Z

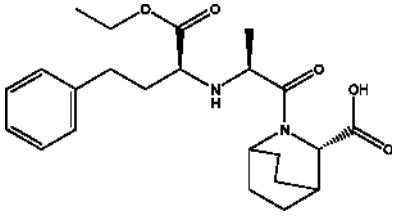
ZABICIPRIL

Therapeutic Function: Antihypertensive

Chemical Name: (3S)-2-((2S)-N-((1S)-1-Carboxy-3-phenylpropyl)alanyl)-2-azabicyclo[2.2.2]octane-3-carboxylic acid, (1-ethyl ester)

Common Name: Zabicipril

Structural Formula:



Chemical Abstracts Registry No.: 83059-56-7

Trade Name	Manufacturer	Country	Year Introduced
Zabicipril	ZYF Pharm Chemical	-	-

Raw Materials

4-Phenyl-2,4-diazatricyclo[5.2.1.0(2,6)]decane-3,5-dione-(1)-hydantoin
DCC-HOBT - dicyclohexylcarbodiimideoxybenztriasole
Tartaric acid
Cyanamide
Benzyl alcohol
4-Toluenesulfonic acid
t-Butylamine

Manufacturing Process

The racemic 2-azabicyclo[2.2.1]heptane-3-carboxylic acid was obtained by alkaline hydrolysis (24 h reflux in 4 N NaOH/MeOH 3/1; yield 78%) of the 4-phenyl-2,4-diazatricyclo[5.2.1.$0^{2,6}$]decane-3,5-dione-(1)- hydantoin obtained

according to Ben Ishai. Starting from 2-azabicyclo[2.2.1]heptane-3-carboxylic acid, the (-)-tartaric acid salt of it crystallized from EtOH (yield 87 %) was obtained from this salt by ion-exchange on Dowex 50 WX 8 (H+ form) and elution with 0.3 N NaOH. (yield 98 %) (GLC after esterification with CH_2N_2 and amidation with (-)-camphanyl chloride). 2-Azabicyclo[2.2.1]heptane-3-carboxylic acid was esterified to benzyl ester with benzyl alcohol in toluene using p-toluenesulfonic acid as catalyst. The second chiral intermediate - 4-phenylbutyric acid ethyl ester; compound with 2-amino-propionic acid (alanine) was prepared according to Kaltenbronn S. It was coupled with the above prepared benzyl ester using dicyclohexylcarbodiimideoxybenztriasole (DCC-HOBT)-Et_3N in DMF, thus producing the benxyl ester 2-[2-(1-ethoxycarbonyl-3-phenylpropylamino)propionyl]-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzyl ester (yield 97 %). The high yield of this coupling is probably due to the high reactivity of the rigid bulky nucleophile 2-[2-(1-ethoxycarbonyl-3-phenylpropylamino)propionyl]-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzyl ester and to the low reactivity of the sterically hindered secondary amine intermediate - 4-phenylbutyric acid ethyl ester; compound with 2-amino-propionic acid, so that the formation of by-products (racemates, diketopiperazine from two acylurea by addition of acid on DCC) was not observed (TLC). Benzyl ester was submitted to hydrogenolysis on palladium charcoal in EtOH at room temperature (yield 98%). It crystallized as its t-butylamine salt from ether and finally transformed to more stable hydrochloride - zabicipril (yield 95 %). Careful saponification of t-butylamine salt with 1 N NaOH at room temperature gave crude zabiciprilate, which was purified by ion-exchange on Dowex 50 WX 8 (H^+ form) and elution with water/pyridine 9:1, then crystallization from 2-propanol (yield 80%). Structure of all described compounds is confirmed with NMR spectrum and X-Ray crystal structure analysis.

References

Ben Ishai, D.; Goldstain, E.; Tetrahedron; 1971; 3119-3127
Vincent M. et al.; Tetrahedron Letters; v. 33, No 48; pp. 7369-7372; 1992

ZACOPRIDE HYDROCHLORIDE

Therapeutic Function: Antiemetic, Peristaltic stimulant

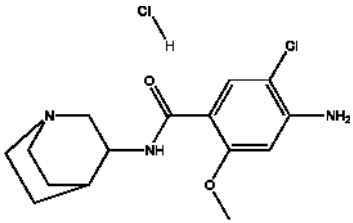
Chemical Name: Benzamide, 4-amino-N-1-azabicyclo[2.2.2]oct-3-yl-5-chloro-2-methoxy- monohydrochloride

Common Name: Zacopride hydrochloride

Chemical Abstracts Registry No.: 90182-92-6 (Base); 99617-34-2

Trade Name	Manufacturer	Country	Year Introduced
Zacopride hydrochloride	ZYF Pharm Chemical	-	-
Zacopride hydrochloride	Biotrend	-	-

Structural Formula:



Raw Materials

4-Amino-5-chloro-2-methoxybenzoic acid
1,1'-Carbonyldiimidazole
3-Aminoquinuclidine

Manufacturing Process

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, fumarate [1:1]:

In a closed system equipped with an oil bubbler, 30 ml of tetrahydrofuran were added to a mixture of 4-amino-5-chloro-2-methoxybenzoic acid, 2.02 g (0.010 mole) and 1,1'-carbonyldiimidazole, 1.62 g (0.010 mole) with stirring. When evolution of carbon dioxide ceased, nitrogen was bubbled through the reaction mixture for 1 hr. A solution of 3-aminoquinuclidine, 1.26 g (0.010 mole) in 10 ml tetrahydrofuran was added dropwise to the stirred reaction mixture and stirring at room temperature continued for 3 hrs. TLC analysis (3% conc. ammonium hydroxide solution in methanol) showed some product formation. The mixture was heated at reflux temperature for 18 hours and then concentraded to an oil. TLC analysis showed the presence of the product, imidazole and 3-aminoquinuclidine. The oil was dissolved in methylene chloride (75 ml) and washed twice with 50 ml portions of aqueous sodium bicarbonate solution. The methylene chloride layer was dried over anhydrous magnesium sulfate and concentrated to yield 2.0 g (67%) of a glassy amorphous solid, the free base of the title compound.

In another reaction on a 0.020 mole scale, 5.18 g (83.8%) of the product as the free base was obtained.

The products were combined, dissolved in methanol (20 ml) and the solution and treated with a solution of fumaric acid (2.73 g) in methanol (50 ml). Absolute ether was added to precipitate the salt which was collected by filtration and recrystallized from methanol-water (200:20) with isopropyl ether added to the point of incipient cloudiness. The recrystallized salt (5.38 g) melted at 223°-225°C.

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride, hydrate (1:1:1):

To an isopropyl alcohol solution of the above free base of the title compound is added in equal molar amount of 37% (conc.) hydrochloric acid. A salt is

separated by addition of acetone followed by filtration which is recrystallized from acetone-water to give the title compound, MP: 158°-160°C.

References

Welstead W.J.; US Patent No. 4,605,652; August 12, 1986; Assigned to A.H.Robins Company, Inc., Richmond, Va.

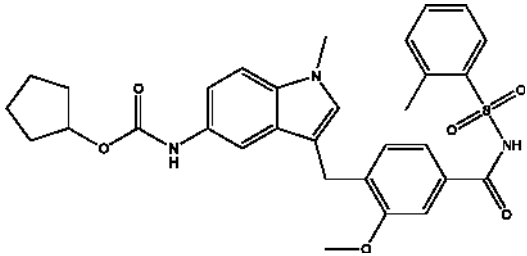
ZAFIRLUKAST

Therapeutic Function: Anti-asthmatic

Chemical Name: Carbamic acid, (3-((2-methoxy-4-((((2-methylphenyl) sulfonyl)amino)carbonyl)phenyl)methyl)-1-methyl-1H-indol-5-yl)-, cyclopentyl ester

Common Name: Zafirlukast

Structural Formula:



Chemical Abstracts Registry No.: 107753-78-6

Trade Name	Manufacturer	Country	Year Introduced
Accolate	AstraZeneca	UK	-
Accolate	Astrazeneca Canada Inc.	Canada	-
Vanticon	Zeneca	-	-

Raw Materials

4-Bromobenzyl-3-methoxy-benzoic acid methyl ester
Silver oxide
Sodium hydride
Methyl iodide
Cyclophentylchloroformate
Lithium hydroxide
o-Toluenesulfonamide

Manufacturing Process

6-Nitroindol with 4-bromobenzyl-3-methoxy-benzoic acid methyl ester gives in presence of silver oxide catalyst the diarilmethane 2-(2,4-dimethoxy-benzyl)-5-nitro-1H-indole. The indole nitrogen is then converted to its anion with sodium hydride; treatment with methyl iodide gives the corresponding N-methyl derivative. Catalitic hydrogenation then converts the nitro group to the amine to give 4-(6-amino-1H-inden-2-ylmethyl)-3-methoxy-benzoic acid methyl ester. Acylation of that amine with cyclophentylchloroformate then gives the urethane [2-(2,4-dimethoxy-benzyl)-1-methyl-1H-indol-5-yl]-carbamic acid cyclopentyl ester. The benzoate ester is then selectively cleaved with lithium hydroxide in dimethyl formamide to the corresponding carboxylic acid. The intermediate is converted to the acyl sulfonamide by coupling with ortho-toluenesulfonamide to give [2-(2-methoxy-4-o-tolylmethanesulfonylaminocarbonyl-benzyl)-1-methyl-1H-indol-5-yl]-carbamic acid cyclopentyl ester (zafirlucast).

References

Lednicer D., The Organic Chemistry of Drug Synthesis, v. 6, p.129-130; 1999, John Wiley and Sons

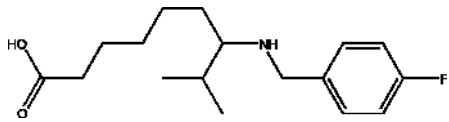
ZAFULEPTINE

Therapeutic Function: Antidepressant

Chemical Name: (+/-)-7-((p-Fluorobenzyl)amino)-8-methylnonanoic acid

Common Name: Thymeon; Zafuleptine

Structural Formula:



Chemical Abstracts Registry No.: 59209-97-1

Trade Name	Manufacturer	Country	Year Introduced
Zafuleptine	ZYF Pharm Chemical	-	-
S 3344	Servier	-	-

Raw Materials

Cyclohexanone
4-Toluenesulfonic acid
Isobutyroyl chloride
Methylamine
Morpholine
Triethylamine
4-Fluorobenzylamine
Platinum oxide

Manufacturing Process

295 g of cyclohexanone and 261 g of morpholine are dissolved in 800 ml of benzene. After the whole has been dissolved, 1.5 g of p-toluene sulfonic acid is added and the mixture is heated under reflux. The water formed is extracted continuously by azeotropic distillation. After 20 hours reflux, the remaining solvent is distilled off and the oily residue is recovered. 379 g of the enamine are so obtained, boiling at 115°C to 117°C/2mm. The yield amounts to 76%. The pure 1-morpholinocyclohex-1-ene has a refractive index of n_D^{22}=1.5122.

To solution of 16.7 g 1-morpholinocyclohex-1-ene in 45 ml chloroform, 10.1 g of triethylamine are added. Over a period of one hour a solution of 1 mole-equivalent of isobutyroyl chloride in 15 ml chloroform is added, with stirring. The mixture is stirred for two hours at room temperature and is thereafter heated at 60°C for 3 hours. It is kept aside for a night, then 150 ml hydrochloric acid are added. The mixture is shaken and is then allowed to settle. The chloroformic phase is discarded. The aqueous phase is partially neutralized with sodium carbonate until the pH value reaches 6 and is then extracted with chloroform three times. The organic phases are united, washed with water, dried over sodium sulfate, filtered and evaporated to dryness. The crude residue is purified by distillation under reduced pressure to give 2-(isobutyroyl)cyclohexanone.

1 mole-equivalent of 2-(isobutyroyl)cyclohexanone is added to 70 ml of a 5% aqueous solution of sodium hydroxide. The mixture is heated under reflux for 2 hours. The aqueous solution is then made acidic with a 4 N solution of hydrochloric acid and is extracted with ether. The ethereous phase is separated, is washed with a saturated solution of sodium chloride, is dried on sodium sulfate, is filtered and is evaporated to dryness. The solid residue is left to stand at room temperature. The crystallization begins quickly. The crystals are recovered and are recrystallized from n-pentane to give 7-oxo-8-methylnonanoic acid.

A fresh solution of 1 mole-equivalent of p-fluorobenzylamine and 1 mole equivalent methylamine is added to a solution of 1 mole-equivalent 7-oxo-8-methylnonanoic acid in 20 ml ethanol. The mixture is warmed at 40°C for a night. 0.1 g of platinum oxide is then added and the mixture is hydrogenated under ordinary pressure at 40°C. After the theoretical amount of hydrogen has been absorbed, the catalyst is filtered off and the solvent is evaporated under reduced pressure. The oily residue crystallized quickly, at room temperature. The product is purified by recrystallizing it from ethyl acetate and is dried over phosphoric anhydride in a closed vessel. (+/-)-7-((p-Fluorobenzyl)amino)-8-methylnonanoic acid is a crystalline solid; MP: 88°-89°C.

References

Malen C. et al.; US Patent No. 4,154,851; May 15, 1979; Assigned to Science Union et Cie, Sciete Francaise de Recherche Medicale, Suresnes, France

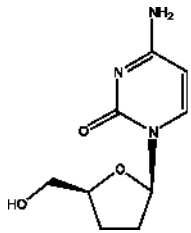
ZALCITABINE

Therapeutic Function: Antiviral, Immunosuppressive

Chemical Name: Cytidine, 2',3'-dideoxy-

Common Name: Dideoxycytidine; Zalcitabine

Structural Formula:



Chemical Abstracts Registry No.: 7481-89-2

Trade Name	Manufacturer	Country	Year Introduced
Hivid	Hoffmann - La Roche Inc.	USA	-
Zalcitabine	Roche Laboratories	USA	-

Raw Materials

2-Acetoxy-2-methylpropanoyl bromide
(S)-(-)-2-Acetoxypropionyl bromide
Poly-4-vinylpyridine
Palladium on charcoal
Ethylenediaminetetraacetic acid disodium salt dihydrate (Fluka)
N-Acetylcytidine
Copper sulfate dihydrate
Acetic anhydride
Triton B
Zinc

Manufacturing Process

Bromoacetylation of N-acetylcytidine with 2-acetoxy-2-methylpropanoyl bromide

A 5 L three-nicked, round-bottomed flask equipped with a mechanical stirrer, thermometer, nitrogen inlet tube, and additional funnel was charge with 142.6 g (0.5 mole) of N-acetylcytidine, and 1.25 L of acetonitrile. The suspension was stirred under nitrogen, cooled to 5°C (ice-bath), and treated dropwise (during 20 min) with 225 ml of 2-acetoxy-2-methylpropanoyl bromide (AIBB) during 30 minutes. At the completion of the addition, a homogeneous solution resulted. It was stirred at room temperature overnight (the reaction was complete within 3 hr), cooled to 5°C, and diluted with 1.25 L of ethyl acetate. After recooling to 5°C, 2.0 L of saturated sodium bicarbonate was added. The mixture was stirred for 5 minutes, the organic phase was separated, and the aqueous phase was back-extracted with 500 ml of ethyl acetate. The combined organic extracts were washed with 1 L of saturated brine, dried ($MgSO_4$), and evaporated to give a gum. Final drying at 40°C (1 mm) for 1 hr

gave 264.7 g (102%) of a white solid. High pressure liquid chromatographic analysis gave the following results (major peaks only): 40% of [2R-[2α,3β,4α,5α(S*)]]-N-[1-[3-(acetyloxy)-5-[(2-(acetyloxy)-1-oxopropoxy] methyl]-4-bromotetrahydro-2-furanyl]-1,2-dihydro-2-oxo-4-pyrimidinyl] acetamide (a) and 24% of its regioisomer (b).

Preparation of [2R-[2α,3β,4α,5α(S*)]]-N-[1-[3-(acetyloxy)-5-[(2-(acetyloxy)-1-oxopropoxy]methyl]-4-bromotetrahydro-2-furanyl]-1,2-dihydro-2-oxo-4-pyrimidinyl]acetamide (a) and its regioisomer (b).

A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and argon inlet was charged with 28.52 g of N-acetylcytidine in 250 ml of acetonitrile. The mixture was cooled to 10°C and treated with 48.75 g of (S)-(-)-2-acetoxypropionyl bromide during 15 minutes. It was stirred at room temperature overnight, cooled to 10°C, treated with 400 ml of cold (0°C) saturated sodium bicarbonate, and extracted with 250 ml of ethyl acetate. The extract was washed with 200 ml of saturated brine, dried ($MgSO_4$) and evaporated to give 45.45 g of a white foam. Reversed phase chromatography (C_{18} column) with 40% methanol in water gave a pure sample of (a).

Zinc-copper couple was prepared by the next way:

A 12 L three-necked, round-bottomed flask equipped with a mechanical stirrer was charged with 4.50 kg of zinc dust. The zinc dust was washed with 3.75 L of 3% aqueous hydrochloric acid by stirring for 3 to 5 minutes. The hydrochloric acid was decanted from the solid. This cycle was repeated with 3x3.75 L of 3% hydrochloric acid. The reaction was slightly exothermic and the volume of the zinc dust increased to double its original volume. The zinc dust was then washed with 4x3.0 L of deionized water to remove any residual hydrochloric acid. After all the water was decanted, the spongy zinc layer was treated with a solution made by dissolving 240.0 g of cupric sulfate dihydrate in 7.5 L of deionized water. The suspension was stirred rapidly as the solution was added. The aquamarine color of the cupric sulfate solution was removed almost immediately and the zinc suspension changed in color from gray to black. The near colorless aqueous layer was decanted and the solid was washed with 4x3.0 L of deionized water. The suspension of zinc-copper couple was filtered through a piece of Whatman No. 1 filter paper, then washed with 4x30 L ethanol and 3x3.0 L of ether. The solid was carefully dried at 25°C and 140 mm overnight to remove ether, then for 3 hr at 130°-140°C (0.5 mm). The solid was cooled to room temperature under vacuum and was stored under argon in amber bottles. The procedure yielded 3.84 kg of zinc-copper couple.

Preparation of [2R-[2α,5α(S*)]]-N-[1-[5-[[2-(acetyloxy)-1-oxopropoxy] methyl]-2-5-dihydro-2-furanyl]-1,2-dihydro-2-oxo-4-pyrimidinyl]acetamide.

A total of 1.47 g of a mixture of bromoacetates in acetonitril was reduced with 800 mg of zinc-copper couple. The mixture was stirred under argon at room temperature overnight. The mixture was deoxygenated by evacuation followed by filling the reaction vessel with argon (oxygen-free nitrogen may be used); this procedure was repeated three times. It was filtered over Celite, the flask was rinsed out with of acetonitrile, and the rinse was used to wash the Celite. The combined filtrate and washing were evaporated (40°C), and the residue was dissolved in of methylene chloride. This was added to a previously

prepared solution of ethylenediaminetetraacetic acid disodium salt dihydrate (Fluka) in deionized water containing of sodium bicarbonate. The mixture was stirred vigorously for 1.5 hr, and filtered over Celite, which was washed with methylene chloride. The organic phase was separated and the aqueous phase was re-extracted with of methylene chloride. The combined organic was washed with of saturated sodium bicarbonate, which was back-extracted with of methylene chloride. The combined organic was dried ($MgSO_4$), filtered, and concentrated. To this was added of acetic anhydride followed by 40 g of poly-4-vinylpyridine, and the mixture was stirred under nitrogen for 3 hr. It was filtered over Celite, which was washed with methylene chloride. The combined filtrate and washing were evaporated, toluene was added, and the mixture was evaporated again, ether was added with vigorous stirring for 15 minutes. The mixture was filtered (some scraping of the flask was necessary) and washed with ether to give 570 mg of after crystallization from hot tetrahydrofuran, melting point 125°C; $[\alpha]_D^{25}$+119.04°(c=0.25, $CHCl_3$).

Preparation of [2R-[2α,5α(S*)]]-N-[1-[5-[[2-(acetyloxy)-1-oxopropoxy] methyl]tetrahydro-2-furanyl]-1,2-dihydro-2-oxo-4-pyrimidinyl]acetamide.

A solution of 720 mg of 2R-[2α,5α(S*)]]-N-[1-[5-[[2-(acetyloxy)-1-oxopropoxy]methyl]-2-5-dihydro-2-furanyl]-1,2-dihydro-2-oxo-4-pyrimidinyl]acetamide set forth in 10 ml L of methanol and 10 ml of tetrahydrofuran was hydrogenated over 200 mg of 10% palladium on charcoal at room temperature and atmospheric pressure until hydrogen uptake ceased (10 ml). The mixture was filtered over Celite and the filtrate was evaporated to give a gum. Chromatography on 10 g of silica (70-230 mesh) with 10% methanol in methylene chloride, gave 290 mg of the product as a foam, $[\alpha]_D^{25}$+88.43° (C=0.99, $CHCl_3$).

Preparation of 2',3'-dideoxycytidine.

A solution of 20.7 g of [2R-[2α,5α(S*)]]-N-[1-[5-[[2-(acetyloxy)-1-oxopropoxy]methyl]tetrahydro-2-furanyl]-1,2-dihydro-2-oxo-4-pyrimidinyl] acetamide in 100 ml of ethanol was treated with 10.0 ml of Triton B (N-benzyltrimethyl-ammonium hydroxide), and the mixture was stirred at room temperature overnight. The mixture was concentrated to 20 ml, cooled to 0°C, and the product was collected by filtration. It was washed with 10 ml of cold ethanol to give 4.48 g of 2',3'-dideoxycytidine, melting point 215°-218°C, as an white solid.

References

Belica P.S. et al.; US Patent No. 4,900,828; Feb. 13, 1990; Assigned to Hoffmann-LaRoche Inc., Nutley, N.J.

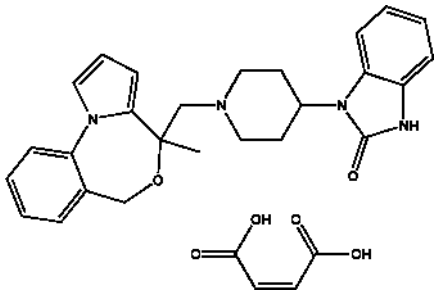
ZALDARIDE MALEATE

Therapeutic Function: Antidiarrheal

Chemical Name: 2H-Benzimidazol-2-one, 1,3-dihydro-1-[1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)methyl]-4-piperidinyl]-, maleate (1:1)

Common Name: Zaldaride maleate

Structural Formula:



Chemical Abstracts Registry No.: 109826-26-8 (Base); 109826-27-9

Trade Name	Manufacturer	Country	Year Introduced
Zaldaride maleate	Ciba-Geigy (Novartis)	-	-

Raw Materials

Methyl anthranilate	2,5-Dimethoxytetrahydrofuran
Butyl lithium	Lithium aluminum hydride
1,1'-Carbonyldiimidazole	Tetramethylethylene diamine
Ethyl pyruvate	1,3-Dihydro-1-(4-piperidyl)-2H-benzimidazol-2-one

Manufacturing Process

A mixture of 500 g of methyl anthranilate and 438 g of 2,5-dimethoxytetrahydrofuran in 670 ml of glacial acetic acid is heated at reflux temperature for 1.5 hours. The acetic acid is then evaporated under reduced pressure and the residue is distilled to yield methyl 2-(1H-pyrrol-1-yl)benzoate, b.p. 109°C/0.1 mm Hg.

To a suspension of 117 g of lithium aluminum hydride in 2 L of anhydrous ether (under an inert atmosphere) is added dropwise a solution of 428 g of methyl 2-(pyrrol-1-yl)benzoate in 1.5 L of ether over a period of 4 hours. The reaction mixture is then heated at reflux temperature for an additional 4 hours and then allowed to cool to room temperature. After cooling in an ice-bath, the excess lithium aluminum hydride is destroyed by the dropwise addition of 117 ml of water over 1 hour, followed by dropwise addition of 117 ml of 15% sodium hydroxide and subsequent addition of 351 ml of water over a 30 minute period. The resultant granular solid is separated by filtration, the ether layer is then dried over magnesium sulfate and the solvent evaporated under reduced pressure to yield 2-(pyrrol-1-yl)benzyl alcohol which may be further purified by distillation in vacuum; BP: 110°-114°C/0.1 mm Hg.

To a solution of 34.6 g of 2-(pyrrol-1-yl)benzyl alcohol in 300 ml of anhydrous tetrahydrofuran and 32 ml of tetramethylethylene diamine is added 183 ml of a 2.4 molar solution of n-butyl lithium in such a manner that the internal temperature of the reaction is maintained below 30°C. On completion of the addition, the reaction mixture is stirred at room temperature for 3 hours. The reaction mixture is then cooled to -70°C by means of a dry-ice/acetone bath, and 24 ml of ethyl pyruvate is added to the mixture over 1 minute. The reaction is then allowed to warm to room temperature and stirred overnight (18 hours). The reaction is then poured into an ice-water/ether mixture and the organic phase separated, dried over magnesium sulfate and the solvent evaporated under reduced pressure to yield ethyl-4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine-4-carboxylate, MP: 94°-96°C, which may be recrystallized from a mixture of ether-hexane (1:1).

The mixture of 41 g thereof, 180 ml of 3 N sodium hydroxide and 150 ml of ethanol is heated at reflux temperature for 6 hours. The ethanol is then removed by evaporation under reduced pressure and the aqueous solution is acidified to pH 5 with 6 N HCl. The resulting product, 4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine-4-carboxylic acid, MP: 182°-183°C, is collected by filtration, and may be recrystallized from aqueous ethanol.

To a solution of 7.5 g thereof, in 300 ml of tetrahydrofuran is added 5 g of 1,1'-carbonyldiimidazole and the resultant mixture stirred at room temperature for 1 hour. To this mixture is added 5 g of 1,3-dihydro-1-(4-piperidyl)-2H-benzimidazol-2-one, and the reaction is heated at reflux temperature for 48 hours. After cooling to room temperature, the reaction mixture is poured into 150 ml of ice-water and extracted into 150 ml of methylene chloride. The organic extracts are washed successively with 150 ml of sodium carbonate solution, 150 ml of water and 150 ml of dilute hydrochloric acid, then dried over magnesium sulfate, filtered, and the solvent is evaporated under reduced pressure to yield 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)carbonyl]-4-piperidinyl}-2H-benzimidazol-2-one, m.p. 208°-210°C.

To a suspension of 3.0 g of 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)carbonyl]-4-piperidinyl}-2H-benzimidazol-2-one in 120 ml of tetrahydrofuran is added 700 mg of lithium aluminum hydride. The reaction mixture is then heated at reflux temperature for 6 hours followed by stirring at room temperature for 18 hours. The reaction mixture is diluted with 150 ml of ether and the excess lithium aluminum hydride destroyed in the usual manner described below. The resulting granular precipitate is removed by filtration. The organic phase is washed with 150 ml of dilute sodium hydroxide and then 150 ml of brine. The organic extracts are then dried over magnesium sulfate, filtered and solvent evaporated under reduced pressure to yield 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one, MP: 199°-201°C. This is then converted into its maleate salt by dissolving separately the free base and a molar equivalent amount of maleic acid in acetone, and combining the solutions. The 1:1 maleate salt crystallizes upon standing, has MP: 183°-185°C.

The 1:1 fumarate salt prepared in a similar manner has a melting point of 125°-127°C.

References

Wasley J.W.F. et al.; US Patent No. 4,758,559; July. 19, 1988; Assigned to Ciba-Geigy Corporation, Ardsley, N.Y.

