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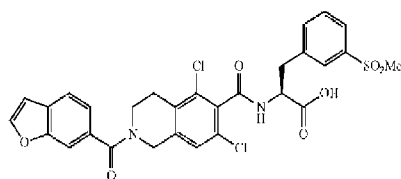
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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF LIFITEGRAST OR SALTS THEREOF

(57) Abstract: Disclosed herein is an improved process for the synthesis of lifitegrast or salts thereof with high yields and purity and its use in the therapy.



Lifitegrast (I)



“AN IMPROVED PROCESS FOR THE PREPARATION OF LIFITEGRAST OR SALTS THEREOF”

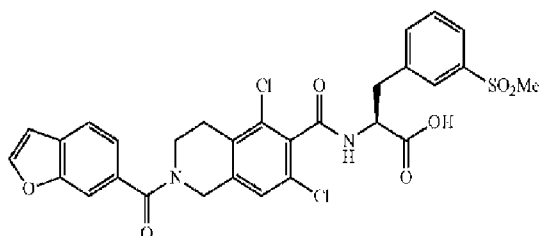
TECHNICAL FILED

The present invention relates to a novel process for synthesis of lifitegrast or salts thereof.

BACKGROUND OF THE INVENTION

Dry eye disease (DED) is a multifactorial disorder of the ocular surface characterized by symptoms of discomfort, decreased tear quality, and chronic inflammation that affects an estimated 20 million patients in the US alone. DED is associated with localized inflammation of the ocular surface and periocular tissues leading to homing and activation of T cells, cytokine release, and development of hyperosmolar tears. This inflammatory milieu results in symptoms of eye dryness and discomfort.

Lifitegrast (trade name Xiidra) is an FDA approved drug indicated for the treatment of both signs and symptoms of dry eye. It is an ophthalmic solution applied in the form of eye drops two times a day. Lifitegrast, the compound of Formula I:



has been found to be an effective inhibitor of Lymphocyte Function-Associated Antigen-1 (LFA-1) interactions with the family of intercellular adhesion molecules (I CAM), and has desirable pharmacokinetic properties, including rapid systemic clearance. Lifitegrast inhibits T cell-mediated inflammation by blocking the binding of two important cell surface proteins (lymphocyte function-associated antigen 1 and intercellular adhesion molecule 1), thus lessening overall inflammatory responses.

Most drugs administered to the ocular surface are rapidly cleared from the tear film within the first 30–60 minutes following topical administration due to the normal tear turnover. Lifitegrast has excellent aqueous solubility (>100 mg/mL). The high solubility allows a relatively large concentration to be administered into the tear film and theoretically allows significant residual concentration despite the normal tear turnover.

The compound was first disclosed in the US 8084047 B2 patent. Different processes for preparing lifitegrast are disclosed in US8080562 B2, US8378105 B2, US8927574 B2, US9353088 B2, US9085553 B2, US8879935 B2 and US2017/0029410. Improved forms, including crystalline forms, and their uses in treatment of disorders mediated by the interaction of LFA-1 and ICAM are described in US 9,353,088 B2.

Thus, there is a pressing need in the art for new low-cost and high-yield processes for the preparation of lifitegrast suitable for industrial scale.

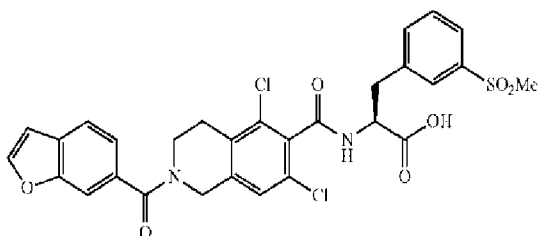
OBJECTS OF THE INVENTION

One object of the present invention is to provide an improved process for preparing lifitegrast of Formula (I) or salts thereof, which is simple, economical and suitable for industrial scale up.

Another object of the present invention is to provide lifitegrast of Formula (I) or salts thereof with high purity without subjecting to further purification.

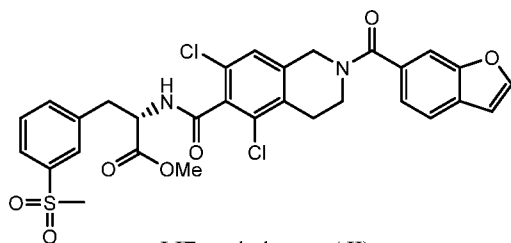
SUMMARY OF THE INVENTION

The present invention discloses an efficient process for the manufacture of enantiomerically pure lifitegrast of Formula (I) or salts thereof, which comprises;



Lifitegrast (I)

(a) hydrolysing LIF methyl ester (II)

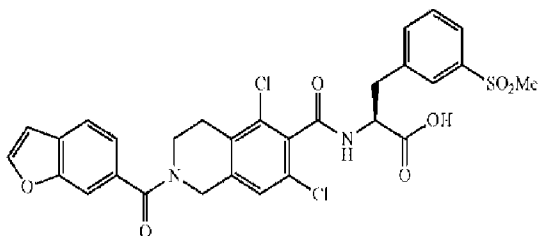


LIF methyl ester (II)

with a suitable base in one or more protic solvent(s); and

(b) isolating Lifitegrast of Formula I, or a salt thereof, with an enantiomeric excess greater than about 95%.

