222 parts of p-nitrobenzenesulfonyl chloride added at 50°C to 55°C. The whole is then warmed for 2 hours to 55°C. Water is added to the crystalline aggregate obtained, the precipitated bis-N-(p-nitrobenzenesulfonyl)-6-amino-2,4-dimethylpyrimidine filtered off by suction and washed with water. It is purified by recrystallizing from methyl ethyl ketone. On slowly heating it decomposes; on rapidly heating it melts at about 210°C to 215°C with decomposition.

49.3 parts of bis-N-(p-nitrobenzenesulfonyl)-6-amino-2,4-dimethylpyrimidine are heated to boiling for one hour with 12.3 parts of 6-amino-2,4-dimethylpyrimidine in 50 parts of dry pyridine. After cooling, the 6-(p-nitrobenzenesulfonamido)-2,4-dimethylpyrimidine formed is precipitated with water and filtered off by suction. It is purified by dissolving in dilute caustic soda and precipitating with acid. On recrystallization from dilute alcohol it melts (with decomposition) at 188°C to 189°C.

On reaction, for example, with iron and hydrochloric acid, 6-(p-aminobenzenesulfonamido)-2,4-dimethylpyrimidine, melting point 236°C is obtained.

References

Merck Index 8831
Kleeman and Engel p. 846
I.N. p. 907
Hartmann, M., von Meyenburg, H. and Druey, J.; US Patent 2,429,184; October 14, 1947; assigned to Ciba Pharmaceutical Products, Inc.

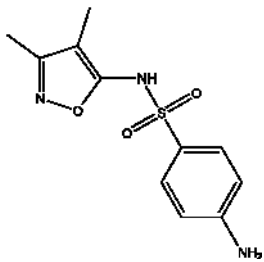
SULFISOXAZOLE

Therapeutic Function: Antibacterial

Chemical Name: 4-Amino-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide

Common Name: Sulfafurazole

Structural Formula:



Chemical Abstracts Registry No.: 127-69-5

Trade Name	Manufacturer	Country	Year Introduced
Gantrisin	Roche	US	1949
Unisulf	Lemmon	US	1964
Entusul	U.S.V.	US	1964
Sosol	Mc Kesson	US	1970
SK-Soxazole	SKF	US	1971
Soxomide	Upjohn	US	1972
Sulfalar	Parke Davis	US	1973
Soxo	Sutcliff/Case	US	1974
Koro-Sulf	Holland Rantos	US	1978
Amidoxal	Polfa	Poland	-
Azo-Gantrisin	Roche	US	-
Dow-Sulfisoxazole	Dow	US	-
Gansol	Abdi Ibrahim	Turkey	-
Isoxamin	Fuso	Japan	-
Novosoxazole	Novopharm	Canada	-
Pancid	Lister	Italy	-
Pediazole	Ross	US	-
Sulfagan	Ohio Medical	US	-
Sulfagen	Verdun	Canada	-
Sulfapolar	Farmos	Finland	-
Sulfazin	Shionogi	Japan	-
Sulfazole	Protea	Australia	-
Sulfizole	I.C.N.	Canada	-
Sulfoxol	Neopharma	Finland	-
Sulsoxin	Reid-Provident	US	-
Thiasin	Yamanouchi	Japan	-
TL-Azole	Zenith	US	-
Urazole	Propan-Lipworth	S. Africa	-
Urogan	Adams	Australia	-
US-67	Saunders	Canada	-
V-Sul	Vangard	US	-

Raw Materials

Hydrogen chloride
3,4-Dimethyl-5-aminoisoxazole
p-Acetaminobenzene sulfonic acid chloride

Manufacturing Process

112 parts of 3,4-dimethyl-5-amino-isoxazole were dissolved in a mixture of 100 volume parts of pyridine and 200 volume parts of acetone. The mixture is cooled with cold water and 240 parts p-acetamino-benzene sulfonic acid chloride are added in small portions under stirring at temperatures of below 30°C. The mixture is left standing overnight at 20° to 30°C and then the 5-acetamino-benzene-sulfonylamino-3,4-dimethyl-isoxazole is precipitated by

the addition of water. Recrystallized from acetic acid or alcohol it forms small prisms of the melting point 210°C.

100 parts of the 5-acetamino-benzene-sulfonyl-amino-3,4-dimethyl-isoxazole are boiled under reflux with 500 volume parts 15 to 20% aqueous hydrochloric acid for 30 to 45 minutes until all is dissolved. 500 parts crystallized sodium acetate are added and the liquid left cooling for crystallization. The sulfanilamido-3,4-dimethyl-isoxazole is sucked off, washed with water and dried. In the pure state it forms white prisms with the melting point of 193°C.

References

Merck Index 8832
Kleeman and Engel p. 837
PDR pp. 1473, 1487, 1558, 1606, 1999
OCDS Vol. 1 p. 124 (1977)
I.N. p. 900
REM p. 1175
Wuest, H.M. and Hoffer, M.; US Patent 2,430,094; November 4, 1947; assigned to Hoffmann-La Roche, Inc.

