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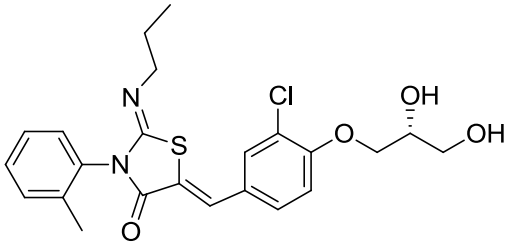
A process for the preparation of (2Z,5Z)-5-[3-chloro-4-[(2R)-2,3-dihydroxypropoxy]benzylidene] -3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one and its intermediate thereof

MSN Laboratories Private Limited; R&D Center; Srinivasan Thirumalai Rajan; Sajja Eswaraiah; Gade Srinivas Reddy; Challa Suresh

A process for the preparation of (2Z,5Z)-5-[3-chloro-4-[(2R)-2,3-dihydroxypropoxy]benzylidene]-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one and its intermediate thereof

Abstract:

Process for the preparation of (2Z,5Z)-5-[3-chloro-4-[(2R)-2,3-dihydroxypropoxy] benzylidene]-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one compound of formula-1, which is represented by the following structural formula:



Formula-1.

Background of the invention:

(2Z,5Z)-5-[3-chloro-4-[(2R)-2,3-dihydroxypropoxy]benzylidene]-3-(2-methylphenyl) -2-(propylimino)-1,3-thiazolidin-4-one compound of formula-1 is commonly known as Ponesimod, which was approved in US and Europe under the brand name of Ponvory for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults in 2021.

U.S patent No. USRE43728E (hereinafter described as US'728E) describes the process for the preparation of Ponesimod.

U.S patent No. US8263780B2 describes the process for the preparation of intermediate compound of Ponesimod.

U.S patent No. US9340518B2 describes the process for the preparation of Ponesimod and its intermediate compound.

However, there is always a need exist for alternative preparative routes, which for example involves fewer steps, use reagents that are less expensive and / or easier to handle, consumes smaller amounts of reagents, provide a higher yield of product, have smaller and/or more ecofriendly waste products, and/or provide a higher purity of the final compound of Formula-1. Hence the inventors of the present invention have developed an improved process for the preparation of Ponesimod and its intermediate compounds.

Brief description of the invention:

The first embodiment of the present invention provides a process for the preparation of Ponesimod of formula-1.

The second embodiment of the present invention provides a process for the preparation of compound of formula-11.

Brief description of the drawings:

Figure-1: Illustrates the powder X-Ray diffraction pattern of amorphous form of compound of formula-1.

Figure-2: Illustrates the powder X-Ray diffraction pattern of amorphous form of compound of formula-1 obtained according to the example-16.

Detailed description of the invention:

As used herein the term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; "ether solvents" such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, methyl t-butyl ether, diisopropyl ether, 1,2-dimethoxy ethane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), diglyme, dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; "polar solvents" such as water or mixtures thereof.

As used herein the present invention the term "suitable base" refers to inorganic bases like "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium