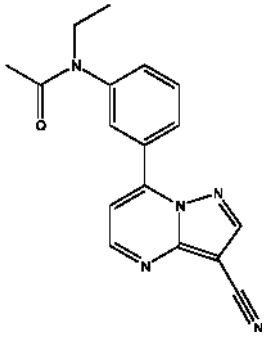
ZALEPLON

Therapeutic Function: Sedative

Chemical Name: Acetamide, N-(3-(3-cyanopyrazolo(1,5-a)pyrimidin-7-yl)phenyl)-N-ethyl

Common Name: Zaleplon; Zelaplon

Structural Formula:



Chemical Abstracts Registry No.: 151319-34-5

Trade Name	Manufacturer	Country	Year Introduced
Sonata	Lundbeck	-	-
Sonata	Wyeth-Ayerst Laboratories	-	-
Starnoc	Servier	France	-
Stilnite	Zydus Neurosciences	India	-
Zalep	Protech Biosystems, Division of Cipla	India	-
Zaplon	Torrent Pharmaceuticals Ltd.	India	-
Zaso	Cadila Pharmaceuticals Ltd.	India	-

Raw Materials

N-(3-Acetylphenyl)ethanamide
Dimethylformamide dimethyl acetal
Acetic acid
Sodium hydride
Ethyl iodide

Manufacturing Process

N-[3-[3-(Dimethylamino)-1-oxo-2-propenyl]phenyl]acetamide amide

A 1 gram-equivalent portion of N-(3-acetylphenyl)ethanamide in equivalent portion of dimethylformamide dimethyl acetal was refluxed for 8 hours, then evaporated. The residue was taken up in 200 ml of dichloromethane, passed through hydrous magnesium silicate, diluted with hexane and concentrated, giving the desired compound.

N-[3-[3-(Dimethylamino)-1-oxo-2-propenyl]phenyl-N-ethylacetamide

A mixture of 1 gram-equivalent of N-[3-[3-(dimethylamino)-oxo-2-propenyl]phenyl]propanamide and equivalent portion of 60% sodium hydride in oil in dimethylformamide was stirred for 0.5 hour under argon, then cooled in an ice bath and a solution of 1gram-equivalent of ethyl iodide in 10 ml of dimethylformamide was added in small portions. The mixture was then stirred at room temperature for 0.5 hour and extracted three times with hexane. The extracts were discarded, water was added and this mixture extracted with dichloromethane. This extract was evaporated and the residue crystallized from hexane giving the desired compound, MP 110°-113°C.

N-[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide

A mixture of 1 gram-equivalent of 3-aminopyrazole-4-carbonitrile and 1 gram-equivalent of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetanamide in 50 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed. The residue was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was separated, dried, passed through a pad of hydrous magnesium silicate and hexane was added to the refluxing filtrate. The mixture was then cooled and the solid collected, giving the desired product, MP 186°-187°C.

References

Dusza J.P. et al.; US Patent No. 4,656,538; Dec. 2, 1986; Assigned to American Cyanamid Company, Stanford, Conn.

ZALOSPIRONE HYDROCHLORIDE

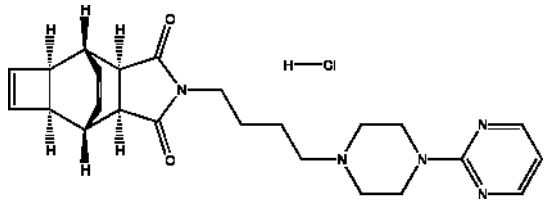
Therapeutic Function: Anxiolytic

Chemical Name: 4,7-Etheno-1H-cyclobut[f]isoindole-1,3(2H)-dione, 3a,4,4a,6a,7,7a-hexahydro-2-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-, (3aα,4aα,4β,6aα,7β,7aα)- monohydrochloride

Common Name: Zalospirone hydrochloride

Chemical Abstracts Registry No.: 114298-18-9 (Base); 114374-97-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Zalospirone hydrochloride	American Home Products (AHP)	-	-

Raw Materials

1,3-Dioxo-4,7-etheno-δ^5-1,3,3a,7a-tetrahydrocyclobut[f]isoindole
Sodium hydride
1,4-Dibromobutane
Triethylamine
1-(2-Pyrimidinyl)piperazine dihydrochloride

Manufacturing Process

To a stirred solution of 0.035 mole of 1,3-dioxo-4,7-etheno-δ^5-1,3,3a,7a-tetrahydrocyclobut[f]isoindole in 70 ml of dimethylformamide is added 0.9 g of sodium hydride. The suspension is stirred at 60°C for 3 hours and is poured into a stirred solution of 1,4-dibromobutane (0.04 mol) in 50 ml of dimethylformamide. The reaction mixture is stirred at room temperature for 24 hours, dimethylformamide is evaporated under reduced pressure and the residue is extracted with methylene chloride (3x200 ml). The methylene chloride extracts are collected, washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue is solidified to a waxy like material. 0.007 mole of this material is dissolved in 50 ml of dimethylformamide, and to this solution is added 6 ml of triethylamine and 0.007 mole of 1-(2-pyrimidinyl)piperazine dihydrochloride. The reaction mixture is stirred at room temperature for 48 hours. Dimethylformamide is removed under reduced pressure and the remaining solid is extracted with 2x100 ml of methylene chloride. The methylene chloride extracts are dried over anhydrous Na_2SO_4, evaporated and the residue is separated by HPLC using 30% methanolethyl acetate as eluent. Evaporation of the solvent from the desired fractions (R_f = 0.5) affords the 3a,4,4a,6a,7,7a-hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4,7-etheno-1H-cyclobut[f]isoindole-1,3(2H)-dione dihydrochloride, which is converted to the dihydrochloride salt by dissolving the free base in ethanol and adding ether saturated with hydrogen chloride; MP: 252°-254°C.

References

Abou-Gharbia M.; US Patent No. 4,892,943; Jan. 9, 1990; Assigned to Amercan Home Products Corporation, New York, N.Y.

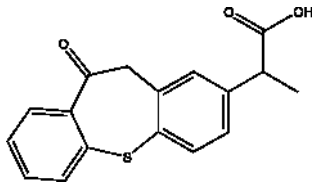
ZALTOPROFEN

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: Dibenzo[b,f]thiepin-2-acetic acid, 10,11-dihydro-α-methyl-10-oxo-

Common Name: Zaltoprofen; Zaxoprofen

Structural Formula:



Chemical Abstracts Registry No.: 89482-00-8

Trade Name	Manufacturer	Country	Year Introduced
Zaltoprofen	ZYF Pharm Chemical	-	-
Soleton	NIPPON CHEMIPHAR CO., LTD.	-	-

Raw Materials

Dimethyl malonate
Palladium on carbon
Sodium nitrite
Polyphosphoric acid
Potassium t-butoxide
Thiophenol
Diethyl 2-(3-chloro-4-nitrophenyl)-2-methylmalonate

Manufacturing Process

Zaltoprofen may be prepared in 4 steps:

1. Preparation of 2-(3-carboxymethyl-4-nitrophenyl)propionic acid:

Dimethyl malonate (4.04 g, 30.6 mmol), potassium t-butoxide (3.43 g, 30.6 mmol) and anhydrous N,N-dimethylformamide (15 ml) were mixed and stirred for 10 minutes in a nitrogen atmosphere at 90°C. The mixture was then cooled to room temperature, and to the cooled mixture was added a solution of diethyl 2-(3-chloro-4-nitrophenyl)-2-methylmalonate (5.04 g, 15.3 mmol) prepared in the manner as described in Japanese Patent Publication No. 47-45, 746) in anhydrous N,N-dimethylformamide (15 ml). The resulting mixture was stirred at 90°C for 3 hours, and then poured into 1 N hydrochloric acid (30 ml). The mixture was subjected to extraction using two portions of diethyl ether. The ether extracts were combined, washed successively with water and an aqueous saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The dried extract was placed under reduced pressure to give 7.97 g of yellow oil. The oil was adsorbed on silica gel (16 g) and subjected to

moderate pressure silica gel column chromatography. The adsorbed oil was eluted using a mixture of ethyl acetate/hexane (1/3, v/v) to give 4.33 g (yield: 66.7%) of diethyl 2-[3-bis(methoxycarbonyl)methyl-4-nitrophenyl]-2-methylmalonate as a yellow oil.

The diethyl 2-[3-bis(methoxycarbonyl)methyl-4-nitrophenyl]-2-methylmalonate obtained above,(4.13 g, 9.71 mmol) was dissolved in acetic acid (40 ml). To the solution were added water (16 ml) and concentrated sulfuric acid (4 ml), and the resulting mixture was heated for 15 hours under reflux. The acetic acid was distilled off under reduced pressure. The residue was concentrated under reduced pressure after addition of toluene. The precipitated crystals were collected by filtration and washed with water to give 2.06 g of the desired compound as a pale brown crystalline product. The filtrate and washing were combined and subjected to extraction using ethyl acetate. The ethyl acetate portion was washed successively with water and an aqueous saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to leave 0.32 g of 2-(3-carboxymethyl-4-nitrophenyl)propionic acid as a yellow crystalline product. The total amount was 2.38 g (yield: 96.8%).

2. Preparation of 2-(4-amino-3-carboxymethylphenyl)propionic acid disodium salt:

In 0.5 N aqueous sodium hydroxide solution (0.8 ml) was dissolved 2-(3-carboxymethyl-4-nitrophenyl)propionic acid (50 mg, 0.2 mmol). The solution was stirred for 18 hours at room temperature in a hydrogen gas atmosphere, after addition of 10% palladium/carbon (10 mg). Insolubles were removed by filtration, and the filtrate was concentrated under reduced pressure to give 55 mg (yield: quantitative amount) of the desired compound as a colorless oil.

3. Preparation of 2-(3-carboxymethyl-4-phenylthiophenyl)propionic acid:

In 2 N hydrochloric acid (0.5 ml) was dissolved 2-(4-amino-3-carboxymethylphenyl)propionic acid disodium salt, 53 mg, 0.2 mmol). Sodium nitrite (14 mg, 0.2 mmol) was added to the resulting solution under stirring and chilling with ice. The mixture was stirred for 30 minutes under chilling with ice. The mixture was then neutralized with a chilled aqueous saturated sodium acetate solution. To the neutralized mixture was added a solution of thiophenol (0.02 ml, 0.2 mmol) in 6 N aqueous sodium hydroxide solution (0.1 ml), and the mixture was stirred for 2 hours at room temperature. The reaction mixture was then made acidic by addition of 2 N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate portion was extracted with an aqueous saturated sodium hydrogen carbonate solution. The aqueous portion was then made acidic by addition of 6 N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate portion was washed successively with water and an aqueous saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give 28 mg (yield: 45%) of the 2-(3-carboxymethyl-4-phenylthiophenyl)propionic acid.

4. Preparation of 2-(10,11-dihydro-10-oxodibenzo[b,f]thiepin-2-yl)propionic acid [i.e., Zaltoprofen]:

2-(3-Carboxymethyl-4-phenylthiophenyl)propionic acid prepared above (174

mg, 0.55 mmol) was mixed with polyphosphoric acid (3.5 g). The mixture was stirred at 60°-70°C for 3 hours. The reaction mixture was then extracted with ethyl acetate after addition of chilled water. The ethyl acetate portion was washed successively with water and an aqueous saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to leave a brown crystalline residue. The residue was recrystallized from benzene-hexane, to give 123 mg (yield: 75%) of the desired compound as a pale yellow crystalline product. MP: 130.5°-131.5°C. The structure of compounds was confirmed with ^{1}H-NMR spectrum.

References

Yamamoto M.; US Patent No. 6,111,115; August 29, 2000; Assigned to Nippon Chemiphar Co., Ltd., Tokyo; Ube Industries, Ltd., Yamaguchi, both of Japan

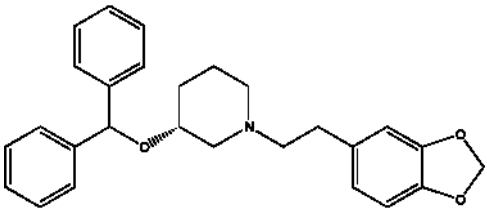
ZAMIFENACIN

Therapeutic Function: Antimuscarinic

Chemical Name: Piperidine, 1-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(diphenylmethoxy)-, (3R)-

Common Name: Zamifenacin

Structural Formula:



Chemical Abstracts Registry No.: 127308-82-1

Trade Name	Manufacturer	Country	Year Introduced
Zamifenacin	Sumitomo Industries	-	-

Raw Materials

Hydroxypiperidine, (3R,S)-
Sodium iodide
Lithium aluminum hydride
Phosphorus tribromide
Benzhydrol
4-Toluenesulfonic acid monohydrate
3,4-Methylenedioxyphenylacetic acid

Manufacturing Process

(3R)-Diphenylmethoxy-1-(3,4-methylenedioxyphenethyl)piperidine:

A mixture of (3R)-diphenylmethoxypiperidine (2.67 g), 3,4-methylenedioxyphenethyl bromide (2.29 g), sodium carbonate (2.10 g) and sodium iodide (0.25 g) in acetonitrile (50 ml) was heated under reflux for 68 hours, diluted with ethyl acetate and water, and the layers were separated. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by chromatography on silica (50 g) using methylene chloride containing 0-5% methanol as the eluant. The title compound (zamifenacin) was obtained as a colourless solid after recrystallisation from hexane (1.25 g, 78%), MP: 52°-55°C, $[\alpha]_D^{25}$= +22.5° (c 1.5 in ethanol).

The starting compounds were prepared next way:

1. (3R)-Diphenylmethoxypiperidine:

A solution of (3R)-hydroxypiperidinium (1S)-camphor-10-sulphonate prepared from (3R,S)-hydroxypiperidine by the method of B. Ringdahl, U. F. W. Ohnsorge and J. C. Craig, [J. Chem. Soc. Perkin II, (1981), 697], $[\alpha]_D^{25}$=+23.1° (c 1.5 in 50% aqueous ethanol; (1 mole-equivalent), benzhydrol (1mole-equivalent) and p-toluenesulphonic acid monohydrate (1 mole-equivalent) in toluene (600 ml) was heated under reflux for four hours using a Dean-Stark apparatus to remove the water formed. The mixture was then partitioned between 2 M aqueous sodium hydroxide solution and ethyl acetate and the organic layer was washed with water and evaporated. The residue was partitioned between ether and 10% aqueous citric acid and the acidic layer was washed with ether, basified with excess solid sodium carbonate and extracted into ether. The organic layer was washed with water, dried over magnesium sulfate and evaporated to give the title compound a colourless oil (2.7 g, 50%), $[\alpha]_D^{25}$=+3.3° (c 1.5 in ethanol), which was characterized by its ^{1}H-NMR spectrum.

2. 3,4-Methylenedioxyphenethyl alcohol:

3,4-Methylenedioxyphenylacetic acid (18.0 g) was added portion wise over 30 minutes to a stirred, ice-cooled suspension of lithium aluminium hydride (4.0 g) in ether (400 ml) and the mixture was stirred at temperature for two hours, quenched by the cautious addition of saturated aqueous ammonium chloride solution and filtered. The filtrate was washed with 10% aqueous sodium carbonate solution, dried over magnesium sulfate and evaporated to give the title compound as a pale yellow oil (15.01 g, 90%), which was characterized by its ^{1}H-NMR spectrum.

3. 3,4-Methylenedioxyphenethyl bromide:

A solution of phosphorus tribromide (8.1 g) in carbon tetrachloride (50 ml) was added dropwise over 30 minutes to a stirred solution of 3,4-methylenedioxyphenethyl alcohol (15.0 g) in carbon tetrachloride (200 ml) and the mixture was heated under reflux for 3 hours, washed sequentially with water (twice), 5 M aqueous sodium hydroxide solution and water, dried

over magnesium sulfate and evaporated. The residue was purified by chromatography on silica (100 g) using carbon tetrachloride as the eluant. Appropriate fractions were combined and evaporated to give the 3,4-methylenedioxyphenethyl bromide as a pale yellow oil (8.3 g, 40%), which was characterized by its ^{1}H-NMR spectrum.

Zamifenacin may be also synthesized from L-proline methyl ester in 4 steps an overall yield of 20% by using a ring enlargement of L-proline derivative.

References

Alker D. et al.; US Patent No. 5,089,505; Feb. 18, 1992; Assigned to Pfilzer Inc., New York, N.Y.
Cossy J. et al.; Bioorganic and Medical Chemistry Letters; v. 7, No 10, pp. 1343-1344, 1997

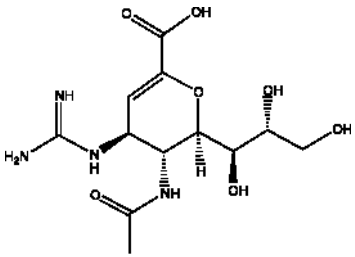
ZANAMIVIR

Therapeutic Function: Antiviral

Chemical Name: D-glycero-D-galacto-Non-2-enonic acid, 5-(acetylamino)-4-(aminoiminomethyl)amino)-2,6-anhydro-3,4,5-trideoxy-

Common Name: Zanamivir

Structural Formula:



Chemical Abstracts Registry No.: 139110-80-8

Trade Name	Manufacturer	Country	Year Introduced
Relenza	GlaxoWellcome	-	-

Raw Materials

5-Acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-glycero-D-galacto-non-2-enonic acid
Sodium acetate
Cyanogen bromide
Hydrazine

5-(Acetylamino)-4-cyanoamino-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enopyranosonic acid
Methylamine

Manufacturing Process

The 1st method of preparation of zanamivir:

5-(Acetylamino)-4-amino-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid (3 g, 10.35 mmol) was suspended in methanol (37.5 ml) and sodium acetate (1.89 g, 23.1 mmol) was added, causing a "caking" of the suspension and making stirring difficult. To this at 21°C with exclusion of moisture was added a solution of cyanogen bromide (1.14 g, 10.8 mmol) in methanol (150 ml), in a dropwise manner. Stirring gradually became easier, until a readily stirrable suspension was obtained. Addition was complete in 3.5 hours. The mixture was then stirred at 21°C with exclusion of moisture for 44 hours. The small amount of remaining solid was filtered off and solvent evaporated in vacuo to an orange-brown foam. The foam was taken up in methanol (125 ml) and with rapid stirring at 21°C was treated dropwise with propan-2-ol (130 ml). The precipitate was filtered off, washed with iso-PrOH/MeOH (3:2), and combined filtrate and washings evaporated to give the 5-(acetylamino)-4-cyanoamino-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid as a pale yellow foam (3.48 g).

5-(Acetylamino)-4-cyanoamino-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid (500 mg, 1.59 mmol) was dissolved in dried (over 3 A mol. sieves) methanol (20 ml) and anhydrous hydrazine (0.5 ml, 15.9 mmol) was added. This was then stirred at 21°C for 18 hours. The white precipitate was filtered off, washed with methanol and air-dried (0.172 g, 31%). The solid was taken up in water (3.2 ml) and with warming and swirling, propan-2-ol (8.1 ml) was added. The cystallised material was filtered off, air-dried then dried under high vacuum to give D-glycero-D-galacto-non-2-enonic acid, 5-(acetylamino)-4-(aminoiminomethyl)amino)-2,6-anhydro-3,4,5-trideoxy as a white solid (0.127 g,); >97% purity; M.P. >180°C.

The 2nd method of preparation of zanamivir:

5-(Acetylamino)-4-cyanoamino-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (500 mg, 1.585 mmol) was dissolved in dried (over 3 A mol. sieves) methanol (12 ml) and methylamine (33 wt. % solution in ethanol, 1.93 ml, 15.85 mmol) was added. This was stirred at 21°C for 18 hours. The precipitate was filtered off and air dried to a white solid (127 mg, 23%). This was recrystallised from water (1.4 ml) and propan-2-ol (6.9 ml). The product was filtered off and dried under high vacuum to give the title compound as a white solid (56 mg, 10.2%). Concentration of mother liquors gave a further 21.3 mg (4%) of D-glycero-D-galacto-non-2-enonic acid, 5-(acetylamino)-4-(aminoiminomethyl)amino)-2,6-anhydro-3,4,5-trideoxy-; 97.7% purity; M.P. >180°C.

References

Laurence M. et al.; US Patent No. 5,639,786; Jun. 17, 1997; Assigned to BIOTA Scientific Manegement, Pty., Ltd., Victoria, Australia

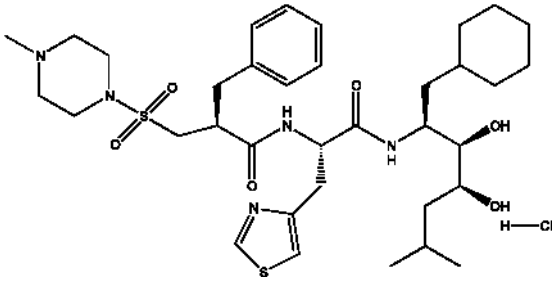
ZANKIREN HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 4-Thiazolepropanamide, N-(1-(cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl)-α-((2-(((4-methyl-1-piperazinyl)sulfonyl) methyl)-1-oxo-3-phenylpropyl)amino)-, (1S-(1R*(R*(R*)),2S*,3R*))-, monohydrochloride

Common Name: Zankiren hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 138742-43-5 (Base); 138810-64-7

Trade Name	Manufacturer	Country	Year Introduced
Zankiren hydrochloride	Abbott	-	-

Raw Materials

Benzaldehyde
1,4-Diazabicyclo[2,2,2]octane
Hydrogen bromide
Sodium sulfite
Hydrogen
N-Methylpiperazine
Diethyl acetamidomalonate
Sodium hydride
Sodium thiosulfate
Lithium hydroxide
Hydrogen chloride
Sodium bicarbonate
1-Hydroxybenzotriazole
Trifluoroacetic acid
Methyl acrylate
Acetic acid
Sulfuric acid
Nickel Raney
Phosphorus pentachloride
Sodium hydroxide
2,3-Dibromopropene
N-Bromosuccinimide
Thioformamide
Sodium
Potassium chloride
Di-t-butyldicarbonate
N-Methylmorpholine
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
(2S,3R,4S)-2-[(t-Butyloxycarbonyl)amino]-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

Manufacturing Process

Producing of (2S)-2-benzyl-3-(1-methyl-piperazin-4-ylsulfonyl)propionic acid:

A mixture of benzaldehyde (82.1 ml, 0.81 mol), methyl acrylate (109.1 ml, 1.211 mol), 1,4-diazabicyclo[2,2,2]octane (13.6 g, 0.12 mol), and acetic acid (1.4 ml, 0.024 mol) was allowed to stir at 35°C for 60 h, at which point the reaction was determined to have proceeded to 70% completion by ^{1}H NMR. Methyl acrylate (20.9 ml, 0.23 mol) was then added and the solution was allowed to react at 35°C for an additional 48 h. The mixture was diluted with diethyl ether (1.0 L) and was washed with 2x200 ml portions of a pH 7 phosphate buffer. After concentration in vacuum, the remaining mixture was distilled at reduced pressure (12 mm) to afford 6.5 g of unreacted benzaldehyde and 130.0 g (90%) of the desired methyl 3-hydroxy-2-methylene-3-phenylpropionate as a colorless oil, boiling point 130°C.

To a 2 L, 3-neck Morton flask fitted with a thermometer, a mechanical stirrer, and an addition funnel was added the methyl 3-hydroxy-2-methylene-3-phenylpropionate (305.9 g, 1.585 mol) followed by addition of 48% HBr (505 ml, 4.46 mol) in one portion. The flask was immersed in an ice-water bath, at which time concentrated sulfuric acid (460 ml, 8.62 mol) was added dropwise over 90 min and the internal temperature of the reaction mixture was maintained at 23°-27°C throughout the addition process. After removal of the ice-water bath, the mixture was allowed to stir at room temperature overnight. The solution was then transferred to a separatory funnel and the organic layer was allowed to separate from the acid layer. The acids were drained and the organic layer was diluted with 2 L of a 1:1 ethyl acetate/hexane solution, washed with saturated aqueous sodium bicarbonate solution (1 L), dried over sodium sulfate, and concentrated to yield 400.0 g (99%) of the desired (Z)-1-bromo-2-carbomethoxy-3-phenyl-2-propene as a light yellow oil, which was used without any additional purification, boiling point 180°C (12 mm).

To a 12 L, 3-neck round bottom flask fitted with a mechanical stirrer, thermometer and an addition funnel was added the (Z)-1-bromo-2-carbomethoxy-3-phenyl-2-propene (400.0 g, 1.57 mol) and methanol (4 L). The mixture was warmed to 50°C and a solution of sodium sulfite (199.0 g, 1.57 mol) dissolved in water (4 L) was added over 75 min while the internal temperature of the flask was maintained at 50°C. After the addition was complete, the clear solution was allowed to stir at 50°C for an additional 45 min. The reaction mixture in solution was taken to the next step without additional purification. The (Z)-2-carbomethoxy-3-phenyl-2-propene-l-sulfonic acid sodium salt may be isolated by concentration to an amorphous powder.

To the 8 L of 1:1 methanol/water mixture containing the (Z)-2-carbomethoxy-3-phenyl-2-propene-l-sulfonic acid sodium salt was added 60.0 g of W-24 raney nickel. The resulting suspension was pressurized under 50 psi of hydrogen and was allowed to shake on a Parr shaker for 24 h, at which time an additional 20.0 g of raney nickel catalyst was added. After 6 h under 50 psi of hydrogen, the catalyst was removed by filtration and the solution was concentrated to dryness. To the dry white solid was added ethyl acetate (6 L) and heptane (4 L) and the solution was vigorously stirred with a mechanical stirrer overnight. The white suspension was removed by filtration yielding 530.0 g (88%) of the desired 2-carbomethoxy-3-phenylpropane-1-sulfonic acid sodium salt as an amorphous powder.

To a 3 L round bottom flask was added the 2-carbomethoxy-3-phenylpropane-1-sulfonic acid sodium salt (530.0 g, 1.39 mol) and toluene (520 ml) followed

by the addition of PCl_5 (317.0 g, 1.52 mol). The mixture was warmed to 50°C with stirring for 45 min. It was then diluted with toluene (1 L) and was filtered through celite. After concentration in vacuum, 371.0 g (96%) of the desired 2-carbomethoxy-3-phenyl-1-propanesulfonyl chloride was obtained as a light brown oil.

To a 1 L round bottom flask was added the 2-carbomethoxy-3-phenyl-1-propanesulfonyl chloride (84.5 g, 0.305 mol) and dichloromethane (305 ml). The mixture was cooled to 0°C in an ice water bath and a solution of N-methylpiperazine (35.5 ml, 32.1 g) dissolved in dichloromethane (305 ml) was added dropwise with vigorous stirring over 90 min. After the addition was completed, the ice-water bath was removed and the mixture was stirred an additional 4 h while warming to room temperature. The solution was then poured into a separatory funnel containing 1 L of a 5% aqueous NaOH solution. The layers were partitioned and the organic layer was dried over potassium carbonate. Concentration in vacuum yielded an oil, which was filtered through 200.0 g of silica gel using 4:1 hexane/ethyl acetate as an eluant. Concentration gave 84.3 g (81%) of the desired methyl 2-benzyl-3-(1-methyl-piperazin-4-ylsulfonyl)propionate as a yellow oil.

The resultant racemic ester methyl 2-benzyl-3-(1-methyl-piperazin-4-ylsulfonyl)propionate (135.0 g, 397 mmol) was suspended in acetone (300 ml) and water (900 ml). While being stirred vigorously at a temperature of 35°C, a crude preparation of Subtilisin Carlsberg (10 ml, Alcalase 2.4 L, Novo Laboratories) was added. Sodium hydroxide solution (6 M) was used to maintain the reaction at pH 7.5-8.0. After 3 days, the acetone was removed under reduced pressure and the aqueous phase was extracted with $CHCl_3$ (1 L) to remove the unreacted ester. The aqueous phase was adjusted to pH 7 with 3 M HCl and was desalted by eluting through a column of Amberlite XAD-16 (2.0 kg, prewashed sequentially with water, methanol, and water) using a water to water-methanol gradient. Evaporation of the solvent afforded 46.0 g (70%) of the (2S)-2-benzyl-3-(1-methyl-piperazin-4-ylsulfonyl)propionic acid as a white solid, melting point 184.5°C.