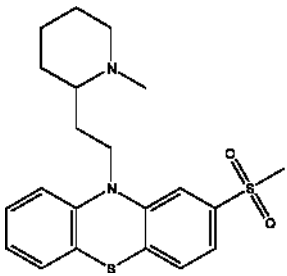
SULFORIDAZINE

Therapeutic Function: Neuroleptic

Chemical Name: 10H-Phenothiazine, 10-(2-(1-methyl-2-piperidyl)ethyl)-2-methylsulfonyl-

Common Name: Solforidazine; Sulforidazine

Structural Formula:



Chemical Abstracts Registry No.: 14759-06-9

Trade Name	Manufacturer	Country	Year Introduced
Sulforidazine	ZYF Pharm Chemical	-	-
Inofal	Sandoz	-	-

Raw Materials

2-Methylsulfonylphenothiazine
Sodium methylate
2-(2-Chloroethyl)-1-methylpiperidine

Manufacturing Process

A mixture of 96.5 g 2-methylsulfonylphenothiazine, 50 g 2-(2-chloroethyl)-1-methylpiperidine, 62 g diethyl carbonate and 2 g sodium methylate was heated at 135°C for 1 hour and then at 180-190°C for 2.5 hours. The product was dissolved in benzene (500 ml) and the solution was extracted with 700 ml of 15% aqueous solution tartaric acid. The extract was washed with benzene. After addition of sodium carbonate solution to the extract was obtained a precipitate which was dissolved in benzene. This solution was washed with water and concentrated. 2-Methylsulfonyl-10-(2-(1-methyl-2-piperidyl)ethyl)phenothiazin was recrystallized from acetone, melting point 121-123°C.

References

Renz J., Bourquin J.-P., Winkler H., Gagnaux P., Ruesch P., Achwarb G.; FR Patent No. 1,459,476; Nov. 30, 1965; Assigned to SANDOZ S.A.

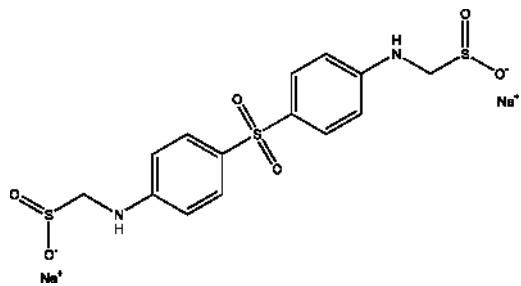
SULFOXONE SODIUM

Therapeutic Function: Antibacterial (leprostatic)

Chemical Name: Disodium [sulfonylbis(p-phenylenimino)]dimethanesulfinate

Common Name: Aldesulfone sodium

Structural Formula:



Chemical Abstracts Registry No.: 144-75-2

Trade Name	Manufacturer	Country	Year Introduced
Diasone Sodium	Abbott	US	1947

Raw Materials

Diaminodiphenyl sulfone
Sodium formaldehyde sulfoxylate

Manufacturing Process

About 20 grams of diamino diphenyl sulfone is dissolved in about 500 cc of ethyl alcohol (3A made up of 5 parts methyl alcohol and 100 parts of ethyl alcohol) by placing the ingredients in a flask provided with a reflux condenser and warming over a water bath. About 24 grams of pure grade, very finely powdered (40 to 60 mesh) sodium formaldehyde sulfoxylate is then rapidly added to the alcohol solution of diamino diphenyl sulfone and the mixture refluxed in the usual manner. It was found that the mixture should be refluxed for a total of 5 hours and that a precipitate starts to form near the 3 hour period. The reaction mixture is then cooled to 15°C and kept at this temperature for about 1 hour. The precipitate formed in the filtrate is filtered off rapidly and drained as much as possible to remove mother liquor and then washed with small amounts of cold alcohol. The solid product is immediately placed in a desiccator and dried over sulfuric acid for about 20 hours.

References

Merck Index 8848
Kleeman and Engel p. 847
OCDS Vol. 1 p. 140 (1977)
I.N. p. 51
REM p. 1217
Rosenthal, S.M. and Bauer, H.; US Patent 2,234,981; March 18, 1941; assigned to the US Secretary of the Treasury
Raiziss, G.W., Clemence, L.R.W. and Freifelder, M.; US Patent 2,256,575; September 23, 1941; assigned to Abbott Laboratories

SULINDAC

Therapeutic Function: Antiinflammatory

Chemical Name: (Z)-5-Fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl] methylene]-1H-indene-3-acetic acid

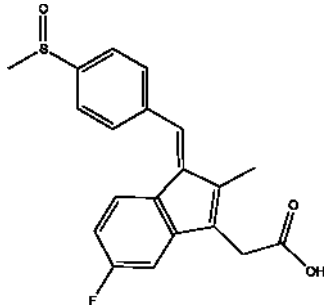
Common Name: -

Chemical Abstracts Registry No.: 38194-50-2

Raw Materials

Hydrogen
Sodium periodate
Propionic anhydride
Cyanacetic acid
p-Fluorobenzaldehyde
p-Methylthiobenzaldehyde
Polyphosphoric acid

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Imbaral	Sharp and Dohme	W. Germany	1976
Clinoril	MSD	Italy	1976
Arthrocine	Chibret	France	1977
Clinoril	MSD	UK	1977
Clinoril	MSD	US	1978
Clinoril	Banyu	Japan	1982
Clinoril	Kyorin	Japan	1982
Aflodac	Benvegna	Italy	1982
Algocetil	Francia	Italy	-
Citireuma	C.T.	Italy	-
Lyndak	Tiber	Italy	-
Mobilin	Teva	Israel	-
Reumofil	Ausonia	Italy	-
Sudac	Errekappa	Italy	-
Sulene	Scalari	Italy	-
Sulic	Crosara	Italy	-
Sulinol	Farnex	Italy	-

