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(54) Title: PROCESS FOR PREPARATION OF LIFITEGRAST

(57) Abstract: The present invention relates to a process for the preparation of lifitegrast, a compound of formula I, the process comprising deprotecting a compound of formula III using a Lewis acid. The present invention also relates to lifitegrast organic amine salt, a compound of formula II, process for its preparation and conversion thereof to lifitegrast.

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PROCESS FOR PREPARATION OF LIFITEGRAST

PRIORITY

[0001] This application claims the benefit of Indian Provisional Applications 201721032941 filed on September 18, 2017 and 201821018016 filed on May 14, 2018, entitled “PROCESS FOR PREPARATION OF LIFITEGRAST”, the contents of which are incorporated herein by reference.

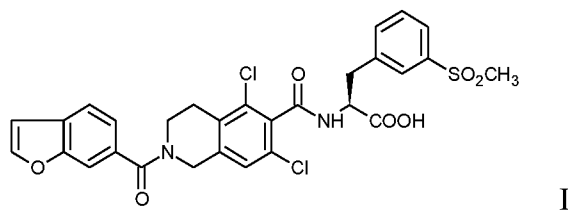
BACKGROUND OF THE INVENTION

Technical Field

[0002] The present invention relates to process for the preparation of lifitegrast.

Description of the Related Art

[0003] Lifitegrast, which is chemically known as (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid is represented by compound of Formula I.

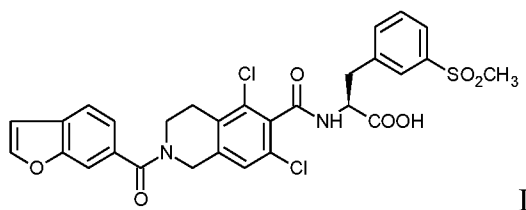


[0004] Xiidra™ Shire's lifitegrast ophthalmic solution 5% for topical ophthalmic use is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of signs and symptoms of dry eye disease.

[0005] The present invention provides a process for lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein the level of R isomer of lifitegrast is less than 1% as determined by HPLC, via a novel organic amine salt of lifitegrast.

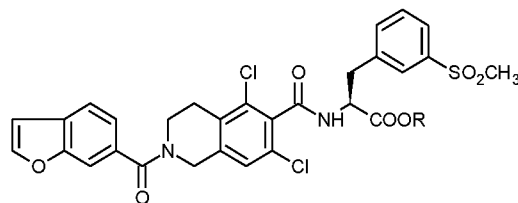
SUMMARY OF THE INVENTION

[0006] The present invention provides a process for the preparation of lifitegrast, a compound of formula I,



the process comprising:

(a) deprotecting a compound of formula III,

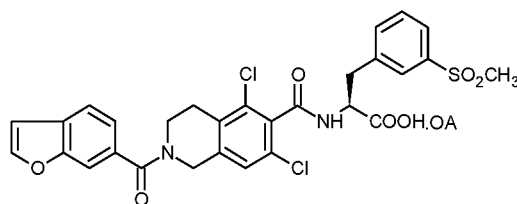


III

wherein R is selected from C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl, and wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl;

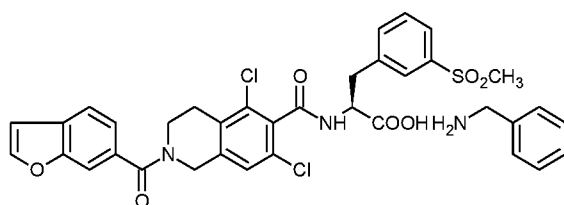
wherein the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof, to obtain lifitegrast; and

(b) optionally, reacting the lifitegrast obtained in step (a) with an organic amine OA to form an organic amine salt thereof, a compound of formula II,



II.

[0007] In another embodiment, the present invention provides lifitegrast benzylamine salt, a compound of formula IIA,

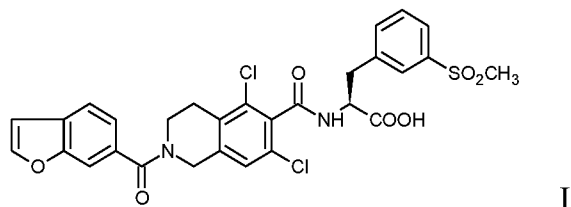


IIA.

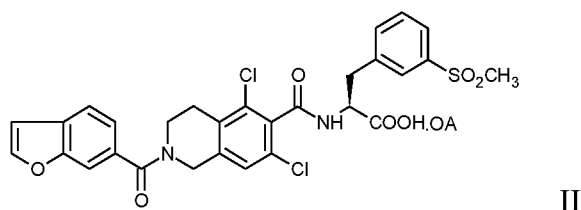
[0008] In another embodiment, the present invention provides a process for the preparation of lifitegrast benzylamine salt, a compound of formula IIA, the process comprising:

- (a) reacting lifitegrast with benzylamine in presence of a solvent to form a reaction mixture;
- (b) obtaining lifitegrast benzylamine salt from the reaction mixture of step (a); and
- (c) isolating the lifitegrast benzylamine salt, the compound of formula IIA.

[0009] In another embodiment, the present invention provides a process for the preparation of lifitegrast, a compound of formula I comprising:



(a) reacting crude lifitegrast, with an organic amine OA, to form an organic amine salt thereof, a compound of formula II; and



(b) treating the compound of formula II with an acid to form lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein the level of R isomer of lifitegrast is less than 1% as determined by HPLC.

[0010] In another embodiment, the present invention provides use of lifitegrast benzylamine salt, compound of formula IIA, in the preparation of lifitegrast.

BRIEF DESCRIPTION OF THE DRAWINGS

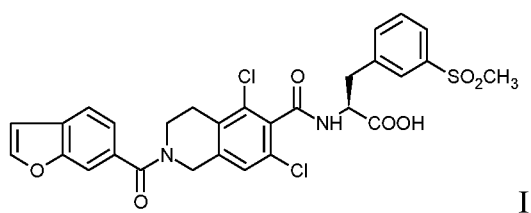
[0011] Figure 1 is ¹H NMR of compound IIA according to example 4.

[0012] Figure 2 is a characteristic XRPD of crystalline compound IIA according to example 4.

[0013] Figure 3 is XRD of amorphous lifitegrast according to example 11.

