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(57) Abstract :
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FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

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The Patents Rules, 2003

COMPLETE SPECIFICATION

(see Section 10 and Rule 13)

TITLE

IMPROVED PROCESS FOR THE PREPARATION OF BILASTINE

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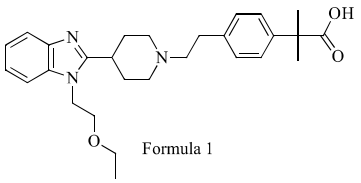
The following specification particularly describes the nature of this invention and the manner in which it is to be performed

FIELD OF THE INVENTION:

The present invention generally relates to the field of organic synthesis. More particularly, the present invention relates to a process for the preparation of 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoicacid represented by the following structural Formula 1.



Formula 1

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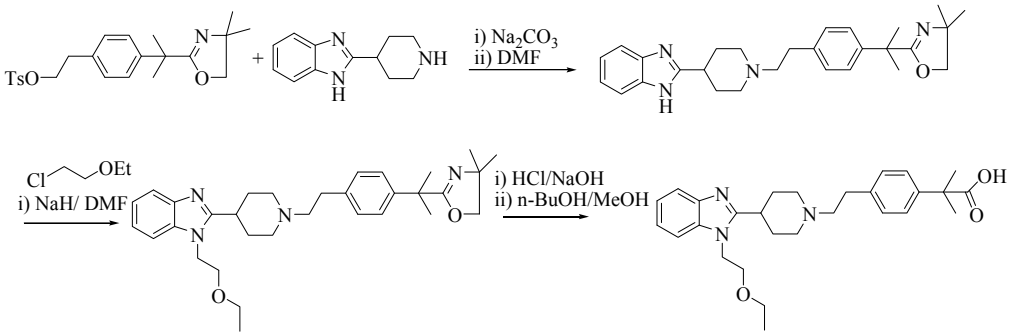
BACKGROUND:

2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoicacid, also known as Bilastine, is an antihistamine drug useful in the treatment of allergic rhinoconjunctivitis and urticaria (hives). It exerts its effect as a selective histamine HI receptor antagonist and has potency similar to cetirizine and is superior to Fexofenadine.

Various processes for preparation of Bilastine and its intermediates are known in the existing art.

For example, United States patent number 5,877,187 discloses 2-[4-(2-{4-[l-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid and its synthesis.

The process disclosed in the said patent is schematically represented in Scheme-A.



Scheme-A

This process involves the reaction of the benzimidazole intermediate with tosylated oxazole intermediate in presence of sodium carbonate followed by reaction of obtained intermediate compound with l-chloro-2-ethoxyethane to provide oxazole protected Bilastine. Cleavage of the said oxazole ring by treating it with 3N HCl gives Bilastine.

However, the above process has several disadvantages like formation of dimer impurity during the formation of intermediate compound i.e. 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole.

Further, the above process produces Bilastine in very low yields with number of by-products.

In view of all these disadvantages, there is a significant need to develop an improved process for the preparation of 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoicacid.

The present inventors overcome all the disadvantages associated with the prior art process by providing an improved process for the preparation of 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid which is able to produce highly pure Bilastine with better yields.

OBJECTS OF THE INVENTION:

The primary object of the present invention is to provide a simple and efficient preparation process of 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoicacid.

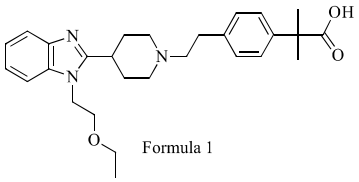
Another object of the present invention is to provide a process to prepare 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoicacidwith high yield and high quality.

Another object of the present invention is to provide a process of reducing the formation of impurities and by-products in the preparation of 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoicacid and its intermediates.

Yet another object of the present invention is to provide process for purification of Bilastine.