Manufacturing Process

The following process sequence is described in US Patent 3,654,349:

p-Fluoro-α-Methylcinnamic Acid: 200 grams (1.61 mols) p-fluorobenzaldehyde, 3.5 grams (2.42 mols) propionic anhydride and 155 grams (1.61 mols) sodium propionate are mixed in a 1 liter three-necked flask which had been flushed with nitrogen. The flask is heated gradually in an oil-bath to 140°C. After 20 hours the flask is cooled to 100°C and the contents are poured into 8 liters of water. The precipitate is dissolved by adding 302 grams potassium hydroxide in 2 liters of water. The aqueous solution is extracted with ether, and the ether extracts washed with potassium hydroxide solution. The combined aqueous layers are filtered, acidified with concentrated HCl, filtered and the collected solid washed with water, thereby producing p-fluoro-α-methylcinnamic acid which is used as obtained.

p-Fluoro-α-Methylhydrocinnamic Acid: To 177.9 grams (0.987 mol) p-fluoro-α-methylcinnamic acid in 3.6 liters ethanol is added 11.0 grams of 5% Pd/C and the mixture reduced at room temperature under a hydrogen pressure of 40 psi. Uptake is 31/32 pounds (97% of theoretical). After filtering the catalyst, the filtrate is concentrated in vacuo to give the product p-fluoro-α-methylhydrocinnamic acid used without weighing in next step.

6-Fluoro-2-Methylindanone: To 932 grams polyphosphoric acid at 70°C on the steam bath is added 93.2 grams (0.5 mol) p-fluoro-α-methylhydrocinnamic acid slowly with stirring. This temperature is gradually raised to 95°C and the mixture kept at this temperature for 1 hour. The mixture is allowed to cool and added to 2 liters of water. The aqueous layer is extracted with ether, the ether solution washed twice with saturated sodium chloride solution, 5% Na_2CO_3 solution, water, and then dried. The ether filtrate is concentrated with 200 grams silica-gel, and added to a five pound silica-gel column packed with 5% ether-petroleum ether. The column is eluted with 5 to 10% ether-petroleum ether and followed by TLC to give 6-fluoro-2-methylindanone.

5-Fluoro-2-Methylindene-3-Acetic Acid: A mixture of 18.4 grams (0.112 mol) of 6-fluoro2-methylindanone, 10.5 grams (0.123 mol) cyanacetic acid, 6.6 grams acetic acid and 1.7 grams ammonium acetate in 15.5 ml dry toluene is refluxed with stirring for 21 hours, as the liberated water is collected in a Dean Stark trap. The toluene is concentrated and the residue dissolved in 60 ml of hot ethanol and 14 ml of 2.2 N aqueous potassium hydroxide solution. 22 grams of 85% KOH in 150 ml of water is added and the mixture refluxed for 13 hours under N_2. The ethanol is removed under vacuum, 500 ml water added, the aqueous solution washed well with ether and then boiled with charcoal. The aqueous filtrate is acidified to pH 2 with 50% hydrochloric acid, cooled and the precipitate collected in this way dried 5-fluoro-2-methyl-indenyl-3-acetic acid (MP 164° to 166°C) is obtained.

5-Fluoro-2-Methyl-1-(p-Methylthiobenzylidene)-3-Indenylacetic Acid: 15 grams (0.072 mol) 5-fluoro-2-methyl-3-indenylacetic acid, 14.0 grams (0.091 mol) p-methylthiobenzaldehyde and 13.0 grams (0.24 mol) sodium methoxide are heated in 200 ml methanol at 60°C under nitrogen with stirring for 6 hours. After cooling the reaction mixture is poured into 750 milliliters of ice-water, acidified with 2.5 N hydrochloric acid and the collected solid triturated with a little ether to produce 5-fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic acid (MP 187° to 188.2°C).

5-Fluoro-2-Methyl-1-(p-Methylsulfinylbenzylidene)-3-Indenylacetic Acid: To a solution of 3.4 grams (0.01 mol) 5-fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic acid in a 250 ml mixture of methanol and 100 ml acetone is added a solution of 3.8 grams (0.018 mol) of sodium periodate in 50 ml water with stirring.

450 ml water is added after 18 hours and the organic solvents removed under vacuum below 30°C. The precipitated product is filtered, dried and recrystallized from ethyl acetate to give 5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-3-indenylacetic acid. Upon repeated recrystallization from ethylacetate there is obtained cis-5-fluoro-2-methyl-1-(p-methylsulfinylbenzylidene)-3-indenylacetic acid (MP 184° to 186°C).

References

Merck Index 8863
Kleeman and Engel p. 847
PDR p. 1147
OCDS Vol. 2 p. 210 (1980)
DOT 12 (2) 496 (1976)
I.N. p. 909
REM p. 1120
Hinkley, D.F. and Conn, J.B.; US Patent 3,647,858; March 7, 1972; assigned to Merck & Co., Inc.
Shen, T.-Y., Greenwald, R.B., Jones, H., Linn, B.O. and Witzel, B.E.; US Patent 3,654,349; April 4, 1972; assigned to Merck and Co., Inc.