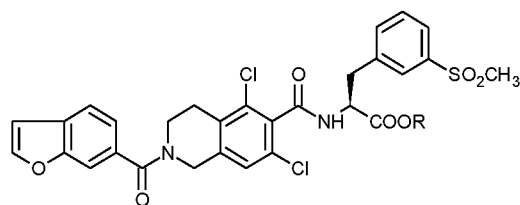
DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention provides a process for the preparation of lifitegrast, a compound of formula I,



the process comprising:

(a) deprotecting a compound of formula III,

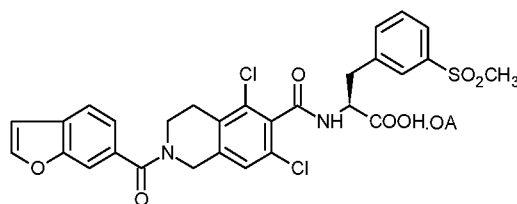


III

wherein R is selected from C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl, and wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl;

wherein the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof, to obtain lifitegrast; and

(b) optionally, reacting the lifitegrast obtained in step (a) with an organic amine OA to form an organic amine salt thereof, a compound of formula II,



II.

[0015] In the present application, the term “room temperature” means a temperature of about 25°C to about 30°C.

[0016] The term "C₁-C₆ alkyl" as used herein refers to an aliphatic hydrocarbon group which may be straight or branched having C₁-C₆ carbon atoms in the chain. The term “branched” means that one or lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. The alkyl groups include but are not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl.

[0017] The term “C₆-C₁₈ aryl” as used herein refers to an aromatic hydrocarbon group having a single ring or multiple aromatic rings fused together. Preferred aryl groups have C₆-C₁₈ carbon atoms, more preferably have C₆-C₁₀ carbon atoms. The aryl groups include but are not limited to phenyl, naphthyl or tetrahydronaphthyl.

[0018] The term “halogen” refers to iodo, bromo, chloro or fluoro.

[0019] The term "C₁-C₆ alkoxy" as used herein refers to C₁-C₆ alkyl group, wherein alkyl is as defined herein, that is linked to the rest of the molecule or to another group

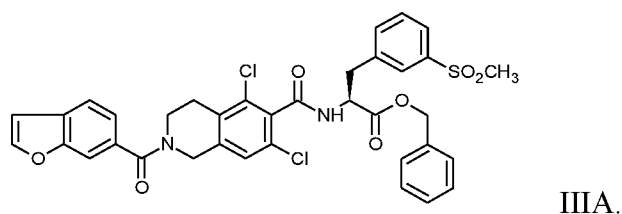
through an oxygen atom. The alkoxy groups include but are not limited to methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *tert*-butoxy, *n*-pentoxy.

[0020] In (a) of the above process for the preparation of lifitegrast, the compound of formula III is deprotected to obtain lifitegrast, wherein the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof.

[0021] In one embodiment, in compound of formula III, when R is C₁-C₆ alkyl optionally substituted with C₆ aryl, and wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl, the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof.

[0022] In another embodiment, in compound of formula III, when R is C₁-C₆ alkyl optionally substituted with C₆ aryl, the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof.

[0023] In one embodiment, in compound of formula III, when R is C₁ alkyl substituted with C₆ aryl, the compound of formula III is lifitegrast benzyl ester represented by compound of formula IIIA,



[0024] In one embodiment, the compound of formula IIIA is deprotected to obtain lifitegrast, wherein the deprotection is carried out by subjecting the compound of formula IIIA to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof.

[0025] In one embodiment, the deprotection is carried out by subjecting the compound of formula III to non-hydrolytic treatment with a Lewis acid.

[0026] In one embodiment, the term “non-hydrolytic” means subjecting the compound of formula III with a Lewis acid in the absence of water.

[0027] In one embodiment, in compound of formula III, when R is C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl, the deprotection is carried out by non-hydrolytic cleavage using a Lewis acid.

[0028] In one embodiment, the term “non-hydrolytic cleavage” means the ester cleavage of the O-R bond in the compound of formula III, is carried out in the absence of water.

[0029] In one embodiment, the term “non-hydrolytic cleavage” means the ester cleavage of the O-R bond in the compound of formula III being facilitated due to the coordination of the ester carbonyl in the compound of formula III with the electrophilic metal ion of the Lewis acid (MX).

[0030] In one embodiment, the term “non-hydrolytic cleavage” means the ester cleavage of the O-R bond in the compound of formula III being facilitated by the nucleophile X of the Lewis acid (MX).

[0031] In one embodiment, the term “non-hydrolytic cleavage” excludes the ester cleavage in the compound of formula III is not by water nucleophile or hydroxide nucleophile.

[0032] In one embodiment, the Lewis acid may be selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof.

[0033] The deprotection reaction may be carried out in the presence of an aprotic solvent.

[0034] In one embodiment, the aprotic solvent includes, but is not limited to esters such as methyl acetate, ethyl acetate, *n*-propyl acetate, *tert*-butyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dioxane, dimethoxy ethane, 2-methyltetrahydrofuran and the like; nitriles such as acetonitrile and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane; sulfur compounds such as carbon disulfide; tertiary amines such as pyridine; amides such as dimethylformamide; or mixtures thereof.

[0035] In one embodiment, the deprotection is carried out at about room temperature to about the reflux temperature of the solvent.

[0036] In one embodiment, the lifitegrast obtained in step (a) is in-situ and carried forward to step (b).

[0037] The term “in-situ” means the intermediates formed in the steps referred to are not isolated. The term “not isolated” means the intermediates referred to are not separated as a solid.

[0038] In one embodiment, the term “in-situ” means the process of the invention is carried out without isolation of lifitegrast in the form of a solid compound.

[0039] In one embodiment, the lifitegrast obtained in step (a) may be present in the filtrate and used for reaction with organic amine, without isolating it from the filtrate.

[0040] In one embodiment, the lifitegrast obtained in (a) and present in the filtrate, may be isolated in a solid form or as a residue by removal of the solvent by evaporation or distillation and then reacted with the organic amine.

[0041] In one embodiment, the lifitegrast obtained in (a) has a chemical purity of 50-99.5% as determined by HPLC.

[0042] In (b) of the above process for the preparation of lifitegrast, the lifitegrast obtained in step (a) is reacted with an organic amine OA to form an organic amine salt thereof, a compound of formula II.

[0043] An organic amine, OA is an organic compound which acts as a base. They usually contain nitrogen atoms, which can easily be protonated.

[0044] In one embodiment, OA is an organic amine of formula $NR_1R_2R_3$, wherein R_1 , R_2 , R_3 may be independently selected from the group consisting of H or C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl; wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl.

[0045] In one embodiment, OA is an organic amine of formula $NR_1R_2R_3$, wherein R_1 is H, R_2 is H, R_3 is C₁-C₆ alkyl group substituted with a C₆ aryl group.

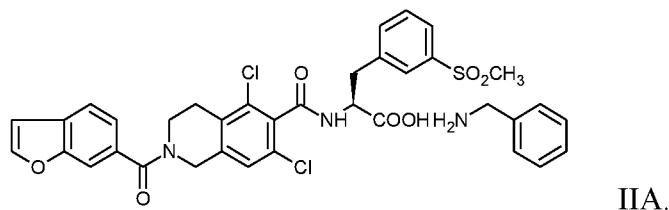
[0046] In one embodiment, OA is an organic amine of formula $NR_1R_2R_3$, selected from the group consisting of benzylamine, methylamine, dimethylamine, trimethylamine, *tert*-butyl amine, ethylamine, diethylamine, triethylamine, diisopropylethylamine.