Producing of H-L-(4-thiazolyl)Ala amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane:

To a stirred mixture of diethyl acetamidomalonate (217.0 g, 1.0 mol) and 2,3-dibromopropene (240.0 g, 1.2 mol) in dry tetrahydrofuran (2.50 L), under nitrogen, was added sodium hydride (26.4 g, 1.1 mol) in several portions. The reaction mixture was stirred at room temperature for 30 min, then heated to reflux. After heating for 18 h, the resultant slurry was cooled to room temperature and suction filtered through a short pad of silica gel. The solid residue was washed with tetrahydrofuran (2x50 ml), and the filtrates were combined and concentrated. The residue was dissolved in ethyl acetate (2.0 L), washed with water and brine, and then was dried over $MgSO_4$. Filtration and concentration gave a yellow oil which solidified upon drying. The resultant solid was recrystallized from a mixture of hot ethyl acetate/hexane to give 301.0 g (89%) of the desired diethyl (2-bromoallyl)acetamidomalonate, melting.point. 85°-87°C.

To a cold (0°C), stirred solution of the diethyl (2-bromoallyl)acetamidomalonate (280 g, 0.83 mol) in a mixture of 2:1 acetonitrile/water (1.68 L) was added solid N-bromosuccinimide (193 g, 1.08

mol) in three portions over a period of 15 min. The resultant orange mixture was stirred at 0°C for an additional period of 1 h and then was allowed to warm to room temperature. After 4 h, the reaction mixture was treated with 10% aqueous sodium thiosulfate, diluted with ethyl acetate, and washed sequentially with water, 10% aqueous $NaHSO_4$ (3 X), water, and brine. Drying ($MgSO_4$) and concentration afforded a yellow solid which was recrystallized from a mixture of ethyl acetate and hexane to give 247.0 g (85%) of the desired diethyl (3-bromo-2-oxo-propyl)acetamidomalonate as a white solid, melting point 97°-98.5°C.

A 5 L, 3-neck round bottom flask equipped with a mechanical stirrer, stopper and a drying tube was charged with the diethyl (3-bromo-2-oxo-propyl)acetamidomalonate (325.0 g, 0.92 mol) and flushed with nitrogen. A freshly prepared solution of thioformamide in tetrahydrofuran (0.8 M, 1.25 L) was added in one portion. The reaction mixture was stirred at room temperature for 4 h. The resultant slurry was then diluted with ether (1.25 L) and cooled to 0°C. The solid was then collected by suction filtration and washed with cold ether (3 X) to give the title compound as the hydrobromide salt. This material was transferred to a 4 L separatory funnel, slurried with ethyl acetate (2 L) and basified by the careful addition of 2 M aqueous NaOH. The organic layer was separated, washed with water and brine, and then dried over $MgSO_4$. Filtration and concentration afforded a pale yellow oil which solidified upon drying to give 242.0 g of the desired compound. This material was recrystallized from an ethyl acetate/hexane mixture to afford 185.6 g (64%) of pure diethyl (4-thiazolylmethyl)acetamidomalonate: melting point 104°-106°C.

To a stirred solution of the diethyl (4-thiazolylmethyl)acetamidomalonate (185.6 g, 0.59 mol) in a mixture of tetrahydrofuran (620 ml) and ethanol (310 ml) was added aqueous 2 M LiOH (325 ml, 0.65 mol) dropwise over 20 min. After stirring at room temperature for 2.5 h, the reaction mixture was concentrated and the resultant aqueous mixture was extracted with ether (3x200 ml), adjusted to pH 3 with 3 M HCl, and concentrated under reduced pressure. Residual water was removed by evaporating portions of toluene (2x200 ml). The residue was diluted with toluene (1.5 L) and the resultant slurry was heated to reflux with separation of residual water (Dean-Stark trap). After 3 h the reaction mixture was cooled to room temperature, diluted with ethyl acetate (1.5 L) and suction filtered through SiO_2 (60.0 g). The solids were washed with additional ethyl acetate (4x500 ml) and the combined organics were concentrated to afford a pale yellow oil which solidified on drying (0.5 torr) to afford 119.6 g (84%) of the desired N-acetyl-3-(4-thiazolyl)-DL-alanine ethyl ester, melting point 58°-62°C.

A 5 L, 3-neck round bottom flask equipped with a mechanical stirrer was charged with the N-acetyl-3-(4-thiazolyl)-DL-alanine ethyl ester (210.0 g, 0.87 mol), distilled water (1.6 L), and 1 M aqueous KCl (0.8 L). The homogeneous solution was adjusted to pH 7.0 with 0.1 M NaOH and then was treated with Subtilisin Carlsberg (1.8 g) dissolved in 0.1 M aqueous KCl (25 ml). The reaction mixture was stirred at room temperature with 1.0 M NaOH added as required to maintain the pH at 6.25-7.25. After 4 h, 430 ml of base had been consumed and the reaction was judged to be complete. The reaction mixture was then extracted with chloroform (4x1.5 L), the aqueous phase was carefully acidified to pH 4 with 2 M HCl and then was concentrated under reduced pressure. Residual water was removed by consecutive evaporation

from toluene (3x500 ml) and ethanol (3x500 ml). The residue was taken up in warm ethanol and suction filtered to remove inorganic salts. The solids were washed with warm ethanol (3x400 ml) and the filtrates were concentrated to afford 92.6 g (50%) of N-acetyl-3-(4-thiazolyl)-L-alanine as a white solid, melting point 186°C. The combined chloroform fractions from the extractions were washed with saturated aqueous NaHCO3, water, and brine and then were dried over $MgSO_4$. Filtration and concentration gave 103.0 g (49%) of N-acetyl-3-(4-thiazolyl)-D-alanine ethyl ester. This material could be further purified by recrystallization from ethyl acetatelhexane, melting point 79°-80.5°C.

A 2 L round bottom flask equipped with a magnetic stirrer was charged with N-acetyl-3-(4-thialzoyl)-L-alanine (92.6 g, 0.43 mol) and 6 M HCl (1 L). The resultant solution was heated to reflux. After 3 h the mixture was allowed to cool to room temperature. The solution was then concentrated under reduced pressure, evaporated from toluene (3x200 ml), and dried under vacuum overnight to give 120.0 g of a slightly wet solid 3-(4-thyazolyl)-L-alanine dihydrochloride.

A 4 L Erlenmeyer flask equipped with a mechanical stirrer was charged with the 3-(4-thiazolyl)-L-alanine dihydrochloride (125.9 g) and tetrahydrofuran (1.5 L) and the mixture was adjusted to pH 6.6 with saturated aqueous sodium bicarbonate. The resultant solution was then adjusted to pH 8.9 with 3.0 M NaOH and a solution of di-tert-butyldicarbonate (117.8 g, 0.51 mol) in tetrahydrofuran (150 ml) was added. The reaction mixture was vigorously stirred at room temperature for 40 h. The tetrahydrofuran was removed under vacuum, the pH of the residue was adjusted to 2.0 with 3.0 M HCl and the mixture was extracted with ethyl acetate (3x300 ml). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to give 150.0 g of a white solid. Recrystallization from hot 1:1 ethyl acetate/hexane (1.06 L) gave 107.6 g (82 %) of the desired N-boc-3-(4-thiazolyl)-L-alanine, melting point 115°C.

(2S,3R,4S)-2-[(tert-Butyloxycarbonyl)amino]-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (5.05 g, 1 4.7 mmol, Luly et al., J. Org. Chem. 1988, 53, 6109) was stirred for 90 min in 4 M HCl in ethanol and then evaporated. Ether was added and evaporated 3 times and the residue was dried under high vacuum. To this residue was added 1-hydroxybenzotriazole (5.57 g, 41.2 mmol), the N-Boc-3-(4-thiazolyl)-L-alanine (4.0 g, 14.7 mmol), dimethylformamide (60 ml) and N-methylmorpholine (3.40 ml, 30.9 mmol). The mixture was cooled to -23°C, treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.03 g, 21.0 mmol). After 2 h at -23°C and 21 h at room temperature the mixture was poured into saturated NaHCO3 solution and extracted into ethyl acetate. The organic layer was washed with water and brine, then dried over Na_2SO_4 and evaporated to a white solid which was recrystallized from 1:15 (v/v) methylenechloride/ether (multiple crops) affording 6.28 g (86%) of the desired Boc-L-(4-thiazolyl)Ala amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane as a flaky white solid, melting point 159°-160°C.

Trifluoroacetic acid (50 ml) was slowly added via cannula to a solution of the Boc-L-(4-thiazolyl)Ala amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (6.27 g, 12.6 mmol) in methylene chloride (50 ml) at 0°C. The reaction was stirred 3 h at 0°C and concentrated in vacuum (40°C bath) to an oil which was basified to pH 10-11 with aqueous K_2CO_3.

The product was extracted into chloroform, dried over Na_2SO_4, filtered, and concentrated to a foam. Recrystallization from 1:4 (v/v) methylene chloride/hexane gave 5.0 g (100%) of the desired H-L-(4-thiazolyl)Ala amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane as a fluffy white solid, melting point 111°-112°C.

Producing of (2S)-2-benzyl-3-(1-methylpiperazin-4-ylsulfonyl)propionyl-(L)-(4-thiazolyl)Ala-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane:

To the (2S)-2-benzyl-3-(1-methylpiperatin-4-ylsulfonyl)propionic acid (1.0 g, 3.064 mmol), the H-L-(4-thiazolyl)Ala amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (1.11 g, 2.792 mmol), and 1-hydroxybenzotriazole (1.022 g, 7.563 mmol) in dimethylformamide (20 ml) was added N-methylmorpholine (0.35 ml, 3.2 mmol). The mixture was cooled to -23°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.760 g, 3.96 mmol). After 2 h at -23°C and 14 h at room temperature, the reaction was poured into saturated $NaHCO_3$ solution (100 ml) and extracted into ethyl acetate (2x50 ml) which was washed with water (2x50 ml) and brine (50 ml) and then was dried over Na_2SO_4 and evaporated to afford 1.94 g. Recrystallization from ethanol (15 ml)/hexane (90 ml) afforded 1.55g (79%) of (2S)-2-benzyl-3-(1-methylpiperazin-4-ylsulfonyl)propionyl-(L)-(4-thiazolyl)Ala-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane as a white solid, melting point 169°-170°C.

References

Rosenberg S.H., Denissen J.F.; EU Patent No. 0,456,185,A2; Nov. 13, 1991; Assigned: ABBOTT LABORATORIES One Abbott Park Road Abbott Park, Illinois 60064-3500 (US)

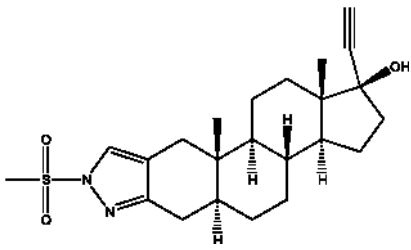
ZANOTERONE

Therapeutic Function: Antiandrogen

Chemical Name: 1'H-Pregn-20-yno[3,2-c]pyrazol-17-ol, 1'-(methylsulfonyl)-, (5α,17α)-

Common Name: Zanoterone

Structural Formula:



Chemical Abstracts Registry No.: 107000-34-0

Trade Name	Manufacturer	Country	Year Introduced
Zanoterone	Sterling Drug (Sanofi-Aventis)	-	-

Raw Materials

Methanesulfonylhydrazide
(2α,5α,17α)-2-(Diethoxymethyl)-17-[(trifluororacetyl)oxy]pregn-20-yn-3-one
(5α,17α)-2-(Acetoxymethylene)-17-hydroxypregn-20-yn-3-one
Acetic acid

Manufacturing Process

1). A solution of methanesulfonylhydrazide (0.0303 mole) in tetrahydrofuran (70 ml, 30 ml for rinsing) was added with stirring to a solution of (2α,5α,17α)-2-(diethoxymethyl)-17-[(trifluororacetyl)oxy]pregn-20-yn-3-one (0.025 mole) in tetrahydrofuran (190 ml). The mixture was allowed to stand for 3 days at room temperature, heated under reflux for 4 h and evaporated. The residue was purified by crystallization and recrystallization from methanol, affording (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol trifluoroacetate (ester), 69% yield, MP: 166°-168°C.

The above ester (10.24 g, 0.0200 mole) in 100 ml of a solution prepared from chloroform (210 ml), ethanol (100 ml) and concentrated aqueous ammonia (10 ml) was allowed to stand at room temperature for 2 h, diluted with chloroform (250 ml), and washed with dilute hydrochloric acid (2 N, 250 ml). The chloroform layer was dried and removed of chloroform under vacuum. A solution of the residue in dichloromethane (95 ml) and ether (5 ml) was passed through silica gel (50 g) using more dichloromethane-ether (19:1, 600 ml). Evaporation of the solvent and recrystallization of the residue from acetonitrile afforded (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol (7.07 g, 85% yield, MP: 202°-203°C). It may be also made another way.

2). A solution of methanesulfonylhydrazide (82.5 g, 0.75 mole) in acetic acid (100 ml) was added with stirring over 5 min to a mixture of (5α,17α)-2-(acetoxymethylene)-17-hydroxypregn-20-yn-3-one (197 g, 0.51 mole) and acetic acid (1 L). The mixture was stirred for 1 h at room temperature, forming a deep yellow solution, which was poured with vigorous stirring into ice-water (6 L). The resulting solid was collected by filtration, washed twice with water (500 ml each time), pressed dry, washed twice again with water (500 ml each time), dried (245 g), recrystallized, first from acetonitrile (2.5 volumes) and then from methanol (6.6 volumes), dried, ground, and redried, affording (5α,17α)-1'-(methylsulfonyl)-1'-H-pregn-20-yno[3,2-c]pyrazol-17-ol (137.8 g, 65% yield, MP: 194°-196°C).

References

Christiansen R. et al.; US Patent No. 4,684,636; Aug. 4, 1987; Assigned to Sterling Drug Inc., New York, N.Y.

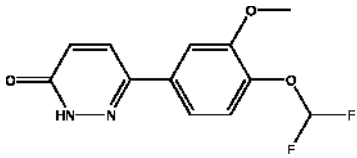
ZARDAVERINE

Therapeutic Function: Bronchodilator

Chemical Name: 6-(4-(Difluoromethoxy)-3-methoxyphenyl)-3(2H)-pyridazinone

Common Name: Zardaverine

Structural Formula:



Chemical Abstracts Registry No.: 101975-10-4

Trade Name	Manufacturer	Country	Year Introduced
Zardaverine	ZYF Pharm Chemical	-	-
Zardaverine	Biotrend	-	-

Raw Materials

Glyoxylic acid monohydrate	4-Hydroxy-3-methoxyacetophenone
Ammonium	Hydrazine hydrate
Sodium hydroxide	Chlorodifluoromethane

Manufacturing Process

20.8 g of 4-hydroxy-3-methoxyacetophenone are dissolved in 350 ml of dioxane and 350 ml of water by the addition of 30.0 g of sodium hydroxide, and the resulting solution is heated to 60°C. While stirring continuously, chlorodifluoromethane is passed into the solution until uptake of the gas stops (about 4 h). The solution is cooled, and the resulting precipitate is filtered off with suction and washed three times with 40 ml of diethyl ether each time. The solution is diluted with water to twice its volume and likewise extracted three times with 100 ml of diethyl ether each time. The combined ether extracts are dried over magnesium sulfate and evaporated in vacuum; the residue is crystallized from petroleum ether (boiling point 50°-70°C), 19.0 g (70.4% of theory) of 4-difluoromethoxy-3-methoxyacetophenone are obtained, melting point 68°C.

15.0 g of 4-difluoromethoxy-3-methoxyacetophenone are heated with 5.9 g of glyoxylic acid monohydrate at 110°C for 2 h. The melt is then cooled to 60°C, 30 ml of water are added, and dissolution is brought about by addition of 10 ml of concentrated aqueous ammonium solution. 3.2 g of hydrazine hydrate are added, and the mixture is boiled under reflux for 2 h, during which the title compound gradually crystallizes out. After cooling, the precipitate is filtered off with suction, thoroughly washed with water, dried and

recrystallized from isopropanol. 10.8 g (58.1% of theory) of the 6-(4-difluoromethoxy-3-methoxyphenyl)-3(2H)pyridazinone are obtained, melting point 204°C.

References

Amschler H; US Patent No. 4,665,074; May 12, 1987; Assigned: Byk Gulden Lomberg Chemische Fabrik GmbH, Constance, Fed. Rep. of Germany

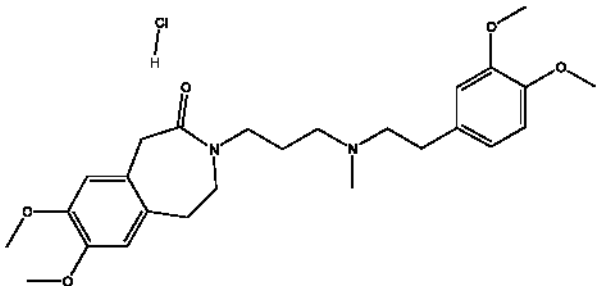
ZATEBRADINE HYDROCHLORIDE

Therapeutic Function: Bradycardic

Chemical Name: 3-(3-((3,4-Dimethoxyphenethyl)methylamino)propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one monohydrochloride

Common Name: Zatebradine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 85175-67-3 (Base); 91940-87-3

Trade Name	Manufacturer	Country	Year Introduced
ZATEBRADINE HYDROCHLORIDE	Boenhringer Ingelheim	-	-

Raw Materials

2-(3,4-Dimethoxyphenyl)acetaldehyde
Hydrochloric acid
Acetic acid
1-[7,8-Dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl]-3-(N-benzylmethylamino)propane
Sodium cyanoborohydride
Palladium on charcoal
Hydrogen
Sodium bicarbonate

Manufacturing Process

A suspension of 1-[7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl]-3-(N-benzylmethylamino)propane and 10% palladium-on-charcoal in glacial acetic acid was hydrogenated at 50°C and at a hydrogen pressure of 5 bar. After the catalyst had been filtered off, the solvent was evaporated in vacuum, and the residue was taken up in methylene chloride. After the solution had been extracted with an aqueous sodium bicarbonate solution and washed with water, it was dried over magnesium sulfate, evaporated and purified over silica gel with methylene chloride and then with increasing amounts of methanol (up to 10%). The N-[3-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-3-yl)propyl]methylamine hydrochloride. Yield: 87% of theory. Melting point: 110°C (dec.).

1.26 g (20 mmols) of sodium cyanoborohydride were added to a solution of 3.29 g (10 mmols) of N-[3-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-3-yl)propyl]methylamine hydrochloride and 1.8 g (10 mmol) of 2-(3,4-dimethoxyphenyl)acetaldehyde in 40 ml of ethanol, while maintaining a pH of 6-7 by the addition of 2 N hydrochloric acid, and stirring was continued for 48 h at room temperature. After evaporating the solution in vacuum, the residue was taken up in dilute hydrochloric acid and extracted twice with ether. Subsequently, the aqueous phase was made alkaline and extracted three times with methylene chloride, and the organic phase was evaporated and purified on silica gel. The 1-[7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on-3-yl]-3-[N-methyl-N-(2-{3,4-dimethoxyphenyl}ethyl)amino]propane was obtained.

References

Reiffen M. et al.; US Patent No. 4,490,369; Dec. 25, 1984; Assigned: Dr. Karl Thomae Gesellschaft mit beschrankter Haftung, Biberach an der Riss, Fed. Rep. of Germany

ZATOSETRON MALEATE

Therapeutic Function: Serotonin antagonist

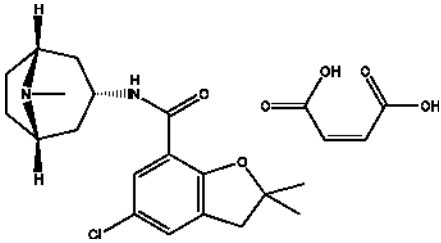
Chemical Name: 7-Benzofurancarboxamide, 5-chloro-2,3-dihydro-2,2-dimethyl-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]- maleate (1:1)

Common Name: Zatosetron maleate

Chemical Abstracts Registry No.: 123482-22-4 (Base); 123482-23-5

Trade Name	Manufacturer	Country	Year Introduced
Zatosetron maleate	Eli-Lilly	-	-
LY53857 maleate	Lilly Research Labs	-	-

Structural Formula:



Raw Materials

5-Chloromethyl salicylate	3-Chloro-2-methylpropene
Potassium carbonate	Sodium chloride
1-Methyl-2-pyrrolidinone	Thionyl chloride
N-Methyltropamine	Sodium hydroxide

Manufacturing Process

A mixture of 5-chloromethyl salicylate, 3-chloro-2-methylpropene, potassium carbonate, and acetone was heated at reflux overnight. After cooling, the mixture was extracted with diethyl ether and ethyl acetate. The organic extracts were combined, washed twice with a 10% sodium chloride solution and water, dried over sodium sulfate, and concentrated in vacuum. The resulting liquid was vacuumed distilled. The fraction collected and the desired 5-chloro-2-(2-methyl-2-propenyloxy)benzoic acid, methyl ester was obtained.

The 5-chloro-2-(2-methyl-2-propenyloxy)benzoic acid, methyl ester was heated at reflux for 6 h in 1-methyl-2-pyrrolidinone. The mixture was then vacuum distilled and the fraction collected and the desired 2-hydroxy-5-chloro-3-(2-methyl-2-propenyl)benzoic acid, methyl ester was obtained.

A mixture of the 2-hydroxy-5-chloro-3-(2-methyl-2-propenyl)benzoic acid, methyl ester and 1 L of methanol was saturated with 90% formic acid and then refluxed overnight. The solution was concentrated in vacuum, added to water, and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and concentrated in vacuum, providing the desired 2,2-dimethyl-5-chloro-2,3-dihydrobenzofuran-7-carboxylic acid, methyl ester as an oil.

The 2,2-dimethyl-5-chloro-2,3-dihydrobenzofuran-7-carboxylic acid, methyl ester were heated at reflux with sodium hydroxide and water for 2-3 h. After cooling, the mixture was extracted with diethyl ether and ethyl acetate. The aqueous layer was acidified with hydrochloric acid and again extracted with ethyl acetate and diethyl ether. These latter organic extracts were combined and washed with water, dried over sodium sulfate, and concentrated in vacuum. Crystallization of the resulting solid from ethyl acetate/hexane provided the desired 2,2-dimethyl-5-chloro-2,3-dihydrobenzofuran-7-carboxylic acid, 71% yield, melting point 158.5°-160°C.

A mixture of 2,2-dimethyl-5-chloro-2,3-dihydrobenzofuran-7-carboxylic acid and thionyl chloride was heated at reflux for 3 h. After the mixture was

concentrated in vacuum and azeotroped with toluene, dry toluene was added and the solution cooled to 5°C. A solution of N-methyl-tropamine in toluene was added in dropwise fashion and the reaction heated at reflux overnight. After cooling, the mixture was added to ice water, made basic, and extracted with diethyl ether/ethyl acetate. The organic layer was washed twice with 6 N hydrochloric acid. The combined aqueous extracts were cooled, made basic with sodium hydroxide solution, and extracted with ethyl acetate. The ethyl acetate solution was washed twice with water, dried over sodium sulfate, and concentrated in vacuum providing of the endo-5-chloro-2,3-dihydro-2,2-dimethyl-N-(8-methyl-8-azabicyclo[3.2.1.]oct-3-yl-7-benzofurancarboxamide, free base, as an oil.

In practice it is usually used as maleate salt.

References

Cohen M.L. et al.; US Patent No. 4,921,982; May 1, 1990; Assigned: Eli Lilly and Company, Indianapolis

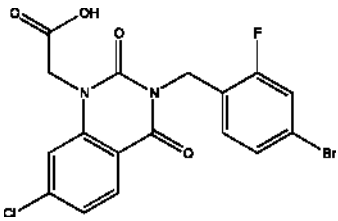
ZENARESTAT

Therapeutic Function: Aldose reductase inhibitor

Chemical Name: 1(2H)-Quinazolineacetic acid, 3,4-dihydro-3-((4-bromo-2-fluorophenyl)methyl)-7-chloro-2,4-dioxo-

Common Name: Fenarestat; Zenarestat

Structural Formula:



Chemical Abstracts Registry No.: 112733-06-9

Trade Name	Manufacturer	Country	Year Introduced
FK 366	Fujisawa Pharmaceutical	-	-

Raw Materials

4-Bromo-2-fluorobenzylamine
4-Chloro-2-nitrobenzoyl chloride
Acetic acid
N,N'-Carbonyldiimidazole
Ethyl bromoacetate
Triethylamine
Hydrochloric acid
Sodium hydroxide
Sodium hydride
Iron

Manufacturing Process

To a solution of 4-bromo-2-fluorobenzylamine and triethylamine in chloroform was added dropwise a solution of 4-chloro-2-nitrobenzoyl chloride in chloroform at 0°C with stirring and the mixture was stirred at the same temperature for 1 h. The reaction mixture was washed in turn with diluted aqueous hydrochloric acid and water, and then dried. Evaporation of the solvent followed by recrystallization from diethyl ether gave N-(4-bromo-2-fluorobenzyl)-4-chloro-2-nitrobenzamide.

A mixture of N-(4-bromo-2-fluorobenzyl)-4-chloro-2-nitrobenzamide and iron (1.45 g) in acetic acid (66 ml) was stirred at 100°C for 30 min. After cooling, iron was filtered off. The filtrate was evaporated to give a residue, which was made alkaline with aqueous 1 N sodium hydroxide and extracted with ethyl acetate. The extract was washed with water and dried. Removal of the solvent gave 2-amino-N-(4-bromo-2-fluorobenzyl)-4-chlorobenzamide.

2-Amino-N-(4-bromo-2-fluorobenzyl)-4-chlorobenzamide and N,N'-carbonyldiimidazole were dissolved in dioxane (50 ml). The solution was evaporated to give a residue, which was stirred at 150°C for 30 min. After cooling, the precipitates were collected by filtration and washed with ethanol to give 3-(4-bromo-2-fluorobenzyl)-7-chloro-1,2,3,4-tetrahydro-2,4-dioxoquinazoline; melting point >280°C.

To a suspension of 3-(4-bromo-2-fluorobenzyl)-7-chloro-1,2,3,4-tetrahydro-2,4-dioxoquinazoline in N,N-dimethylformamide was added sodium hydride (60% in mineral oil) with stirring at 0°C and the mixture was stirred for 15 min at the same temperature. To this mixture was added ethyl bromoacetate and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to give a residue. Thus obtained product was purified by recrystallization from isopropyl ether to give 2-[3-(4-bromo-2-fluorobenzyl)-7-chloro-1,2,3,4-tetrahydro-2,4-dioxoquinazolin-1-yl]acetic acid melting point 223°-224°C.

References

Hashimoto M et al.; US Patent No. 4,734,419; March 29, 1988; Assigned: Fujisawa Pharmaceutical Co., Ltd.

ZENIPLATIN

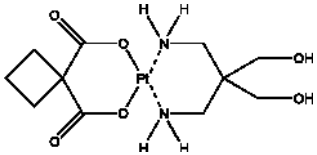
Therapeutic Function: Antineoplastic

Chemical Name: Platinum, (2,2-bis(aminomethyl)-1,3-propanediol-N,N')(1,1-cyclobutanedicarboxylato(2-))-, (SP-4-2)-

Common Name: Zeniplatin

Chemical Abstracts Registry No.: 111490-36-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Zeniplatin	American Cyanamid (AHP)	-	-

Raw Materials

Sodium azide	2,2-Dibromomethyl-1,3-propanediol
Platinum dioxide	Potassium dichloroplatinate
Hydrogen	Disilver salt of 1,1-cyclobutane dicarboxylic acid

Manufacturing Process

The compound of 2,2-dibromomethyl-1,3-propanediol was prepared by the method M. Saivier (et al.), Can. J. Chem; 44, 1599 (1966).

A mixture of 13.1 g of 2,2-dibromomethyl-1,3-propanediol, 6.5 g of sodium azide and 750 ml of dimethylformamide was stirred and heated at 110°-120°C for 20 h, then clarified and the filtrate evaporated. The residue was extracted three times with dichloromethane. The extracts were combined and evaporated, giving 13.65 g of 2,2-bis(azidomethyl)-1,3-propanediol, compound with dimethylformamide.