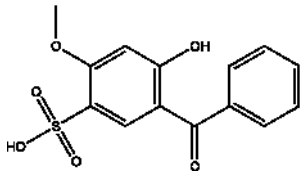
SULISOBENZONE

Therapeutic Function: Sunscreen agent

Chemical Name: 5-Benzoyl-4-hydroxy-2-methoxybenzenesulfonic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 4065-45-6

Trade Name	Manufacturer	Country	Year Introduced
Uval	Dome	US	1965
Cyasorb	Cyanamid	US	-
Spectra-Sorb	Cyanamid	US	-
Sungard	Miles	US	-
Uvinul	G.A.F.	US	-

Raw Materials

2-Hydroxy-4-methoxybenzophenone
Chlorosulfonic acid

Manufacturing Process

663 g of dichloroethane and 74.6 g 2-hydroxy-4-methoxybenzophenone were

charged into a 3-neck flask equipped with stirrer, thermometer, reflux condenser and dropping funnel and a heating mantle. The solution was heated to the reflux temperature (85°C to 86°C) and was dehydrated by distilling off 66.5 g 1,2-dichloroethane. While maintaining at reflux, 30 g chlorosulfonic acid was added slowly over a period of about two hours. The rate of addition was regulated by the speed of evolution of the HCl. After all the chlorosulfonic acid was added, the charge was still maintained at reflux for an additional 15 minutes to remove traces of HCl. It was then cooled to 5°C and filtered. The filter cake was washed with 500 g cold 1,2-dichloroethane and dried. 98 g of product were obtained.

References

Merck Index 8865
I.N. p. 909
Cofrancesco, A.J.; British Patent 1,136,525; December 11, 1968; assigned to General Aniline & Film Corp.

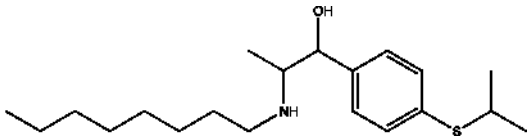
SULOCTIDIL

Therapeutic Function: Spasmolytic, Vasodilator

Chemical Name: 1-(4-Isopropylthiophenyl)-2-n-octylaminopropanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54063-56-8

Trade Name	Manufacturer	Country	Year Introduced
Sulocton	Cooper	Switz.	1978
Flavisco	Searle	France	1980
Locton	Lepetit	Italy	1980
Fluversin	Searle	W. Germany	1980
Bemperil	Sidus	Argentina	-
Cerebro	Sidus	Italy	-
Circleton	I.B.I.	Italy	-
Dulasi	Durron	Italy	-
Duloctil	Searle	UK	-
Euvasal	Selvi	Italy	-
Ibisul	I.B.I.	Italy	-

Trade Name	Manufacturer	Country	Year Introduced
Locton	Lepetit	Italy	-
Polivasal	Coli	Italy	-
Sudil	Errekappa	Italy	-
Sulc	Tosi	Italy	-
Sulodene	Alfa Farm.	Italy	-
Suloktil	Yurtoglu	Turkey	-
Sutidil	Krka	Yugoslavia	-
Tamid	Serpero	Italy	-

Raw Materials

α-Bromo-4-isopropylthiopropiophenone
n-Octylamine
Sodium borohydride

Manufacturing Process

(a) To 28.7 g of α-bromo-4-isopropylthiopropiophenone (0.1 mol) in 100 ml of isopropanol there are rapidly added 14.2 g of n-octylamine while stirring, and then the mixture is brought to 80°C for 1 hour. The solvent is evaporated under vacuum, the residue is diluted with 1 liter of ether and is left to stand overnight in the refrigerator. The precipitate obtained is filtered and dried. There are thus obtained 25 g of α-n-octylamino-4-isopropylthiopropiophenone hydrobromide. Yield: 60%; melting point: 162°C to 164°C.

(b) 41.6 g of the preceding product (0.1 mol) in 200 ml of methanol are cooled in an ice bath to 0°C. There is added drop by drop while stirring a solution of 4.1 g of $NaBH_4$ in 50 ml of water and 2 ml of 5% NaOH. Next, the mixture is stirred for 2 hours at room temperature. The methanol is evaporated under vacuum, diluted with 200 ml of water and extracted with methylene chloride or ether. The organic phase is dried on $MgSO_4$ and the solvent is evaporated under vacuum. The oily residue obtained solidifies rapidly and is recrystallized in pentane. 33.2 g are thus obtained. Yield: 90%; melting point: 62°C to 63°C.

References

Merck Index 8870
Kleeman and Engel p. 849
OCDS Vol. 3 p. 26 (1984)
DOT 13 (3) 107 (1977)
I.N. p. 910
Lambelin, G.E., Gillet, C.L. and Roba, J.L.; US Patent 4,228,187; October 14, 1980; assigned to Continental Pharma

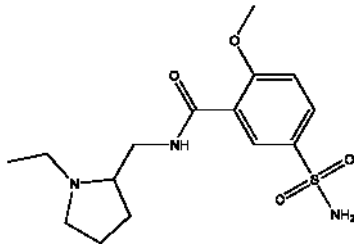
SULPIRIDE

Therapeutic Function: Tranquilizer, Digestive aid

Chemical Name: 5-(Aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxybenzamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15676-16-1