[0047] In one embodiment, the organic amine is benzylamine.

[0048] In one embodiment, OA organic amine is a cyclic amine like pyridine, piperidine, piperazine and the like.

[0049] In one embodiment, OA is an organic amine selected from the group consisting of meglumine, tromethamine, choline, ethanolamine, dibenzylethylenediamine.

[0050] In one embodiment, compound of formula II is lifitegrast benzylamine salt, a compound of formula IIA,

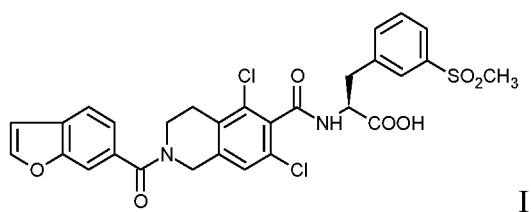


[0051] In one embodiment, the reaction of lifitegrast with organic amine is carried out in an organic solvent.

[0052] In one embodiment, the organic amine salt, a compound of formula II is separated from the reaction mass by filtration and if required subjected to purification by recrystallization.

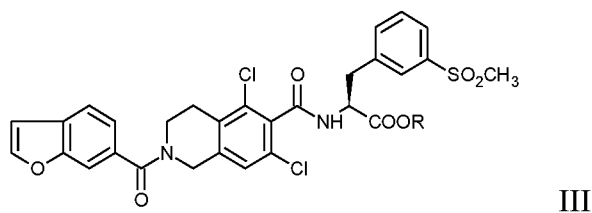
[0053] The recrystallization may be carried out in a solvent selected from the group consisting of alcohol such as methanol, ethanol, isopropanol and the like; ketone such as acetone, methyl isobutyl ketone, ethyl methyl ketone and the like; nitrile such as acetonitrile, propionitrile and the like; water; and mixtures thereof.

[0054] In one embodiment, the present invention provides a process for the preparation of lifitegrast, a compound of formula I,



the process comprising:

(a) deprotecting a compound of formula III,

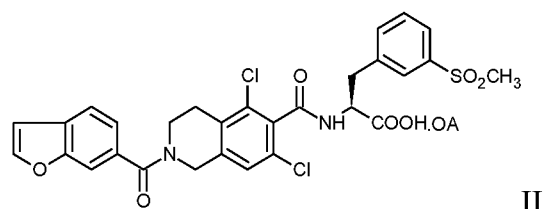


wherein R is selected from C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl, and wherein the aryl group may be optionally substituted with one or more substituents

selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl;

wherein the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof, to obtain lifitegrast; and

(b) reacting the lifitegrast obtained in step (a) with an organic amine OA to form an organic amine salt thereof, a compound of formula II,



[0055] In one embodiment, the organic amine salt of lifitegrast, the compound of formula II, is treated with an acid to form lifitegrast, the compound of formula I.

[0056] In one embodiment, the acid may be an inorganic acid or an organic acid.

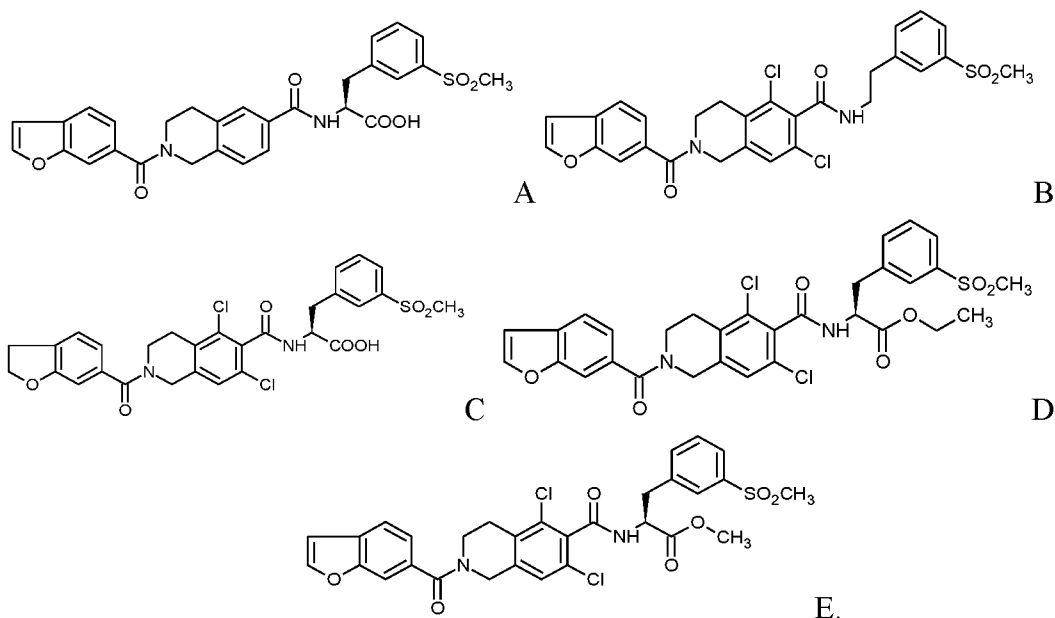
[0057] In one embodiment, the inorganic acid may be selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid and the like.

[0058] In one embodiment, the organic acid may be selected from the group consisting of acetic acid, trifluoroacetic acid, methanesulfonic acid, *p*-toluenesulfonic acid and the like.