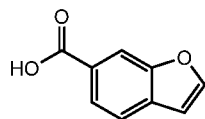
Accordingly, in an aspect of the present invention, there is provided a process for preparing lifitegrast of Formula (I) or a salt thereof,



Lifitegrast (I)

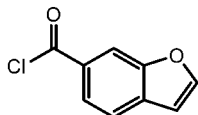
comprising steps of:

a) treating benzofuran-6-carboxylic acid of Formula (VI)



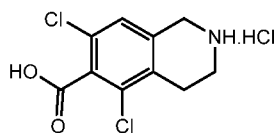
benzofuran-6-carboxylic acid (VI)

with a suitable chlorinating agent, to yield benzofuran-6-carboxylic chloride of Formula (VII)



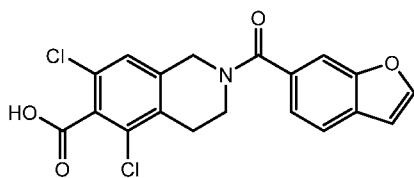
benzofuran-6-carboxylic chloride (VII)

and further condensing with 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (V) or a salt thereof



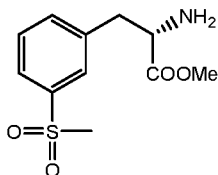
5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid hydrochloride (V)

to yield 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (III);



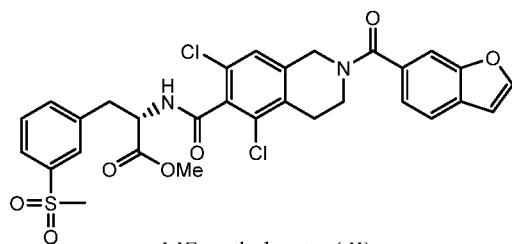
2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (III)

b) coupling the 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (III) with methyl (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoate of Formula (IV)



methyl (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoate (IV)

in the presence of suitable condensing agent to yield LIF methyl ester of Formula (II);



LIF methyl ester (II)

and

c) hydrolysing the LIF methyl ester of Formula (II) with a suitable base in one or more protic solvent to yield lifitegrast (I) or a salt thereof.

In another aspect, the present invention provides a safe, high-yielding, high-purity and industrially-viable method than any method known in the art.

The lifitegrast formed by the process described above may be combined with a suitable carrier to make a pharmaceutical composition. Such compositions may be used to treat inflammatory eye disorder. According to another aspect of the present invention, there is provided a pharmaceutical composition comprising lifitegrast prepared by the process described above together with one or more pharmaceutically-acceptable excipients.

According to another aspect of the present invention, there is provided lifitegrast prepared by the process described above for use in medicine. Suitably, the lifitegrast is for use in treating inflammatory eye disorder.

According to another aspect of the present invention, there is provided the use of lifitegrast prepared by the process described above in the manufacture of a medicament for treating inflammatory eye disorder.

According to another aspect of the present invention, there is provided a method of treating inflammatory eye disorder in patients comprising administering to a patient