Trade Name	Manufacturer	Country	Year Introduced
Dogmatil	Delagrange	France	1969
Dogmatil	Schurholz	W. Germany	1972
Dogmatil	Delagrange	Italy	1972
Dogmatil	Delagrange	Switz.	1972
Dogmatil	Fujisawa	Japan	1973
Dogmatil	Squibb	UK	1983
Abilit	Sumitomo	Japan	-
Betamac	Sawai	Japan	-
Chamionil	Vita	Italy	-
Coolspan	Hishiyama	Japan	-
Digton	Areu	Spain	-
Dobren	Ravizza	Italy	-
Eglonyl	Alkaloid	Yugoslavia	-
Equilid	Lepetit	Italy	-
Eusulpid	C.T.	Italy	-
Guastil	Uriach	Spain	-
Isnamide	Isardi	Italy	-
Kapiride	Kappa	Spain	-
Lavodina	Turro	Spain	-
Lusedan	Bryan	Spain	-
Meresa	Dolorgiet	W. Germany	-
Miradol	Mitsui	Japan	-
Misulvan	Bernabo	Argentina	-
Modal	Rafa	Israel	-
Neogama	Hormosan	W. Germany	-
Neuromyfar	Emyfar	Spain	-
Normum	Serpero	Italy	-
Omperan	Taiho	Japan	-
Paratil	Medica	Finland	-
Psicosen	Centrum	Spain	-

Trade Name	Manufacturer	Country	Year Introduced
Pyrikappl	Isei	Japan	-
Quiridil	Zoja	Italy	-
Sato	Scharper	Italy	-
Seeglu	Teikoku	Japan	-
Sicofrenol	Basileos	Spain	-
Sulpiril	Leiras	Finland	-
Sulpisidan	Llano	Spain	-
Suprium	Orion	Finland	-
Sursumid	Sarm	Italy	-
Tepavil	Prodes	Spain	-
Tonofit	Europa	Spain	-
Trilan	Esseti	Italy	-
Ulpir	Lesvi	Spain	-
Vipral	Roemmers	Argentina	-

Raw Materials

1-Ethyl-2-aminomethylpyrrolidine
2-Methoxy-5-sulfamylbenzoic acid

Manufacturing Process

1-Ethyl-2-aminomethylpyrrolidine is reacted with 2-methoxy-5-sulfamoylbenzoic acid to give sulpiride.

References

Merck Index 8875
Kleeman and Engel p. 849
OCDS Vol. 2 p. 94 (1980)
DOT 9 (6) 244 (1973)
I.N. p. 911
Miller, C.S., Engelhardt, E.L. and Thominet, M.L.; US Patent 3,342,826; Sept. 19, 1967; assigned to Societe d'Etudes Scientifiques et Industrielles de L'Ile-de-France, France

SULPROSTONE

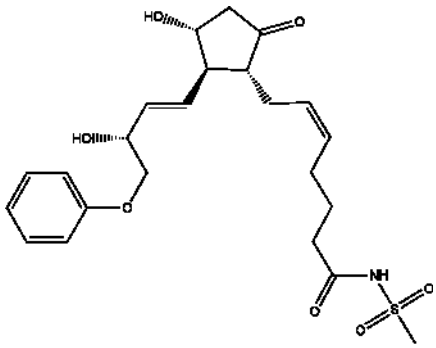
Therapeutic Function: Contraceptive

Chemical Name: N-Methanesulfonyl-9-oxo-11α,15α-dihydroxy-5-cis-13-trans-16-phenoxy-α-tetranorprostadienamide

Common Name: -

Chemical Abstracts Registry No.: 60325-46-4

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Nalador	Schering	W. Germany	1981
Nalador	Schering	Switz.	1983

Raw Materials

Chromic anhydride
(4-Carbohydroxy-n-butyl)triphenylphosphonium bromide
Acetic acid
Methanesulfonyl isocyanate
Sodium methylsulfinylmethide
2-[5α-Hydroxy-3α(tetrahydropyran-2-yloxy)-2β-(3α-tetrahydropyran-2-yloxy-4-
phenoxy-trans-1-buten-1-yl)cyclopent-1α-yl]-acetaldehyde α-hemiacetal

Manufacturing Process

9α-Hydroxy-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoicacid: To a solution of 1.6 g (3.6 mmols) (4-carbohydroxy-n-butyl)triphenylphosphonium bromide in a dry nitrogen atmosphere in 6.0 ml dry dimethyl sulfoxide was added 3.24 ml (6.5 mmols) of a 2.0 M solution of sodium methylsulfinylmethide in dimethyl sulfoxide. To this red ylide solution was added dropwise a solution of 613 mg (1.29 mmols) 2-[5α-hydroxy-3α-(tetrahydropyran-2-yloxy)-2α-(3α-tetrahydropyran-2-yloxy-4-phenoxytrans-1-buten-1-yl)cyclopent-1α-yl] acetaldehyde, γ-hemiacetal in 5.0 ml dry dimethyl sulfoxide over a period of 20 minutes.

After an additional 2 hours stirring at room temperature, the reaction mixture was poured onto ice water. The basic aqueous solution was washed twice with ethyl acetate (20 ml) and acidified to pH 3 with 10% aqueous hydrochloric acid.

The acidic solution was extracted with ethyl acetate (3 x 20 ml) and the combined organic extracts washed once with water (10 ml), dried ($MgSO_4$) and evaporated to a solid residue. This solid residue was triturated with ethyl acetate and the filtrate concentrated. Yield: 754 mg of 9α-hydroxy-11α,15α-

bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ωtetranorprostadienoic acid was collected.