A 13.0 g portion of the 2,2-bis(azidomethyl)-1,3-propanediol was reduced with 0.1 g of platinum dioxide in ethanol, using 50 lb of hydrogen pressure for 20 h. The mixture was then filtered and the filtrate concentrated to dryness, giving 9.34 g of 2,2-bis(aminomethyl)-1,3-propanediol as a pale yellow oil.

A mixture of 1.34 g of 2,2-bis(aminomethyl)-1,3-propanediol, 4.15 g of potassium dichloroplatinate and 22 ml of water was stirred for 2 h, then cooled, the solid collected and washed three times with cold water. This solid was recrystallized from 60 ml of hot water, giving 890.0 mg of the desired [2,2-bis(aminomethyl)-1,3-propanediol-N,N']dichloroplatinum as beige crystals, melting point 223°-225°C (dec.).

A mixture of 0.8 g of [2,2-bis(aminomethyl)-1,3-propanediol-N,N']dichloroplatinum and 0.78 g of the disilver salt of 1,1-cyclobutane dicarboxylic acid in 50 ml of water was stirred in the dark overnight and then filtered. The filtrate was evaporated to dryness, giving 0.72 g of the desired [2,2-bis(aminomethyl)-1,3-propanediol-N,N'][[1,1'-cyclobutanedicarboxylato](2-)-O1,O1]platinum as a beige powder, melting point 202°-205°C (dec.).

References

Child R.G. et al.; US Patent No. 4,760,157; July 26, 1988; Assigned: American Cyanamid Company, Stamford, Conn.

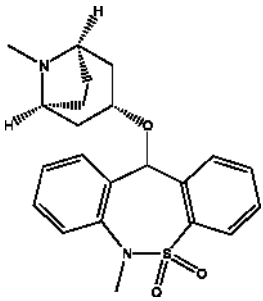
ZEPASTINE

Therapeutic Function: Antihistaminicá Anticholinergic

Chemical Name: 6,11-Dihydro-6-methyl-11-[(1αH,5αH-tropan-3α-yl)-oxy]dibenzo[c,f][1,2]thiazepine 5,5-dioxide

Common Name: Zepastine

Structural Formula:



Chemical Abstracts Registry No.: 28810-23-3

Trade Name	Manufacturer	Country	Year Introduced
Zepastine	ZYF Pharm Chemical	-	-

Raw Materials

5,11-Dihydro-11-methyl-5,10,10-trioxodibenzo[c,f][1,2]thiazepine
Sodium borohydride
Tropine
Maleic acid

Manufacturing Process

5,11-Dihydro-11-methyl-5,10,10-trioxodibenzo[c,f][1,2]thiazepine 16 g is suspended at 300 ml of methanol and treated with of 3 g of sodium borohydride. The reaction mixture is kept at room temperature overnight, heated to dissolve precipitated material, acidified with 10% acetic acid and allowed to cool. The crystalline product is collected on a filter, washed with water and recrystallized from isopropanol, MP: 138°C.

5-Chloro-5,11-dihydro-10,10-dioxo-11-methyldibenzo[c,f][1,2]thiazepine:

A portion of the above product, 5 g, is dissolved in 50 ml of benzene and the solution is saturated with hydrogen chloride. External cooling is supplied in order to maintain the temperature near room temperature. The product crystallizes from the solution during this process. The mixture is kept at room temperature for one hour and the product is collected on a filter, yield 5 g; MP: 224-225°C. This material is purified by recrystallization from toluene, MP: 230°C.

3-(5,11-Dihydro-10,10-dioxo-11-methyldibenzo[c,f][1,2]thiazepin-5-yloxy)tropane and the hydrogen maleate salt thereof. (This name was given by the authors of U. S. Patent No 3 700 633. It corresponds to endo-6,11-dihydro-6-methyl-11-[(8-methyl-6-azabicyclo[3.2.1]oct-3-yl)oxy]dibenzo[c,f][1,2]thiazepine 5,5-dioxide and 6,11-dihydro-6-methyl-11-(8-methyl-8-azabicyclo[3.2.1]octan-3α-yloxy)dibenzo[cf][1,2]thiazepin-5,5-dioxide).

The above chloro intermediate product, 3 g and 3.5 g of tropine with 25 ml of toluene as reaction medium are refluxed for 3 hrs. The reaction mixture is then concentrated in a vacuum until the solvent and other volatile materials are removed. The residue is treated with dilute aqueous hydrochloric acid, and ether. The aqueous layer is separated and neutralized with aqueous sodium hydroxide. Insoluble material, which thereupon separates is dissolved in ether, and the ether solution separated. It is washed several times with water, dried and evaporated, leaving the free base form of the desired product (zepastine) which crystallizes on standing, MP: 157°C. It is recrystallized from ethyl acetate, MP: 162°C.

The base is converted to the hydrogen maleate salt by treatment in ethyl acetate solution with one molecular proportion of maleic acid. This material is recrystallized from ethanol, MP: 215°C.

References

Weber A. et al.; US Patent No. 3,700,663; October 24, 1972; Assigned to Mead Johnson and Company, Evansville, Ind.

ZERANOL

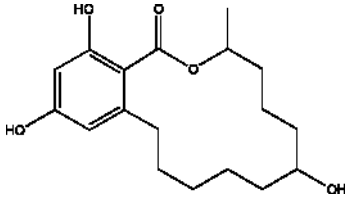
Therapeutic Function: Estrogen

Chemical Name: 3,4,5,6,7,8,9,10,11,12-Decahydro-7,14,16-trihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1-one

Common Name: Zearalanol; Tetrahydro F.E.S. (fermentation estrogenic substance)

Chemical Abstracts Registry No.: 26538-44-3

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Ralone	I.C.I.	Italy	1975
Frideron	Sandoz	Italy	-
Ralgro	Comm. Solvents	Italy	-

Raw Materials

Bacterium *Gibberella zeae*
Nutrient medium
Hydrogen

Manufacturing Process

A spore sand culture containing *Gibberella zeae* (Gordon) NRR L-2830 was aseptically placed in a sterile tube containing 15 ml of Czapek's-Dox solution and a small amount of agar. This medium was then incubated for about 168 hours at approximately 25°C. At the end of the incubation period, the medium was washed with 5 ml of sterile deionized water and transferred to a sterile tube containing 45 ml of Czapek's-Dox solution. The contents of the tube were then incubated for about 96 hours at about 25°C after which the material was available for use in inoculation of a fermentation medium.

To a 2-liter flask were added 300 g of finely divided corn. The flask and its contents were then sterilized and after sterilization 150 ml of sterile deionized water were added. To the mixture in the flask were then added 45 ml of the inoculum prepared by the process and the material was thoroughly mixed. The mixed material was then incubated for about 20 days at 25°C in a dark room in a water-saturated atmosphere. The following illustrates the recovery of the anabolic substance from the fermentation medium.

A 300 g portion of fermented material was placed in 500 ml of deionized water and slurried. The slurry was then heated for about 15 minutes at 75°C, 300 g of filter aid were then added and the material was filtered. The solid filtered material containing the anabolic substance was then air dried, and 333 g of the dried cake were then extracted with 500 ml of ethanol. This procedure was repeated three more times. The ethanol extract was then dried under vacuum to give 6.84 g of solid material. This solid material was then dissolved in 20 ml of chloroform and extracted with 30 ml of an aqueous solution containing 5% by weight of sodium carbonate having an adjusted pH of about 11.2. The extraction process was repeated seven more times. The pH of the sodium carbonate extract was then adjusted to 6.2 with hydrochloric acid, to yield an anabolic substance containing precipitate. The precipitate and the aqueous sodium carbonate extract were then each in turn extracted with

75 ml of ethyl ether. This procedure was repeated three more times to yield a light yellow ethereal solution, which was then dried to yield 116 mg of solid anabolic substance. This material was then subjected to multiple transfer countercurrent distribution using 100 tubes and a solvent system consisting of two parts chloroform and two parts methanol and one part water as the upper phase, all parts by volume. The solid material obtained from the multiple transfer counter-current distribution was then tested for physiological activity according to the well-known mouse-uterine test. The fermentation estrogenic substance produced has the formula:

Tetrahydro F.E.S. was produced by dissolving 0.5 g F.E.S. in 200 ml of ethanol. The F.E.S. was reduced by contacting the solution with hydrogen for 3 hours at 30°C and 1,000 psi using 2 g of Raney nickel as a catalyst. After filtering and concentrating the reaction mixture, the product was washed with 2 to 3 ml of 2-nitropropane and crystallized. It was found to have a melting point from 143°C to 160°C.

References

Merck Index 9923
Kleeman and Engel p. 953
DOT 12 (6) 243 (1976)
I.N. p. 1023
Hodge, E.B., Hidy, P.H. and Wehrmeiser, H.L.; US Patent 3,239,345; March 8, 1966; assigned to Commercial Solvents Corp.
Andrews, F.N. and Stob, M.; USPatent 3,196,019; July 20, 1965; assigned to Purdue Research Foundation

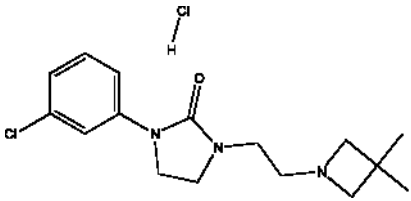
ZETIDOLINE HYDROCHLORIDE

Therapeutic Function: Antipsychotic, Neuroleptic

Chemical Name: 2-Imidazolidinone, 1-(3-chlorophenyl)-3-(2-(3,3-dimethyl-1-azetidinyl)ethyl)- monohydrochloride

Common Name: Zetidoline hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 51940-78-4 (Base); 74315-62-1

Trade Name	Manufacturer	Country	Year Introduced
MDL 308	Dow Chemical	-	-

Raw Materials

1-(m-Chlorophenyl)-2-imidazolidinone
3,3-Dimethyl-1-(2-chloroethyl)azetidine
Sodium carbonate
Sodium hydride
Hydrogen chloride

Manufacturing Process

A solution of 5.0 g of 1-(m-chlorophenyl)-2-imidazolidinone in 30 ml of dimethylformamide is added at room temperature to a mixture of 1.5 g of 50% NaH (mineral oil emulsion) in 30 ml of dimethylformamide. The reaction mixture is stirred for 1 h at room temperature and then 4.5 g of 3,3-dimethyl-1-(2-chloroethyl)azetidine are added. The mixture is stirred again at room temperature for 2 h and then it is heated for 5 h at 80°-85°C. The salts are filtered off and the solvent is removed under vacuum. The residue is taken up with 8 ml of 18% HCl and 16 ml of water and extracted with diethyl ether. The water solution is alkalinized by addition of 15% sodium carbonate and then extracted with diethyl ether. By evaporation of the organic layer a residue is obtained that is triturated in light petroleum. Yield of 1-(m-chlorophenyl)-3-[2-(3,3-dimethylazetidin-1-y1)ethyl]-2-imidazolidinone 7.25 g, melting point 84°-85°C (after recrystallization from hexane).

References

Fontanella L., Maffii G.; GB Patent No. 1,383,619; June 13, 1973; Assigned: Gruppo Lepetit S.p.A., an Italian Body Corporate, of Via Roberto Lepetit 8, Milan, Italy

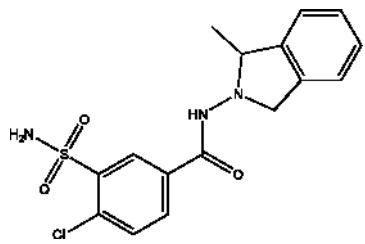
ZIDAPAMIDE

Therapeutic Function: Antihypertensive

Chemical Name: 4-Chloro-N-(1-methyl-2-isoindolinyl)-3-sulfamoylbenzamide

Common Name: Isodapamide; Zidapamide

Structural Formula:



Chemical Abstracts Registry No.: 75820-08-5

Trade Name	Manufacturer	Country	Year Introduced
Zidapamide	ZYF Pharm Chemical	-	-
Zidapumide	Shanghai Chemfrom Chemical Co., Ltd.	-	-

Raw Materials

Triethylamine
t-Butylcarbazate
Hydrogen chloride
α-Methyl-α,α-dibromo-o-xylene
4-Chloro-3-sulfamidobenzoic acid chloride

Manufacturing Process

5.6 ml of triethylamine are added to a solution of 5.0 g (0.018 m) of α-methyl-α,α-dibromo-o-xylene and 2.38 g (0.018 m) of t-butylcarbazate in 15 ml of dimethylformamide heated to 50-60°C. After the addition, the mixture is left stirring for 3 h at room temperature, the solution volume is then made up to about 60 ml by diluting with H_2O and the solution is left for a further hour under stirring. The solid which separates is filtered off, washed with water and dried to give 3.14 g (70%) of 1-methyl-N-(t-butyloxycarbonylamino) isoindoline, melting point 143-145°C.

A suspension of 2.6 g (0.0104 m) of the 1-methyl-N-(t-butyloxycarbonylamino)isoindoline in 7 ml of concentrated HCl is kept stirring at room temperature for 1 h. The final solution is evaporated to dryness under vacuum by heating to 60-70°C to give a solid residue (1.97 g) which crystalises from EtOH+Et_2O (1/1) to give 1.5 g (77.6%) of 1-methyl-2-amine isoindoline hydrochloride, melting point 140-145°C.

3.44 g (0.0 135 m) of 4-chloro-3-sulfamidobenzoic acid chloride are added to a solution of 2.5 g (0.0135 m) of 1-methyl-2-aminoisoindoline hydrochloride and 3.5 g (0.0314 m) of triethylamine in 30 ml of tetrahydrofuran. The mixture is kept stirring at room temperature for 15 h. The abundant solid which separates is filtered off, and is suspended in water in order to remove the triethylamine hydrochloride present. The residue is collected by filtration and dried in a drier to give 3.0 g of 1-methyl-2-(3'-sulfamyl-4'-chlorobenzamido)isoindoline, melting point 208-210°C (the analytical sample crystallizes from 10 volumes of ethyl alcohol, and has a melting point of 210-212°C).

A further amount (0.4 g) of product can be isolated by evaporating the tetrahydrofuran reaction solution, mixing the oily residue with ethyl alcohol and allowing it to crystallize in a refrigerator. The overall yield is 3.4 g, equal to 68.6%.

References

Scalesciani J.B.A.; US Patent No. 4,338,331; July 6, 1982; Assigned: Farmatis S.p.A., Milan, Italy

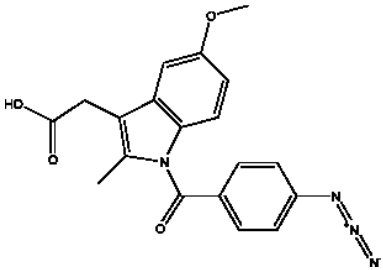
ZIDOMETACIN

Therapeutic Function: Antiinflammatory

Chemical Name: 1H-Indole-3-acetic acid, 1-(4-azidobenzoyl)-5-methoxy-2-methyl-

Common Name: Zidometacin

Structural Formula:



Chemical Abstracts Registry No.: 62851-43-8

Trade Name	Manufacturer	Country	Year Introduced
Zidometacin	ZYF Pharm Chemical	-	-

Raw Materials

Methyl-5-methoxy-2-methyl-3-indolylacetate
Sodium nitrite
4-Nitrobenzoyl chloride
4-Toluenesulfonic acid
Palladium on charcoal

Manufacturing Process

A hot solution of 5.2 g (15.4 mmol) of 1-(p-aminobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid in 65 ml of acetic acid is rapidly cooled to 25-30°C (try to avoid crystallization). This cold solution and a solution of 1.145 g (16.6 mmol) of sodium nitrite in 40 ml of water are added simultaneously to 18 ml of concentrated hydrochloric acid at -5°C with stirring. The resulting solution (about 25°C) is red colored and on cooling to 0°C a crystalline solid begins to separate. After 10 minutes at 0°C, an ice-cold solution of 1.057 g (16.25 mmol) of sodium azide in 40 ml of water is added in portions. A cream colored precipitate forms immediately, accompanied by copious evolution of nitrogen. The reaction is completed when no more red color is visible. If necessary, a further little excess of NaN3 solution may be added. Stirring is continued for 10 minutes at 0°C and then the mixture is extracted with ethylacetate. The organic phase is separated, washed with water, dried over Na_2SO_4 and concentrated in vacuum to give 5.67 g (100%) of 1-(p-azidobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid. Thin layer chromatography on silica gel gives one spot in the system chloroform-ethanol

95:5. An analytical sample is obtained by crystallization from methanol-water: MP: 170-172°C (with gas evolution). The structure of zidometacin is confirmed by IR spectrum.

The starting compounds were synthesized next way:

Preparation of methyl 1-(p-nitrobenzoyl)-5-methoxy-2-methyl-3-indolylacetate:

To a solution of 23.3 g (0.1 mole) of methyl-5-methoxy-2-methyl-3-indolylacetate in 50 ml of dry toluene are added 3 g of 80% sodium hydride. The mixture is stirred at room temperature for 4 hours and then a solution of 18.56 g (0.1 mole) of p-nitrobenzoylchloride in 80 ml of dry toluene is added slowly thereto over a 30-minute period. The reaction mixture is boiled for 30 hours. After cooling it is poured into 400 ml of ice-water and 15 ml of acetic acid. The separated toluene solution is washed with a large quantity of water, dried over sodium sulfate and evaporated to a syrup which is dissolved in ether. Slow evaporation of this solution in an open beaker gives 10 g of methyl-1-(p-nitrobenzoyl)-5-methoxy-2-methyl-3-indolylacetate as yellow prisms. Another quantity may be recovered from the oily residue after chromatography on a silica gel column (elution with benzene). MP: 134-135°C (crystallization from MeOH).

Preparation of 1-(p-nitrobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid:

A solution of 4.9 g (12.8 mmol) of methyl-1-(p-nitrobenzoyl)-5-methoxy-2-methyl-3-indolylacetate in 40 ml of acetic acid containing 400 mg of p-toluene-sulfonic acid is refluxed for 20 hours and then concentrated in vacuum. The gummy residue is extracted with ethyl acetate. The extract is filtered from insoluble material, washed with water and dried over sodium sulfate. Removal of the solvent under reduced pressure affords the desired product as yellow crystals; MP: 185-186°C.

Preparation of 1-(p-aminobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid:

20 g (54.3 mmol) of 1-(p-nitrobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid is dissolved in 1200 ml of hot methanol and hydrogenated in the presence of 2.64 g of 10% palladium on charcoal as catalyst. After 164 mmol of hydrogen have been consumed, the hydrogenation is stopped, and the solution filtered to remove the catalyst. The filtrate is concentrated in vacuum to give, in nearly theoretical yield, the title p-amino derivative. A crystallization from methanol-water gave an analytical sample: MP 198-200°C (dec.) crystals from MeOH-H_2O.

References

Tricerri Zumin S. et al.; US Patent No. 4,181,740; January 1, 1980; Assigned to Pirrel S.p.A., Italy

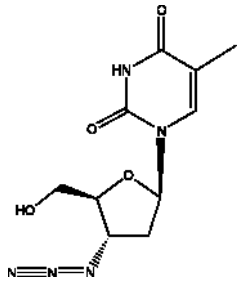
ZIDOVUDINE

Therapeutic Function: Antiviral, Antineoplastic

Chemical Name: Thymidine, 3'-azido-3'-deoxy-

Common Name: Azidothymidine; Azidotimidine; Compound S; Zidovudine

Structural Formula:



Chemical Abstracts Registry No.: 30516-87-1

Trade Name	Manufacturer	Country	Year Introduced
Retrovir	Glaxo Operations UK Ltd.	UK	-
Retrovir	GlaxoSmithKline	India	-
Retrovor	GlaxoWellcome	-	-
Zidovir	Cipla Limited	India	-
Zidovudine	Matrix Laboratories Limited	India	-
Zidovudine	NorthEast General Pharmaceutical Factory	China	-
Zidovudine	GlaxoSmithKline	USA	-
Zilion	Le Sante	India	-
ZIV-100	Samarth Pharma Pvt. Ltd.	India	-
Zoylex	VHB Life Sciences	India	-
Zydowin	Cadila Healthcare	India	-
Zydowin	Zydus Biogen	India	-

Raw Materials

Thymidine
N-(2-Chloro-1,1,2-trifluoroethyl)diethylamine
Sodium azide

Manufacturing Process

Preparation of 2,3'-anhydrothymidine

Thymidine (85.4 g; 0.353 mol) was dissolved in 500 mL dry DMF (dimethyl formamide) and added to N-(2-chloro-1,1,2-trifluoroethyl)diethylamine (100.3 g; 0.529 mol) [prepared according to the method of D. E. Ayer, J. Med. Chem. 6, 608 (1963)]. This solution was heated at 70°C for 30 minutes then poured into 950 mL ethanol with vigorous stirring. The product precipitated from this solution and was filtered. The ethanol supernatant was refrigerated then filtered to yield a total of 47.75 g (0.213 mol; 60.3%) of 2,3'-anhydrothymidine; melting point 228°-230°C.

Preparation for 3'-azido-3'-deoxythymidine

2,3'-Anhydrothymidine (25 g; 0.1115 mol) and NaN_3 (29 g; 0.446 mol) was suspended in a mixture of 250 mL DMF and 38 mL H_2O. The reaction was refluxed for 5 hours at which time it was poured into 1 liter of H_2O. This aqueous solution was extracted with ethyl acetate (EtOAc) (3x700 ml). The EtOAc was dried over Na_2SO_4, filtered, and then EtOAc was removed in vacuo to yield a viscous oil. This oil was stirred with 200 mL water resulting in a solid, 3'-azido-3'-deoxythymidine, 9.15 g (0.0342 mol); 30.7%; melting point 116°-118°C.

References

Rideout et al.; US Patent No. 4,724,232, Feb. 9, 1988; Assigned to Burroughs Wellcome Co., Research, Triangle Park, N.C.

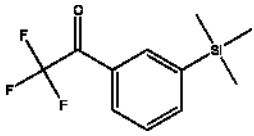
ZIFROSILONE

Therapeutic Function: Acetylcholinesterase inhibitor

Chemical Name: Ethanone, 2,2,2-trifluoro-1-(3-(trimethylsilyl)phenyl)-

Common Name: Zifrosilone

Structural Formula:



Chemical Abstracts Registry No.: 132236-18-1

Trade Name	Manufacturer	Country	Year Introduced
Zifrosilone	Marion Merrell Dow	-	-
MDL 73745	Marion Merrell Dow	-	-

Raw Materials

1,3-Dibromobenzene	Trimethylsilyl chloride
Butyl lithium	Ethyl fluoroacetete

Manufacturing Process

3-Trimethylsilyl-bromobenzene:

A mixture of 1,3-dibromobenzene (25.0 g, 106.4 mmol) and trimethylsilylchloride (11.6 g, 106.4 mmol) in diethyl ether (50 ml) was added dropwise in 1.5 hours on magnesium (2.59 g, 106.4 mmol) in diethyl ether (25 ml). Then the mixture was refluxed for 18 hours, cooled to 0°C, treated with 4 N HCl (75 ml). The organic layer was separated, washed with water, brine, dried over $MgSO_4$ and concentrated. 3-Trimethylsilylbromobenzene was obtained by fractional distillation as a colorless oil (13.4 g, 55% yield, b.p.: 55-62°C/0.8 mmHg.

2,2,2-Trifluoro-1-(3-trimethylsilylphenyl)ethanone:

To a solution of 3-trimethylsilylbromobenzene (7.62 g, 33.3 mmol) in diethyl ether (35 ml) was added 1.5 M n-butyl lithium in hexane (22.2 ml, 33.3 mmol) at 0°C over 10 min. Then the mixture was allowed to react 15 min at room temperature, cooled to -78°C and ethyl trifluoroacetate (14.2 g, 100 mmol) was added over 5 min. Then the mixture was allowed to react 15 min at -78°C, the cooling bath was removed and when the temperature rose to 0°C. 3 N HCl (35 ml) was added dropwise. The organic layer was separated, washed with water, brine, dried over $MgSO_4$ and concentrated. Chromatography (silica gel, cyclohexane/diethyl ether: 90/10) followed by distillation under reduced pressure afforded the expected compound (zifrosilone) as a colorless oil (4.32 g, 53% yield), boiling point 120°C/0.8 mm Hg; Rf: 0.28 (cyclohexane/diethyl ether: 95/5).

References

Schirlin D. et al.; European Patent No. 0,409,676 A1; June 20, 1990; Merrel Dow Pharmaceuticals Inc.

ZILANTEL

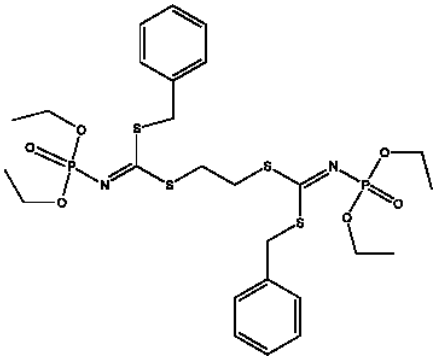
Therapeutic Function: Anthelmintic, Pesticide

Chemical Name: (Diethoxyphosphinyl)carbonimidodithioic acid 1,2-ethanediyl bis(phenylmethyl) ester

Common Name: Zilantel

Chemical Abstracts Registry No.: 22012-72-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Zilantel	ZYF Pharm Chemical	-	-

Raw Materials

Ethanedithiol
Benzyl bromide
Sodium hydroxide
Triethylamine
Diethoxyphosphinyl isothiocyanate

Manufacturing Process

To a mixture of 1.48 parts of ethanedithiol and 3.4 parts of triethylamine in 30 ml of benzene is added, with cooling, 5.7 parts of diethoxyphosphinyl isothiocyanate. After an hour, this mixture is added to 5.7 parts of benzyl bromide in 25 parts by volume of toluene in several portions over a 10 min period (mild temperature rise to 29°C). After stirring over night, the mixture is diluted with more benzene, washed (including dilute sodium hydroxide), and concentrated to give 10.7 parts of oil. Column chromatography on a total of 150 parts of silica gel yields, on sequential elution with 1:1 carbon tetrachloride:chloroform, chloroform and 2-10% methanol in chloroform, 4.5 parts (42%) crude product. The 2.0 parts of colorless crystalline of S,S'-ethylene-S,S'-dibenzyl-diethoxyphosphinylimidodithiocarbonate, melting point 67.5-68.5°C (recrystallization from ether) are obtained.

References

Doscher M.E.; US Patent No. 3,691,283; September 12, 1972; Assigned: American Cyanamid Company, Stamford, Conn.

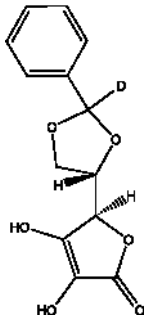
ZILASCORB

Therapeutic Function: Antineoplastic

Chemical Name: L-Ascorbic acid, 5,6-O-(phenylmethylene-d)-

Common Name: Zilascorb (2H); Zoxxoz

Structural Formula:



Chemical Abstracts Registry No.: 122431-96-3

Trade Name	Manufacturer	Country	Year Introduced
Zilascorb (2H)	Norsk Hydro	-	-

Raw Materials

Ascorbic acid
Benzaldehyde
Palladium on barium sulfate
Deuterium
Zinc chloride
Deuterated ethyl benzene
Benzoyl chloride
Trimethylorthoformate

Manufacturing Process

Ascorbic acid (89.2 g) was slurred in 400 ml of p-dioxane, 200 g of zinc chloride were added slowly and the resulting mixture was stirred for one hour. Next, 100 ml (104 g) of benzaldehyde were added. This reaction mixture was stirred at ambient temperature for about 24 hours and was then extracted with 500 ml of ethyl acetate. The ethyl acetate extract was itself extracted with three portions of saturated aqueous sodium chloride. The ethyl acetate solution was dried and the dried solution treated with activated charcoal and then filtered through cellulose. Concentration of the filtrate caused 5,6-O-benzylidene-L-ascorbic acid to crystallize. The above prepared compound has proven effective in treatment of various cancers of carcinoma type, but it isn't very stable and effective. The using of deuteroaldehyde improved the anticancer activity and showed greater biological activity. It has the prolonged presence in blood and could also reduce the need for frequent iv administration. This effect explains the slower reaction kinetics of compounds containing deuterium then for compounds containing hydrogen since a bond to deuterium is broken slower than a bond to hydrogen.