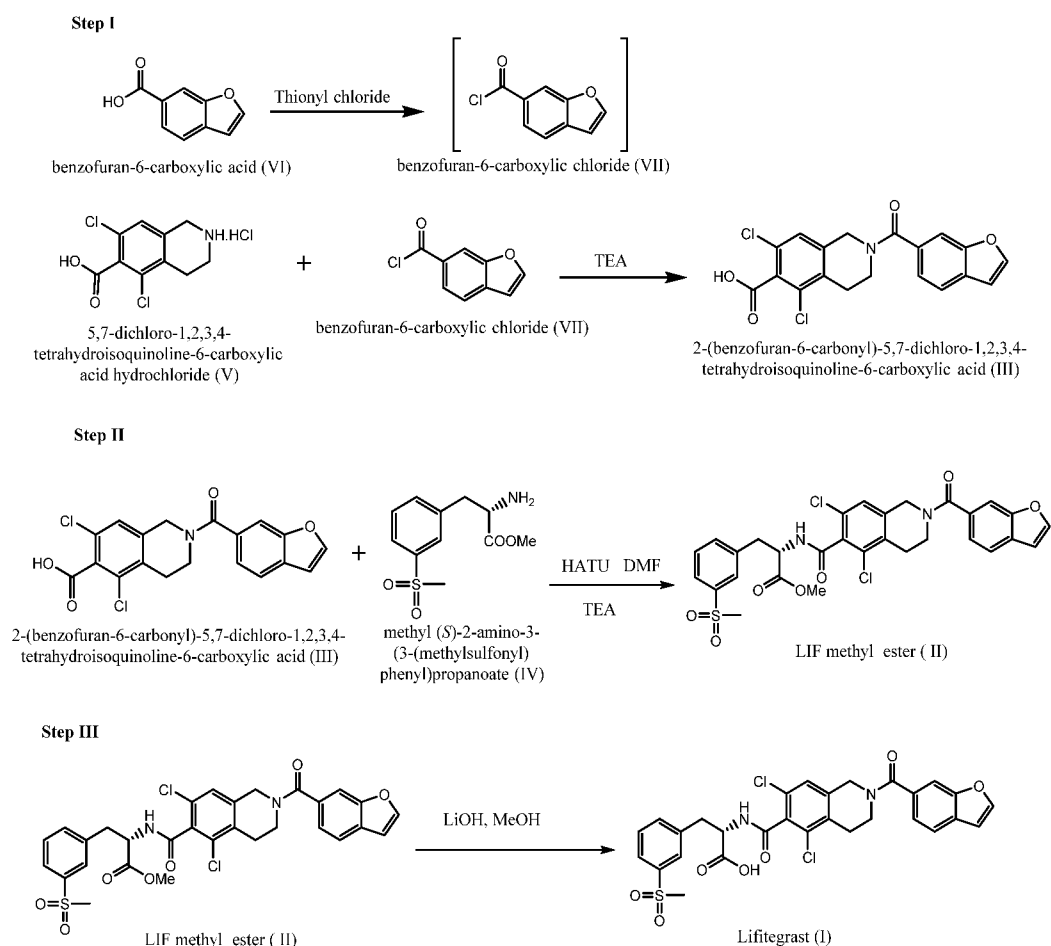
in need thereof an effective amount of lifitegrast prepared by the process described above.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be fully understood and appreciated.

The process according to the present invention will now be described in more detail herein below.

In a preferred embodiment, the process for the preparation of lifitegrast according to the present invention is depicted in the reaction scheme below.



Accordingly, in an embodiment, the present invention provides a process for the synthesis of lifitegrast (I) or a salt thereof, which comprises the following process steps.

In the first step, benzofuran-6-carboxylic acid of Formula (VI) is treated with a suitable chlorinating agent, to yield benzofuran-6-carboxylic chloride of Formula (VII), which is further condensed with 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (V) or a salt thereof to yield 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (III).

Suitable chlorinating agents for the above reaction are selected from, for example, thionyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, phosgene and oxalyl chloride. The chlorination is performed in a manner known to those skilled in the art of organic synthesis. In general it is preferred to stir the benzofuran-6-carboxylic acid of Formula (VI) with the chlorinating agent, which will either be used neat or in solution with a suitable aprotic solvent such as, for example, toluene, methylenechloride (MDC), acetonitrile, tetrahydrofuran, diglyme, dimethylformamide (DMF) or dioxane or the like and the mixture thereof. It is preferred to perform the chlorination by stirring with a suitable solvent, any excess of which can later be conveniently removed by evaporation. More preferably the chlorination is performed in the presence of MDC. Optionally catalytic amount of DMF may be added to enhance the rate of the reaction.

Typically, the reaction mixture is preferably maintained at a temperature of about 0° C to about 80° C, preferably about 10° C to about 50° C, and most preferably about 20° C to about 40° C, preferably for about 1 hour to about 20 hours, more preferably about 2 hours to about 10 hours, and most preferably about 2 hours to about 7 hours.

In an embodiment, the process is carried out without isolating the intermediate benzofuran-6-carboxylic chloride of Formula (VII). In the context of the present invention, the term “without isolation” means that the product being referred to as not being isolated is not isolated as a solid, for example it is not isolated from the reaction mass and dried to form a solid. Thus, “without isolation” may mean that the product remains in solution and is then used directly in the next synthetic step, or it may mean that solvent is substantially removed from a solution of the product such that the product is present as a residue, but not as a solid.

As most chlorinating agents produce hydrochloric acid, it is essential to first remove any remaining chlorinating agent, as this would react with 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (V). If a highly volatile chlorinating agent, such as thionyl chloride, is used neat, then it may be removed by evaporation to leave the benzofuran-6-carboxylic chloride of Formula (VII) as a solid. If the chlorination is done in a solvent, then it is preferable to employ a solvent that is high boiling, so that chlorinating agent may be removed by evaporation, leaving the acid chloride dissolved in the solvent. In any event, the benzofuran-6-carboxylic chloride of Formula (VII) is to be maintained under anhydrous conditions.

In an embodiment, benzofuran-6-carboxylic chloride of Formula (VII) and 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (V) or a salt thereof are reacted by dissolution in a suitable anhydrous solvent such as, for example acetonitrile, tetrahydrofuran, diglyme, dimethylformamide, dioxane, methylene chloride, or toluene.

Optionally a base, either organic or inorganic, such as triethylamine diisopropylethylamine, potassium phosphate, potassium hydrogen phosphate, sodium carbonate, sodium hydroxide, potassium hydroxide or the like, may be added to the reaction mixture as an acid scavenger.