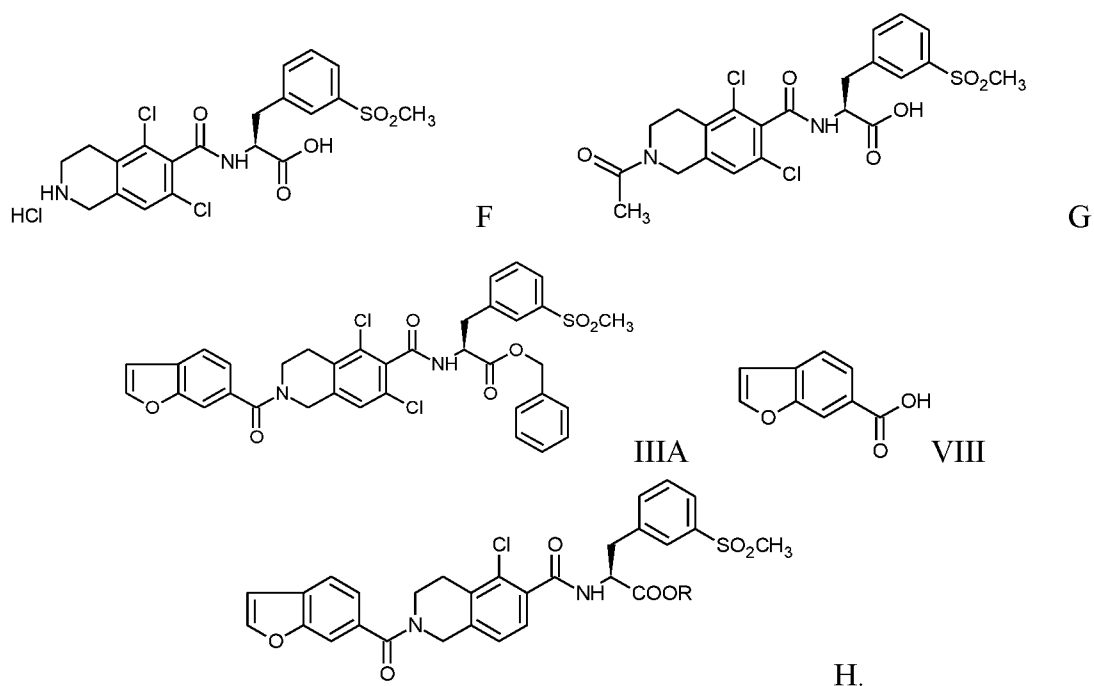
[0059] In one embodiment, the present invention provides a process for lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein the level of *R* isomer of lifitegrast is less than 1% as determined by HPLC.

[0060] In one embodiment, the present invention provides a process for lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein corresponding *R* isomer of lifitegrast is not detected, as determined by HPLC.

[0061] In one embodiment, the present invention provides a process wherein lifitegrast, a compound of formula I, is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC,



[0062] In another embodiment, the present invention provides a process wherein lifitegrast, a compound of formula I, is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula F, G, IIIA, VIII or H is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC,



[0063] In one embodiment, the present invention provides compound of formula A, B, C, D and E and a process for preparation thereof.

[0064] In one embodiment, the present invention provides a process wherein lifitegrast, a compound of formula I is obtained in a chiral purity of at least 99% and wherein

corresponding R isomer is less than 1% as determined by HPLC and in a chemical purity of at least 99% and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC.

[0065] In one embodiment, the present invention provides a process wherein lifitegrast, a compound of formula I is obtained in a chiral purity of at least 99% and wherein corresponding R isomer is not detected as determined by HPLC and in a chemical purity of at least 99% and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC.

[0066] The present invention provides lifitegrast obtained by above process, as analyzed by chemical purity using high performance liquid chromatography (HPLC) with the conditions described below:

Reagents and Solvents: O-Phosphoric acid (AR grade, Merck), Acetonitrile (Gradient grade, Rankem), Methanol (HPLC grade, Rankem), Water (Milli Q or equivalent)

Chromatographic Conditions:

Apparatus: A High Performance Liquid Chromatograph equipped with quaternary gradient pumps, variable wavelength UV detector attached with data recorder and integrator software.

Column: Inertsil ODS 3V, 250 x 4.6mm, 5 μ

Column temperature: 50°C

Sample Cooler temperature: 25°C

Mobile Phase A: Buffer

Mobile Phase B: Acetonitrile

Buffer: 0.1% O-Phosphoric acid in water

Time (min.)	% Mobile Phase A	% Mobile Phase B
0.01	85	15
15	70	30
60	55	45
70	25	75
85	25	75
88	85	15
95	85	15

Diluent: Water : Methanol (80:20, v/v)

Flow Rate: 1.0mL/minute

Detection: UV 210nm

Injection Volume: 50 μ L

Run time: 95minutes

Needle wash: Water: Methanol (20:80 v/v)

The retention time of lifitegrast is about 41.0 minutes under these conditions.

Relative retention time for compound of formula A is about 0.82, compound of formula D is about 1.54, compound of formula E is about 1.34, compound of formula F is about 0.13, compound of formula G is about 0.45, compound of formula IIIA is about 1.72 and compound of formula V is about 0.53 with respect to lifitegrast.

[0067] In one embodiment, the present invention provides a process for the preparation of lifitegrast comprising:

- (a) providing a solution of lifitegrast, prepared by the process as described above, in a solvent; and
- (b) isolating lifitegrast by
 - (i) removing the solvent from the solution obtained in (a); or
 - (ii) combining the solution obtained in (a) with an antisolvent followed by optional cooling; or
 - (iii) slurring the compound obtained from (b) (i); or
 - (iv) cooling the solution obtained in (a);

wherein the lifitegrast obtained is in amorphous form.

[0068] In one embodiment, providing a solution of lifitegrast in a solvent in (a) comprises a solution obtained from reaction mixture in the final stage of process for preparation of lifitegrast.

[0069] In one embodiment, providing a solution of lifitegrast in a solvent in (a) comprises a solution obtained after dissolving lifitegrast in a solvent.

[0070] Solvent used in (a) includes, but is not limited to esters such as methyl acetate, ethyl acetate, propyl acetate, butyl acetate, *tert*-butyl acetate and the like; haloalkanes such as methylene dichloride, ethylene dichloride, chloroform and the like; acyclic ethers such as diethyl ether, dimethyl ether, ethyl methyl ether, diisopropyl ether, methyl *tert*-butyl ether, and the like; cyclic ethers such as tetrahydrofuran, dioxane, and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; aliphatic hydrocarbons such as hexane, heptane,

cyclohexane and the like; aromatic hydrocarbons such as toluene, xylene, chlorobenzene and the like; nitriles such as acetonitrile, propanenitrile and the like; dimethyl sulfoxide; dimethyl formamide; dimethyl acetamide; water; or mixtures thereof.

[0071] In one embodiment, the solvent may be selected from the group consisting of esters, haloalkanes, alcohols, ketones, cyclic ethers, nitriles, dimethyl sulfoxide; dimethyl formamide; dimethyl acetamide; and mixtures thereof. Preferably the solvent selected is ethyl acetate.

[0072] Removal of solvent in (b)(i) may be carried out by solvent distillation, concentration, spray drying, fluid bed drying, lyophilization, flash drying, spin flash drying, or thin-film drying.

[0073] In one embodiment, removal of solvent in (b)(i) may be carried out by solvent distillation, preferably under vacuum.

[0074] In one embodiment, removal of solvent in (b)(i) may be carried out by spray drying.

[0075] In one embodiment, the spray drying is performed at a temperature of about 50-75°C.

[0076] Antisolvent used in (b)(ii) is a solvent which on addition to a solution of lifitegrast in (a) causes precipitation of lifitegrast owing to insolubility of lifitegrast in the solvent system generated.

[0077] In one embodiment, the antisolvent used in b(ii) may include an acyclic ether such as diethyl ether, dimethyl ether, ethyl methyl ether, diisopropyl ether, methyl *tert*-butyl ether, and the like; an aliphatic hydrocarbon such as hexane, heptane, cyclohexane and the like; water; or mixtures thereof.