The deutero-5,6-O-benzylidene ascorbic acid may be prepared next way:

To 300 ml deuterated ethyl benzene (degree of deuteration: 99.4%), in which was suspended 7.6 g of 5% Pd on $BaSO_4$ catalyst, was added 54.7 g of freshly distilled benzoylchloride. Via a gas inlet tube, D_2-gas was bubbled

through the reaction mixture with rapid stirring. The D_2-gas was introduced at a rate of approximately 15 L per hour. The reduction was carried out at the reflux temperature of the reaction mixture, which was 140°-145°C. After 4-5 hr reaction time all the benzoylchloride had been consumed, and the D_2-supply was removed, and the reaction mixture cooled to room temperature. The deuterobenzaldehyde was then distilled under reduced pressure and gave 24 g of chemically pure deuterobenzaldehyde-d_1, B.p. 74°C/22 mm Hg, n_D =1.5436. Degree of deuteration: 99.4 atom % D.

56 g of deuterobenzaldehyde as above prepared are reacted with 50 g of methanol and 61 g of trimethylorthoformate in the presence of 0.8 g hydrochloric acid, while stirring the reaction mixture. After 0.5 hr reaction time at 50°C, the low boiling components of the reaction mixture were removed under vacuum, followed by distilling off the formed deuterated benzaldehyde-dimethylacetate (α,α-dimethoxy-α-d_1-toluene). After redistilling 75 g of pure α,α-dimethoxy-α-d_1-toluene was obtained. BP: 195°C.

40 g dry L-ascorbic acid was dissolved in 60 ml dry dimethylformamide and reacted with 41 g of deuterated-α,α-dimethoxytoluene in the presence of 300 mg p-toluene sulfonic acid. The reaction mixture was held at 60°C while continuously removing the formed methanol under reduced pressure. After the reaction had come to completion (all the calculated quantity of methanol has been removed), the DMF was distilled off under high vacuum. The oily residue was stirred with ice-cold water to obtain white crystals of deuterated-5,6-O-benzylidene ascorbic acid. The crystals can be further purified by recrystallization from benzene, but due to instability of the deuteron-5,6-O-benzylidene ascorbic acid, it is recommended that the free acid be converted to the much more stable mono-basic salt by reacting the deuteron-5,6-O-benzylidene-L-ascorbic acid with 13.5 g of sodium hydrogen carbonate in 300 ml water to obtain a clear solution of the mono-sodium salt of deutero-5,6-O-benzylidene-L-ascorbic acid.

References

Kochi et al.; Cancer Treat. Rep.; 64: 21-23, (1980)
Koppel et al.; US Patent No. 4,552,888; Nov. 12, 1985; Assigned to Eli Lilly and Company, Indianapolis, Ind.
Borretzen B. et al.; US Patent No. 4,874,780; Oct. 17, 1989; Assigned to Norsk Hydro a.s., Oslo, Norway

ZILEUTON

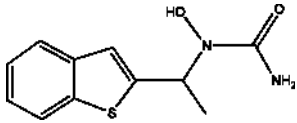
Therapeutic Function: Antiallergic, Antiinflammatory

Chemical Name: Urea, N-(1-benzo[b]thien-2-ylethyl)-N-hydroxy-, (+/-)-

Common Name: Zileuton

Chemical Abstracts Registry No.: 111406-87-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Zyflo	Abbott Laboratories	USA	-

Raw Materials

Benzo[b]thiophene	Butyl lithium
Acetaldehyde	N,O-Dimethyl acetohydroxamic acid
Borane pyridine complex	Hydroxylamine hydrochloride
Trimethylsilyl isocyanate	Phosgene

Manufacturing Process

N-Hydroxy-N-(1-benzo[b]thien-2-ylethyl) acetamide

1. 2-Acetyl benzo[b]thiophene.

Method a. Benzo[b]thiophene (10 g, 75 mmole) was dissolved in THF (50 ml) and cooled to -78°C. n-Butyl lithium (28 ml, 2.7 M in hexanes) was added. The mixture was stirred for 15 minutes and N,O-dimethyl acetohydroxamic acid was added. Following an additional 30 minutes of stirring, the reaction was quenched at -78°C with ethanol and 2 N HCl solution and extracted into ether. The solvent was removed in vacuo and the residue chromatographed on silica gel eluting with 20% ether in pentane to yield 6.9 g of the desired product as a white solid.

Method b. To a solution of benzo[b]thiophene (10.0 g, 75 mmole) in THF (50 ml) was added n-butyl lithium (33 ml, 2.5 M in hexanes) at -70°C under N_2. The mixture, containing a white precipitate, was stirred at 70°C for 1 hour. Acetaldehyde (4.6 ml, 82 mmole) was added dropwise. After a few minutes the reaction was quenched with saturated NH_4Cl solution. The layers were separated, the organic layer dried over MgSO4, filtered, and evaporated to give a white solid (10 g) which was used directly for the next step.

The alcohol prepared as described above (1.0 g) in acetone (50 ml) was cooled to 5°C and Jones Reagent was added dropwise until the orange yellow color persisted (1.4 ml). The reaction mixture was diluted with water and the desired product precipitated. It was collected by filtration to give 0.85 g.

2. 2-Acetyl benzo[b]thiophene oxime.

2-Acetyl benzo[b]thiophene (5 g, 28.4 mmole), prepared as described in step 1 above, and hydroxylamine hydrochloride (3.0 g, 42.6 mmole) were dissolved in a mixture of ethanol (50 ml) and pyridine (50 ml) and allowed to stir at room temperature for 2 hours. Most of the solvent was removed in vacuo and the residue dissolved in ether. After washing with 2 N HCl (100 ml), the solution was dried over $MgSO_4$ and evaporated. A white crystalline solid

was obtained and was carried on without further purification. An alternative work-up may also be used. The reaction mixture was diluted with water (300 ml) and the product precipitated. It was filtered off and dried in vacuo.

3. 1-Benzo[b]thien-2-ylethyl hydroxylamine. The oxime prepared as in step 2 above (3.5 g, 18.5 mmole) was dissolved in ethanol (25 ml) and cooled to 0°C. Borane pyridine complex (3.7 ml, 37 mmole) was added via syringe under nitrogen followed 10 minutes later by 20% HCl in ethanol (30 ml). Within 30 minutes the reaction was complete and was brought to pH 9 with the addition of solid sodium carbonate or 2 N NaOH. The mixture was extracted into ether and dried over $MgSO_4$. After evaporation a white solid (3.0 g) was obtained. This was carried on without further purification.

N-Hydroxy-N-(1-benzo[b]thien-2-ylethyl)urea

Method A. 1-Benzo[b]thien-2-yl ethyl hydroxyl amine prepared as described above, step 3 (2.0 g, 10 mmole), was refluxed for 30 minutes with trimethylsilyl isocyanate (1.65, 14.2 mmole) in dioxane (30 ml). The reaction mixture was then washed with saturated NH_4Cl solution, dried with $MgSO_4$, and evaporated.

Method B. 1-Benzo[b]thien-2-yl ethyl hydroxyl amine prepared as described in step 3, was dissolved in toluene (100 ml) and HCl gas was bubbled through the mixture at a moderate rate for about 4 minutes. The solution was then heated to reflux and phosgene was bubbled through for another 4 minutes. After an additional one hour reflux, the mixture was allowed to cool to room temperature and then added to excess cold ammonium hydroxide solution. The precipitate was collected and recrystallized. Melting point: 157°-158°C. NMR (300 MHz), and mass spectrum confirmed the structure of the prepared compound.

References

Summers, Jr. et al.; US Patent No. 4,873,259; Oct. 10, 1989; Assigned to Abbott Laboratories, Abbot Park, Ill.

ZILPATEROL HYDROCHLORIDE

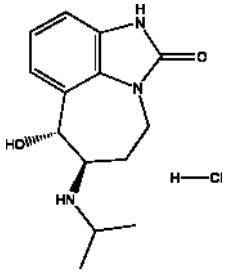
Therapeutic Function: Beta-adrenergic blocker

Chemical Name: trans-(+/-)-4,5,6,7-Tetrahydro-7-hydroxy-6-[(1-methylethyl)amino]imidazo[4,5,1-jk][1]benzazepin-2-(1H)-one monohydrochloride

Common Name: Zilpaterol hydrochloride

Chemical Abstracts Registry No.: 117827-79-9

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Zilpaterol hydrochloride	LONZA LTD.	-	-

Raw Materials

Sodium hydride
Hydrochloric acid
Aluminum chloride
o-Phosphoric acid
Sodium hydroxide
Palladium on carbon
Sodium borohydride
1,3-Dihydro-1-benzyl-2H-benzimidazol-2-one
Ethyl 4-bromobutyrate
Thionyl chloride
Potassium carbonate
Phenol
tert-Butyl nitrite
Hydrogen
Sodium cyanoborohydride

Manufacturing Process

7.6 g of sodium hydride as a 50% suspension in oil were added over 30 min with stirring to a mixture of 29.6 g of 1,3-dihydro-1-benzyl-2H-benzimidazol-2-one [described in Helv., Vol. 44 (1961), p. 1278] in 296 ml of dimethylformamide and the mixture was stirred for another 30 min and was cooled to 5°C. 33.9 g of ethyl 4-bromobutyrate were added dropwise to the mixture over 30 min and the mixture was stirred at room temperature for 3 h and was poured into 900 ml of iced water. The mixture was extracted with ether and the organic phase was washed with water, dried and evaporated to dryness. The oil residue was dissolved in 50 ml of isopropyl ether and the solution was allowed to crystallize for 16 h and was then vacuum filtered to obtain 22.6 g of ethyl 1,3-dihydro-2-oxo-3-benzyl-1H-benzimidazol-1-butanoate, melting point 52°C (crystallization from cyclohexane).

A mixture of 40.6 g of the ethyl 1,3-dihydro-2-oxo-3-benzyl-1H-benzimidazol-1-butanoate and 400 ml of 1 N methanolic sodium hydroxide was refluxed for 3 h under an inert atmosphere and was then concentrated to 0.5 its value and was poured into 1 L of iced water. The pH was adjusted to 2 by addition of concentrated hydrochloric acid and the mixture was vacuum filtered. The product was washed and dried to obtain 35.2 g of 1,3-dihydro-2-oxo-3-benzyl-1H-benzimidazol-1-butanoic acid, melting point 168°C (crystallization from ethyl acetate).

21.5 ml of thionyl chloride were added to a suspension of 21.5 g of the

product of 1,3-dihydro-2-oxo-3-benzyl-1H-benzimidazol-1-butanoic acid in 430 ml of chloroform and the mixture was refluxed for 75 min and was evaporated to dryness under reduced pressure. The residue was dissolved in 860 ml of dichloroethane under an inert atmosphere and after cooling the mixture to 15°C, 18.67 g of aluminum chloride were added thereto. The mixture was stirred at 20°C for 4 h and was poured into 1 L of iced water. 43 ml of concentrated hydrochloric acid were added thereto and the mixture was stirred for 10 min and was filtered. The decanted aqueous phase was extracted with methylene chloride and the combined organic phases were washed with aqueous 10% potassium carbonate to a pH of 6 and were dried and evaporated to dryness under reduced pressure. The residue was crystallized from ethyl acetate and dried to give 8.7 g of 5,6-dihydro-1-benzyl-imidazo[4,5,1-j-k][1]benzazepin-2,7-[1H,4H]-dione, melting point 135°C (crystallization from isopropanol).

A mixture of 29.2 g of the 5,6-dihydro-1-benzyl-imidazo[4,5,1-j-k][1]benzazepin-2,7-[1H,4H]-dione, 292.0 g of o-phosphoric acid and 14.1 g of phenol were heated at 150°C under an inert atmosphere for 2 h, was cooled to about 35°C and was poured into 1200 ml of iced water with stirring. 2 L of methylene chloride were added to the mixture which was then made alkaline with sodium hydroxide. The mixture was filtered and the solids were washed with methylene chloride. The combined organic phases were washed, dried and evaporated to dryness under reduced pressure. The residue was crystallized and was chromatographed over silica gel. Elution with a 90:2:2 ethyl acetate-methanol-triethylamine mixture yielded 9.7 g of 5,6-dihydro-imidazo[4,5,1-j-k][1]benzazepin-2,7-[1H,4H]-dione, melting point 235°C.

42.5 ml of 1.8 N ethanolic hydrochloric acid and 10.5 ml of tert-butyl nitrite were added at 5°C under an inert atmosphere to a suspension of 15.5 g of the 5,6-dihydro-imidazo[4,5,1-j-k][1]benzazepin-2,7-[1H,4H]-dione in 620 ml of tetrahydrofuran and the mixture was stirred at 5°C for 3 h and was vacuum filtered. The product was washed with tetrahydrofuran and with a 1:1 chloroform-methanol mixture to obtain 16.5 g of 6-oxime of 4,5-dihydroimidazo[4,5,1-j-k][1]benzazepin-2,6,7[1H]-trione, melting point >280°C.

A suspension of 4.0 g of the 6-oxime of 4,5-dihydroimidazo[4,5,l-j-k][1]benzazepin-2,6,7[1H]-trione 2.0 g of 10% palladium carbon and 150 ml of methanol was stirred under hydrogen for 2,5 h and was then filtered. The filtrate was cooled in an ice bath while slowly adding with mild stirring 0.66 g of sodium borohydride and the mixture was stirred at 5°C for 90 min. The mixture was evaporated to dryness under reduced pressure at 30°C and the residue was dissolved in 15 ml of methanol. The solution was acidified to a pH of 1-2 by addition of hydrogen chloride in ethyl acetate and the mixture was vacuum filtered to obtain 3.6 g of (6RS, trans)-6-amino-7-hydroxy-4,5,6,7-tetrahydro-imidazo[4,5,l-j-k][1]benzazepin-2[1H]-one hydrochloride melting at >260°C (crystallization from methanol and then from ethanol). The base (6RS, trans)-6-amino-7-hydroxy-4,5,6,7-tetrahydro-imidazo[4,5,l-j-k][1]benzazepin-2[1H]-one may be produced from (6RS,trans)-6-amino-7-hydroxy-4,5,6,7-tetrahydro-imidazo[4,5,l-j-k][1]benzazepin-2[1H]-one hydrochloride by treatment of salt with sodium hydroxide.

3.0 g of sodium cyanoborohydride were added over 15 min at 0-5°C to a mixture of 6.0 g of (6RS, trans)-6-amino-7-hydroxy-4,5,6,7-tetrahydro-

imidazo[4,5,l-j-k][1]-benzazepin-2(1H)-one, 60 ml of methanol and 30 ml of acetone and the mixture was stirred at room temperature for 3 h and was evaporated to dryness under reduced pressure. The residue was added to 60 ml of water and the mixture was extracted with chloroform. The organic phase was dried and evaporated to dryness to obtain 3.6 g of (6RS,trans)-6-isopropylamino-7-hydroxy-4,5,6,7-tetrahydro-imidazo[4,5,l-j-k][1]-benzazepin-2(1H)-one, melting point 166°C.

References

Frechet D. et al.; US Patent No. 4,585,770; April 29, 1986; Assigned: Roussel Uclaf, Paris, France

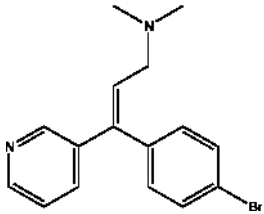
ZIMELIDINE

Therapeutic Function: Antidepressant

Chemical Name: 3-(4-Bromophenyl)-N,N-dimethyl-3-(3-pyridinyl)-2-propen-1-amine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 56775-88-3

Trade Name	Manufacturer	Country	Year Introduced
Normud	Astra	W. Germany	1981
Zelmid	Astra	UK	1982
Normud	Astra	Switz.	1982
Zelmid	Astra	Sweden	1983

Raw Materials

3-Bromopyridine
Butyl lithium
ω-Dimethylamino-4'-bromopropiophenone
Sulfuric acid

Manufacturing Process

To 9 g of n-butyl lithium in 200 ml of dry ether 20 g of 3-bromopyridine is added as quickly as possible at -40°C without raising the temperature. When

the addition is finished the mixture is stirred for another 30 minutes. Thereafter 32.5 g of ω-dimethylamino-4'-bromopropiophenone is added in such a way that the temperature does not exceed -40°C. The cooling is discontinued and the mixture is stirred during the night whereupon the reaction mixture is poured onto ice and diluted HCl, which is washed with ether and is extracted with 20 ml of methylene dichloride. The methylene dichloride is dried and evaporated. The crystals are dissolved in water, which then is made alkaline with a solution of Na_2CO_3, is extracted with ether, dried, and evaporated and recrystallized from isopropyl ether, petroleum ether 1:1. Yield 4 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(3''-pyridyl)-propanol. Melting point 67°C.

3.6 g of 1-(4'-bromophenyl)-3-(N,N-dimethylamino)-1-(3''-pyridyl)-propanol are dissolved in 15 ml of 85% H_2SO_4 and heated at 170°C for 10 minutes. The reaction mixture is poured into 60 ml of water, which is then made alkaline with 10 N NaOH, and is extracted with 2 x 25 ml of ether. The ether is dried with Na_2SO_4, treated with active carbon and evaporated. The residue is dissolved in 25 ml of acetone and an equivalent amount of oxalic acid dissolved in 25 ml of acetone is added. The precipitate obtained is filtered off, is dissolved in 50 ml of water, which is made alkaline with 10 N NaOH and is extracted with 2 x 25 ml of ether. The ether solution is dried with Na_2SO_4 and is filtered, whereupon dry HCl is introduced. The precipitate obtained is filtered off. Yield 1.2 g of 3-(4'-bromophenyl)-3-(3''-pyridyl)-dimethylallylamine dihydrochloride (H 102/09). Melting point 193°C.

References

Merck Index 9924
DFU 3 (1) 71 (1978)
OCDS Vol. 3 p. 49 (1984)
DOT 18 (9) 449 (19821
I.N. p. 1023
Berntsson, P.B., Carlsson, P.A.E. and Corrodi, H.R.; US Patent 3,928,369; December 23, 1975; assigned to AB. Hassle (Sweden)

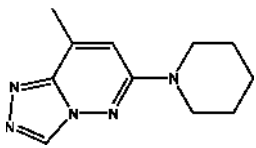
ZINDOTRINE

Therapeutic Function: Bronchodilator

Chemical Name: 1,2,4-Triazolo[4,3-b]pyridazine, 8-methyl-6-(1-piperidinyl)-

Common Name: Zindotrine

Structural Formula:



Chemical Abstracts Registry No.: 56383-05-2

Trade Name	Manufacturer	Country	Year Introduced
Zindotrine	Dow Chemical Co., USA	-	-
Zindotrine	Hoechst-Marion-Roussel	-	-

Raw Materials

3-Hydrazino-4-methyl-6-piperidinopyridazine
Formic acid
Sodium carbonate

Manufacturing Process

A mixture of 20.0 g of 3-hydrazino-4-methyl-6-piperidinopyridazine in 100 ml of aqueous 99% formic acid was heated at the boiling temperature under reflux for 3 h and then evaporated to dryness. The residue, containing 8-methyl-6-piperidino-s-triazolo[4,3-b]pyridazine formate was taken up in excess aqueous sodium carbonate and extracted with chloroform. After evaporation of the chloroform solvent the 8-methyl-6-piperidino-s-triazolo[4,3-b]pyridazine was crystallized from ethyl acetate. Yield 4.4 g, melting point 118-120°C.

References

Bellasio E., Campi A.; US Patent No. 3,915,968; Oct. 28, 1975; Assigned: Gruppo Lepetot S.p.A., Milan, Italy

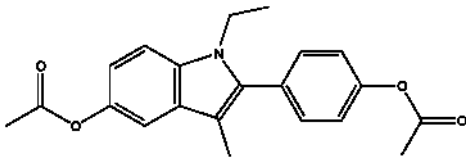
ZINDOXIFENE

Therapeutic Function: Antiestrogen

Chemical Name: 1H-Indol-5-ol, 2-(4-(acetyloxy)phenyl)-1-ethyl-3-methyl-, acetate (ester)

Common Name: Zindoxifene

Structural Formula:



Chemical Abstracts Registry No.: 86111-26-4

Trade Name	Manufacturer	Country	Year Introduced
Zindoxifene	GASTHAUS	-	-

Raw Materials

Boron tribromide
1-Methyl-2-(4-methoxyphenyl)-6-methoxy-1-ethylindole
Acetic anhydride
Sodium bicarbonate
Pyridine
Hydrogen chloride

Manufacturing Process

At 70°C there were added BBr_3 with the injector into a solution of 1-methyl-2-(4-methoxy-phenyl)-6-methoxy-1-ethylindole in water free methylene chloride. After 30 min the cold bath was removed and the mixture stirred overnight. The reaction mixture is carefully poured into a saturated sodium bicarbonate solution with ice cooling. The product is extracted three times with ethyl acetate, the combined organic extracts washed with sodium bicarbonate solution and water, dried and the solvent removed on a rotary evaporator. The 3-methyl-2-(4-hydroxyphenyl)-6-hydroxy-1-ethylindole was produced, melting point 142-143°C.

There are added acetic anhydride and of pyridine to the thus obtained 3-methyl-2-(4-hydroxyphenyl)-6-hydroxy-1-ethylindole and the mixture heated for 2 h at the boiling point. After cooling the mixture is poured onto ice, extracted with methylene chloride and the organic phase washed twice with 2 N HCl. After drying and removal of solvent in the rotary evaporator the residue is chromatographed with methylene chloride via silica and subsequently 3-methyl-2-(4-acetoxyphenyl)-6-acetoxy-1-ethylindole is obtained, melting point 150-152°C (recrystallized from ethanol).

References

Angerer E., Schonenberger H.; US Patent No. 4,661,511; April 28, 1987; Assigned: Deguss Aktiengesellschaft, Frankfurt, Fed.Rep. of Germany

ZINOSTATIN

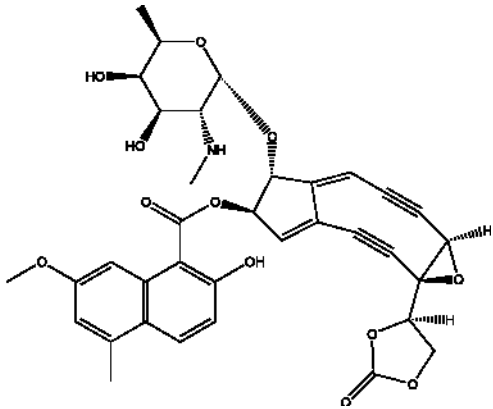
Therapeutic Function: Antineoplastic

Chemical Name: Neocarzinostatin (combination with apoprotein)

Common Name: Neocarcinostatin; Neocarzinostatin K; Zinostatin

Chemical Abstracts Registry No.: 9014-02-2

Trade Name	Manufacturer	Country	Year Introduced
Zinostatin	Yamanouchi	-	-



Structural Formula:

Raw Materials

Starch	Streptomyces carzinostaticus var. neocarzinostaticus
Soybean powder	Yeast
Sodium chloride	Copper sulfate
Zinc sulfate	Manganese chloride
Glucose	Calcium carbonate
Peptone	Meat extract
Oxalic acid	Ammonium sulfate

Manufacturing Process

Neocarzinostatin is produced by the cultivation of a strain of Streptomyces carzinostaticus var. neocarzinostaticus under suitable conditions as the cultivation of other Actinomycetes.

An aqueous culture medium was prepared containing the following ingredients (%): starch 2.0, exoleated soybean powder 2.0, dry yeast 0,5, sodium chloride 0.25, manganese chloride 0.0005, copper sulfate 0.0005, zinc sulfate 0.0005, calcium carbonate 0.2.

After sterilizing, and adjusting to pH 7.0, 100 ml of the medium was placed in each of several test tubes, 500 ml capacity, and sterilized. Streptomyc carzinostaticus var.neocarzinostaticus strain F-41 was inoculated therein, and fermented with agitation for 24 h at 27°C and then used as the stock culture. Next, an aqueous production culture medium was prepared containing (%): glucose 3.0, peptone 0.5, meat extract 0.5, sodium chloride 0.5, calcium carbonate 0.2.

After sterilization, the medium was adjusted to pH 7.0. 100 ml of the production medium was placed in each of 70 test tubes, 500 ml capacity and sterilized. 5 % by volume of the above-mentioned stock culture was added to the production culture medium in each test tube and fermented with agitation at 27°C. The pH be came 6.6 after an incubation period of 36 h, and 6.8-7.2 after 48 h. After that, the pH showed no further change. When the amount of

neocarzinostatin in the liquid was measured by its action on Sarcina lutea, it had reached 40 mkg/ml by 24 h culture, 73 mkg/ml by 36 h, 100 mkg/ml by 48 h, and 130 mkg/ ml by 64 h. Fermentation was suspended after 64 h, and solids containing the mycelium were separated by filtration. Filter paper was used and 5 L of culture liquid containing 130 mkg/ml of the active ingredient were obtained.

The culture liquid obtained above was adjusted to pH 3.0 with a saturated oxalic acid solution and the precipitate formed therein collected by filtration. The filtrate was added to 50.0 g each of kaolin and Celite 545 powder (diatomaceous earth), and stirred for 15 h at 4°C and after chromoprotein was allowed to adsorb as much as possible, it was filtered. The resulting filtrate was divided and placed in cellophane bags; dry air was blown on them at 27°C for 24 h condensing them to about 600 ml. This concentrated solution at 4°C was desalted by cellophane dialysis for 24 h in distilled water. The yield of desalted concentrated solution from the culture liquid was approximately 80% (867 mkg/ml, 600 ml).

The concentrated solution obtained above was thoroughly stirred at 4°C solid ammonium sulfate was added, amounting to 25% (150.0 g) by volume; the resulting brown precipitate was collected by centrifugation and thoroughly washed. Ammonium sulfate (150.0 g) was again added, and after leaving it for 15 h at 4°C the greyish white precipitate formed was isolated by a refrigeration-centrifugation method. The precipitate was washed several times with a cool aqueous ammonium sulfate solution, dissolved in 20 ml of distilled water and dialyzed overnight at 4°C against distilled water. After desalting, the liquid was passed through a column of Sephadex G-25. The passage solution was lyophilized and 660.0 mg of a light yellow coarse powder, neocarzinostatin, was produced (the yield from the culture liquor was 56%).

References

Ishida N.; US Patent No. 3,334,022; August 1, 1967

ZINTEROL HYDROCHLORIDE

Therapeutic Function: Bronchodilator

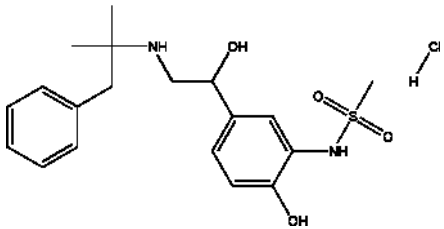
Chemical Name: Methanesulfonamide, N-(5-(2-((1,1-dimethyl-2-phenylethyl) amino)-1-hydroxyethyl)-2-hydroxyphenyl)- monohydrochloride

Common Name: Zinterol hydrochloride

Chemical Abstracts Registry No.: 37000-20-7 (Base); 38241-28-0

Trade Name	Manufacturer	Country	Year Introduced
Zinterol Hydrochloride	ZYF Pharm Chemical	-	-

Structural Formula:



Raw Materials

5'-Bromoacetyl-2'-hydroxymethanesulfonanilide
α,α-Dimethylphenthylamine
Hydrogen bromide
Palladium on carbon
2-Butanone

Manufacturing Process

A). 2'-Hydroxy-5'-([N-(2-methyl-1-phenyl-2-propyl)glycyl]methane-sulfonanilide hydrobromide:

To a solution of α,α-dimethylphenthylamine (120 g, 0.8 mole) in 1.1 liter of acetonitrile is added 5'-bromoacetyl-2'-hydroxymethanesulfonanilide (108 g, 0.35 mole) in a period of 5 minutes. The resulting solution is refluxed for 5 minutes on a steam bath and then permitted to stand for 25 minutes at room temperature after which it is chilled and acidified with 5 N ethanolic hydrogen bromide. The acidified mixture is concentrated in vacuum until a thick slurry is obtained. After standing overnight at room temperature, the slurry is filtered and the crude product triturated with 2-butanone, filtered, washed with 2-butanone and dried to 86.3 g, (54%), MP: 217.5-221°C (dec.).