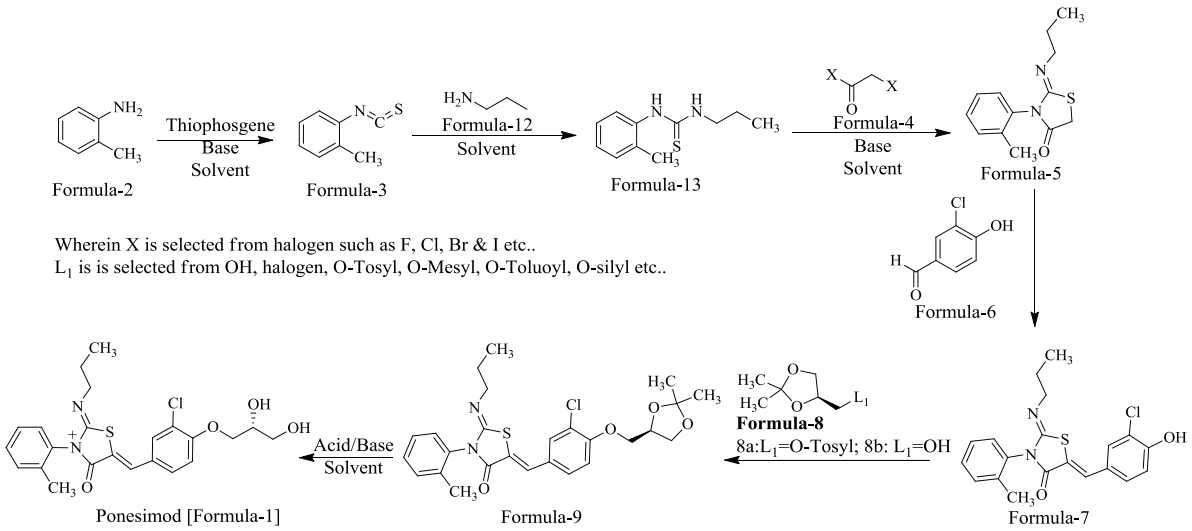
carbonate and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate and the like; “alkali metal hydroxides” such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride, lithium hydride and the like; ammonia such as liquor ammonia, ammonia gas, alcoholic ammonia and the like; and organic bases like dimethylamine, diethylamine, diisopropyl amine, diisopropylethylamine, diisobutylamine, triethylamine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), 2,6-lutidine, lithium diisopropylamide; “alkali metal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; alkali metal amides such as sodium amide, potassium amide, lithium amide and the like; organosilicon bases such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) or mixtures thereof.

As used herein the term “Protecting agent” used in the present invention is selected from but not limited to alkyl, cycloalkyl, arylalkyl, aryl, ethers, esters, cyclic ethers, cyclic esters, acetal, cyclic acetal, ketal, and cyclic ketal groups and the like that can be removed under either acidic or basic conditions so that the protecting group is removed and replaced with a hydrogen atom. Specific hydroxyl protecting groups include, but are not limited to, methyl, ethyl, acetate, ethylacetate, propionate, ethylene glycol, propylene glycol, 4-methoxybenzyl, benzyl, trityl, trimethylsilyl, tetrahydropyranyl, and benzoyl.

As used herein the term “silyl” used in the present invention refers to trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethyl-silyl (DPMS), t-butylmethoxyphenylsilyl (TBMPS),

The term "substantially pure" or “pure” means compound of formula-1 prepared by the process of the present invention is substantially free from the impurities. The compound of formula-1 obtained according to the present invention is substantially pure having a purity about >95% by HPLC, preferably about >97% by HPLC, more preferably about >99% by HPLC.

The first embodiment of the present publication is schematically represented below in Scheme-I:



Scheme-I

First embodiment of the present invention provides a process for the preparation of Ponesimod of formula-1 comprising:

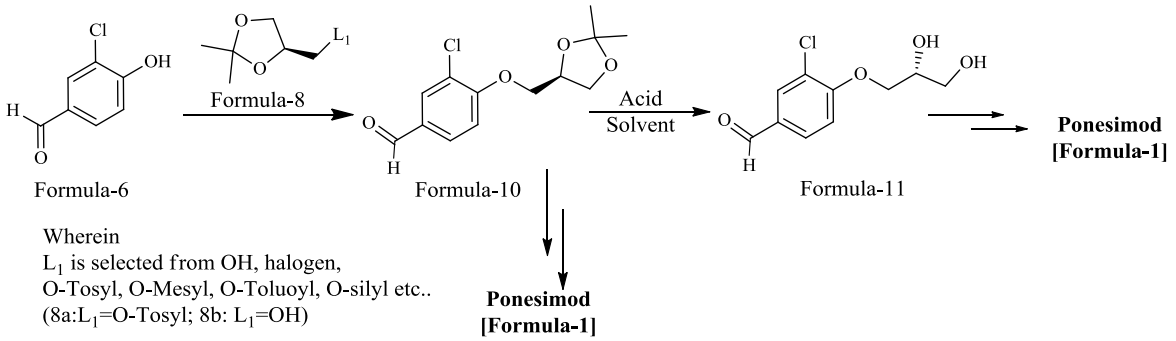
a) reacting the compound of formula-7 with compound of formula-8 to provide compound of formula-9,
b) deprotecting the compound of formula-9 to provide Ponesimod of formula-1.
c) optionally purifying the obtained Ponesimod in step-b).