SUMMARY:

The present invention provides a process for preparing 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of Formula 1,



Formula 1

(herein after referred to as Bilastine) comprising the steps of:

a) N-alkylation of2-Piperidin-4-yl-1H-Benzoimidazolecompound of Formula 3 with Benzeneethanol,4-[1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-1-methylethyl]-,4-methylbenzenesulfonate compound of Formula2 in presence of a suitable base in

a suitable solvent to provide 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 4 and optionally purifying the obtained intermediate to provide pure compound of Formula 4,

b) reacting the compound of Formula 4 with 2-Ethoxyethyl 4-methylbenzenesulfonate compound of Formula 5 in presence of suitable base in a suitable solvent to provide 2-(2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 6,

c) cleaving the oxazoline protected Bilastine of compound of Formula 6 with suitable acid, suitable base and suitable solvent to provide Bilastine compound of Formula 1, and

d) purifying the crude Bilastine compound of Formula 1 with a suitable solvent to provide Pure Bilastine.

The present invention has the advantages of simple operation, use of mixture of alcohol and water as a reaction solvent for important intermediate (Formula 4), high purity, high yield and very less formation of impurities and by-products.

Other objectives, advantages and features of the present invention will become more apparent from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention deals with an improved process for preparation of 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of Formula 1, which provides intermediates and final drug substance having low level of impurities thereby increasing the yields and purity substantially.

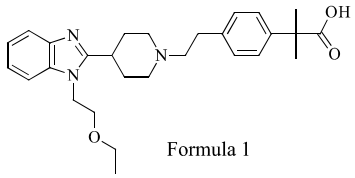
As used herein the term "suitable solvent" is selected from "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-

butyl ether, 1,2-dimethoxy ethane, tetrahydrofuran, 1,4-dioxane and the like; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n- butyl acetate, isobutyl acetate, tert-butyl acetate and the like; "polar-aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, 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 isobutyl ketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcohol solvents" such as methanol, ethanol, n-propanol, iso- propanol, n-butanol, iso-butanol, tert-butanol, ethane- 1,2-diol, propane- 1,2-diol and the like; "polar solvents" such as water; acetic acid, formicacid or mixture thereof.

As used herein the term "suitable base" is selected from inorganic bases selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; "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 hydrides such as sodium hyd ride, potassium hydride, lithium hydride and the like; alkali metal amides such as sodium amide, potassium amide, lithium amide and the like; ammonia, alkali metal and alkaline earth metal salts of acetic acid such as sodium acetate, potassium acetate, magnesium acetate, calcium acetate and the like; "organic bases" like dimemylamine, diethylamine, diisopropyl amine, diisopropylemylamine, di n-butylamine, diisobutylamine, triethylamine, tributylamine, tert- butyl amine, pyridine, 4-dimethylaminopyridine (DMAP), l,8-diazabicyclo[5.4.0]undec-7- ene (DBU), l,5-diazabicyclo[4.3.0]non-5-ene (DBN), N-methylmorpholine (NMM), l,4-diazabicyclo[2.2.2]octane(DABCO), 2,6-lutidine, lithium diisopropylamide; "organolithium bases" such as n-butyl lithium, "organosilicon bases" such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) or mixture thereof.

As used herein the term "suitable acid" is selected from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or mixture thereof.

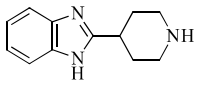
The first aspect of the present invention is to provide an improved process for the preparation of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid (hereinafter referred to as Bilastine) compound of Formula 1,



Formula 1

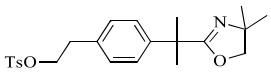
The process comprising the steps of;

a) N-alkylation of 2-Piperidin-4-yl-1H-Benzoimidazolecompound of Formula 3,



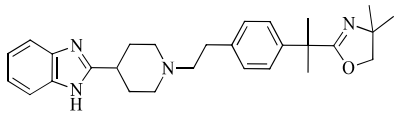
Formula 3

With Benzeneethanol, 4-[1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-1-methylethyl]-, 4-methylbenzenesulfonate compound of Formula 2,



Formula 2

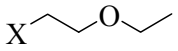
In presence of a suitable base and a suitable solvent to provide 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 4,



Formula 4

In this step, effluent is reduced by replacing DMF with methanol.

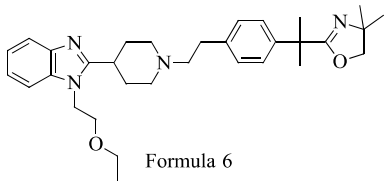
b) reacting the compound of Formula 4 with compound of Formula 5,



Formula 5

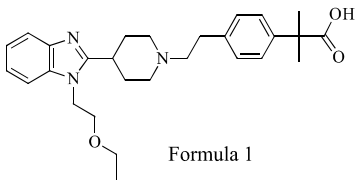
Where in X is a good leaving group in nucleophilic substitution reactions such as Cl, Br, I, R_4SO_2, R_2SO_3 where R_4 and R_2 is a methyl, phenyl etc.