The reaction rate may be increased by heating up to the boiling point of the solvent. The reaction is carried out at a temperature of about 0°C to about 150°C, preferably about 20°C to about 100°C, more preferably about 25°C to about 50°C; preferably, for about an hour to about 40 hours, more preferably about 2 hours to about 30 hours, most preferably about 2 hours to about 25 hours.

2-(benzofuran-6-carbonyl) -5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (III) thus obtained may be isolated by any method known in the art.

In step II, the coupling reaction of the 2-(benzofuran-6-carbonyl) -5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (III) with methyl (S)-2-amino-3-(3-(methylsulfonyl) phenyl) propanoate of Formula (IV) is carried out in the presence of suitable coupling agent to yield LIF methyl ester of Formula (II).

In an embodiment, suitable coupling agent is selected from one or more of but not limited to for e.g. DCC or other dialkyl carbodiimides, 1,1'-carbonyldiimidazole (CDI), 1,2-oxazolinium compounds, e.g. 2-ethyl-5-phenyl-1,2-oxazolium-3'-sulfonate and 2-tert-butyl-5-methylisoxazolium perchlorate, or a suitable acylamino compound, e.g. 2-ethoxy-1-ethoxy-carbonyl-1,2-dihydroquinoline, or activated phosphoric acid derivatives, bis(2-oxo-3-oxazolidinyl)phosphinic acid chloride or 1-benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluorophosphate, phenylsilane, benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (BOP), 1-hydroxy benzotriazole hydrate (HOBt), PyBOP (Analog of the BOP), n-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC HCl), 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), 4-

Dimethylaminopyridine (DMAP) and the like. A particularly suitable coupling reagent for use in the above process according to the present invention is HATU.

The reaction is preferably conducted in the presence of a base. The reaction is preferably conducted in the presence of an organic solvent.

A suitable base either organic or inorganic, for use in a process according to the present invention can be selected from the group comprising of such as triethylamine, diisopropylethylamine, potassium phosphate, potassium hydrogen phosphate, sodium carbonate, sodium hydroxide, potassium hydroxide and the like. A particularly suitable base for use in the above process according to the present invention is triethylamine.

A suitable organic solvent for use in a process according to the present invention can be selected from the group comprising of dimethylformamide, dimethylacetamide, dimethyl sulfoxide, N-methyl pyrrolidone, sulfolane, diglyme; 1,4-dioxane, tetrahydrofuran, acetonitrile, acetone and other inert organic solvents known in the art. A particularly suitable inert organic solvent for use in the above process according to the present invention is dimethylformamide.

The coupling reaction is preferably carried out at a temperature of about 0°C to about the boiling point of the reaction mass, preferably about 0°C to about 80°C, more preferably about 10°C to about 50°C; for about an hour to about 20 hours, preferably about an hour to about 10 hours, most preferably about an hour to about 8 hours.

The LIF methyl ester (II) thus obtained may be isolated by any method known in the art.

In step III, hydrolysis of LIF methyl ester of Formula (II) is carried out with a suitable base in one or more protic solvent(s) to yield lifitegrast of Formula (I) or a salt thereof.

A suitable protic solvent can be selected from the group comprising of water, C1-C6 alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol and isobutanol or the mixture thereof. Preferably, the protic solvent used is selected from water or aqueous alcohol.

The hydrolysis is preferably carried out using an aqueous mixture of a strong base, such as a hydroxide of an alkali metal or an alkaline earth metal. Examples of the hydroxide of an alkali metal or an alkaline earth metal to be used in the reaction of the present invention include potassium hydroxide, lithium hydroxide, sodium hydroxide, caesium hydroxide, calcium hydroxide, barium hydroxide and strontium hydroxide, as well as hydrates thereof. More preferred bases are potassium hydroxide, lithium hydroxide, calcium hydroxide, and hydrates thereof, and even more preferred bases are potassium hydroxide, lithium hydroxide and hydrates thereof.

Most preferably, the hydrolysis is carried out using either water-KOH or aqueous methanol- lithium hydroxide and hydrates thereof.

The hydrolysis is preferably carried out at a temperature of about 0°C to about the boiling point of the reaction mass, preferably about 0°C to about 80°C, more preferably about 10°C to about 50°C; for about 30 minutes to about 10 hours, preferably about an hour to about 8 hours, most preferably about an hour to about 5 hours.

Lifitegrast is isolated from the reaction mixture as a free acid. The product may be purified if desired by conventional methods such as recrystallization, purification by slurry or by conversion to suitable salt such as sodium, potassium, calcium,

lithium, magnesium, zinc and the like of the free acid followed by regeneration of free acid. Recrystallization involves providing a solution of crude Lifitegrast or a salt thereof in a suitable solvent or mixture of solvents and then crystallizing the solid from the solution.

The present invention includes substantially pure lifitegrast or its salts. As used in this instance, substantially pure refers to chemical and optical purity of lifitegrast greater than 90 %, preferably 92 %, and more preferably 95 % by weight.