In the first aspect of the first embodiment, reaction in step-a) is carried out in presence of reagent and in a solvent, weherein reagent is selected from but not limited to a base or azodicarboxylate such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) combination with triphenylphosphine; solvent selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents such as water and/or their mixtures thereof as described above, the base is selected from inorganic bases or organic bases as described herein above.

The second aspect of the first embodiment, deprotection in step-b) is carried out in presence of deprotecting agent which is selected from an acid or a base; wherein an acid such as hydrochloric acid, hydrobromic acid, hydrofluoric acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, trifluoroacetic acid, formic acid, substituted/unsubstituted alkyl/aryl sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, pyridinium p-toluene sulfonic acid, trifluromethane sulfonic acid

and "hydrogen fluoride (HF) sources" such as ammonium fluoride, tetrabutyl ammonium fluoride, pyridine-HF, Et_3N-3HF etc; metal catalysts in presence of hydrogen source and the like.

The second embodiment of the present publication is schematically represented below in Scheme-II:



Scheme-II

Second embodiment of the present invention provides a process for the preparation of compound of formula-11 comprising:

a) Reacting compound of formula-6 with the compound of formula-8 to provide formula-10,
b) deprotecting compound of formula-10 to provide formula-11.

In the first aspect of the second embodiment, reaction in step-a) and step-b) is carried out in presence of a solvent which is defined in first aspect of first embodiment.

In the second aspect of the second embodiment, the base in step-a) is selected from inorganic bases or organic bases as described herein above.

The third aspect of the second embodiment, the deprotecting agent used in step-b) is same as described in third aspect of first embodiment.

The fourth aspect of the second embodiment, compounds of formula-10 and formula-11 are further converted to Ponesimod by known processes such as US7435828B2, USRE43728E or any other literature.

Ponesimod obtained according to the present invention is having a purity of greater than about 98%, preferably greater than about 99%, more preferably greater than about 99.5% by HPLC.

Ponesimod intermediates obtained according to the present invention is having a

purity of greater than about 98%, preferably greater than about 99%, more preferably greater than about 99.5% by HPLC.

The third embodiment of the present invention provides pharmaceutical composition comprising Ponesimod and at least one pharmaceutically acceptable excipient. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Ponesimod prepared according to the present invention can be further micronized or milled in conventional techniques to get the desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball milling, roll milling and hammer milling, and jet milling. Milling or micronization may be performed before drying, or after the completion of drying of the product.

In another embodiment of the present invention provides a pharmaceutical composition comprising Ponesimod prepared according to the present invention and one or more pharmaceutically acceptable carriers for the treatment.

The best mode of carrying out the present invention was illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be considered as limitation of the scope of the invention.

Examples:

Example-1: Preparation of 1-propyl-3-(o-tolyl)thiourea of Formula-13

Aqueous potassium carbonate solution (386.3 g of Potassium carbonate in 1000 ml of water) was slowly added to the precooled the solution of o-Toluidine of formula-2 (100 g) in cyclohexane (1000 ml) at 15-20°C and stirred. Thiophosgene (139 ml) was added to the obtained mixture at 15-20°C and stirred the reaction mixture at the same temperature. Separated the organic layer from the reaction mixture and the aqueous layer was extracted with cyclohexane. Combined the organic layers and washed with aqueous potassium carbonate solution followed by water and by with aqueous sodium chloride solution. Distilled off solvent completely from the organic layer and co-distilled with cyclohexane to get residue. Cyclohexane (800 ml) was added to the obtained residue at the 25-30°C and cooled to 10-15°C. n-propyl amine of formula-12 (81.6 ml) was added slowly to above mixture at

the same temperature and stirred the reaction mixture at the same temperature. Filtered the solid, washed with cyclohexane and dried to get the title compound.