In presence of a suitable base in a suitable solvent to provide 2-(2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 6,



Formula 6

c) cleaving the oxazoline protected Bilastine of compound of Formula 6 with suitable acid and suitable base and suitable solvent to provide Bilastine compound of Formula 1



Formula 1

, and

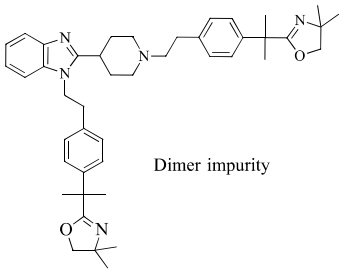
d) Purifying the crude Bilastine compound of Formula 1 with a suitable solvent to provide Pure Bilastine compound of Formula 1.

Wherein, in steps a) to c), the suitable base is selected from hydroxides, alkoxides, carbonates and bicarbonates of alkali metals or mixture thereof.

In step c), the suitable acid is selected from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and mixture thereof.

In steps a) to d), the suitable solvent is selected from chloro solvents, ketone solvents, ether solvents, ester solvents, hydrocarbon solvents, polar solvents, polar-aprotic solvents, nitrile solvents, alcohol solvents, acetic acid, formic acid or mixture thereof.

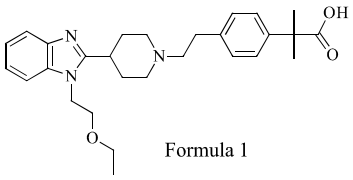
In one embodiment of the present invention, the compound of Formula 4 is optionally purified with a solvent selected from alkyl ester (e.g. ethyl acetate, methyl acetate and propyl acetate), water or mixture thereof to provide pure compound of Formula 4, with reduced level of dimer impurity.



Dimer impurity

In an embodiment, a mixture of alcohol and water (preferably methanol and water) is used as reaction solvent in the production of 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 4 (in step a).

The preferred embodiment of the present invention provides an improved process for the preparation of Bilastine compound of Formula 1,



Formula 1

Comprising the steps of:

a) N-alkylation ofBenzene ethanol, 4-[1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-1-methylethyl]-, 4-methylbenzenesulfonate compound of Formula 2 with 2-Piperidin-4-yl-1H-Benzoimidazole compound of Formula 3 in presence of sodium carbonate in methanol and water mixture provides 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole

compound of Formula 4 and purifying the compound of Formula 4 with ethyl acetate and water mixture to provide pure compound of Formula 4,

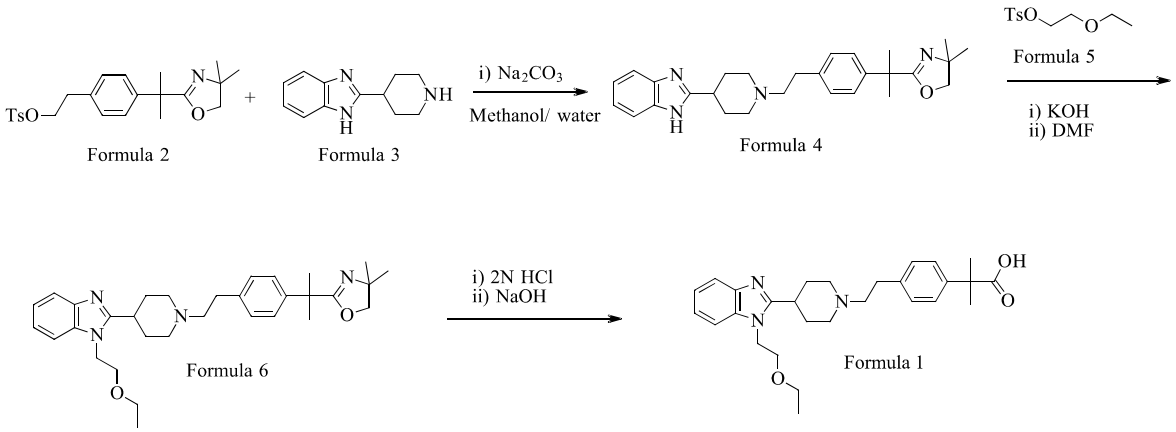
b) reacting the compound of Formula 4 with 2-Ethoxyethyl 4-methylbenzenesulfonate compound of Formula 5 in presence of potassium hydroxide in DMF provides 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 6,