Lifitegrast and its pharmaceutically acceptable salts described herein and/or prepared in accordance with the processes described herein may contain less than about 0.5 %, or less than about 0.1 %, by weight of process, optical, or structural impurities as characterized by high performance liquid chromatography (HPLC) and chiral HPLC.

The process of the present invention is advantages over prior art processes.

Prior art teaches use of protected 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (V) either as N-Boc or trityl, in the condensation steps and hence required subsequent deprotection, whereas the process of the present invention uses 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (V) as a free amine base. Thus the process of the present invention avoids protection and subsequent deprotection steps thereby reduce number of steps. This forms one aspect of the present invention.

Further, the above process steps do not require high temperature for the reaction as reported in the prior art, but are carried out under mild conditions such as room temperature whereby very little by-products are produced in the reaction. This forms another aspect of the present invention.

Further, the hydrolysis reaction is carried out using water as a green solvent. Water, not only is a natural solvent but also the most inexpensive and environmentally

benign solvent. The hydrolysis reaction is greatly accelerated by using water as a solvent instead of organic solvents as reported in the prior art. The use of water as a solvent also implies the elimination of tedious extraction, distillation/evaporation processes, simplifies work up procedure and thus contributes to the overall synthetic efficiency, chemical and optical purity of lifitegrast.

Furthermore, the above process is suitable for large-scale production and is economical to operate.

The example are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples:-

Example 1: Preparation of 2-(benzofuran-6-carbonyl) -5,7-dichloro-1,2,3 ,4-tetrahydroisoquinoline-6-carboxylic acid (III)

Benzofuran-6-carboxylic acid (VI) (7.5 gms , 0.046 moles) was suspended in 100 ml MDC and cooled to 0-5°C. 1 ml DMF was added at 0-5°C followed by thionyl Chloride (3.8 ml , 0.02moles). The temperature was raised to 25-30°C and the reaction mixture was further stirred for 4 hours. The solvent was removed under vacuum at 45 °C. The residue was stirred in 50 ml MDC and the solution was cooled to 5-10°C. The solution of 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid HCl (V) (10 gms , 0.035moles) and triethyl amine (25 ml , 0.34 moles) in 50 ml MDC , was cooled to 5-10°C. To this solution was added benzofuran-6-carboxylic chloride (VII) maintaining temperature at 5-10°C. The temperature was raised to 25-30°C and the reaction mixture was further stirred overnight. The reaction mixture was quenched in 100 ml of water. The organic layer was separated, washed with water and evaporated. The residue was stirred in 30 ml ethyl acetate and stirred for an hour at 25-30°C. The solid was isolated by filtration and dried to yield titled compound.

Yield: 90-95%

Example 2: Preparation of LIF methyl ester (II)

To a stirred mixture of 2-(benzofuran-6-carbonyl) -5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (III) (2 gms, 0.05 moles), methyl (S)-2-amino -3-(3-(methylsulfonyl) phenyl) propanoate (IV) (1.8 gms, 0.006 moles) and triethyl amine (3.6 ml, 0.05 moles) in 10 ml of DMF was added HATU (2.5 gms, 0.007 moles). The reaction mixture was further stirred for 3 hours at 25-30°C. The reaction mixture was quenched in 50 ml of water and stirred for 15 mins. Ethyl acetate (25 ml) was added. The organic layer was separated, washed with 10 % sodium carbonate solution and evaporated to yield titled compound.

Yield: 75-80%

Example 3: Preparation of lifitegrast (I)

LIF methyl ester (II) (1 gm, 0.002 moles) was stirred in 10 ml methanol. To this was added LiOH (0.13 gm, 0.003 moles) and 1 ml water. The reaction mixture was stirred for 3.0 hours at 25-30°C. To the reaction mixture was added 5 ml water and the solvent was evaporated at 40-45 °C. The reaction mixture was acidified using aq. HCl and stirred further for an hour at 25-30°C. The solid was isolated by filtration and dried to yield titled compound.

Yield: 75-80%

HPLC purity: > 99%

Example 4: Preparation of sodium salt of Lifitegrast

To a stirred solution of Lifitegrast (2 gms, 0.00325 moles) in 10 ml methanol was added sodium methoxide solution (0.2g, 0.0037 moles in 10 ml methanol) The reaction mixture was stirred for an hour at 25-30°C. The solvent was removed under vacuum at 40-45°C and the residue was stirred in 10 ml ethyl acetate for an hour at 25-30°C. The solid was isolated by filtration and dried to yield titled compound.