Yield: 164 g.

Example-2: Preparation of 2-[(Z)-(Propylimino)-3-o-tolyl-thiazolidin-4-one of formula-5

o-Toluidine of formula-2 (5 g) was added slowly to the solution of thiophosgene (7 ml) in water (25 ml) at 25-30°C and stirred the mixture at the same temperature. Ethyl acetate was added to above reaction mixture at the same temperature. Separated the organic layer from the mixture and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with aqueous sodium carbonate solution followed by water and by with aqueous sodium chloride solution. Distilled off solvent completely from the organic layer. Ethyl acetate was added to the above obtained compound at the 25-30°C and cooled to 15-20°C. n-Propyl amine of formula-12 (5 ml) was added to the above mixture at 15-20°C and stirred. Cooled the reaction mixture to 0-5°C. Dimethylaniline (14.8 ml) followed by bromoacetyl bromide of formula-4a (4.9 ml) were added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred at the same temperature. Distilled off solvent completely from the mixture to get title compound as residue.

Example-3: Preparation of 5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)(propy-limino]-3-(o-tolyl)-thiazolidin-4-one of Formula-7

N-Methylmorpholine (105.5 ml) was added to pre-cooled solution of compound of formula-13 (100 g) in Dichloromethane (500 ml) at -5to 0°C and stirred the reaction mixture at the same temperature. Bromoacetyl bromide of formula-4a (46.3 ml) was added slowly to above mixture at -5°C to 0°C and stirred the reaction mixture at the same temperature. Distilled off solvent and cooled the obtained compound to 25-30°C. Acetic acid (1000 ml) was added to the obtained compound at 25-30°C. 3-chloro-4-hydroxy benzaldehyde of formula-6 (56.7 g) and sodium acetate (78.7 g) were added to the mixture at 25-30°C and stirred the mixture at the same temperature. Heated the reaction mixture to 65-70°C and stirred at the same temperature. Cooled the reaction mixture to 15-20°C. Water was added to above reaction mixture at the same temperature and stirred it. Filtered the solid and washed with water. The obtained compound was slurried in the ethyl acetate and dried to get title compound.

Yield: 110 g.

Example-4: Purification of 5-(3-Chloro-4-hydroxy-benz-(Z)-ylidene)-2-[(Z)(propy-limino]-3-(o-tolyl)-thiazolidin-4-one of Formula-7

Compound of formula-7 (170 g) was added to isopropyl alcohol (850 ml) at 25-30°C and

stirred the mixture at the same temperature. Heated the reaction mixture to 75-80°C and stirred the mixture at the same temperature. Cooled the reaction mixture to 0-5°C and stirred. Filtered the solid and washed with isopropyl alcohol and dried to get title compound.

Yield: 149 g.

Example-5: Preparation of (2Z,5Z)-5-(3-Chloro-4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)benzylidene)-2-(propylimino)-3-(o-tolyl)thiazolidin-4-one of Formula-9

Mixture of compound of formula-7 (50 g) and (S)-(2,2-dimethyl-1,3-dioxolan-4-yl) methyl 4-methylbenzenesulfonate of formula-8a (55.5 g) were stirred at the 25-30°C. Potassium carbonate (178 g) and Dimethylsulfoxide (500 ml) were added to the above mixture at the same temperature. Heated the reaction mixture to 105-110°C and stirred it at the same temperature. Cooled the reaction mixture to 25-30°C. Water and ethyl acetate were added to above reaction mixture at the same temperature. Organic layer was separated from the mixture and it was washed with aqueous sodium chloride solution and followed by water. Distilled off solvent completely from the organic layer and co-distilled with n-heptane. n-Heptane was added to the above obtained compound at the 25-30°C and stirred. Filtered the obtained solid, washed with n-heptane and dried to get the title compound.

Yield: 58 g.