[0078] In one embodiment, the antisolvent used in b(ii) may be diisopropyl ether.

[0079] In one embodiment, the antisolvent used in b(ii) may be *n*-hexane, *n*-heptane or cyclohexane.

[0080] In one embodiment, the antisolvent used in b(ii) may be water.

[0081] In one embodiment, the present invention provides a process for the preparation of amorphous form of lifitegrast comprising:

(a) providing a solution of lifitegrast, prepared by the process as defined above, in a solvent; and

(b) isolating the amorphous form of lifitegrast by combining the solution obtained in (a) with an antisolvent followed by optional cooling.

[0082] In one embodiment, the present invention provides a process for preparation of amorphous lifitegrast wherein the solvent used in (a) is ethyl acetate and the antisolvent used in (b) is cyclohexane.

[0083] After the addition of the antisolvent as in b(ii), optional cooling may be performed to obtain the precipitate.

[0084] In one embodiment, the present invention provides a process for preparation of amorphous form of lifitegrast comprising:

(a) providing a solution of lifitegrast in a solvent; and

(b) isolating the amorphous form of lifitegrast by cooling the solution obtained in (a) to a temperature of about -5°C to 10°C.

[0085] In one embodiment, the present invention provides a process for the preparation of lifitegrast comprising:

(a) providing a mixture of lifitegrast, prepared by the as described above, in water, optionally in presence of an organic solvent; and

(b) isolating lifitegrast by

(i) treating the mixture obtained in (a) with a base to give a solution;

(ii) treating the solution obtained in (b)(i) with an acid to form lifitegrast; and

(iii) filtering the lifitegrast obtained in (b)(ii);

wherein the lifitegrast obtained is in amorphous form.

[0086] In one embodiment, the organic solvent used in step (a) may be selected from the group consisting of esters, haloalkanes, alcohols, ketones, cyclic ethers, nitriles, dimethyl sulfoxide; dimethylformamide; dimethyl acetamide; and mixtures thereof.

[0087] In one embodiment, the base used in (b)(i) may be selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, sodium bicarbonate and potassium bicarbonate.

[0088] In one embodiment, the acid used in (b)(ii) may be selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, citric acid, phosphoric acid.

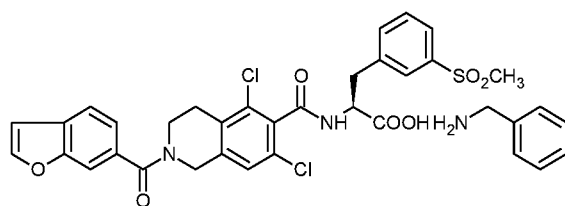
[0089] In one embodiment, the amorphous lifitegrast obtained in (b) may, optionally, be filtered and dried. Drying may be performed at a temperature of about 55°C to about 110°C. Drying may be performed preferably in the presence of vacuum.

[0090] In one embodiment, the amorphous lifitegrast is obtained in a chiral purity of at least 99% and wherein corresponding *R* isomer of lifitegrast is less than 1%, as determined by HPLC.

[0091] In one embodiment, the amorphous lifitegrast is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC.

[0092] In one embodiment, the amorphous lifitegrast, the compound of formula I obtained by the process of the present invention is converted to crystalline forms A, B, C, D, and E.

[0093] In one embodiment, the present invention provides lifitegrast benzylamine salt, a compound of formula IIA,



IIA.

[0094] In one embodiment, the present invention provides compound of formula IIA characterized by a proton NMR spectrum having peaks at δ 8.11-8.12, 8.04-8.06, 7.71-7.83, 7.62-7.64, 7.43-7.52, 7.3-7.39, 7.05, 4.74, 4.41-4.46, 3.95, 3.62, 3.26-3.30, 3.08-3.16, 2.77-2.80.

[0095] In one embodiment, the present invention provides compound of formula IIA in crystalline form.

[0096] In one embodiment, the present invention provides compound of formula IIA in crystalline form characterized by 2 θ peaks at 15.0, 19.1, 19.8, 20.6 and 21.1 $\pm$ 0.2°.

[0097] In one embodiment, the present invention provides a process for the preparation of lifitegrast benzylamine salt, a compound of formula IIA, the process comprising:

- (a) reacting lifitegrast with benzylamine in presence of a solvent to form a reaction mixture;
- (b) obtaining lifitegrast benzylamine salt from the reaction mixture of step (a); and
- (c) isolating the lifitegrast benzylamine salt, the compound of formula IIA.

[0098] In (a) of the above process for preparation of lifitegrast benzylamine salt, lifitegrast is reacted with benzylamine in presence of a solvent to form a reaction mixture.

[0099] The solvent includes but is not limited to esters such as methyl acetate, ethyl acetate, *n*-propyl acetate, isopropyl acetate, *tert*-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane and the like; ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dioxane and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols such as methanol, ethanol, *n*-propyl alcohol, isopropyl alcohol, *n*-butyl alcohol, isobutyl alcohol, *sec*-butyl alcohol, *tert*-butyl alcohol, pentanol, octanol and the like; haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; dimethyl sulfoxide; dimethyl acetamide; water; or mixtures thereof.

[0100] The reaction may be carried out at a temperature of about 25°C to about 100°C. The stirring time may range from about 30 minutes to about 10 hours, or longer.

[0101] In (b) of the above process for preparation of lifitegrast benzylamine salt, lifitegrast benzylamine salt is obtained from the reaction mixture of step (a), the process comprising:

- (i) cooling and stirring the mixture obtained in (a); or
- (ii) removing the solvent from the mixture obtained in (a); or
- (iii) treating the mixture of step (a) with an anti-solvent optionally, cooling and stirring the obtained mixture.

[0102] In one embodiment, the lifitegrast benzylamine salt is obtained by cooling and stirring the solution of step (a). The stirring time may range from about 30 minutes to about 10 hours, or longer. The temperature may range from about -20°C to about 30°C.

[0103] In one embodiment, the lifitegrast benzylamine salt is obtained by removing the solvent from the solution obtained in (a). Removal of solvent may be accomplished by substantially complete evaporation of the solvent; or concentrating the solution, cooling the solution if required and filtering the obtained solid. The solution may also be completely evaporated in, for example, a rotavapor, a vacuum paddle dryer or in a conventional reactor under vacuum above about 720mm Hg.

[0104] In one embodiment, the lifitegrast benzylamine salt is obtained by adding an anti-solvent to the solution obtained in (a) to form a mixture and optionally, cooling and

stirring the obtained mixture. The stirring time may range from about 30 minutes to about 10 hours, or longer. The temperature may range from about -10°C to about 120°C.