Yield: 80-85%

Example 5: Preparation of 2-(benzofuran-6-carbonyl) -5,7-dichloro-1,2,3 ,4-tetrahydroisoquinoline-6-carboxylic acid (III)

Benzofuran-6-carboxylic acid (VI) (50 gms , 0.3086 moles) was suspended in 250 ml MDC and cooled to 15-20°C. 5 ml DMF was added at 15-20°C followed by thionyl Chloride (34 ml , 0.4629 moles). The temperature was raised to 35-40°C and the reaction mixture was further stirred for 2 hours. The solvent was removed under vacuum at 45°C. The residue was stirred in 250 ml MDC and the solution was cooled to 5-10°C. The solution of 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid HCl (V) (74.12 gms , 0.2623 moles) and triethyl amine (215 ml , 1.5432 moles) in 500 ml MDC , was cooled to 5-10°C. To this solution was added benzofuran-6-carboxylic chloride (VII) maintaining temperature at 5-10°C. The temperature was raised to 25-30°C and the reaction mixture was further stirred for 2 hours. The reaction mixture was quenched in 500 ml of water. The organic layer was separated, washed with water and stirred with 2.5 gms of charcoal for 30 minutes. The reaction mixture was filtered over hyflo and the clear filtrate evaporated under vacuum at 40-45°C. The residue was stirred in 250 ml ethyl acetate and stirred for an hour at 25-30°C. The solid was isolated by filtration and dried to yield titled compound.

Yield: 95-98%

Example 6: Preparation of LIF methyl ester (II)

To a stirred mixture of 2-(benzofuran-6-carbonyl) -5,7-dichloro-1,2,3 ,4-tetrahydroisoquinoline-6-carboxylic acid (III) (100 g , 0.2562 moles) , and triethyl amine (148.8 gms , 1.475 moles) in 500 ml of DMF was added HATU (121.76 gms, 0.320 moles). The reaction mixture was further stirred for 1 hour at 25-30°C. Added methyl (S)-2-amino -3-(3-(methylsulfonyl) phenyl) propanoate (IV) (79.94 gms, 0.006moles) and the reaction mixture was further stirred for 6 hours at 25-30°C. The reaction mixture was filtered and quenched in 6% sodium carbonate solution at 5-10°C and stirred for 30 mins. The solids were filtered and stirred in 1.0 lit water at 25-30°C for 1 hour. The solids were isolated by filtration and dried to yield titled compound.

Yield: 150 gms

HPLC Purity: 95-97%

Example 7: Preparation of lifitegrast (I)

To a stirred solution of KOH (16.04 gms, 0.286 moles) in 1.0 lit water was added, LIF methyl ester (II) (120 gms, 0.1906 moles). The reaction mixture was stirred for 4.0 hours at 25-30°C. To the reaction mixture was added 200 ml water and the reaction mixture was acidified using 50% HCl solution (70 ml) and stirred further for an hour at 25-30°C. The solids were filtered and stirred in 600 ml water at 25-30°C for 30 minutes. The solids were isolated by filtration and dried under vacuum at 40-45°C for about 20 hours to yield titled compound.

Yield: 80 gms

HPLC purity: 96-98%

Example 8: Preparation of lifitegrast (I)

LIF methyl ester (II) (2 gms, 0.003 moles) was stirred in 10 ml methanol. To this was added KOH (0.27 gm, 0.004 moles) and 6 ml water. The reaction mixture was stirred for 3.0 hours at 25-30°C. To the reaction mixture was added 5 ml water and the solvent was evaporated at 40-45°C. The reaction mixture was acidified using aq. HCl and stirred further for an hour at 25-30°C. The solid was isolated by filtration and dried to yield titled compound.

Yield: 71.5%

HPLC purity: 97.47%

Chiral Purity: 86.8% ee

Example 9: Preparation of lifitegrast (I)

To a stirred solution of KOH (26.7 gms, 0.47 moles) in 1.0 lit water was added, LIF methyl ester (II) (200 gms, 0.32 moles). The reaction mixture was stirred for 4.0 hours at 25-30°C. To the reaction mixture was added 1.0 lit water and the reaction mixture was acidified using 50% HCl solution (100 ml) and stirred further for an hour at 25-30°C. The solids were filtered and stirred in 1.0 lit water at 25-

30°C for 30 minutes. The solids were isolated by filtration and dried under vacuum at 40-45°C for about 20 hours to yield titled compound.

Yield: 178 gms

Efficiency: 91.28%

HPLC purity: 98.04%

Example 10: Preparation of lifitegrast (I)

To a stirred solution of KOH (14 gms, 0.25 moles) in 525 ml water was added, LIF methyl ester (II) (105 gms, 0.16 moles). The reaction mixture was stirred for 4.0 hours at 25-30°C. To the reaction mixture was added 500 ml water and the reaction mixture was acidified using 50% HCl solution (50 ml) and stirred further for an hour at 25-30°C. The solids were filtered and stirred in 500 ml water at 25-30°C for 30 minutes. The solids were isolated by filtration and dried under vacuum at 40-45°C for about 20 hours to yield titled compound.