Example-6: Preparation of (2Z,5Z)-5-(3-Chloro-4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)benzylidene)-2-(propylimino)-3-(o-tolyl)thiazolidin-4-one of Formula-9

Diisopropyl azodicarboxylate (208.8 g) and triphenylphosphine (271.1 g) were added to the mixture of R-(2,2-dimethyl-1,3-dioxolan-4-yl) methanol of formula-8b (95.6 g), Compound of formula-7 (200 g) and toluene (300 ml) at 25-30°C. Heated the reaction mixture to 40-45°C and stirred. Cooled the reaction mixture to 25-30°C. Magnesium chloride was added to above mixture and heated the mixture to 45-50°C and stirred. Cooled the reaction mixture to 25-30°C. Filtered the unwanted solid and washed with toluene. The filtrate was washed with aqueous sodium hydroxide solution. Obtained organic layer was washed with aqueous sodium chloride solution. Distilled off solvent completely from the organic layer and co-distilled with n-heptane. The obtained compound was slurried in the mixture of ethyl acetate and n-heptane and dried to get title compound.

Yield: 152 g.

Example-7: Preparation of (2Z,5Z)-5-(3-Chloro-4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)benzylidene)-2-(propylimino)-3-(o-tolyl)thiazolidin-4-one of Formula-9

R-(2,2-dimethyl-1,3-dioxolan-4-yl) methanol of formula-8b (47.8 g), triphenylphosphine (135.5 g) were added to the mixture of ethyl acetate (1300 ml) and compound of formula-7

(100 g) at 25-30°C. Cooled the reaction mixture to 10-15°C and Diisopropyl azodicarboxylate (104.4 g) was slowly added to reaction mixture at the same temperature and stirred the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and filtered the solid and washed with ethyl acetate. Obtained filtrate washed with aqueous sodium carbonate solution and followed by water and then with aqueous sodium chloride solution and followed by water. Distilled off solvent completely from the organic layer and co-distilled with isopropyl alcohol. The obtained compound was slurried in the ethyl acetate and dried to get title compound.

Yield: 91 g.

Example-8: Preparation of (2Z,5Z)-5-(3-Chloro-4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)benzylidene)-2-(propylimino)-3-(o-tolyl)thiazolidin-4-one of Formula-9

Preparation of Compound of formula-9 from 25 grams of compound formula-7 is similar to the process described in example-7 using toluene as a solvent in place of ethyl acetate.

Yield: 21.5 g.

Example-9: Preparation of Ponesimod of Formula-1

Water (150 ml) and p-Toluenesulfonic acid (51.55 g) were added to the solution of compound of formula-9 (150 g) in methanol (750 ml) at 25-30°C and stirred. Heated the above reaction mixture to 75-80°C and stirred at the same temperature. Cooled the above reaction mixture to 25-30°C. Water and ethyl acetate were added to above reaction mixture at the same temperature. The organic layer was separated from the mixture. The aqueous layer was extracted with ethyl acetate and combined the organic layers. The obtained organic layer was washed with aqueous sodium bicarbonate solution, followed by aqueous sodium chloride solution and then with water. Distilled off solvent completely from the organic layer and co-distilled with methanol followed by n-heptane. Isopropyl alcohol and n-heptane were added to the obtained compound at 25-30°C and stirred at the same temperature. Heated the mixture to 65-70°C and cooled to 25-30°C. Filtered the obtained solid, washed with n-heptane and dried to get the title compound.

Yield: 110 g.

Example-10: Preparation of 3-Chloro-4-hydroxybenzaldehyde of Formula-6

Heated the mixture of chloroform (500 ml), 4-hydroxybenzaldehyde (50 g), N-chloro succinimide (61.6 g) to 50-55°C and stirred the reaction mixture. Distilled off solvent completely from the reaction mixture and cooled to 25-30°C. The obtained compound was recrystallized from water and dried to get pure title compound.

Yield: 52 g.