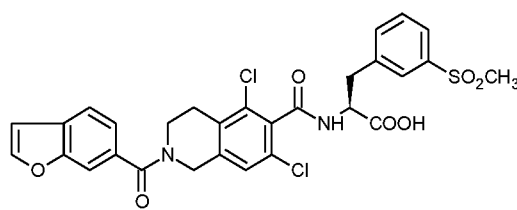
[0105] The anti-solvent is selected such that the lifitegrast benzylamine salt is precipitated out from the solution.

[0106] The anti-solvent includes but is not limited to esters such as methyl acetate, ethyl acetate, *n*-propyl acetate, isopropyl acetate, *tert*-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane and the like; ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dioxane and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols such as methanol, ethanol, *n*-propyl alcohol, isopropyl alcohol, *n*-butyl alcohol, isobutyl alcohol, *sec*-butyl alcohol, *tert*-butyl alcohol, pentanol, octanol and the like; haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; dimethyl sulfoxide; dimethyl acetamide; water; or mixtures thereof.

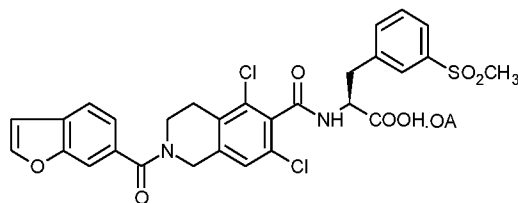
[0107] In (c) of the process for the preparation of lifitegrast benzylamine salt, the lifitegrast benzylamine salt is isolated by any method known in the art. The method, may involve any of techniques, known in the art, including filtration by gravity or by suction, centrifugation, and the like.

[0108] The isolated lifitegrast benzylamine salt may be further dried. The drying may be carried out at temperature from about room temperature to about 100°C with or without vacuum. The drying may be carried out for any desired time until the required product quality is achieved. The drying time may vary from about 1 hour to about 25 hours, or longer.

[0109] In one embodiment, the present invention provides a process for the preparation of lifitegrast, a compound of formula I comprising:



(a) reacting crude lifitegrast, with an organic amine OA, to form an organic amine salt thereof, a compound of formula II; and



II

(b) treating the compound of formula II with an acid to form lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein the level of R isomer of lifitegrast is less than 1% as determined by HPLC.

[0110] An organic amine, OA is an organic compound which acts as a base. They usually contain nitrogen atoms, which can easily be protonated.

[0111] In one embodiment, OA is an organic amine of formula $NR_1R_2R_3$, wherein R_1 , R_2 , R_3 may be independently selected from the group consisting of H or C_1 - C_6 alkyl optionally substituted with C_6 - C_{18} aryl; wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C_1 - C_6 alkoxy and C_1 - C_6 alkyl.

[0112] In one embodiment, OA is an organic amine of formula $NR_1R_2R_3$, wherein R_1 is H, R_2 is H, R_3 is C_1 - C_6 alkyl group substituted with a C_6 aryl group

[0113] In one embodiment, OA is an organic amine of formula $NR_1R_2R_3$, selected from the group consisting of benzylamine, methylamine, dimethylamine, trimethylamine, *tert*-butyl amine, ethylamine, diethylamine, triethylamine, diisopropylethylamine.

[0114] In one embodiment, the organic amine is benzylamine.

[0115] In one embodiment, OA organic amine is a cyclic amine like pyridine, piperidine, piperazine and the like.

[0116] In one embodiment, OA is an organic amine selected from the group consisting of meglumine, tromethamine, choline, ethanolamine, dibenzylethylenediamine.

[0117] In one embodiment the “crude lifitegrast” means lifitegrast having a chemical purity of 50-99.5% as determined by HPLC.

[0118] In one embodiment the “crude lifitegrast” means lifitegrast having a chemical purity of 80-95% as determined by HPLC.

[0119] In one embodiment, the crude lifitegrast obtained from an earlier reaction may be present in the filtrate and used for reaction with organic amine, without isolating it from the filtrate.

[0120] In one embodiment, the crude lifitegrast obtained from an earlier reaction and present in the filtrate, may be isolated in a solid form or as a residue by removal of the solvent by evaporation or distillation and then reacted with the organic amine.

[0121] In one embodiment, the reaction of crude lifitegrast with organic amine is carried out in an organic solvent.

[0122] In one embodiment, the organic amine salt, a compound of formula II is separated from the reaction mass by filtration and if required subjected to purification by recrystallization.

[0123] The recrystallization may be carried out in a solvent selected from the group consisting of alcohol such as methanol, ethanol, isopropanol and the like; ketone such as acetone, methyl isobutyl ketone, ethyl methyl ketone and the like; nitrile such as acetonitrile, propionitrile and the like; water; and mixtures thereof.

[0124] In one embodiment, the organic amine salt compound of formula II is treated with an acid selected from an inorganic acid or an organic acid, to form lifitegrast.

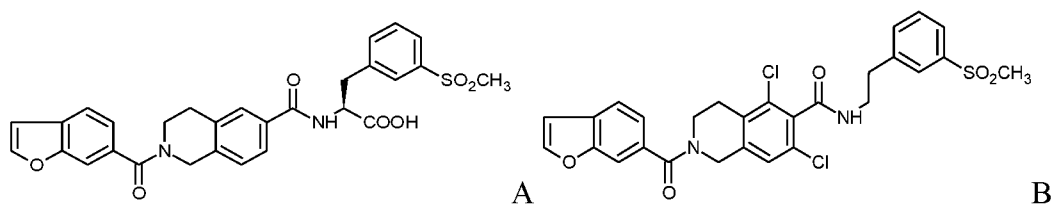
[0125] The inorganic acid may be selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid and the like.

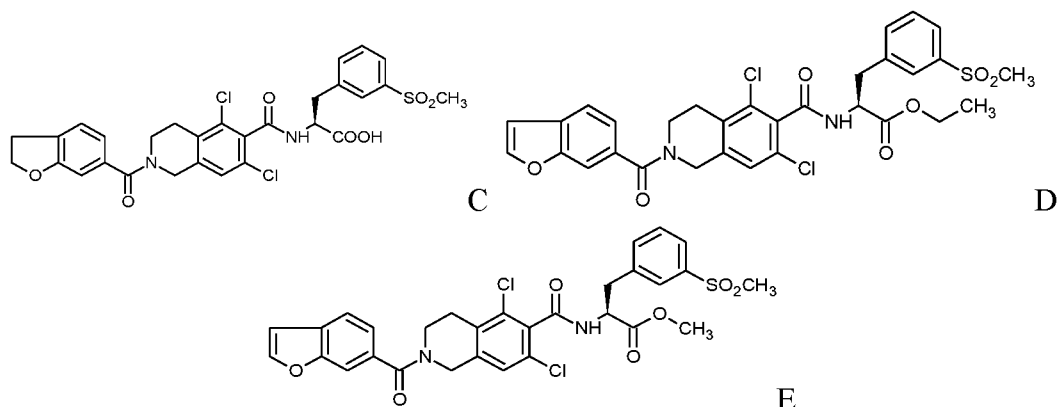
[0126] The organic acid may be selected from the group consisting of acetic acid, trifluoroacetic acid, methanesulfonic acid, *p*-toluenesulfonic acid and the like.