Yield : 78.8 gms

% Yield: 76%

HPLC purity : 96.2%

Chiral purity: 99.44%

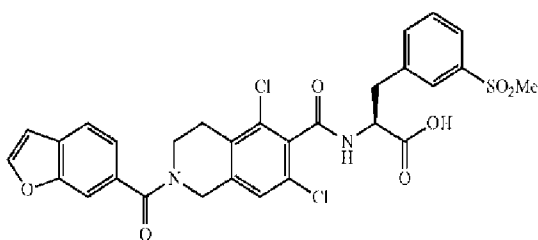
Lifitegrast prepared using various protic solvents by following example 8, is summarized in Table 1

Table 1

Sr.no.	Solvent	Input qty. of LIF methyl ester (II)	HPLC Purity %area	Yield- of Lifitegrast (I) %area	Chiral purity. %
1.	Methanol.	2.0gm	97.47%	53.1%	90.5%
2.	Ethanol.	2.0gm.	95.69%	56.2%	94.0%
3.	IPA	2.0gm.	96.39%	69.5%	97.0%
4.	n-Butanol	2.0gm.	95.74%	73.6%	95.7%
5.	Water	105.0gm.	96.2%	76.0%	99.44%

We claim,

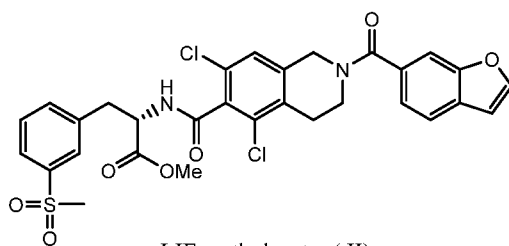
1. A process for preparing Lifitegrast of formula (I)



Lifitegrast (I)

or a salt thereof comprising the steps of :

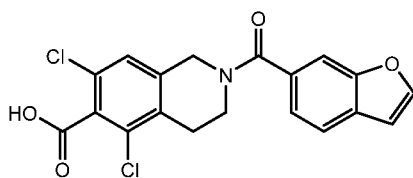
- a) hydrolysing LIF methyl ester (II)



LIF methyl ester (II)

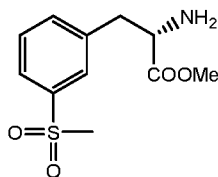
- with a suitable base in one or more protic solvent(s) and
 - b) isolating Lifitegrast of Formula I, or a salt thereof, with an enantiomeric excess greater than about 95%.
2. The process according to claim 1, wherein the protic solvent(s) is selected from water, C1-C6 alcohol or the mixture thereof.
 3. The process according to claim 2, wherein alcohol is selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol and isobutanol.

4. The process according to any one of the preceding claims, wherein the protic solvent(s) is water or aqueous alcohol.
5. The process according to claim 1, wherein the base is selected from hydroxide of an alkali metal or an alkaline earth metal.
6. The process according to claim 5, wherein the base is selected from the group consisting of potassium hydroxide, lithium hydroxide, sodium hydroxide, caesium hydroxide, calcium hydroxide, barium hydroxide and strontium hydroxide, as well as hydrates thereof.
7. A process for preparing Lifitegrast of formula (I), further comprising coupling 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (III)



2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (III)

with methyl (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoate of Formula (IV)



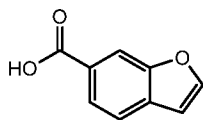
methyl (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoate (IV)

in the presence of suitable coupling agent to yield LIF methyl ester of Formula (II).

8. The process according to claim 7, wherein the reaction is carried out at a temperature of about 0°C to about the boiling point of the reaction mass, preferably about 0°C to about 80°C.
9. The process according to claim 7, wherein the coupling agent is selected from dialkyl carbodiimides such as N,N'-dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole (CDI); 1,2-oxazolinium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium-3'-sulfonate and 2-tert-butyl-5-methylisoxazolium perchlorate, acylamino compound, such as 2-ethoxy-1-ethoxy-carbonyl-1,2-dihydroquinoline; activated phosphoric acid derivatives such as, bis(2-oxo-3-oxazolidinyl)phosphinic acid chloride or 1-benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluorophosphate, phenylsilane, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP), 1-hydroxybenzotriazole hydrate (HOBt), PyBOP, n-Ethyl-N'-(3-dimethylaminopropyl) carbodidimide hydrochloride (EDC HCl), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), 4-Dimethylaminopyridine (DMAP) and the like.
10. The process according to claim 9, wherein the condensing agent is HATU.
11. The process according to any one of the claims 7, 8, 9 or 10, wherein the reaction is conducted in the presence of an organic or inorganic base.
12. The process according to claim 11, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, potassium

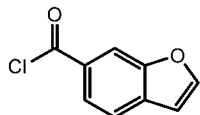
phosphate, potassium hydrogen phosphate, sodium carbonate, sodium hydroxide, potassium hydroxide and the like.