c) cleaving the compound of Formula 6 with hydrochloric acid and sodium hydroxide provides Bilastine compound of Formula 1, and

d) Purifying the crude Bilastine compound of Formula 1 using n-Butanol and DM water provides the pure Bilastine.

In one preferred embodiment, the present invention provides pure Bilastine with a purity of about 99.89% w/w, as determined by HPLC.

The present invention is schematically represented below in Scheme-B.



Scheme-B

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

The Bilastine obtained according to the present invention is free flowing and non-Solvated Solid. Hence, it is well suited for pharmaceutical applications.

The following examples are provided for the purpose of giving the man of the art a sufficiently clear and complete explanation of the present invention, but must not be deemed to be limitations on the essential aspects of the object of the invention, Such as those indicated in the foregoing paragraphs hereof.

Examples:

Example-l: Preparation of 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole (Formula 4)

Benzeneethanol,4-[1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-1-methylethyl]-, 4-methylbenzenesulfonate compound of Formula 2 (50.0 gm),2-Piperidin-4-yl-1H-Benzoimidazole compound of Formula 3 (26.6 g) and sodium carbonate (15.3 g) were added to a methanol (135.0 mL) and water (15.0 mL) mixture at 25-30°C. Heated the reaction mixture temperature to 65-70°C and stirred for 16 hours at the same temperature. Cooled the reaction mixture to 25-35°C and quenched with DM water (225.0 mL) at 25-35°C and stirred for 2 hours at the same temperature. Filtered the solid, washed with water and followed by purification in ethyl acetate (225.0 mL) and water (25.0 mL) mixture at 70-75°C. Filtered the solid, washed with ethyl acetate and dried the material to get the title compound.

Yield: 40.5 gm.

Example-2: Preparation of 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole (Formula 6)

Sodium hydride in 60% mineral oil (1.05 g) was added to the mixture of 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 4 (10.0 g) and DMF (60.0 mL) at 25-35°C. Stirred the reaction mixture for 2 hrs at 25-35°C. Added slowly 2-chloroethylethyl ether compound of Formula 5 (3.66 g) at 25-35°C. Heated the reaction mass temperature to 80-85°C.Stirred the reaction mixture at 80-85°C for 16 hours. Cooled the reaction mass temperature to 0-5°C and quenched the reaction mixture with DM water (100.0 mL) at 0-5°C stirred for 1 hour at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound.

Yield: 9.8 g.

Example-3: Preparation of 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole (Formula 6)

Potassium hydroxide (7.51 g) was added to the mixture of 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 4 (30.0 g) and DMF (120.0 mL) at 25-35°C. Stirred the reaction mixture for 1 hour at 25-35°C. Added slowly 2-Ethoxyethyl 4-methylbenzenesulfonate compound of Formula 5 (19.5 g) at 25-35°C. Stirred the reaction mixture at 25-35°C for 18 hours. Quenched the reaction mixture with DM water (120.0 mL) at 25-35°C stirred for 2 hours at the same temperature. Filtered the solid, washed with water and to get the title compound.

Yield: 33.6 gm.

Example-4: Preparation of Bilastine (Formula1)

Aqueous 2NHCl solution (120.0 mL) was added to 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 6 (30.0 g)at 25-35°C.Heated the reaction mixture to 80-85°C and stirred for 1 hour at the same temperature. Cooled to 25-35°C and adjusted the pH with 50% aqueous sodium hydroxide and extracted the compound in to n-butanol (150.0 mL). Separated the n-butanol layer and treated with aqueous sodium hydroxide solution (120.0 mL). Heated the reaction mixture to reflux temperature and stirred for 3 hours at the same temperature. Cooled the reaction mass temperature to 25-35°C. Separated the organic layer adjusted the pH to 6.5 to 7.0 with dilute HCl solution. Separated the organic layer and distilled and cooled to 25-35°C.Filtered the solid and washed with isopropylalcohol (30.0 mL) and dried the material to get the title compound.