[0127] In one embodiment, the present invention provides a process for lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein the level of R isomer of lifitegrast is less than 1% as determined by HPLC.

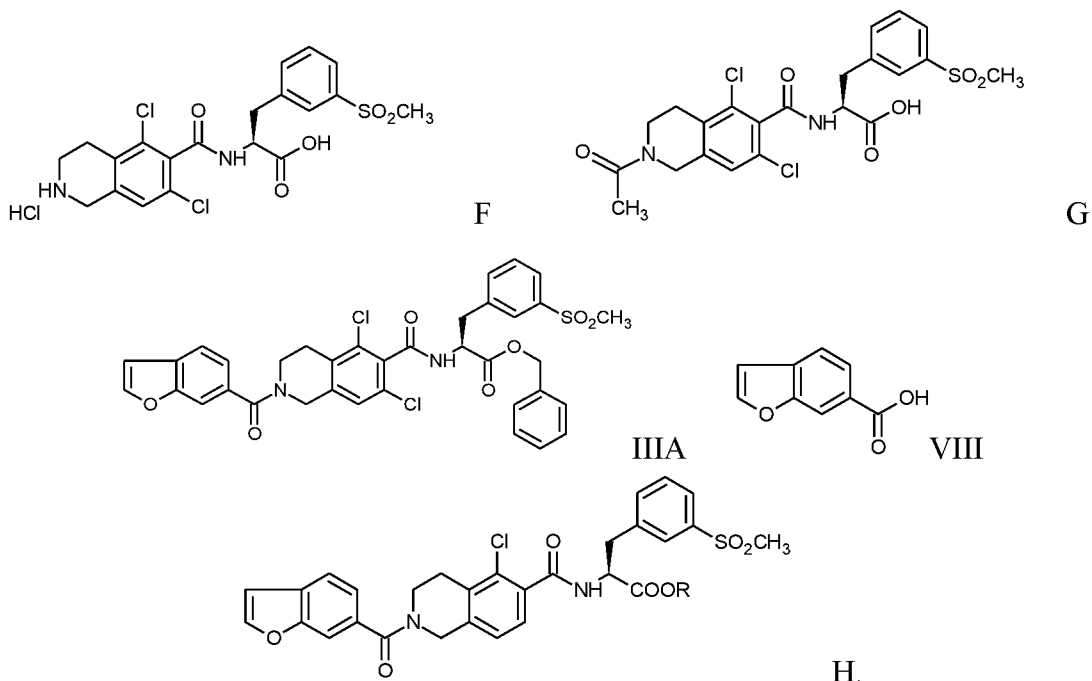
[0128] In one embodiment, the present invention provides a process for lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein corresponding R isomer of lifitegrast is not detected, as determined by HPLC.

[0129] In one embodiment, the present invention provides a process wherein lifitegrast, a compound of formula I is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC,



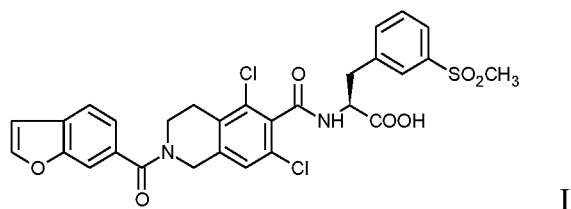


[0130] In another embodiment, the present invention provides a process wherein lifitegrast, a compound of formula I, is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula F, G, IIIA, VIII or H is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC,

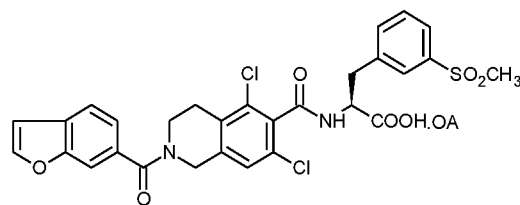


[0131] In one embodiment, the present invention provides compound of formula A, B, C, D and E and a process for preparation thereof.

[0132] In one embodiment, the present invention provides a process for the preparation of lifitegrast, a compound of formula I comprising:



(a) reacting crude lifitegrast, with an organic amine OA, of formula $NR_1R_2R_3$, wherein R_1 is H, R_2 is H, R_3 is C_1 - C_6 alkyl group substituted with a phenyl group to form an organic amine salt thereof, a compound of formula II; and

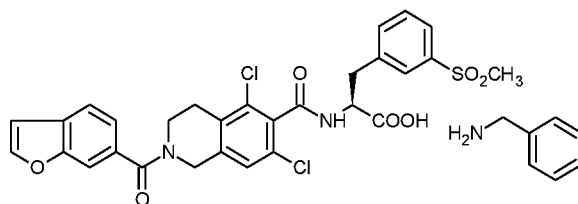


II

(b) treating the compound of formula II with an acid to form lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein the level of R isomer of lifitegrast is less than 1% as determined by HPLC.

[0133] In one embodiment, the present invention provides a process wherein lifitegrast, a compound of formula I is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC in a chiral purity of at least 99% and wherein corresponding R isomer is not detected, as determined by HPLC.

[0134] In one embodiment, the present invention provides a process for lifitegrast, wherein the compound of formula II is lifitegrast benzylamine salt, a compound of formula IIA,



IIA.

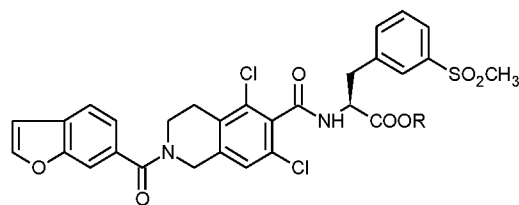
[0135] In one embodiment, the present invention provides a process for the preparation of lifitegrast, compound of formula I comprising:

(a) reacting crude lifitegrast with alkali/alkaline earth metal hydroxide or carbonate or bicarbonate of alkali/alkaline earth metal to obtain lifitegrast alkali/alkaline earth metal salt; and

(b) treating the lifitegrast alkali/alkaline earth metal salt with an acid to form lifitegrast, a compound of formula I.

[0136] In one embodiment, the present invention provides a process for the preparation of crude lifitegrast, comprising deprotecting a compound of formula III, wherein R is selected from C_1 - C_6 alkyl optionally substituted with C_6 - C_{18} aryl and wherein the aryl

group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl,



III.

[0137] In one embodiment, in compound of formula III, when R is C₁-C₆ alkyl group, the deprotection is carried out by acid or base hydrolysis.