9-Oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoicacid: To a solution cooled to -10°C under nitrogen of 754 mg (1.3 mmols) 9α-hydroxy-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid in 13 ml reagent grade acetone was added dropwise to 0.56 ml (1.41 mmols) of Jones' reagent (chromic anhydride). After 20 minutes at -10°C, 0.260 ml 2-propanol was added and the reaction mixture was allowed to stir an additional 5 minutes at which time it was combined with 75 ml ethyl acetate, washed with water (3 x 10 ml), dried ($MgSO_4$)and concentrated to give 752 mg of 9-oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid, which was chromatographed on silica gel using ethyl acetate as eluent to afford 505 mg of pure intermediate.

N-Methanesulfonyl-9-oxo-11α,15α-dihydroxy-5-cis-13-trans-16-phenoxy-ω-tetranorprostadienamide:To 1.0 mmols of 9-oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienoic acid in 40 ml THF is added 2 ml triethylamine. After 15 minutes of stirring at room temperature 10.0 ml of 0.1 M methanesulfonylisocyanate in THF is added. After a further 1 hour of stirring, the reaction mixture is neutralized with acetic acid and the solvent removed by evaporation (in vacuo). The resultant residue is taken up in methylene chlorine and washed successively with water and sodium bicarbonate to yield, after drying and solvent evaporation, N-methanesulfonyl-9-oxo-11α,15α-bis-(tetrahydropyran-2-yloxy)-16-phenoxy-cis-5-trans-13-ω-tetranorprostadienamide. This intermediate is then hydrolyzed overnight with acetic acid/water and purified by column chromatography to give the desired N-methanesulfonyl-9-oxo-11α,15α-dihydroxy-5-cis-13-trans-16-phenoxy-ω-tetranorprostadienamide.

References

Merck Index 8877
DFU 3 (1) 59 (1978)
OCDS Vol. 3 p. 9 (1984)
DOT 18 (7) 331 (1982)
I.N. p. 911
Bindra, J.S. and Johnson, M.R.; US Patents 4,024,179; May 17, 1977; and 4,244,887; January 13, 1981; both assigned to Pfizer, Inc.

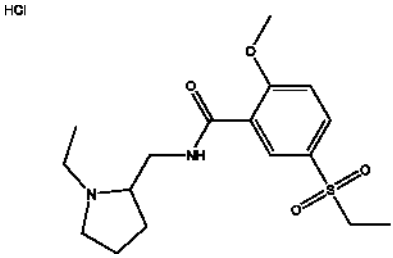
SULTOPRIDE HYDROCHLORIDE

Therapeutic Function: Neuroleptic

Chemical Name: N-(1-Ethyl-2-pyrrolidylmethyl)-2-methoxy-5-ethylsulfonylbenzamide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53583-79-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Barnetil	Delagrange	France	1976
Barnotil	Vita	Italy	1983
Topral	Alkaloid	Yugoslavia	-

Raw Materials

Phosphorus trichloride
N-Ethyl-α-aminomethylpyrrolidine
2-Methoxy-5-ethylsulfonylbenzoic acid

Manufacturing Process

A solution of 17.22 g of N-ethyl-α-aminomethylpyrrolidine in 360 ml of pyridine is placed in a 1 l balloon flask. A solution of 3.51 g of phosphorus trichloride in 40 ml of pyridine is added at ambient temperature. After the mixture has been stirred for 1 hour, 10 g of 2-methoxy-5-ethylsulfonylbenzoic acid is introduced. The mixture is heated under reflux for 4 ½ hours. After cooling, the solvent is evaporated under vacuum and the residue is dissolved in 200 ml of 20% sodium hydroxide. The solution is extracted with 200 ml of chloroform.

The organic solution is dried and filtered and the solvent is evaporated under vacuum; the residue is dissolved in 150 ml of ethanol and the solution is acidified with hydrochloric acid. The hydrochloride is dried without heating and recrystallized from 100 ml of absolute ethanol. 7.2 g of N-(1-ethyl-2-pyrrolidyl-methyl-2-methoxy-5-ethylsulfonylbenzamide hydrochloride is produced. Melting point: 190°C to 193°C.

References

Merck Index 8879
DFU 1 (2) 83 (1976)
Kleeman and Engel p. 851
DOT 13 (4) 154 (1977)
I.N. p. 911
Societe D'Etudes Scientifiques et Industrielles de L'Ile-de-France; British Patent 1,394,559; May 21, 1975

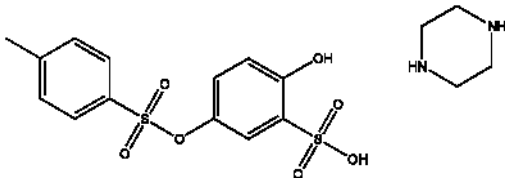
SULTOSILIC ACID PIPERAZINE SALT

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2-Hydroxy-5-[[(4-methylphenyl)sulfonyl]oxy] benzenesulfonic acid, piperazine salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 57775-27-6; 57775-26-5 (Free acid)

Trade Name	Manufacturer	Country	Year Introduced
Mimedran	Esteve	Spain	1982

Raw Materials

2,5-Dihydroxybenzenesulfonic acid
Pyridine
Tosyl chloride
Piperazine

Manufacturing Process

The monotosylation of 2,5-dihydroxybenzenesulfonic acid is carried out in a pyridine medium by treating it with tosyl chloride, thus preferably isolating the 2-hydroxy-5-tosyloxybenzenesulfonic acid, pyridine salt. This product subjected to reflux with an alcoholic solution of piperazine yields 2-hydroxy-5-tosyloxybenzenesulfonic acid, piperazine salt.