Yield: 22.9gm.

HPLC Purity: 99.79%

Bilastine crude compound was purified by slurry from solvents like DMF, n-Butanol, a mixture of n-Butanol, DM water and a mixture of DMF, alcohol.

Example-5: Purification of Bilastine (Formula 1)

Crude Bilastine compound of Formula1 (17.0 g) was dissolved in n-Butanol (153.0 mL) and DM water (17.0 mL) at 25-35°C. Heated the reaction mixture to 55-65°C stirred for 10 min at the same temperature. Filtered the reaction mass through 0.45 micron filtration setup. Distilled the filtrate up to 5.0 v, stirred the resulting slurry for 2 hours at 25-30°C. Filtered the solid, washed with isopropylalcohol (17.0 mL) and dried the material to get the title compound.

Yield: 16.3 g

HPLC Purity: 99.89%

Example-6: Purification of Bilastine (Formula 1)

Crude Bilastine compound of Formula 1(5.0 g) was added to IPA (30.0 mL) and DMF (2.5 mL) at 25-35°C. Heated the reaction mixture to reflux temperature and stirred for 1 hour at the same temperature. Cooled to 25-35°C and stirred for 1 hour at the same temperature. Filtered the solid, washed with IPA (5.0 mL) and dried the material to get the title compound.

Yield: 4.8 g

HPLC purity: 99.63%

Example-7: Purification of Bilastine (Formula1)

Crude Bilastine compound of Formula1 (5.0 g) was added to methanol (30.0 mL) and DMF (2.5 mL) at 25-35°C. Heated the reaction mixture to reflux temperature and stirred for 1 hour at the same temperature. Cooled to 25-35°C and stirred for 1 hour at the same temperature. Filtered the solid, washed with methanol (5.0 mL) and dried the material to get the title compound.

Yield: 4.3 g

HPLC Purity: 99.65%

Example-8: Purification of Bilastine (Formula1)

Crude Bilastine compound of Formula1 (5.0 g) was added to n-butanol (30.0 mL) and DMF (2.5 mL) at 25-35°C. Heated the reaction mixture to reflux temperature and stirred for 1 hr at the same temperature. Cooled to 25-35°C and stirred for 1 hour at the same temperature. Filtered the solid, washed with n-butanol (5.0 mL) and dried the material to get the title compound.

Yield: 4.4 g

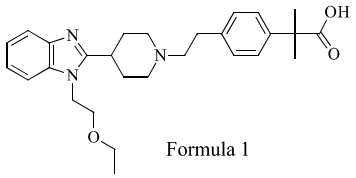
HPLC Purity: 99.66%

The advantages of present invention including, but not limited to, are: simple, cost effective, eco-friendly, amenable for scale up, less formation of dimer impurity during the production of 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 4 and the additional purification of Formula 4 has controlled the dimer impurity, less formation of process impurities and degradation impurities during the production of 2-(2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 6 and Bilastine compound of Formula 1, and high yield & high quality in the production of Bilastine and its intermediate compounds(Formula 4 and Formula 6).

While the foregoing written description of the invention enables one of ordinary skill to make and use what is considered presently to be the best mode thereof, those of ordinary skill will understand and appreciate the existence of variations, combinations, and equivalents of the specific embodiment, method, and examples herein. The invention should therefore not be limited by the above described embodiment, method, and examples, but by all embodiments and methods within the scope and spirit of the invention as claimed.

We Claim:

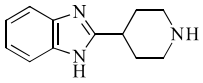
1. A process for preparing 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of Formula 1



Formula 1

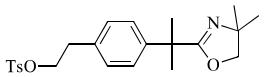
, the process comprising the steps of:

a) N-alkylation of 2-Piperidin-4-yl-1H-Benzoimidazolecompound of Formula 3,



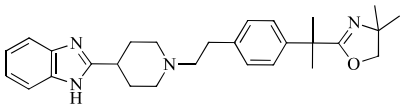
Formula 3

With Benzene ethanol, 4-[1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-1-methylethyl]-, 4-methylbenzenesulfonate compound of Formula 2,