13. A process for preparing Lifitegrast of formula (I), further comprising treating benzofuran-6-carboxylic acid of Formula (VI)



benzofuran-6-carboxylic acid (VI)

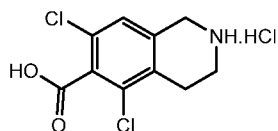
with a suitable chlorinating agent, to yield benzofuran-6-carboxylic chloride of Formula (VII)



benzofuran-6-carboxylic chloride (VII)

and;

condensing with 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (V)



5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid hydrochloride (V)

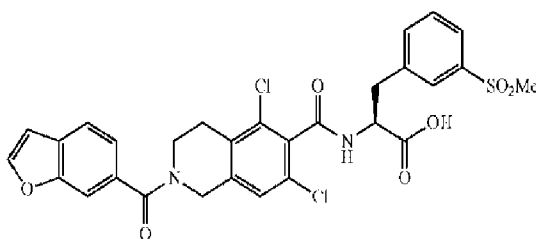
or a salt thereof to yield 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (III).

14. The process according to claim 13, wherein the intermediate benzofuran-6-carboxylic chloride of Formula (VII) is not isolated.

15. The process according to claim 13 or 14, wherein the chlorinating agent is selected from the group consisting of, thionyl chloride, phosphorus

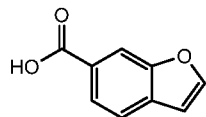
oxychloride, phosphorus trichloride, phosphorus pentachloride, phosgene and oxalyl chloride.

16. The process according to any one of claims 13,14 or 15, wherein the chlorination is carried in the presence of an aprotic solvent selected from the group comprising of, toluene, methylenechloride (MDC), acetonitrile, tetrahydrofuran, diglyme, dimethylformamide (DMF) or dioxane or the like and the mixture thereof and at a temperature of 0°C to about 80°C.
17. The process according to any one of the preceding claims 13,14,15 or 16, wherein the condensation is carried out in the presence of a suitable solvent selected from the group consisting of acetonitrile, tetrahydrofuran, diglyme, dimethylformamide, dioxane, methylene chloride, and toluene and at a temperature of about 0°C to about 150°C.
18. The process according to claim 17, wherein the condensation is conducted in the presence of an organic or inorganic base.
19. The process according to claim 18, wherein the base is selected from the group comprising of triethylamine diisopropylethylamine, potassium phosphate, potassium hydrogen phosphate, sodium carbonate, sodium hydroxide, potassium hydroxide or the like.
20. The process for preparing Lifitegrast of formula (I) according to any one of the preceding claims wherein, the said process comprises;



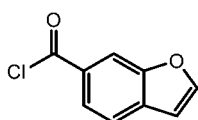
Lifitegrast (I)

a) treating benzofuran-6-carboxylic acid of Formula (VI)



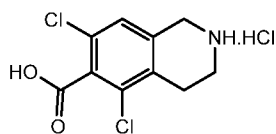
benzofuran-6-carboxylic acid (VI)

with a suitable chlorinating agent, to yield benzofuran-6-carboxylic chloride of Formula (VII)



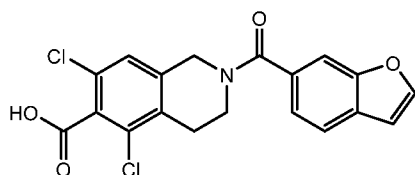
benzofuran-6-carboxylic chloride (VII)

and further condensing with 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (V) or a salt thereof



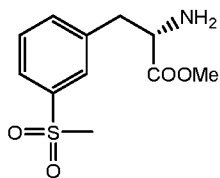
5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid hydrochloride (V)

to yield 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid of Formula (III);

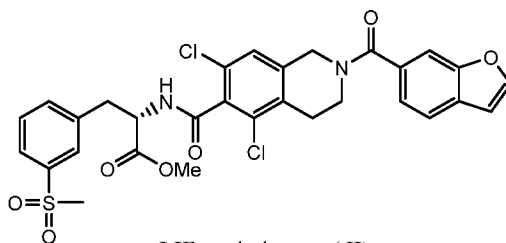


2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (III)

b) coupling the 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (III) with methyl (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoate of Formula (IV)

methyl (*S*)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoate (IV)

in the presence of suitable condensing agent to yield LIF methyl ester of Formula (II); and



LIF methyl ester (II)

c) hydrolysing the LIF methyl ester of Formula (II) with a suitable base in one or more protic solvent(s) to yield lifitegrast (I) or a salt thereof.

21. The process according to any one of the preceding claims wherein, the Lifitegrast has chemical purity more than 95 % by weight and optical purity more than 95 % by weight.

22. A pharmaceutical composition comprising Lifitegrast prepared by the process according to any one of the preceding claims together with one or more pharmaceutically-acceptable excipients, for the treatment of inflammatory eye disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2018/050756

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D405/06 A61P29/02 A61P27/02 A61K31/4725
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	paragraph [00160] - paragraph [00162] -----	7-12
A	CN 106 995 439 A (ZHENJIANG SHENG'AN MEDICINE CO LTD; JIANGSU JIBEIER PHARMACEUTICAL CO) 1 August 2017 (2017-08-01) paragraph [0128]; figure 3 ----- -/-	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

23 January 2019

Date of mailing of the international search report

01/02/2019

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2018/050756

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	figure 1	1-6, 13-22
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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