Example-11: Preparation of (R)-3-chloro-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy) benzaldehyde of Formula-10

Potassium carbonate (44 g) and (S)-(2,2-dimethyl-1,3-dioxolan-4-yl) methyl 4-methylbenzenesulfonate of formula-8a (20.11 g) were added to the mixture of compound of formula-6 (10 g) and dimethyl sulfoxide (100 ml) at 25-30°C and stirred the mixture at the same temperature. Heated the above reaction mixture to 80-85°C and stirred the mixture at the same temperature. Cooled the above reaction mixture to 25-30°C. Water and ethyl acetate were added to above reaction mixture at the same temperature. Separated the organic layer. The Aqueous layer was extracted with ethyl acetate and combined the organic layers. The organic layer was washed with sodium bicarbonate solution, water and followed by aqueous sodium chloride solution. Distilled off solvent completely from the organic layer to get the title compound. Yield: 16.0 g.

Example-12: Preparation of (R)-3-chloro-4-(2,3-dihydroxypropoxy)benzaldehyde of Formula-11

Water (27.2 ml) and p-Toluenesulfonic acid (10.2 g) were added to the solution of compound of formula-10 (16 g) in methanol (320 ml) at 25-30°C and stirred the mixture at the same temperature. Heated the above reaction mixture to 80-85°C and stirred. Cooled the above reaction mixture to 25-30°C. Ethyl acetate and water were added to above reaction mixture at the same temperature. The organic layer was separated from the mixture and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with water followed by sodium chloride solution. Distilled off solvent completely from the organic layer. Water and dichloromethane were added to the obtained compound. The organic layer was separated from the mixture. Distilled off solvent completely from the organic layer. The obtained compound was slurried in water and dried to get the title compound.

Yield: 11.0 g.

Example-13: Preparation of Ponesimod of Formula-1

Hydrochloric acid (180 ml) was added to pre-cooled mixture of Compound of formula-9 (90 g) and water (450 ml) at 10-15°C and stirred the reaction mixture at the same temperature. Toluene was added to the mixture at the same temperature. Separated the organic layer from the mixture and the aqueous layer washed with toluene. Neutralized the aqueous layer using aqueous sodium bicarbonate solution. Ethyl acetate was added to the obtained mixture and stirred. Organic layer was separated from the mixture and aqueous layers was extracted with ethyl acetate. Combined the organic layers and washed with water. Distilled off solvent

completely from the organic layer. The obtained compound was slurried in the mixture of tetrahydrofuran and n-heptane, filtered the solid and dried to get title compound.

Yield: 60 g.

Example-14: Preparation of Ponesimod of Formula-1

Compound of formula-5 (7.20 g) was added to the mixture of compound of formula-11 (5 g), ethanol (60 ml), sodium acetate (6.3 g) at 25-30°C. Heated the reaction mixture to 80-85°C and stirred. Partially distilled off the solvent from the reaction mixture. Stirred the reaction mixture at the same temperature and cooled the mixture to 30-35°C. Water was added to the mixture at 25-30°C and stirred. Cooled the mixture to 0-5°C and stirred at the same temperature. Filtered the solid, washed with ethanol and dried to get the title compound.

Yield: 6 g.

Example-15: Purification of Ponesimod of Formula-1

Dissolved Ponesimod (5 g) in ethanol (20 ml) at 70-75°C and cooled the mixture to 45-50°C, then further mixture cooled to 0-5°C and stirred at the same temperature. Heated the mixture to 45-50°C and stirred at the same temperature, further cooled to 0-5°C and stirred at the same temperature. Filtered the solid and washed with ethanol and dried to get the title compound.

Yield: 2.8 g.

Example-16: Preparation of amorphous form of Ponesimod of Formula-1

Ponesimod (55 g) was dissolved in dichloromethane (275 ml) at 25-30°C and filtered the solution to make it particle free and washed with dichloromethane. Distilled off solvent completely from the filtrate and dried to get the title compound.

Yield: 50 g. PXRD of the obtained compound is illustrated in figure-2.