B). 2'-Hydroxy-5'-(1-hydroxy-2-(2-methyl-1-phenyl-2-propylamino)ethyl) methanesulfonanilide hydrobromide:

2'-Hydroxy-5'-([N-(2-methyl-1-phenyl-2-propyl)glycyl]methanesulfonanilide hydrobromide (132 g, 0.29 mole is dissolved in 2 liters of hot methanol, the methanolic solution is allowed to cool to room temperature and 13 g 10% palladium on carbon catalyst suspended in 50 ml of water is added. Hydrogenation of the stirred mixture is carried out under 1-3 atm. of pressure for 17 hours during which time 0.31 mole of hydrogen is absorbed. The catalyst is filtered and the filtrate concentrated under reduced pressure until a thick slurry is obtained. Isoptopanpl is added tothed slurry and the mixture is again concentrated in vacuum to remove water by azeotropic distillation. Trituration of residual solid with 2-propanol and collection on a filter affords 100.5 g (76% yield) of desired product, MP: 194.5-195.5°C (dec.).

2'-Hydroxy-5'-(1-hydroxy-2-(2-methyl-1-phenyl-2-propylamino)ethyl) methanesulfonanilide base:

2'-Hydroxy-5'-(1-hydroxy-2-(2-methyl-1-phenyl-2-propylamino)ethyl)

methanesulfonanilide hydrobromide (47.7 g) is refluxed with 100 ml of methanol. The material only partly dissolves. A solution of 6.5 g of potassium hydroxide in 25 ml of methanol is then added to the suspension followed by 1 L of water. The mixture is thoroughly stirred and cooled to 5-10°C. The precipitate is collected on a filter and washed with water until a negative test for bromide using silver nitrate is obtained. The product is dried in an oven at 65°C, yield 36 g.

References

Comer W.T. et al.; US Patent No. 3,801,631; April 2, 1974; Assigned to Mead Johnson and Company, Evansville, Ind.

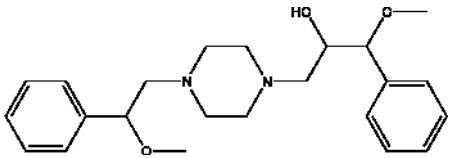
ZIPEPROL

Therapeutic Function: Bronchodilator

Chemical Name: 4-(2-Methoxy-2-phenylethyl)-α-(methoxyphenylmethyl)-1-piperazine-ethanol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 34758-83-3; 34758-84-4 (Dihydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Respilene	Winthrop	France	1973
Respilene	Sigma Tau	Italy	1979
Antituxil	Ghimas	Italy	-
Bronx	Lisapharma	Italy	-
Citizeta	C.T.	Italy	-
Mirsol	Mepha	Switz.	-
Respirase	Gibipharma	Italy	-
Respirex	Inibsa	Spain	-
Sanotus	Krka	Yugoslavia	-
Talasa	Andromaco	Argentina	-
Zitoxil	Farmochimica	Italy	-

Raw Materials

1-(2-Phenyl-2-methoxy)ethyl piperazine
3-Phenyl-3-methoxy propylene oxide

Manufacturing Process

In a reactor provided with a mechanical stirrer, a reflux refrigerant and a thermometer, there is introduced: 393 grams 1-[2-phenyl, 2-methoxy]ethyl piperazine and 22 grams 3-phenyl-3-methoxy propylene oxide in 750 ml of absolute ethanol.

When the slightly exothermic reaction (rise in temperature of about 20°C) has ceased, heating is effected for 1.5 hours at 60°C. The product is then cooled to 4°C and left to crystallize for about 12 hours. The precipitate is centrifugated then recrystallized in 500 ml of absolute ethanol.

420 grams of the desired compound is thus obtained in the form of a white, crystalline powder, melting point 83°C.

References

Merck Index 9976
Kleeman and Engel p. 953
DOT 10 (3) 104 (1974)
I.N. p. 1024
Mauvernay, R.Y., Eusch, N., Moleyre, J. and Simond, J.; US Patent 3,718,650; February 27, 1973; assigned to Societe Anonyme Centre Europeen de Recherches Mauvernay, France

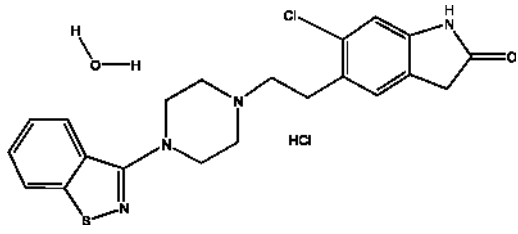
ZIPRASIDONE HYDROCHLORIDE

Therapeutic Function: Antipsychotic

Chemical Name: 2H-Indol-2-one, 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-, monohydrochloride monohydrate

Common Name: Ziprasidone hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 122883-93-6; 146939-27-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Geodon	Pfizer	USA	-

Raw Materials

2-Chloroethyl-6-chloro-oxindole
3-Piperazinyl-1,2-benzisothiazole hydrochloride
5-(2-Chloroethyl)-6-chloro-oxindole
1-(1,2-Benzisothiazol-3-yl)piperazine

Manufacturing Process

Preparation of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one

A 20-gallon glass lined tank, under a nitrogen atmosphere, was charged with 33.5 liters of water and 9.4 kilograms (kg) of sodium carbonate (dense, 89.1 moles, 3.4 eq.). The resulting mixture was stirred to give a solution. To the solution 6.4 kg of 2-chloroethyl-6-chloro-oxindole (27.8 moles, 1.06 eq.) was charged, followed by 6.7 kg of 3-piperazinyl-1,2-benzisothiazole hydrochloride (26.2 moles, 1.0 eq.). This was stirred and heated to reflux (100°C). After 11 hours the reaction was sampled for high pressure liquid chromatography (HPLC) assay. The reflux was continued for another 2 hours then the reaction was cooled to 25°C and the slurry stirred for 1 hour. The product was observed and found to be essentially free from lumps and gummy matter. The product was collected by filtration. A 14 liter water was added to the tank and cooled to 12°C and then used to wash the product. The cake was pulled as dry as possible, and the product was returned to the tank along with 40 liters of isopropyl alcohol (IPO). This was cooled and then stirred for 2 hours and the product was collected by filtration. The cake was washed with 13.4 liters of fresh IPO, then dried under vacuum at 30° to 40°C. After drying, 17.3 kg of the title compound was obtained. This was in excess of the theoretical weight yield due to some residual carbonate in the crude product.

Recrystallization of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one

To a clean and dry 100-gallon glass lined tank was charged 9.0 kg of the material obtained above and 86 gallons of tetrahydrofuran (THF). The slurry was heated to reflux and held for 1 hour. The hazy solution was then filtered through a 14" sparkler precoated with filter aid and backed with a Fulflo filter to a clean, dry, and "spec free" glass-lined tank on a lower level. The batch was concentrated by vacuum distillation. Another 8.3 kg of the material obtained in above was dissolved in 83 gallons of THF in the upper tank. This was filtered to the lower tank. The tank lines and sparkler were rinsed with 10 gallons of THF. The batch was concentrated to about 22 gallons, then cooled to 5°C and stirred for 1 hour. The product was collected by filtration. Then 20 gallons of fresh IPO were cooled in the tank and used to rinse the product cake. The product was collected and dried under vacuum at 45°C; yielding 9.05 kg of product (83.8% yield for the coupling and recrystallization. The product matched the spectra of a standard NMR and showed the correct retention time by HPLC with 99.7% assay. Another way for preparation of 5-

(2-(4-(1,2-benzisothiazol-3-yl)-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2-H-indol-2-one.

A clean and dry 20-gallon glass lined tank was charged with 19 L of water and 4.44 kg of sodium carbonate, after the carbonate had dissolved 4.29 kg (17.5 moles) of 5-(2-chloroethyl)-6-chloro-oxindole and 3.62 kg (16.5 moles) of 1-(1,2-benzisothiazol-3-yl)piperazine were added. The aqueous slurry was heated to reflux and the temperature maintained for 14 hours. When the reaction was complete the solution was cooled to 20°C and filtered. The wet product was reslurried in 23 L of isopropyl alcohol at room temperature for 2 hours. The product was collected by filtration on 2 large Buchner funnels, each was washed with 3.4 L of fresh isopropyl alcohol. The product was vacuum dried at 30° to 40°C. until no isopropyl alcohol remained, giving 5.89 kg (86.4% yield) of the desired free base which matched a standard sample by high performance liquid chromatography (HPLC).

A clean and dry 20-gallon reactor was charged with 17.4 gallons of deionized water and 4.44 L of concentrated hydrochloric acid, to give a 0.77 M solution. To the solution was added 4.44 kg of the anhydrous 5-(2-(4-(1,2-benzisothiazol-yl)-1-piperazinyl)-ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one free base. The slurry was warmed to 65°C and held for 18 hours. The slurry was cooled to room temperature. The product was filtered and washed with 2x5-gallon portions of deionized water, and then air dried at 50°C for 30 hours. The dried product contained 4.4% water and the x-ray diffraction method confirmed that the desired product was obtained.

References

Bush F. et al.; US Patent No. 5,338,846; Aug, 16, 1994; Assigned to Pfizer Inc. (New York, N.Y)
Allen D. et al.; US Patent No. 5,312,925; May, 17, 1994; Assigned to Pfizer Inc. (New York, N.Y)

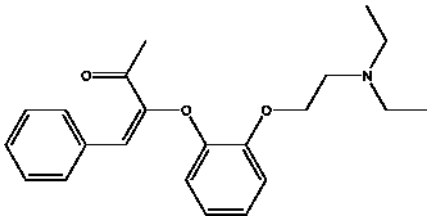
ZOCAINONE

Therapeutic Function: Antiarrhythmic

Chemical Name: (E)-3-[2-[2-(Diethylamino)ethoxy]phenoxy]-4-phenyl-3-buten-2-one

Common Name: Zocainone

Structural Formula:



Chemical Abstracts Registry No.: 68876-74-4

Trade Name	Manufacturer	Country	Year Introduced
Zocainone	ZYF Pharm Chemical	-	-

Raw Materials

N,N-Diethylaminoethyl chloride
Sodium salt of 3-o-hydroxyphenoxy-4-phenyl-3-butene-2-one

Manufacturing Process

21.0 g of N,N-diethylaminoethyl chloride are added drop by drop to 35.0 g of the sodium salt of 3-o-hydroxyphenoxy-4-phenyl-3-butene-2-one suspended in 600 ml of anhydrous acetone. The mixture is heated under reflux for 4 h, the sodium chloride is filtered off, and the filtrate is evaporated to dryness. The residue is dissolved in water and extracted a number of times with diethyl ether. The ether phase, after drying over Na_2SO_4, is evaporated to dryness and purified by distillation in a bulb apparatus, and 3-[o-(β-N,N-diethylaminoethoxy)phenoxy]-4-phenyl-3-buten-2-one was obtained, boiling point 200-210°C/0.6 mm Hg).

References

Manghisi E. et al.; US Patent No. 3,988,475; Oct. 26, 1976; Assigned: Istituto Luso Farmaco d'Italia S.r.l., Milan, Italy

ZOFENOPRIL CALCIUM

Therapeutic Function: Antihypertensive

Chemical Name: L-Proline, 1-(3-(benzoylthio)-2-methyl-1-oxopropyl)-4-(phenylthio)-, (1(R*),2α,4α)- calcium salt (2:1)

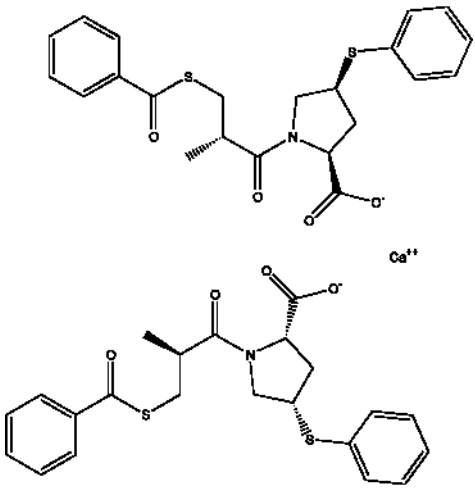
Common Name: Zofenopril calcium; Zofenil

Chemical Abstracts Registry No.: 81872-10-8 (Base); 81938-43-4

Trade Name	Manufacturer	Country	Year Introduced
Zofenopril Calcium	ZYF Pharm Chemical	-	-
Zofen	Berlin-Chemie AG Menarini Group	-	-
Zofenopril Calcium	Menarini	-	-
Zofenopril Calcium	Shanghai abochem chemical co., Ltd.	-	-
Bifril	Laboratorios Silesia S.A.	-	-
Bifril	Menarini	-	-
Zantipre	FIRMA-Fabbr. Ital. Ritrov. Medic. Aff. Spa	-	-

Trade Name	Manufacturer	Country	Year Introduced
Zantipress	FIRMA-Fabbr. Ital. Ritrov. Medic. Aff. Spa	-	-
Zofepril	Menarini	-	-
Zopranol	Laboratori Guidotti spa	-	-

Structural Formula:



Raw Materials

Sodium bicarbonate
cis-4-Phenylthio-L-proline
Hydrogen chloride
Dicyclohexylamine
Potassium bisulfate
(D)-3-(Benzoylthio)-2-methylpropanoic acid chloride

Manufacturing Process

9.9 g (0.031 mole) of cis-4-phenylthio-L-proline is suspended in 100 ml of water (pH 5.6) and the pH is adjusted to 10.2 by the addition of about 20 ml of 10% sodium bicarbonate to provide a clear solution. The pH is then adjusted to 9.5 by the addition of about 4.5 ml of concentrated HCl. The solution is kept at 30°C while 8.1 g (0.033 mole) of (D)-3-(benzoylthio)-2-methylpropanoic acid chloride in 30 ml of toluene is added simultaneously with 100 ml of 10% sodium bicarbonate to keep the pH at 9.3. After about 1/4 of the acid chloride is added, a slimy precipitate begins to form which persists throughout the reaction. After stirring the reaction mixture at pH 9.3 for 2.5 h, it is made strongly acidic by adding 20% HCl in the presence of ethyl acetate. The aqueous layer is extracted twice with 350 ml portions of ethyl acetate and the combined organic layers are washed with 300 ml of saturated brine and dried ($MgSO_4$). The solvent is removed to yield 11.8 g of foamy solid cis-1-[D-3-(benzoylthyo)-2-methyl-1-oxopropyl]-4-(phenylthio)-L-

proline hydrochloride.

To a solution of this cis-1-[D-3-(benzoylthyo)-2-methyl-1-oxopropyl]-4-(phenylthio)-L-proline hydrochloride 11.8 g (0.027 mole) in 70 ml of acetonitrile there is added about 6.0 g of dicyclohexylamine in 25 ml of ether. A white crystalline precipitate forms immediately. After standing overnight in the cold room, the solid is filtered and washed with ether to yield (cis)-1-[D-3-(benzoylthio)-2-methyl-1-oxopropyl]-4-(phenylthio)-L-proline, dicyclohexylamine salt (1:1).

The slightly moist (cis)-1-[D-3-(benzoylthio)-2-methyl-1-oxopropyl]-4-(phenylthio)-L-proline dicyclohexylamine salt is stirred for 2.5 h in a mixture of 300 ml of ethyl acetate and 200 ml of 10% potassium bisulfate. Two clear layers form. The aqueous layer is extracted with two 200 ml portions of ethyl acetate and the combined organic layers are dried ($MgSO_4$). The solvent is removed to yield 10.1 g of foamy solid (cis)-1-[D-3-(benzoylthio)-2-methyl-1-oxopropyl]-4-(phenylthio)-L-proline; melting point 42-44°C.

In practice it is usually used as calcium salt (2:1).

References

Ondetti M.A., Krapcho J.; US Patent No. 4,316,906; February 23, 1982; Assigned: E.R. Squibb and Sons, Inc., Princeton, N.J.

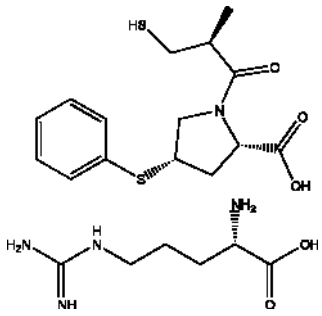
ZOFENOPRILAT ARGININE

Therapeutic Function: Antihypertensive

Chemical Name: L-Proline, 1-(3-mercapto-2-methyl-1-oxopropyl)-4-(phenylthio)-, (1(R*),2α,4α)- compd. with arginine (1:1)

Common Name: Zofenoprilat arginine

Structural Formula:



Chemical Abstracts Registry No.: 75176-37-3 (Base); 81872-09-5

Trade Name	Manufacturer	Country	Year Introduced
Zofenil arginine	Menarini	-	-
Bifril	Silesia S.A.	-	-

Raw Materials

Sodium
Thiophenol
Hydrochloric acid
Hydrogen bromide
Potassium bisulfate
Ammonia
N-Carbobenzyloxy-trans-4-tosyloxy-L-proline, methyl ester
Ethanol
Sodium hydroxide
Cyclohexylamine
Acetic acid
D-3-Acetylthio-2-methylpropionyl chloride
Sodium carbonate

Manufacturing Process

Sodium metal (0.85 g, 0.037 mole) is dissolved in 40 ml of absolute ethanol. To this there is added with stirring 3.7 ml (0.036 mole) of thiophenol followed by 7.5 g (0.017 mole) of N-carbobenzyloxy-trans-4-tosyloxy-L-proline, methyl ester [J. Am. Chem. Soc., 79, 191 (1957)]. After stirring for 4 h and standing overnight at room temperature, the bulk of the ethanol is removed on a rotary evaporator. The mostly solid residue is stirred with 120 ml of dichloromethane and 60 ml of water. The layers are separated (some methanol is added to help break up emulsions) and the aqueous phase is extracted with additional dichloromethane (2x60 ml). The combined organic phase are washed with 100 ml of saturated sodium chloride solution, dried ($MgSO_4$), and the solvent evaporated to give 6.5 g (100%) of N-carbobenzyloxy-cis-4-phenylthio-L-proline, methyl ester as a pale yellow viscous oil.

The N-carbobenzyloxy-cis-4-phenylthio-L-proline, methyl ester (6.5 g, 0.017 mole) is dissolved in 55 ml of methanol, treated portionwise at -1° to 4°C with 13 ml (0.026 mole) of 2 N sodium hydroxide, stirred at 0°C for 1 h, and kept at room temperature for approximately 16 h. After removing about half of the solvent on a rotary evaporator, the cooled solution is diluted with 100 ml of water, washed with 60 ml of ether (wash discarded), layered over with 70 ml of ethyl acetate, stirred, cooled, and acidified with 4.8 ml of 1:1 hydrochloric acid. After separating, the aqueous phase is extracted with additional ethyl acetate (3x40 ml) and the combined organic layers are dried ($MgSO_4$) and evaporated to give 5.9 g of a light yellow viscous oil. The latter is dissolved in 30 ml of ethanol, treated with 1.9 g of cyclohexylamine in 3 ml of ethanol and diluted to 330 ml with ether. On seeding, the crystalline cyclohexylamine salt separates. The latter, after cooling for approximately 16 h, weighs 5.3 g; melting point 148-151°C. This material is combined with 1.5 g of identical product from a previous experiment, stirred with 200 ml of boiling acetonitrile, and cooled to yield 6.3 g of colorless N-carbobenzyloxy-cis-4-phenylthio-L-proline cyclohexylamine salt; melting point 152-155°C.

This N-carbobenzyloxy-cis-4-phenylthio-L-proline cyclohexylamine salt is suspended in 25 ml of ethyl acetate, stirred, and treated with 25 ml of 1 N hydrochloric acid. When two clear layers are obtained, they are separated and the aqueous phase is extracted with additional ethyl acetate (3x25 ml). The combined organic layers are dried ($MgSO_4$) and the solvent evaporated to give

5.0 g (65%) of N-carbobenzyloxy-cis-4-phenylthio-L-proline as a nearly colorless, very viscous syrup.

N-Carbobenzyloxy-cis-4-phenylthio-L-proline (4.9 g, 0.014 mole) is treated with 25 ml of hydrogen bromide in acetic acid (30-32%), stoppered loosely, and stirred magnetically. After 1 h the orange-yellow solution is diluted to 250 ml with ether to precipitate the product as a heavy oil which gradually crystallizes on seeding, rubbing and cooling After stirring in an ice-bath for 1 h, the material is filtered under nitrogen, washed with ether, suspended in fresh ether, cooled for approximately 16 h, and filtered again to give 3.2 g (77%) of colorless solid (cis)-4-phenylthio-L-proline hydrobromide; melting point 106-109°C.

A solution of 3.0 g (0.0094 mole) of (cis)-4-phenylthio-L-proline hydrobromide in 25 ml of water is stirred, cooled to 5°C and 15 ml of 20% sodium carbonate are added. This mixture is treated with 2.0 g (0.011 mole) of D-3-acetylthio-2-methylpropionyl chloride in 5 ml of ether during the course of 10 min with the intermittent addition of 3.0 g of sodium carbonate to maintain the pH at 8.0 to 8.4). The mixture is stirred in the ice-bath for an additional hour, 25 ml of water are added and then a solution of 5 ml of concentrated hydrochloric acid in 25 ml of water. The strongly acid solution is saturated with sodium chloride and extracted with 50 ml of ethyl acetate (four times). The organic phases are combined, dried, filtered and solvent evaporated to give 3.8 g of a pale yellow viscous oil. The dicyclohexylamine salt following trituration with 15 ml of acetonitrile one obtains 2.4 g of colorless solid 1-[D-3-(acetylthio)-2-methyl-1-oxopropyl]-cis-4-phenylthio-L-proline dicyclohexylamine salt; melting point 184-186°C.

This 1-[D-3-(acetylthio)-2-methyl-1-oxopropyl]-cis-4-phenylthio-L-proline dicyclohexylamine salt is treated with 30 ml of 10% potassium bisulfate and extracted into ethyl acetate, cooled in an ice bath and treating portionwise with 60 ml of 10% potassium bisulfate. The clear layers are separated and the aqueous portion extracted with 60 ml of ethyl acetate (2 times). The organic phases are combined, dried ($MgSO_4$), filtered and the solvent is evaporated to give 2.0 g (59%) of glass-like 1-[D-3-(acetylthio)-2-methyl-1-oxopropyl]-cis-4-phenylthio-L-proline, melting point 103-105°C (from ether-hexane).

The 1-[D-3-(acetylthio)-2-methyl-1-oxopropyl]-cis-4-phenylthio-L-proline (2.0 g, 0.0042 mole) is treated with 3.5 ml of concentrated ammonia in 8.5 ml of water. The base dissolves in about 30 min and the resulting solution (under Argon) is allowed to stand for 2 h at room temperature. This solution is cooled, extracted with 25 ml of ethyl acetate (2 times) and the ethyl acetate extract is discarded. The solution is again layered with 25 ml of ethyl acetate and acidified with 17 ml of 1:1 hydrochloric acid. The mixture is shaken, separated and the aqueous phase extracted with 25 ml of ethyl acetate (3 times). The organic phases are combined, dried ($MgSO_4$), filtered and the solvent removed on the rotary evaporator to give to give 1.35 g (100%) of viscous syrupy 1-(D-3-mercapto-2-methyl-1-oxopropyl)-cis-4-phenylthio-L-proline.

In practice it is usually used as arginine salt.

References

Ondetti M.A., Krapcho J.; US Patent No. 4,316,906; February 23, 1982; Assigned: E.R. Squibb and Sons, Inc., Princeton, N.J.

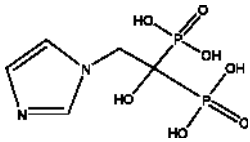
ZOLEDRONIC ACID

Therapeutic Function: Bone calcium regulator

Chemical Name: Phosphonic acid, (1-hydroxy-2-(1H-imidazol-1-yl) ethylidene)bis-

Common Name: Acidium zoledronicum; Zoledronic acid

Structural Formula:



Chemical Abstracts Registry No.: 118072-93-8

Trade Name	Manufacturer	Country	Year Introduced
Zometa	Novartis Pharma	Switz.	-

Raw Materials

Imidazol-4-yl acetic acid hydrochloride
Phosphoric acid
Phosphorus trichloride

Manufacturing Process

With stirring and under reflux, 8.6 g (0.053 mole) of imidazol-4-yl acetic acid hydrochloride, 7.1 ml of 85% phosphoric acid and 25 ml of chlorobenzene are heated to 100°C. Then 13.9 ml of phosphorus trichloride are added dropwise at 100°C, whereupon evolution of gas occurs. Over the course of 30 min a dense mass precipitates from the reaction mixture. The batch is heated for 3 hours to 100°C and the supernatant chlorobenzene is removed by decantation. With stirring and under reflux, the residual viscous mass is heated to the boil for 3 hours with 40 ml of 9 N hydrochloric acid. The batch is filtered hot with the addition of carbon and the filtrate is diluted with acetone, whereupon the crude 2-(imidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid precipitates. This product is recrystallised from water. Melting point: 238-240°C (dec.).

References

EP 0,275,821
Jaeggin K.A., Widler L., US Patent No. 4,939,130; Jul. 3, 1990; Assigned to Ciba-Geigy Corporation, Ardsley, N.Y.

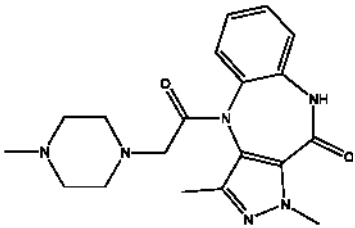
ZOLENZEPINE

Therapeutic Function: Antiulcer

Chemical Name: 4,9-Dihydro-1,3-dimethyl-4-[(4-methyl-1-piperazinyl) acetyl]pyrazolo[4,3-b][1,5]benzodiazepin-10-(1H)-one

Common Name: Zolenzepine

Structural Formula:



Chemical Abstracts Registry No.: 78208-13-6

Trade Name	Manufacturer	Country	Year Introduced
Zolenzepine	ZYF Pharm Chemical	-	-

Raw Materials

N-Methylpiperazine
Sodium bicarbonate
4-Chloroacetyl-1,3-dimethyl-1,4,9,10-tetrahydropyrazolo[4,3-b][1,5] benzodiazepin-10-one

Manufacturing Process

3.5 g of 4-chloroacetyl-1,3-dimethyl-1,4,9,10-tetrahydropyrazolo[4,3-b][1,5]benzodiazepin-10-one, 8.1 g of N-methylpiperazine and 50 ml of toluene are stirred at 80°C for 2 h. 60 ml of dilute sodium bicarbonate solution are added to the mixture, the layers are separated and the aqueous phase is extracted by shaking it with toluene several times more before concentrating it to dryness in vacuum. The residue is stirred with 100 ml of isopropanol and is filtered; the filtrate is concentrated in vacuum. The residue (4.0 g) is purified by stirring it with diethyl ether and by recrystallizing it from toluene, which yields 2.2 g of 1,3-dimethyl-4-[(4-methylpiperazin-1-yl)acetyl]-

1,4,9,10-tetrahydropyrazolo[4,3-b][1,5]benzodiazepin-10-one, melting point 186-188°C.