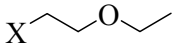
Formula 2

In presence of a suitable base in a suitable solvent to provide 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 4,



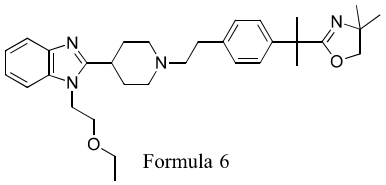
Formula 4

b) reacting the compound of Formula 4 with compound of Formula 5,



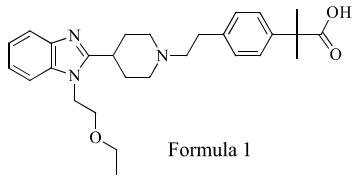
Formula 5

In presence of a suitable base in a suitable solvent to obtain2-(2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 6,



Formula 6

c) cleaving the oxazoline protected compound of Formula 6 with a suitable acid, suitable base and suitable solvent to provide Bilastine compound of Formula 1,



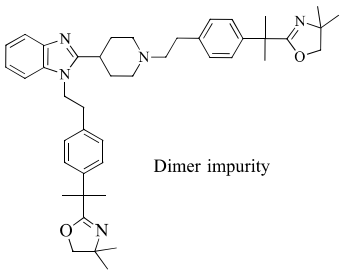
Formula 1

, and

d) purifying the Bilastine compound of Formula 1 with a suitable solvent to provide Pure Bilastine compound of Formula 1.

Where in step b), X is a good leaving group selected from Cl, Br, I, R_4SO_2, or R_2SO_3 where R_4 and R_2 is methyl or phenyl.

2. The process as claimed in claim 1, comprising purifying the compound of Formula 4 with a suitable solvent or mixture of solvents to provide pure compound of Formula 4, with less formation of dimer impurity.



Dimer impurity

3. The process as claimed in claim 1, wherein the suitable base of steps a) to c) is selected from hydroxides, alkoxides, carbonates and bicarbonates of alkali metals or mixture thereof.

4. The process as claimed in claim 1, wherein the suitable solvent of steps a) to d) is selected from chloro solvents, ketone solvents, ether solvents, ester solvents, hydrocarbon solvents, polar solvents, polar- aprotic solvents, nitrile solvents, alcohol

solvents, acetic acid, formic acid or mixture thereof.

5. The process as claimed in claim 1, wherein the suitable solvent of step a) is a mixture of alcohol selected from methanol, ethanol, isopropyl alcohol and n-Butanol and water.

6. The process as claimed in claim 1, wherein the suitable solvent of step a) is a mixture of methanol and water.

7. The process as claimed in claim 1, wherein the suitable acid of step c) is hydrochloric acid.

8. The process as claimed in claim 1, wherein the suitable solvent of step d) is selected from methanol, DMF, IPA, n-Butanol, DM water or mixture thereof.

9. The process as claimed in claim 2, wherein the suitable solvent is selected from ethyl acetate, methyl acetate, propyl acetate, water or mixture thereof.

10. The process as claimed in claim 2, wherein the suitable solvent mixture is ethyl acetate and water.

Dated this the 10th day of September 2021

ELIZABETH PUTHRAN
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ADVOCATE / AGENTS FOR THE APPLICANTS

ABSTRACT:

IMPROVED PROCESS FOR THE PREPARATION OF BILASTINE

The present invention relates to a new, improved process for the preparation of 2-[4-(2-{4-[l-(2-ethoxyethyl)-lH-benzimidazol-2-yl]-l-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid (Formula 1), that comprises the N-alkylation of 2-Piperidin-4-yl-1H-Benzoimidazole with Benzeneethanol,4-[1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-1-methylethyl]-,4-methylbenzenesulfonate in suitable solvent system to provide 2-(2-(4-(2-(4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound (Formula 4) with reduced formation of dimer impurity. Further, the compound of Formula 4 is reacted with2-Ethoxyethyl 4-methylbenzenesulfonate compound of Formula 5 in presence of suitable base in a suitable solvent to provide 2-(2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl) piperidin-1-yl) ethyl) phenyl) propan-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole compound of Formula 6, and cleavage of the oxazoline protected Bilastine of compound of Formula 6 with suitable acid, suitable base and suitable solvent provides Bilastine compound of Formula 1.