References

DFU 6 (11) 688 (1981)
Esteve-Subirana, A.; US Patent 3,954,767; May 4, 1976

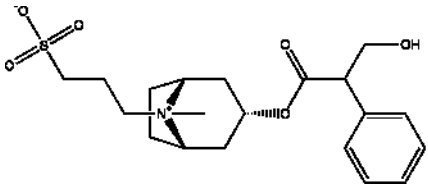
SULTROPONIUM

Therapeutic Function: Spasmolytic

Chemical Name: Endo(+/-)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(3-sulfopropyl)-8-azoniabicyclo[3.2.1]octane hydroxide, inner salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15130-91-3

Trade Name	Manufacturer	Country	Year Introduced
Sultroponium-B	Biotherax	France	1970

Raw Materials

Atropine
Propane-1,3-sultone

Manufacturing Process

To a cold solution of 29 g of atropine in 250 ml of acetone a solution of 13 g of propane-1,3-sultone in 100 ml of acetone is generally added. The combined solution is left for 48 hours. The white precipitate of fine crystalline needles is separated, washed several times with acetone, and then recrystallized from ethanol. It melts at 220°C.

References

Merck Index 8880
Kleeman and Engel p. 851
DOT 6 (3) 97 (1970)
I.N. p. 912
Raudnitz, J.P.M. and Wahl, H.; British Patent 1,082,445; September 6, 1967

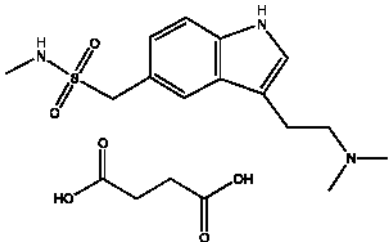
SUMATRIPTAN SUCCINATE

Therapeutic Function: Serotoninergic

Chemical Name: 1H-Indole, 3-(2-(dimethylamino)ethyl)-N-methyl-5-methanesulfonamide, butanedioic acid salt (1:1)

Common Name: Sumatriptan succinate

Structural Formula:



Chemical Abstracts Registry No.: 103628-48-4; 103628-46-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Imigran	GlaxoSmithKline	UK	-
Imitrex	Glaxo Wellcome	UK	-
Sumatriptan Succinate	Chemo Iberica	Spain	-
Suminat	Sun Pharmaceuticals Industries Ltd.	India	-

Raw Materials

Hydrogen chloride
Nickel Raney
Dimethylamine
(Phenylthio)acetaldehyde
Sodium borohydride
Succinic acid
4-Hydrazino-N-methylbenzenemethanesulphonamide hydrochloride

Manufacturing Process

A solution of (phenylthio)acetaldehyde (6.05 g) in absolute ethanol (180 ml) was added over 10 min to a solution of 4-hydrazino-N-methylbenzenemethanesulphonamide hydrochloride (10 g) in water (180 ml) with cooling. After addition of the aldehyde was complete, the mixture was stirred at 5°C for a period of 14 h. The precipitated solid was filtered off, washed with water (200 ml), hexane (200 ml) and dried in vacuo to give the N-methyl-4-[2-[2-(phenylthio)ethylidene]hydrazino]benzenemethane-sulphonamide (10.95 g), melting point 110°-112°C.

A solution of the N-methyl-4-[2-[2-(phenylthio)ethylidene]hydrazino]benzenemethane-sulphonamide in absolute ethanol (300 ml) was saturated with hydrogen chloride gas (ca. 30 min) whilst being cooled in an ice-water bath, allowed to stir at room temperature for 3 h and filtered. The filtrate was concentrated in vacuo and chromatographed to afford a foam, which solidified on trituration with ether to an amorphous powder (2.17 g). A sample was recrystallized from hexane-dichloromethane to give the N-methyl-3-(phenylthio)-1H-indole-5-methanesulphonamide, melting point 133°-134°C.

To a solution of N-methyl-3-(phenylthio)-1H-indole-5-methanesulphonamide (460 mg) in absolute ethanol (50 ml) was added Raney nickel [4.6 g, 50% slurry in water, washed to neutrality with deionized water (60 ml)] and the reaction mixture refluxed for 16 h under an atmosphere of nitrogen. On

cooling to room temperature, the supernatant was removed and the Raney nickel extracted with ethanol (2x50 ml, which was brought to a gentle reflux for 15 min under an atmosphere of nitrogen). The combined extracts were filtered through a sand-celite pad and concentrated in vacuo. Chromatography of the residue, afforded an oil (87 mg) which crystallized from ether-hexane to give the N-methyl-1H-indole-5-methanesulphonamide (90 mg), melting point 127°-129°C.