References

Rainer G.; US Patent No. 4,317,823; March 2, 1982; Assigned: Byk Gulden Lomberg Chemische Fabrik GmbH, Constance, Fed. Rep. of Germany

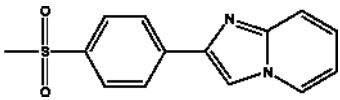
ZOLIMIDINE

Therapeutic Function: Antiulcer

Chemical Name: 2-[4-(Methylsulfonyl)phenyl]imidazo[1,2-a]pyridine

Common Name: Zoliridine

Structural Formula:



Chemical Abstracts Registry No.: 1222-57-7

Trade Name	Manufacturer	Country	Year Introduced
Solimidin	Selvi	Italy	1974
Gastronilo	Aristegui	Spain	-
Mutil	Lakeside	US	-

Raw Materials

2-Aminopyridine
p-Methylsulfonyl-ω-bromoacetophenone

Manufacturing Process

190 g of 2-aminopyridine were dissolved in 350 ml of dioxane and the solution was reacted with 277 g of p-methylsulfonyl-ω-bromoacetophenone. After two hours at room temperature the 2-(4'-methylsulfonylphenyl)[1,2-a]imidazopyridine was filtered, washed and recrystallized by alcohol.

References

Merck Index 9992
Kleeman and Engel p. 954
DOT 10 (6) 210 (1974)
I.N. p. 1024
Almirante, L., Murmann, W. and Friz, L.P.; US Patent 3,318,880; May 9, 1967; assigned to Laboratorio Bioterapico Milanese Selvi and Co. S.a.S. (Italy)

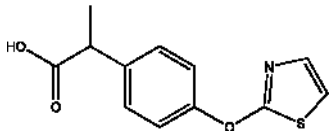
ZOLIPROFEN

Therapeutic Function: Antiinflammatory, Analgesic

Chemical Name: Benzeneacetic acid, α-methyl-4-(2-thiazolyloxy)-, stereoisomer

Common Name: Zoliprofen, Zoxiprofen

Structural Formula:



Chemical Abstracts Registry No.: 56355-17-0

Trade Name	Manufacturer	Country	Year Introduced
Zoliprofen	ZYF Pharm Chemical	-	-

Raw Materials

2-Chlorothiazole
Ethyl 2-(4-hydroxyphenyl)propionate
Potassium carbonate

Manufacturing Process

A mixture of 2-chlorothiazole (5.0 g), ethyl 2-(4-hydroxyphenyl)propionate (8.1 g), potassium carbonate powder (8.65 g) and dimethylformamide (80 ml) is stirred at 150°-155°C for 2.5 hours. The solvent is distilled out under reduced pressure. To the residue is added water and extracted with ether. The extract is washed with a 10% aqueous solution of sodium hydroxide and water and dried. The ether is evaporated. The residue is subjected to chromatography using silica gel and eluted with 50% benzene-hexane, benzene and 10% ether-benzene to yield ethyl 2-[4-(2-thiazolyloxy)-phenyl]propionate (5.8 g).

The product is dissolved in a mixture of a 20% aqueous solution of potassium hydroxide (30 ml) and 95% ethanol (30 ml). The solution is kept at room temperature for 30 minutes. The solvent is evaporated. The residue is acidified with hydrochloric acid after addition of water, and extracted with ether. The extract is washed with water and dried over magnesium sulfate. The solvent is distilled out. The residue is recrystallized from ether-hexane to give 2-[4-(2-thiazolyloxy)phenyl]propionic acid (4.8 g).

The product (5.0 g) is dissolved in an aqueous solution (30 ml) of sodium hydroxide (0.82 g). To the solution washed with ether is added an aqueous solution (5 ml) of calcium chloride 2 hydrate (1.6 g) to form a precipitate. The precipitate washed with water gives calcium 2-[4-(2-

thiazolyloxy)phenyl]propionate (5.5 g) melting at 143°-145°C.

References

Maeda R. et al.; US Patent No. 4,025,528; May 24, 1977; Assigned to Shionogi and Co., Ltd., Osaka, Japan

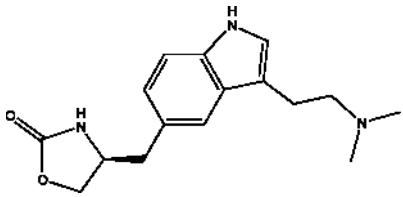
ZOLMITRIPTAN

Therapeutic Function: Serotoninergic

Chemical Name: 2-Oxazolidinone, 4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)-, (S)-

Common Name: Zolmitriptan

Structural Formula:



Chemical Abstracts Registry No.: 139264-17-8

Trade Name	Manufacturer	Country	Year Introduced
Zomig	AstraZeneca	UK	-
Zolmitriptan	AstraZeneca	UK	-

Raw Materials

α-Keto-γ-valerolactone
Ethoxyalyl-γ-butyrolactone
Dimethylaminopyridine
Copper oxide
(S)-4-(4-Aminobenzyl)-1,3-oxazolidyne-2-one hydrochloride
Methanesulfonic acid
Dimethylamine
Dowex 5OWX8-400
Quinoline
Sodium nitrite

Manufacturing Process

(S)-4-(4-[N'-(2-Oxotetrahydropyran-3-iliden)hidrazino]benzyl}-1,3-oxazolidin-2-one

A solution of 2.8 g (40.6 mmoles) of sodium nitrite in 12 ml of water was added slowly to a solution of 9.1 g (39.8 mmoles) of (S)-4-(4-aminobenzyl)-1,3-oxazolidyne-2-one hydrochloride in 17 ml of water and 29 ml of concentrated HCl, keeping the reaction temperature below 0°C. The mixture

was stirred at this temperature for 15 minutes. Once that time had elapsed the diazonium salt solution was added rapidly to a suspension of 30 g (239 mmoles) of sodium sulphite in 106 ml of water precooled to 0°C under nitrogen atmosphere. The red solution was stirred at 0°C for 10 minutes and then left to reach 65°C in 1 hour. It was stirred at 65°C for 30 minutes, and 18.2 ml of concentrated HCl then added. The mixture was stirred at the same temperature under nitrogen atmosphere for 3 hours and then left to cool to room temperature. To this solution was added a solution of 35 mmoles of α-keto-γ-valerolactone (prepared by decarboxylation of 11.8 g (63.7 mmoles) of a ethoxyalyl-γ-butyrolactone in 15.2 ml of 2 N H_2SO_4 at reflux) and left under stirring at room temperature for 12 hours. When that time had elapsed the mixture was cooled to 0°C and stirred for one hour. The precipitate formed was filtered, washed with cold water and dried in an hotair oven at 40°C, giving a white solid which was crystallised from ethanol/water to give 10.5 g (87%) of the title hydrazone as a white solid. Melting point 223.3°-224.7°C.

(S)-6-(2-Oxo-1,3-oxazolidin-4-ylmethyl)-4,9-dihydro-3H-pyrano-[3,4-b]indol-1-one

3.8 g (12.5 mmoles) of (S)-4-{4-[N'-(2-oxotetrahydropyran-3-iliden) hydrazino]benzyl}-1,3-oxazolidin-2-one were suspended in 32 ml of a saturated solution of hydrogen chloride in acetic acid. The mixture was stirred at room temperature for 16 h, 10 ml of water/ice was added to the reaction mixture and stirred at 0°C for 20 min. The precipitate was filtered, washed with cold water and dried in hot-air oven at 40°C. The residue was crystallised with methanol to yield 3.3 g (92%) of the title indole as a yellow crystalline solid. Melting point 215°-217°C.

(S)-3-(2-Hydroxyethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1-H-indol-2-carboxylicacid methyl ester

To a suspension of 500 mg (1.74 mmoles) of the (S)-6-(2-oxo-1,3-oxazolidin-4-ylmethyl)-4,9-dihydro-3-pyrano-[3,4-b]indol-1-one in 10 ml of methanol were added 0.12 ml (1.9 mmoles) of methanesulfonic acid. The mixture was left under stirring at the reflux temperature for 3 hours. The solvent was evaporated to dryness under reduced pressure, the residue dissolved with 10 ml of a saturated bicarbonate solution and extracted three times with dichloromethane. The combined organic phases were dried and evaporated to dryness and the evaporated solid recrystallised from ethanol to give 517 mg (93%) of the title ester as a yellow crystalline solid. Melting point 178°-180°C.

(S)-3-(2-Hydroxyethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-2-carboxylicacid ethyl ester

9.5 g (31.3 mmoles) of (S)-4-{4-[N'-(2-oxotetrahydropyran-3-ilyden) hydrazine]benzyl}-1,3-oxazolidin-2-one were suspended in 76 ml of a 2 N solution of hydrogen chloride in absolute ethanol. The mixture was left under stirring at 75°C for 30 min. The solvent was evaporated to dryness under reduced pressure, 50 ml of a saturated solution of potassium carbonate added, and then extracted three times with 50 ml of dichloromethane. The combined organic phases were dried on anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised from isopropyl alcohol/heptane to give 9.25 g (89%) of the title indole. The product was

recrystallised from methanol to give a yellow crystalline solid. Melting point 154°-156°C.

(S)-5-(2-Oxo-1,3-oxazolidin-4-ylmethyl)-3-[(2-toluen-4-sulphonyloxy)ethyl]-1-indol-2-carboxylicacid ethyl ester

To a stirred suspension of 4.6 g (13.8 mmoles) of the (S)-3-(2-hydroxyethyl)-5-(2-oxo-1,3-oxazolidin-4- ylmethyl)-1H-indol-2-carboxylic acid ethyl ester in 42 ml of dichloromethane were added 4.2 ml of pyridine, 3.9 g (20.7 mmoles) of tosyl chloride and 170 mg (1.38 mmoles) of dimethylaminopyridine and the stirring continued at room temperature for 20 hours. The reaction mixture was poured over 20 ml of 3 N, HCl precooled to 0°C and extracted twice with dichlormethane. The organic phases were washed with brine, dried on anhydrous sodium sulphate and the solvent evaporated to dryness. The evaporated solid was crystallised with isopropyl alcohol to give 6.4 g (95%) of the title compound as a white crystalline solid. Melting point 166.4°-168.2°C.

(S)-3-(2-Dimethylaminoethyl)-5-[2-oxo-1,3-oxazolidin-4-ylmethyl]-1H-indol-2-carboxylicacid ethyl ester

A stirred suspension of 5 g of (S)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-3-[(2-toluen-4-sulphoniloxy)ethyl]-1H-indol-2-carboxylic acid ethyl ester in 30 ml of a 2 N solution of dimethylamine in ethanol was stirred at 50°C for 20 hours in a closed reactor. The solvent was evaporated to dryness, the residue dissolved in 20 ml of 2 N HCl and washed three times with 15 ml of dichloromethane. The washed aqueous phase was cooled and adjusted to pH 12 with a 40% sodium hydroxide solution and extracted three times with 20 ml of dichloromethane. The combined organic phases were washed with brine and dried above anhydrous sodium sulphate. The solvent was evaporated to dryness and the residue recrystallised from ethyl acetate to give 3.4 g (91%) of the title dimethylamine as a yellow solid. Melting point 67°-70°C.

(S)-3-(Z-Dimethylaminoethyl-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-2-carboxylicacid

To a solution of 1.4 g (24.9 mmoles) of KOH in 10 ml of ethanol was added 2.8 g (7.8 mmoles) of (S)-3-(2- dimethylaminoethyl)-5-[2-oxo-1,3-oxazolidin-4-ylmethyl]-1H-indol-2-carboxylic acid ethyl ester. The resulting solution was heated at reflux temperature for one hour. It was cooled and the solvent evaporated to dryness. The residue was dissolved in 6 ml of water and washed three times with 10 ml of dichloromethane. The aqueous solution was cooled to 5°C, adjusted to pH 6 with glacial acetic acid, stirred for 30 minutes at that temperature and the water evaporated to dryness. The residue was redissolved in 30 ml of water and 5 g of ionic exchange resin (Dowex5OWX8-400) added. The mixture was left under stirring at room temperature for 24 hours. The resin was filtered and it was washed with water. For desorbtion the resin was suspended with 20 ml of a 10% aqueous solution of ammonia and stirred at room temperature for 5 hours. After that it was filtered and washed with water, water was evaporated to dryness under reduced pressure to give 7.75 g (94%) of the title acid as a yellow crystalline solid. Melting point 230°C.

(S)-4-[3-(2-Dimethylaminoethyl)-1H-indol-5-ylmethyl]-1,3-oxazolidin-2-one

15.1 g (3.02 mmoles) of the (S)-3-(2-dimethylaminoethyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-2-carboxylic acid was suspended in 10 ml of dry quinoline. 20 mg of cuprous oxide was added and the stirred suspension heated to 200°C under dry nitrogen stream. The reaction mixture was kept at this temperature until no more CO_2 was released (15-20 min). It was left to cool to room temperature and the reaction mixture filtered through decalite. The filtrate was concentrated by vacuum distillation of the solvent, providing a residue which was dissolved with a succinic acid solution and washed three times with 15 ml of dichloromethane. The washed aqueous phase was cooled, the pH adjusted to 12 with a 40% sodium hydroxide solution and extracted three times with 20 ml of dichloromethane. The combined organic phases were dried on anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised with isopropyl alcohol to give 780 mg (90%) of zolmitriptan as a white solid. Melting poimt 138°-140°.

The structure of all described compounds was confirmed by IR and NMR spectrums.

References

Pere D.B., Montserrat A.A.; WO 2004014901; Feb. 19, 2004; Assigned to Laboratorios Vita, Spain

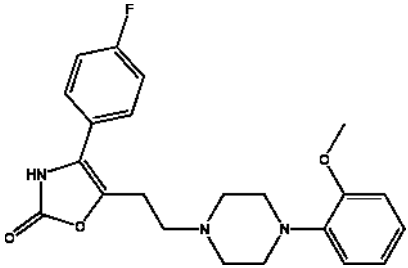
ZOLOPERONE

Therapeutic Function: Neuroleptic

Chemical Name: 2(3H)-Oxazolone, 4-(4-fluorophenyl)-5-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-

Common Name: Zoloperone

Structural Formula:



Chemical Abstracts Registry No.: 52867-74-0

Trade Name	Manufacturer	Country	Year Introduced
Zoloperone	ZYF Pharm Chemical	-	-

Raw Materials

Phosgene
Triethylamine
1-p-Fluoro-benzoyl-1-hydroxy-3-N-[N'-(2-methoxy-phenyl)] piperazinopropane

Manufacturing Process

To 20% solution of phosgene in toluene, agitated and cooled to 0°C, are added over 30 min a solution of 1-p-fluoro-benzoyl-1-hydroxy-3-N-[N'-(2-methoxyphenyl)]piperazinopropane and triethylamine in anhydrous chloroform. It is agitated at ambient temperature for 5 h, cooled to 0°C and the solution saturated with gaseous ammonia. The solution is agitated at ambient temperature for 3 h, filtered and the filtrate dried under reduced pressure, 4-ρ-fluorophenyl-5-β-(4-o-methoxyphenylpiperazino)ethyl-4-oxazolin-2-one, melting point 154°C (by alcohol) was obtained.

References

Manghisi E, Cascio G.; US Patent No. 3,930,008; December 30, 1975; Assigned: Istituto Luso Farmaco d'Italia S.r.l., Milan, Italy

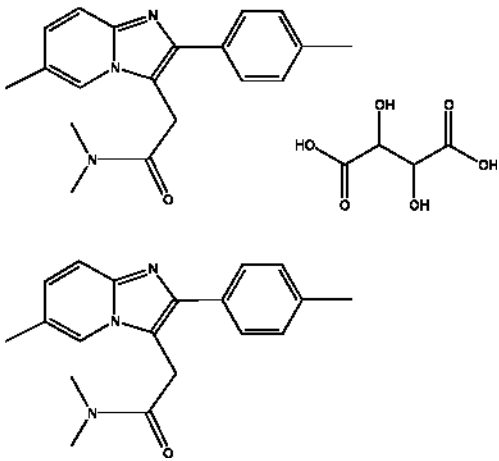
ZOLPIDEM TARTRATE

Therapeutic Function: Hypnotic

Chemical Name: Imidazo(1,2-a)pyridine-3-acetamide, N,N,6-trimethyl-2-(4-methylphenyl)-, (2R,3R)-2,3-dihydroxybutanedioate (2:1)

Common Name: Zolpidem tartrate

Structural Formula:



Chemical Abstracts Registry No.: 99294-93-6

Trade Name	Manufacturer	Country	Year Introduced
Ambien	Sanofi-Synthelabo	France	-
Eudorm	Rontag	-	-
Zolpidem tartrate	Gador S.A.	Argentina	-

Raw Materials

Bromine
Acetic acid
3-(4-Methyl-benzoyl)propyldimethylamide
6-Amino-3-picoline

Manufacturing Process

18.6 g (84.8 mmol) of 3-(4-methylbenzoyl)propyldimethylamide are dissolved in 50 ml of glacial acetic acid. A solution of 13.55 g (84.8 mmol) of bromine and 45 ml of glacial acetic acid is added dropwise within 50 min at ambient temperature and the mixture is then stirred overnight. The suspension formed is filtered and washed with 30 ml of glacial acetic acid. The filter residue is added to 200 ml of distilled water, triturated thoroughly and stirred for 1 hour. The product is filtered again and washed with another 200 ml of water. The crystals obtained (21.16 g) are dried for 6 hours in a vacuum at 70°C. Yield of 3-(4-methylbenzoyl)-2-bromopropyldimethylamide is 18.18 g of white crystals (71.9% of theory), melting point: 119-121°C.

Synthesis of N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide

1). 50 g (167.7 mmol) of 3-(4-methylbenzoyl)-2-bromopropyldimethylamide are placed in 500 ml of acetonitrile. A solution of 36.27 g (335.4 mmol) of 6-amino-3-picoline and 350 ml of acetonitrile is added dropwise at 60°C within 1.75 hours and once the solution has all been added the mixture is stirred for another 4 hours. The resulting solution is diluted with 1000 ml of dichloromethane and washed three times with 2000 ml of distilled water. Then the organic phase is extracted three times with 1000 ml of 2 N hydrochloric acid. The combined acid phases are adjusted to pH 8 with 20% sodium hydroxide solution and, after being cooled, extracted three times with 1 L of dichloromethane. The organic phases are combined, dried with magnesium sulphate and concentrated by evaporation. The crystals of N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide obtained are triturated with 500 ml of distilled water, stirred overnight, filtered off, washed again with 50 ml of distilled water and the residue is dried in a vacuum for 5 hours at 60°C. Yield: 17.94 g of light-brown crystals (45.7% of theoretical).

2).10.0 g (33.5 mmol) of 3-(4-methylbenzoyl)-2-bromopropyldimethylamide and 7.25 g (67.0 mmol) of 6-amino-3-picoline are dissolved in 170 ml of 1,3-dimethyl-2-imidazolidinone and stirred for 3 hours at 60°C. The reaction mixture is cooled and diluted with 100 ml of dichloromethane. It is then washed five times with 150 ml of distilled water. The organic phase is washed twice with 150 ml of 2 N hydrochloric acid. The combined acid phases are adjusted to pH 8 with 2 N sodium hydroxide solution. The mixture is extracted twice with 150 ml of dichloromethane, the organic phases are dried with $MgSO_4$ and concentrated by evaporation. The brown oil obtained is mixed with 50 ml of n-heptane and stirred for 30 min. The supernatant diluent is

decanted off from the precipitated product which is then washed twice with 10 ml of n-heptane. The residue is evaporated down again, combined with 200 ml of distilled water and stirred for 30 min. The N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide is filtered off, washed with 50 ml of distilled water and dried. Yield: 2.38 g of beige crystals (23.1% of theoretical.), melting point: 194-195°C.

3). 100 g (0.456 mol) of 3-(4-methylbenzoyl)propyldimethylamide are dissolved in 400 ml of dichloromethane. 2 g (0.025 mol) of hydrogen bromide are piped into the solution which is then refluxed. Then 86.1 g (0.539 mol) of bromine is added dropwise within 45 min and the mixture is stirred for 30 min. It is then cooled to ambient temperature and washed with 600 ml of distilled water. The aqueous phase is discarded. The organic phase is evaporated down to about 10% (v/v) and then diluted with 300 ml of acetonitrile. This solution is added dropwise within 45 min to a solution of 66.62 g (0.616 mol) of 6-amino-3-picoline in 150 ml of acetonitrile at 70°C and stirred for 1.5 hours. Then 400 ml of toluene are added at 20-30°C and the mixture is then extracted with 500 ml of 2 N hydrochloric acid. The toluene phase is discarded, the aqueous phase is again combined with 400 ml of toluene and adjusted to pH 4 with 20% sodium hydroxide solution. The toluene phase is discarded, the aqueous phase is combined with 400 ml of toluene and adjusted to pH 8.5 with 20% sodium hydroxide solution. The toluene phase is separated off and evaporated down to 10% (v/v). The residue is combined with MTBE and stirred for 2 hours at 5°C. The crystals of N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide are suction filtered, washed with MTBE and dried. Yield: 43 g of zolpidem (30.7%).

17.94 g (94%) (54.9 mmol) of N,N,6-trimethyl-2-(4-methylphenyl)imidazo [1,2-a]pyridine-3-acetamide are placed in 90 ml of methanol. A solution of 4.13 g (27.5 mmol) of (2R,3R)-(+)-tartaric acid and 125 ml of methanol are added, followed by 28 ml of methyl-tert-butyl-ether (MTBE) within 30 seconds. The mixture is stirred for 15 hours at ambient temperature. The light-brown suspension formed is stirred for another 1 hour at 5°C, filtered off, the residue is washed with 50 ml of MTBE, and the crystals are dried for 5 hours in a vacuum at 50°C. Yield: 18.3 g crystals of N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide semitartrate (87.2% of theoretical).

References

Sauter M., Wohlleben W.; US Patent No. 6,562,975, May 13, 2003; Assigned to Boehringer Ingelheim Pharma KG, Ingelheim (DE)

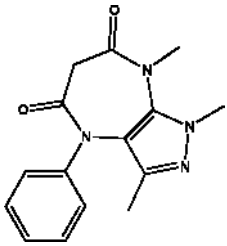
ZOMEBAZAM

Therapeutic Function: Anxiolytic, Nootropic

Chemical Name: 1,3,8-Trimethyl-4-phenyl-4,8-dihydro-1H-pyrazolo[3,4-b][1,4]diazepine-5,7-dione

Common Name: Zomebazam

Structural Formula:



Chemical Abstracts Registry No.: 78466-70-3

Trade Name	Manufacturer	Country	Year Introduced
Zomebazam	ZYF Pharm Chemical	-	-
Zomebazam	Hoechst	-	-

Raw Materials

Nickel Raney
Sodium methanolate
Copper
4-Benzeneazo-1,3-dimethyl-5-methylaminopyrazole
Methyl malonate chloride
Potassium acetate
Bromobenzene

Manufacturing Process

(a) 1,3,8-Trimethyl-4-phenyl-5,6,7,8-tetrahydropyrazolo[3,4-b][1,5]diazepine-1H ,4H-5,7-dione:

23 g (0.1 mole) of 4-benzene-azo-1,3-dimethyl-5-methylaminopyrazole are hydrogenated in 250 ml of ethanol with 60 g of Raney nickel, at 60°C; a hydrogen pressure of 50 atmospheres. When the uptake of hydrogen has ended, the catalyst is filtered off and the reaction solution is evaporated in vacuum. The residue is triturated with ether/petroleum ether and the precipitate of 4-amino-1,3-dimethyl-5-methylaminopyrazole is filtered off. The product is sufficiently pure for the subsequent reactions. MP: 87°C.

(b) 4-α-Ethoxycarbonylacetylamino-1,3-dimethyl-5-methylaminopyrazole:

1.4 g (0.01 mole) of 4-amino-1,3-dimethyl-5-methylaminopyrazole are dissolved in 20 ml of toluene, 1 ml (0.012 mole) of monomethyl malonate chloride is slowly added dropwise, whilst cooling with ice, and the mixture is subsequently stirred at room temperature for one hour. The toluene is stripped off in vacuum, the residue is taken up in chloroform and the mixture is washed with ice-cold $NaHCO_3$ solution and water and dried with Na_2SO_4. After evaporating off the solvent, 4-α-ethoxycarbonylacetylamino-1,3-dimethyl-5-methylaminopyrazole remains as an yellowish oil.

(c) 1,3,8-Trimethyl-5,6,7,8-tetrahydropyrazolo[3,4-b][1,5]diazepine-1H,4H-

5,7-dione:

15 ml of a 1 molar sodium methanolate solution are added to 2.4 g (0.01 mole) of 4-α-ethoxycarbonylacetylamino-1,3-dimethyl-5-methyl-aminopyrazole, dissolved in 100 ml of ethanol, and the mixture is stirred at room temperature for 8 hours. It is then neutralized with alcoholic HCl and evaporated in vacuum, the residue is taken up in $CHCl_3$, the mixture is filtered and the filtrate is again evaporated. After adding ether to the residue, the latter becomes crystalline and can be filtered off. It is recrystallized from isopropanol/diisopropyl ether. MP: 202°C.

(d) 1,3,8-Trimethyl-4-phenyl-5,6,7,8-tetrahydropyrazolo[3,4-b][1,5]diazepine-1H,4H-5,7-dione:

A mixture of 1 g of 1,3,8-trimethyl-5,6,7,8-tetrahydropyrazolo[3,4-b][1,5]diazepine-1H,4H-5,7-dione, 1 g of potassium acetate and 1.5 g of copper powder in 100 ml of bromobenzene is boiled under reflux, whilst stirring, until the reaction has ended (monitoring by thin layer chromatography, 3-4 hours). The mixture is then allowed to cool to room temperature and is diluted with CH_2Cl_2 (200 ml), the inorganic constituents are filtered off, the organic phase is washed with water and dried and the solvent is stripped off in vacuum. Recrystallization of the residue from diisopropyl ether gives the analytically pure 1,3,8-trimethyl-4-phenyl-5,6,7,8-tetrahydropyrazolo[3,4-b][1,5]diazepine-1H,4H-5,7-dione. MP: 168°C.

References

Rackur G. et al.; US Patent No. 4,302,468; November 24, 1981; Assigned to Hoechst Aktiengesellshaft, Frankfurt an Main, Fed. Rep. of Germany

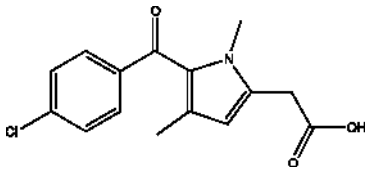
ZOMEPIRAC

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: 5-(p-Chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 33369-31-2

Trade Name	Manufacturer	Country	Year Introduced
Zomex	Cilag	Switz.	1979
Zomax	McNeil	US	1980
Zomax	Cilag	France	1981
Zomax	Cilag	W. Germany	1981
Zomax	Ortho	UK	1981
Zomaxin	Cilag	Italy	1982
Calmador	Finadiet	Argentina	-
Dolgenal	Exa	Argentina	-
Dolwas	Wassermann	Spain	-
Zopirac	Sintyal	Argentina	-

Raw Materials

Ethyl 5-(p-chlorobenzoyl)-1,4-dimethyl-3-ethoxypyrrole-2-acetate
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

5-(p-Chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetic acid: A suspension of 17.3 g (0.0435 mol) of ethyl 5-(p-chlorobenzoyl)-1,4-dimethyl-3-ethoxypyrrole-2-acetate in 170 g of 25% hydroxide is heated under reflux for 3 hours. The suspension is poured into ice and the resulting yellow solution is added to ice-hydrochloric acid with stirring. The precipitated solid is collected by filtration, air dried and recrystallized from acetone containing 10% water to give 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetic acid as a white solid; melting point 253°C to 254°C.

Ethyl 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetate: A suspension of 2.0 g of 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetic acid in 20 ml of 0.5% ethanolic hydrogen chloride is heated under reflux. The solid gradually dissolves. After 40 minutes a white crystalline solid precipitates. The solution is cooled and the solid product, ethyl 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetate, is filtered and dried, melting point 197°C to 198°C.