Drawings

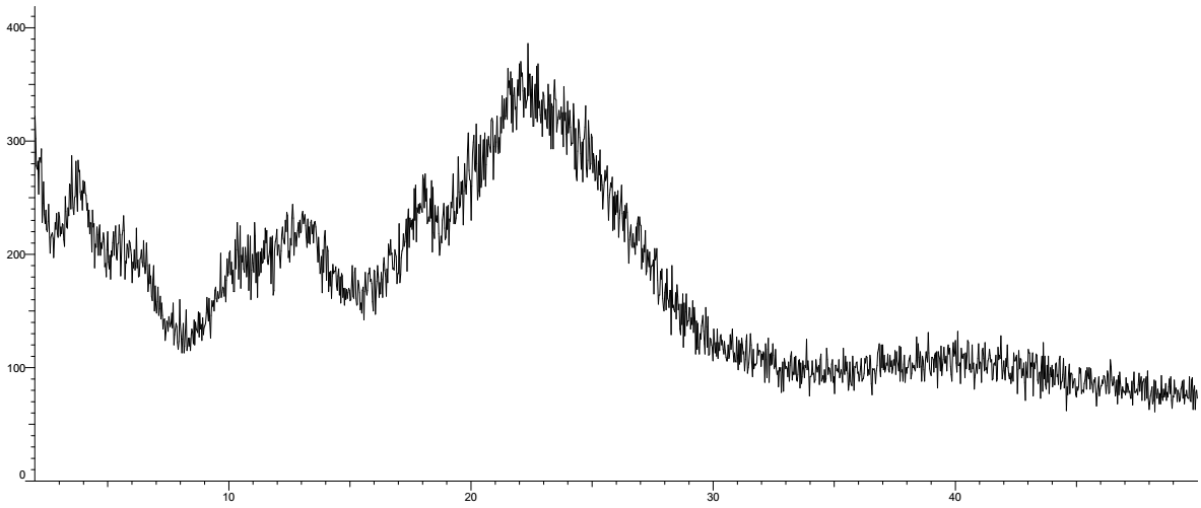


Figure-1

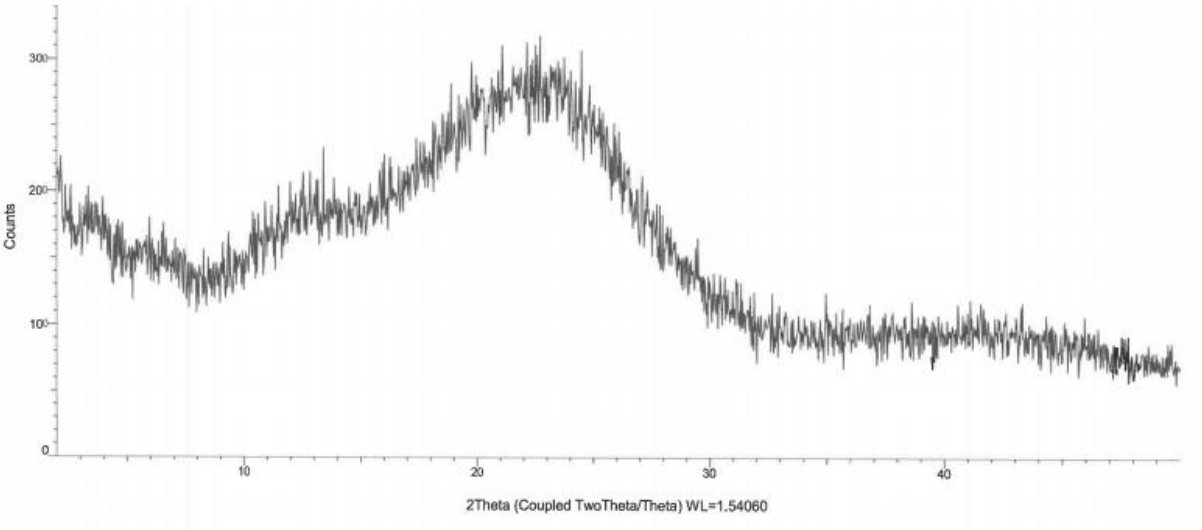


Figure-2

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