To N,N-diethyl chloroacetamide (800 mg) at 0°C was added phosphorous oxychloride (250 μl) over a period of 30 sec. After the addition was complete, the mixture was allowed to stir at 0°C for 15 min and then at room temperature for 20 min. The N-methyl-1H-indole-5-methanesulphonamide (300 mg) was added at 0°C and the mixture warmed to 65°C, whereupon it dissolved. The mixture was stirred for 2 h at this temperature then poured onto ice (ca. 5 g) and chloroform (5 ml) and stirred vigorously for 1 h. A solid was filtered off, washed with water (50 ml), and hexane (100 ml) and dried in vacuo to give the 3-(chloroacetyl)-N-methyl-1H-indole-5-methanesulphonamide (192 mg).

A solution of the 3-(chloroacetyl)-N-methyl-1H-indole-5-methanesulphonamide (160 mg) in ethanolic dimethylamine (30 ml, 33% w/v solution in ethanol) was heated to reflux for 2 h. On cooling to room temperature the solvent was removed in vacuo and the residue was chromatographed to afford the 3-[(dimethylamino)acetyl]-N-methyl-1H-indole-5-methanesulphonamide, melting point 230°C, dec.

To a suspension of the 3-[(dimethylamino)acetyl]-N-methyl-1H-indole-5-methanesulphonamide (46.5 mg) in 1-propanol (5 ml) was added sodium borohydride (62 mg). The reaction mixture was brought to reflux for a period of 3 h, then an additional quantity of borohydride (60 mg) was added. After refluxing for a further 1 h, the mixture was allowed to cool to room temperature and quenched with 2 N HCl (10 ml). The aqueous solution was washed with ethyl acetate (5 ml) then neutralized ($NaHCO_3$ solution) and extracted with ethyl acetate (3 x 15 ml). The combined extracts were concentrated in vacuo and the residue chromatographed to give the 3-[2-(dimethylamino)ethyl]-N-methyl 1H-indole-5-methanesulphonamide as a gum (2 mg) which was shown by TLC.

Succinic acid in hot methanol was added to a hot solution of the the 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide in absolute ethanol and the mixture was heated to reflux with stirring to give a solution. The solution was allowed to cool with stirring to room temperature, and the resultant suspension was farther cooled in an ice-bath for 2 h. The solid was filtered off, washed with ethanol, and dried in vacuo to give the 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide, salt with succinic acid (1:1).

References

William A.; GB Patent No. 2162 522 A; Feb. 5 1986; Assigned: Glaxo Group Limited (United Kingdom), Clarges House, 6-12 Clarges Street, London W 1Y 8DH

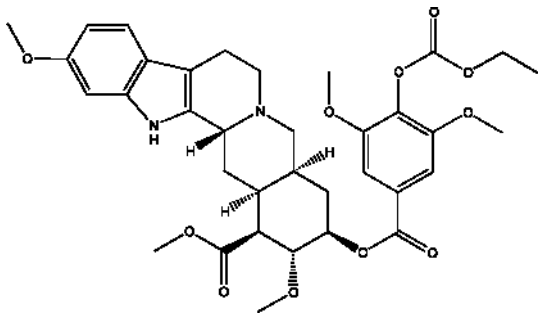
SYROSINGOPINE

Therapeutic Function: Antihypertensive

Chemical Name: 18-[[4-[(Ethoxycarbonyl)oxy]-3,5-dimethoxybenzoyl]oxy]-11,17-dimethoxyyohimban-16-carboxylic acid methyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 84-36-6

Trade Name	Manufacturer	Country	Year Introduced
Singoserp	Ciba	US	1958
Syringia	Toyo Jozo	Japan	1975
Aurugopin	Nisshin	Japan	-
Elumonon	Tatsumi	Japan	-
Hipotensor Zambe	Zambeletti	Italy	-
Neoreserpan	Panthox and Burck	Italy	-
Nichiserpine-S	Nichiiko	Japan	-
Novoserpina	Ghimas	Italy	-
Raunova	Zambeletti	Italy	-
Rosidil	Nippon Chemiphar	Japan	-
Siroshuten	Isei	Japan	-
Tesamurin	Zensei	Japan	-

Raw Materials

Methyl reserpate
O-Carbethoxysyringoyl chloride

Manufacturing Process

1 part by weight of methyl reserpate and 1.9 parts by weight of O-carbethoxysyringoyl chloride were dissolved in 20 parts by volume of anhydrous pyridine and allowed to stand at 5°C for 3 days. An equal volume

of ice was then added, and the mixture evaporated to dryness in vacuo. The residue was dissolved in 50 parts by volume of chloroform and washed in succession with three 50 parts by volume portions of 2% sodium hydroxide solution and two 50 parts by volume portions of water. The chloroform solution was dried over sodium sulfate and evaporated to dryness. The residue was dissolved in 15 parts by volume of benzene and chromatographed on a 10 part by weight column of II-III grade alumina. Eluates of benzene, 90 benzene: 10 acetone, 80 benzene: 20 acetone, 60 benzene: 40 acetone; and acetone were removed. From the 90 benzene: 10 acetone eluate there was recovered crystalline methyl O-(O'-carbethoxysyringoyl)-reserpate, melting point 175°C to 178°C, on crystallization from acetone.

References

Merck Index 8901
Kleeman and Engel p. 853
OCDS Vol. 1 p. 319 (1977)
I.N. p. 917
Lucas, R.A.; US Patent 2,813,871; November 19,1957; assigned to Ciba Pharmaceutical Products, Inc.