Ethyl 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetate: A 9.0 g (0.0255 mol) sample of ethyl 5-(p-chlorobenzoyl)-3-carboxy-1,4-dimethylpyrrole-2-acetate is heated under nitrogen at 210°C to 230°C for 2 hours. Gas is evolved. The residue is molecularly distilled in a sublimator at 195°C, 0.05 mm/Hg. The sublimate is recrystallized from cyclohexane to give ethyl 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetate as a white solid, melting point 107°C to 109°C.

5-(p-Chlorobenzoyl)-1,-4dimethylpyrrole-2-ecetic acid: A suspension of 4.0 g (0.0125 mol) of ethyl 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetate in 26 ml of 0.5 N sodium hydroxide (0.013 mol) is heated under reflux for 30 minutes. The resulting solution is acidified with dilute hydrochloric acid, and the precipitated solid is collected by filtration, air dried and recrystallized from 2-propanol to give 5-(p-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid as a

white crystalline solid, melting point 178°C to 179°C.

References

Merck Index 9993
DFU 2 (10) 698 (1977)
Kleeman and Engel p. 955
OCDS Vol. 3 p. 128 (1984)
DOT 16 (12) 434 (1980)
I.N. p. 1025
Carson, J.R.; US Patents 3,752,826; August 14,1973 and 3,865,840; February 11, 1975; both assigned to McNeil Laboratories, Inc.

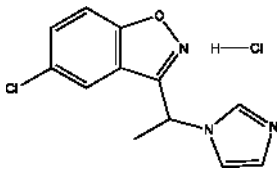
ZONICLEZOLE HYDROCHLORIDE

Therapeutic Function: Anticonvulsant

Chemical Name: 1,2-Benzisoxazole, 5-chloro-3-(1-(1H-imidazol-1-yl)ethyl)-monohydrochloride

Common Name: Xonicezole hydrochloride; Zoniclezole hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 121929-20-2(Base); 121929-46-2

Trade Name	Manufacturer	Country	Year Introduced
Zoniclezole hydrochloride	GASTHAUS	-	-

Raw Materials

Butyl lithium
Diisopropylamine
5-Chloro-3-[(1H-imidazol-1-yl)ethyl]-1,2-benzisoxazole

Manufacturing Process

A solution of n-butyl lithium in hexane (2.1 M, 9.2 ml, 0.019 mole) is added dropwise to a solution of diisopropylamine (0.021 mole) in anhydrous tetrahydrofuran (40 ml) at -40°C (dry ice/isopropanol bath). After standing at this temperature for 10 minutes, the cold solution is added dropwise to a stirred, cooled (-60°C) solution of 5-chloro-3-[(1H-imidazol-1-yl)ethyl]-1,2-

benzisoxazole (0.019 mole) in anhydrous tetrahydrofuran (40 ml). The resulting deep red colored reaction mixture is stirred at -60°C for 30 minutes and then iodomethane (4.1 g, 0.029 mole) is added all at once. The reaction is stirred at -60°C for 1 hour and then without external cooling for a further 2 hours. Water (100 ml) and ethyl acetate (100 ml) are then added and the organic solution is separated and extracted with 3 N hydrochloric acid (2x30 ml). The combined acid extracts are subsequently made basic (pH 8) with 2 N sodium hydroxide and the product is extracted into ethyl acetate (2x50 ml). The combined extracts are dried over anhydrous sodium sulfate, filtered and evaporated in vacuum to afford an oil which solidifies on standing. The crude 5-chloro-3-[1-(1H-imidazol-1-yl)ethyl]-1,2-benzisoxazole, is recrystallised from isopropanol, When a warm solution of this material in isopropanol is treated with a small excess of ethereal hydrogen chloride, the hydrochloride salt 5-chloro-3-[1-(1H-imidazol-1-yl)ethyl]-1,2-benzisoxazole hydrochloride is obtained, MP: 168-170°C.

References

Bowman R.W.; US Patent No. 4,859,691; August 22, 1989; Assigned to Ciba-Geigy Corporation, Ardsley, N.Y.

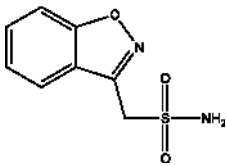
ZONISAMIDE

Therapeutic Function: Anticonvulsant; Antiepileptic

Chemical Name: 1,2-Benzisoxazole-3-methanesulfonamide

Common Name: Fenisoxine; Zonisamide

Structural Formula:



Chemical Abstracts Registry No.: 68291-97-4

Trade Name	Manufacturer	Country	Year Introduced
Zonegran	Elan Pharmaceuticals, Inc.	-	-

Raw Materials

3-Bromomethyl-1,2-benzisoxazole
Sodium sulfite
Phosphorus oxychloride

Manufacturing Process

To a solution of 8.0 of 3-bromomethyl-1,2-benzisoxazole (m.p. 64-66°) in 130 ml of methanol was added a solution of 8.1 g of sodium sulfite in 130 ml of water. The mixture was heated with stirring at 50°C for 4 hours and concentrated under reduced pressure. The crystalline residue was dissolved in 250 ml of methanol with warming and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure and the crystalline residue of 1,2-benzisoxazole-3-methanesulfonyl chloride was washed with diethyl ether to give crude sodium 1,2-benzisoxazole-3-methanesulfonate (10.5 g).

To 100 ml of phosphorus oxychloride was added 10.5 g of the above-mentioned sodium salt and the mixture was heated under reflux for 3 hours. The excess of phosphorus oxychloride was distilled off under reduced pressure. The residue was dissolved in 200 ml of ethyl acetate and the removal of the insoluble material by filtration gave the solution of the 1,2-benzisoxazole-3-methanesulfonyl chloride.

The solution of 1,2-benzisoxazole-3-methanesulfonyl chloride in ethyl acetate, was cooled on an ice bath, saturated with dry ammonia gas, and allowed to stand at room temperature for one hour. After the removal of the insoluble material by filtration, the filtrate was concentrated to yield a crystalline solid, which was washed with a small amount of ethyl acetate and recrystallized from ethyl acetate to give the 3-sulfamoylmethyl-1,2-benzisoxazole (5.2 g), m.p. 160-163°C.

References

Uno H. et al.; US Patent No. 4,172,896; Oct. 30, 1979; Assigned to Dainippon Pharmaceutical Co., Ltd., Osaka, Japan

ZOPICLONE

Therapeutic Function: Sedative, Hypnotic

Chemical Name: 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester

Common Name: Zopiclone; Amoban; Amovane; Imovane

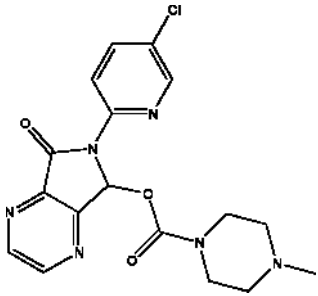
Chemical Abstracts Registry No.: 43200-80-2

Raw Materials

Sodium hydride
1-Chlorocarbonyl-4-methylpiperazine
Sodium hydroxide
1-Methylpiperazine

6-(5-Chloropyrid-2-yl)-7-oxo-5-phenoxycarbonyloxy-5,6-dihydropyrrolo[3,4-b]pyrazine
6-(5-Chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Zopiclone	Pliva	-	-
Zopiclone	ZYF Pharm Chemical	-	-
Zopiclone	Guangzhou Zhensu Fine Chemical Co., Ltd.	-	-
Zopiclone	Vision Group	-	-
Novo-Zopiclone	Novopharm	-	-
Zo-tab	Pacific Pharmaceuticals Ltd.	-	-
Zopiclone	Grindeks	-	-
Zopiclone Biogaran	Biogaran	-	-
Alpaz	Beta	-	-
Alpaz	ROYAL PHARMA	-	-
Amoban	Rhone-Poulenc Rorer S.A.	-	-
Datolan	Faes	-	-
Espa-Dorm	Espana	-	-
Imozop	Durascan	-	-
Limovan	Rhone-Poulenc Rorer	-	-
Limovan	Aventis	-	-
Mozop	Durascan	-	-
Optidorm	Dolorgiet	-	-
Rhovane	Rhodiapharm	-	-
Siaten	Italfarmaco	-	-
Somnosan	Hormosan Pharma	-	-
Sopivan	Formenti	-	-
Ximovan	Rhone-Poulenc	-	-
Ximovan	Aventis Pharma	-	-
Zinovane	Rhone-Poulenc Rorer	-	-

Trade Name	Manufacturer	Country	Year Introduced
Dormex	Pharmalab	-	-
Somnosan	Hormosan-Kwizda	-	-
Imovane	Aventis Pharma	-	-

Manufacturing Process

Producing of 6-(5-chloropyrid-2-yl)-5-(4-methylpiperazin-1-yl)-carbonyloxy-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine by two methods.

1). A solution of 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine (12.0 g) in anhydrous dimethylformamide (360 ml) is added to a suspension of sodium hydride (50% dispersion in mineral oil) (2.4 g) in anhydrous dimethylformamide (60 ml), whilst maintaining the temperature at about -10°C. When the evolution of gas has ceased, a solution of 1-chlorocarbonyl-4-methylpiperazine (8.1 g) in anhydrous dimethylformamide (20 ml) is added, whilst maintaining the temperature at about -10°C. The reaction mixture is stirred for a further 3 h whilst allowing it to heat up gradually to a temperature of about 20°C, and then it is poured into ice-water (1540 ml). The product which crystallizes is filtered off, washed with water (150 ml) and then with diisopropyl ether (100 ml). After drying, a product is obtained and is dissolved in ethyl acetate (600 ml). The solution obtained is filtered through silica gel (250.0 g). Elution is then carried out with ethyl acetate (3200 ml) followed by a mixture of ethyl acetate and methanol The eluates are combined and concentrated to dryness under reduced pressure. So 8.3 g of the 6-(5-chloropyrid-2-yl)-5-(4-methylpiperazin-1-yl)-carbonyloxy-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine are obtained, melting point 178°C (recrystallisation from a mixture of acetonitrile and diisopropyl ether 1:1; 190 ml).

2). 1-Methylpiperazine (155.0 g) is added to a suspension of 6-(5-chloropyrid-2-yl)-7-oxo-5-phenoxycarbonyloxy-5,6-dihydropyrrolo[3,4-b]pyrazine (194.0 g) in acetone (970 ml) cooled to a temperature of about 3°C. The reaction mixture is stirred for 3 h at a temperature of about 3°C and is then poured into water (5000 ml). The product which precipitates is filtered off and then washed with water (600 ml) and dried. This product is treated with methylene chloride (1100 ml) at a temperature of about 20°C. The insoluble material is filtered off and then the filtrate is washed with 1 N sodium hydroxide solution (3x200 ml) and with water (3x200 ml). The organic phase is treated with decolorizing charcoal (10.0 g), dried over potassium carbonate, filtered and then concentrated to dryness under reduced pressure. The oily residue obtained is dissolved in boiling acetonitrile (500 ml). The 101.0 g of 6-(5-chloropyrid-2-yl)-5-(4-methylpiperazin-l-yl)carbonyloxy-7-oxo-5,6-dihydropyrrolo[3,4-b]-pyrazine are obtained, melting point 178°C (washed with ice cold acetonitrile, 50 ml, and then crystallizes with diisopropyl ether, 50 ml).

References

Cotrel C. et al.; US Patent No. 3,862,149; January 21, 1975; Assigned: Rhone-Poulenc S.A., Paris, France

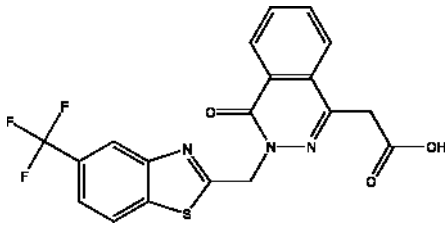
ZOPOLRESTAT

Therapeutic Function: Aldose reductase inhibitor

Chemical Name: 1-Phthalazineacetic acid, 3,4-dihydro-4-oxo-3-((5-(trifluoromethyl)-2-benzothiazolyl)methyl)-

Common Name: Xedia; Zopolrestat

Structural Formula:



Chemical Abstracts Registry No.: 110703-94-1

Trade Name	Manufacturer	Country	Year Introduced
Alond	Pfizer	-	-

Raw Materials

N-Bromosuccinimide
Benzoyl peroxide
Sodium hydride
2-Methyl-5-trifluoromethylbenzothiazole
4-Oxo-3H-phthalazin-1-ylacetate

Manufacturing Process

A mixture of 2-methyl-5-trifluoromethylbenzothiazole (1 mole-equivalent), N-bromosuccinimide (1 mole-equivalent), carbon tetrachloride (700 ml) and a catalytic amount of benzoyl peroxide (0.2 g) was refluxed under irradiation by an UV lamp for 14 hours. The reaction mixture was cooled to room temperature, filtered to remove the precipitated succinimide and the filtrate was evaporated to dryness. The resulting solid was chromatographed over silica gel to obtain the 2-bromomethyl-5-trifluoromethyl-benzothiazole.

To a mixture of ethyl 4-oxo-3H-phthalazin-1-ylacetate (1 mole-equivalent) and sodium hydride (50% w/w dispersion in mineral oil) in dimethylformamide (150 ml) was added 2-bromomethyl-5-trifluoromethylbenzothiazole (1 mole-equivalent) and the resulting mixture stirred at room temperature for 1 hour. This reaction mixture was poured over ice-water (500 ml); sufficient 10% HCl was added to adjust the pH to about 4.0 and the precipitated crude solid was collected. This was chromatographed over silica gel to obtain the ethyl[4-oxo-3-(5-trifluoromethylbenzothiazol-2-yl)-3,4-dihydro-phthalazin-1-yl]acetate; MP: 134°-136°C.

A solution of methyl or ethyl [4-oxo-3-(5-trifluoromethylbenzothiazol-2-yl)-3,4-dihydrophthalazin-1-yl]acetate (1 mole-equivalent) in methanol (50 ml)

containing 10% aqueous potassium hydroxide (5 ml) was stirred at room temperature for 4 hours. The solution was concentrated to remove methanol and the concentrate was diluted with water (75 ml) and then extracted with ethyl acetate. The aqueous portion was separated and acidified with concentrated hydrochloric acid to pH 2.0. The precipitated solid was collected and crystallized from isopropyl alcohol to give [4-oxo-3-(5-trifluoromethylbenzothiazol-2-yl)-3,4-dihydrophthalazin-1-yl]acetic acid; MP: 197°-198°C.

References

Larson E.R. et al.; US Patent No. 4,939,140; July 3, 1990; Assigned to Pfizer Inc., New York, N.Y.

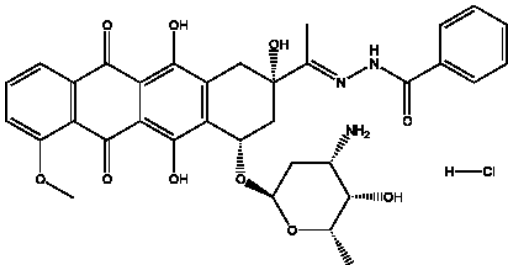
ZORUBICIN HYDROCHLORIDE

Therapeutic Function: Antineoplastic, Antileukemic

Chemical Name: Benzoic acid, (1-(4-((3-amino-2,3,6-trideoxy-α,L-lyxohexopyranosyl)oxy)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl)ethylidene)hydrazide, (2S-cis)-, monohydrochloride

Common Name: Rubidazone; Zorubicin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 54083-22-6 (Base); 36508-71-1

Trade Name	Manufacturer	Country	Year Introduced
Zorubicin Hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

Daunorubicin hydrochloride
Aminoguanidine

Manufacturing Process

9.024 g daunorubicin-hydrochloride (its preparation and physicochemical properties have been described in British Patent Specification No 985 598) was dissolved in 800 ml ethanol and mixed with 2.5 ml acetic acid and 2.162 g benzoyl hydrazide and heated for 24 hours at 60°C. On cooling the obtained precipitate was filtered off, washed with 100 ml of ethanol and dried in vacuum at 20°C. It was dissolved in water and small quantity of insoluble product was filtered off, the filtrate was lyophilized. (1-(4-((3-Amino-2,3,6-trideoxy-α,L-lyxohexopyranosyl)oxy)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl)ethylidene)hydrazide dihydrochloride (zorubicin) was obtained as red-orange crystalline powder; $[\alpha]_D^{20}$= -50° (c=0.2 in water). The compound may be employed in the form of different non-toxic salts such as benzoates, fumarates, maleates, tartrates and so on. The best among these compounds proves to be daunorubicin benzoylhydrazone (rubidazone), which is less cardiotoxic (French Pat. No. 1,578,722 published in 1967, Class CO7d).

References

Jolles G.; GB Patent No. 1,212,459; October 18, 1967; in France (FR); Rhone-Pouleng S.A., a French Body Corporate of 22, Avenue Montaigne, Paris 8e, France

Jolles G.; D.B. Patent No. 2,327,211; May 28, 1973; Sceaux Haunts-de-Seine, (Frankreich)

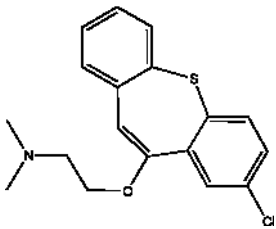
ZOTEPINE

Therapeutic Function: Tranquilizer

Chemical Name: 2-[(8-Chlorodibenzo[b,f]thiepin-10-yl)oxy]-N,N-dimethylethanamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 26615-21-4

Trade Name	Manufacturer	Country	Year Introduced
Lodopin	Fujisawa	Japan	1982

Raw Materials

8-Chlorodibenzo[b,f]thiepin-10(11H)one
2-Dimethylaminoethyl chloride

Manufacturing Process

A suspension of 30 g of sodium hydride in benzene (30 ml) was added dropwise to 52 g of 8-chlorodibenzo[b,f]thiepin-10(11H)-one dissolved in dimethylformamide (800 ml), and the mixture was heated at 100°C for 2 hours. To this, there were added 68 g of 2-dimethylaminoethyl chloride, and the mixture was heated at 60°C for 39 hours. The reaction mixture, after cooled, was poured into ice-water, and the solution was extracted with ethyl acetate. The ethyl acetate layer, after washed with water, was extracted with 10% hydrochloric acid, when oil was precipitated. The aqueous layer, in which oil was precipitated, was washed with ether, made neutral with concentrated sodium hydroxide solution and then extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over magnesium sulfate, and concentrated to give oil, which was allowed to stand to provide solid. The solid was washed with petroleum ether and recrystallized from cyclohexane to yield 42.5 g of 8-chloro-10-(2-dimethylaminoethyl)-oxydibenzo[b,f]thiepin as crystals, melting point 90°C to 91°C. Maleate as colorless needle, melting point 204°C to 204.5°C.

References

Merck Index 9997
DOT 19 (3) 155 (1983)
I.N. p. 1025
Umio, S., Uedo, I., Sato, Y. and Maeno, S.; US Patent 3,704,245; November 28, 1972

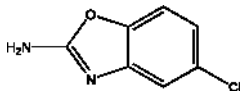
ZOXAZOLAMINE

Therapeutic Function: Muscle relaxant, Uricosuric

Chemical Name: 5-Chloro-2-benzoxazolamine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 61-80-3

Trade Name	Manufacturer	Country	Year Introduced
Flexin	McNeil	US	1956
Contrazole	Millot	France	-
Deflexol	Millot	France	-
Zoxine	Millot	France	-

Raw Materials

2-Amino-4-chlorophenol
Ferric chloride
Ammonium hydroxide
Ammonium thiocyanate
Hydrogen chloride

Manufacturing Process

To a solution of 106 g (0.74 mol) of 2-amino-4-chlorophenol in 500 ml of water containing 69 ml of concentrated hydrochloric acid (29.2 g, 0.8 mol) are added 60.8 g (0.8 mol) of ammonium thiocyanate. The solution is placed in an evaporating dish and heated on a steam bath for 5 hours. The solid which results is then removed from the concentrated solution by filtration, washed with a small amount of water and dried. The filtrate is placed in an evaporating dish and heated on a water bath for 2 hours. At the end of this time, the mixture is cooled, and the solid which precipitates out is removed by filtration. Both solid products are 5-chloro-2-hydroxyphenylthiourea melting at 157°C, and may be combined. The calculated N content for $C_7H_7ClN_2OS$ is 13.8; that found is 13.6.

To a solution of 10 g (0.05 mol) of 2-hydroxy-5-chlorophenylthiourea in 50 ml of methanol is added a solution of 11 g (0.04 mol) of ferric chloride hexahydrate in 50 ml of methanol. The initial purple-red color changes in a few minutes to amber. After stirring for one half hour, the solution is treated with 16.5 ml of 57% ammonium hydroxide solution (0.24 mol). A brown, flocculent precipitate of ferric sulfide appears. The mixture is then refluxed with stirring for one hour, cooled and centrifuged. The centrifugate is evaporated to dryness, and the residue is shaken with ether and water to separate the organic material from the ammonium chloride. The ether layer is extracted three times with 25 ml portions of 1 N hydrochloric acid. The acid solution is then poured into excess ammonium hydroxide, and the resulting solid collected, washed with water and dried. This gives a light tan solid melting at 183°C to 185°. The material is then dissolved in 25 ml of acetone and 50 ml of benzene are added. After treatment of the solution with activated charcoal, the light yellow solution is evaporated to 25 ml and cooled. The white crystals of 2-amino-5-chlorobenzoxazole which separate melt at 185°C to 186°C.

References

Merck Index 9998
I.N. p. 1025
Sam, J.; US Patent 2,780,633; February 5, 1957; assigned to McNeil Laboratories, Inc.

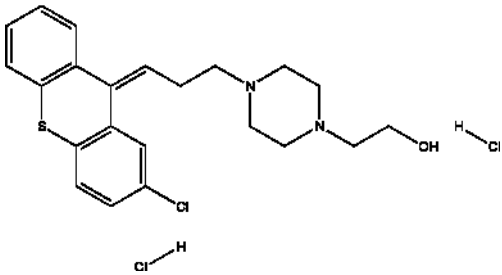
ZUCLOPENTHIXOL HYDROCHLORIDE

Therapeutic Function: Neuroleptic, Antipsychotic

Chemical Name: 4-(3-(2-Chlorothioxanthen-9-ylidene)propyl)-1-piperazineethanol dihydrochloride

Common Name: Zuclopenthixol hydrochloride; Clopixol; Cisordinol

Structural Formula:



Chemical Abstracts Registry No.: 58045-23-1

Trade Name	Manufacturer	Country	Year Introduced
Zuclopenthixol Hydrochloride	ZYF Pharm Chemical	-	-
Ciatyl	Bayer Vital	-	-
Cisordinol	Lundbeck	-	-
Cisordinol-Acufase	Duphar	-	-
Clopixol	Lundbeck	-	-
Sordinol	Lundbeck	-	-

Raw Materials

2-Chlorothiaxanthone
Triethylamine
Piperazine
Ethylene oxide
Allyl magnesium bromide
Thionyl chloride
Hydrochloric acid

Manufacturing Process

288.0 g of 2-chloro-9-allylthiaxanthenol-(9), melting at 77-78°C, are prepared by adding 2-chloro-thiaxanthone to an ether solution of allyl magnesium bromide followed by hydrolysis.

The 2-chloro-9-allylthiaxanthenol-(9) is dissolved in 2 L of anhydrous ether, whereafter 360.0 g triethylamine are added. While stirring and cooling, 150.0 g thionyl chloride dissolved in 500 ml ether are added gradually, allowing the temperature to rise to a maximum of -10°C. After completion of addition, the

ether solution is shaken 3 times with ice water, each time with 0.3 L, whereafter it is dried with potassium carbonate. Thereafter, the ether is evaporated in vacuum and the 2-chloro-9-(propene-3-ylidene-1)-thiaxanthene formed is obtained as a light yellow syrup.

2 methods of producing of 2-chloro-9-[3'-(N'-2-hydroxyethylpiperazino-N)propylidene]thiaxanthene from 2-chloro-9-(propene-3-ylidene-1) thiaxanthene:

1). 27.0 g of 2-chloro-9-(propene-3-ylidene-1)thiaxanthene, are mixed with 50.0 g anhydrous piperazine and 10 ml absolute ethanol and the mixture is heated for 12 h at 120°C under reflux. After cooling, the solidified reaction mixture is treated with 500 ml of water and the mixture extracted with ether. From the ether solution, the 2-chloro-9-(3'-N-piperazino)propylidene) thiaxanthene formed is extracted with dilute hydrochloric acid and precipitated as the base from the aqueous solution by rendering the solution alkaline. By extraction with ether, drying of the ether solution with potassium carbonate and evaporation of the ether, the free base 2-chloro-9-(3'-N-piperazino) propylidene)thiaxanthene is obtained as a colorless oil in a yield of 21.0 g.

35.0 g of the base 2-chloro-9-(3'-N-piperazino)propylidene)thiaxanthene are dissolved in 200 ml of methanol. 5.0 g ethylene oxide are added and the mixture is left standing at room temperature for 3 h. Thereafter, the reaction mixture is evaporated, dried and the 2-chloro-9-[3'-(N'-2-hydroxyethylpiperazino-N)propylidene]thiaxanthene is obtained.

2). 27.0 g of 2-chloro-9-(propene-3-ylidene-1)thiaxanthene, are mixed with 50.0 g anhydrous N-2-hydroxyethylpiperazine and 10 ml absolute ethanol and the mixture is heated for 12 h at 120°C under reflux. After cooling, the solidified reaction mixture is treated with 500 ml of water and the mixture extracted with chloroform. From the chloroform solution, the 2-chloro-9-[3'-(N'-2-hydroxyethylpiperazino-N)-propylidene]thiaxanthene formed is extracted with dilute hydrochloric acid and precipitated as the base from the aqueous solution by rendering the solution alkaline. By extraction with chloroform, drying of the organic solution with potassium carbonate and evaporation of the chloroform, the base 2-chloro-9-[3'-(N'-2-hydroxyethylpiperazino-N)propylidene]thiaxanthene is obtained as colorless syrup.

By dissolving the base in petrol and leaving the solution to stand the trans form crystallize out as a white crystalline substance, from the mother liquor from the trans base, the corresponding cis base can be obtained as a white crystalline substance.

In practice it is usually used as dihydrochloride.

References

Petersen P.V. et al.; US Patent No. 3,116,291; December 31, 1963; Assigned: Kefalas, A/S, Copenhagen-Valby, Denmark

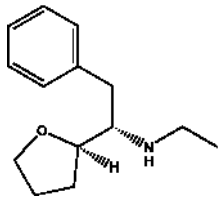
ZYLOFURAMINE

Therapeutic Function: Psycho-analeptic

Chemical Name: 2-Furanmethanamine, N-ethyltetrahydro-α-(phenylmethyl)-, (S-(R*,R*))-

Common Name: Zylofuramine

Structural Formula:



Chemical Abstracts Registry No.: 3563-92-6

Trade Name	Manufacturer	Country	Year Introduced
Zylofuramine	ZYF Pharm Chemical	-	-

Raw Materials

Furfurylbenzyl ketone
Nickel Raney
Sodium caused
N-Ethyl-α-benzylamine
Hydrochloric acid

Manufacturing Process

A mixture of furfurylbenzyl ketone and of N-ethyl-α-benzylamine in methanol was hydrogenated over Raney nickel at 150°C and at a pressure of 1500 p.s.i. The catalyst was removed by filtration and the solvent removed by vacuum distillation. The oily residue was taken up in ether, the ether solution washed with dilute hydrochloric acid and the aqueous layer separated. Addition of 35% sodium solution caused the separation of an oil which was taken up in ether. Removal of the ether by evaporation followed by distillation of the residue gave N-ethyl-α-benzyltetrahydrofurfurylamine, boillin point 101°C/0.07 mm.

References

Clarke R.L.; US Patent No. 3,194,818; July 13, 1965; Assigned: Sterling Drug Inc., New York, N.Y., a corporation of Delaware