[0138] In one embodiment, the acid hydrolysis may be carried out by using hydrochloric acid, sulfuric acid and the like.

[0139] In one embodiment, the base hydrolysis may be carried out using sodium hydroxide, potassium hydroxide and lithium hydroxide or by using carbonates or bicarbonates of alkali metal or alkaline earth metals.

[0140] In one embodiment, the deprotection using base may be carried out in a protic solvent.

[0141] In one embodiment, the deprotection using acid may be carried out in a protic solvent.

[0142] The protic solvent may be selected from alcohols like methanol, ethanol, isopropanol, propanol, butanol, isobutanol, glycols like ethylene glycol, propylene glycol or water or mixtures thereof.

[0143] In one embodiment, the deprotection using base may be carried out in an aprotic solvent.

[0144] In one embodiment, the deprotection using acid may be carried out in an aprotic solvent.

[0145] The aprotic solvent may be dioxane, tetrahydrofuran or acetone.

[0146] In one embodiment, in compound of formula III, when R is C₁-C₆ alkyl group substituted with C₆-C₁₈ aryl, the deprotection is carried out by acid or base hydrolysis or by hydrogenolysis.

[0147] The hydrogenolysis of compound of formula III may be carried out using metal catalysts such as platinum, palladium, nickel, rhodium or ruthenium supported on solid

supports like calcium carbonate, alumina, barium sulfate, silica or activated charcoal carbon.

[0148] In one embodiment, the hydrogenolysis catalyst may be palladium/carbon.

[0149] In an embodiment, the step of contacting compound of formula III with the hydrogenolysis catalyst may be performed in a solvent.

[0150] The hydrogenolysis of compound of formula III may be carried out in a solvent system selected from alcohols, esters and the like.

[0151] The alcohols may be selected from the group consisting of methanol, ethanol, *n*-propyl alcohol, isopropyl alcohol, *n*-butyl alcohol, isobutyl alcohol, *sec*-butyl alcohol, *tert*-butyl alcohol, pentanol, octanol and the like.

[0152] The esters solvent may be selected from the group consisting of ethyl acetate, isopropyl acetate, isobutyl acetate, *tert*-butyl acetate and the like.

[0153] The hydrogenolysis of compound of formula III may be carried out in the presence of hydrogen or hydrogen transfer reagents selected from formic acid, salts of formic acid, phosphonic acid, triethylsilane, hydrazine, where hydrogen is preferred.

[0154] In one embodiment, formic acid and triethylamine are used in the hydrogenolysis step.

[0155] In one embodiment, in compound of formula III, when R is C₁-C₆ alkyl, or C₁-C₆ alkyl group substituted with C₆-C₁₈ aryl, the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid.

[0156] In one embodiment, when R is C₁-C₆ alkyl, or C₁-C₆ alkyl group substituted with C₆-C₁₈ aryl, the deprotection is carried out by subjecting the compound of formula III to non-hydrolytic treatment with a Lewis acid.

[0157] In one embodiment, the term “non-hydrolytic cleavage” means the ester cleavage of the O-R bond in the compound of formula III, carried out in the absence of water.

[0158] In one embodiment, the term “non-hydrolytic cleavage” means the ester cleavage of the O-R bond in the compound of formula III being facilitated due to the coordination of the ester carbonyl in the compound of formula III with the electrophilic metal ion of the Lewis acid (MX).

[0159] In one embodiment, the term “non-hydrolytic cleavage” means the ester cleavage of the O-R bond in the compound of formula III being facilitated by the nucleophile X of the Lewis acid (MX).

[0160] In one embodiment, the term “non-hydrolytic cleavage” excludes the ester cleavage in the compound of formula III is not by water nucleophile or hydroxide nucleophile.

[0161] In one embodiment, the Lewis acid may be selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide.

[0162] The deprotection reaction may be carried out in the presence of an aprotic solvent.

[0163] In one embodiment, the aprotic solvent includes, but is not limited to esters such as methyl acetate, ethyl acetate, *n*-propyl acetate, *tert*-butyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dioxane, dimethoxy ethane, 2-methyltetrahydrofuran and the like; nitriles such as acetonitrile and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane; sulfur compounds such as carbon disulfide; tertiary amines such as pyridine; amides such as dimethylformamide; or mixtures thereof.

[0164] In one embodiment, the deprotection is carried out at room temperature to the reflux temperature of the solvent.

[0165] In one embodiment, the present invention provides a process for the preparation of lifitegrast comprising:

(a) providing a solution of lifitegrast, prepared by the process as defined above, in a solvent; and

(b) isolating lifitegrast by

(i) removing the solvent from the solution obtained in (a); or

(ii) combining the solution obtained in (a) with an antisolvent followed by optional cooling; or

(iii) slurring the compound obtained from (b) (i); or

(iv) cooling the solution obtained in (a);

wherein the lifitegrast obtained is in amorphous form.

[0166] The steps (a) and (b) are as discussed supra.

[0167] In one embodiment, the present invention provides a process for preparation of amorphous lifitegrast wherein the solvent used in (a) is ethyl acetate and the antisolvent used in (b) is cyclohexane.

[0168] In one embodiment, the present invention provides a process for the preparation of lifitegrast comprising:

(a) providing a mixture of lifitegrast, prepared by the as defined above, in water, optionally in presence of an organic solvent; and

(b) isolating lifitegrast by

(i) treating the mixture obtained in (a) with a base to give a solution;

(ii) treating the solution obtained in (b)(i) with an acid to form lifitegrast; and

(iii) filtering the lifitegrast obtained in (b)(ii);

wherein the lifitegrast obtained is in amorphous form.

[0169] The steps (a) and (b) are as discussed supra.

[0170] In one embodiment, the amorphous lifitegrast obtained in (b) may, optionally, be filtered and dried. Drying may be performed at a temperature of about 55°C to about 110°C. Drying may be performed preferably in the presence of vacuum.

[0171] In one embodiment, the present invention provides use of lifitegrast benzylamine salt, compound of formula IIA, in the preparation of lifitegrast.

[0172] In another embodiment, the present invention provides use of lifitegrast benzylamine salt, compound of formula IIA, in the preparation of amorphous lifitegrast.

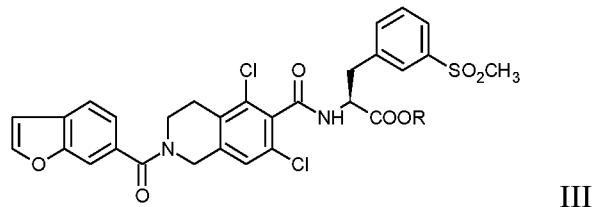
[0173] In one embodiment, the present invention provides a process wherein amorphous lifitegrast is obtained with a chemical purity of at least 99.5% and wherein the level of corresponding *R* isomer is less than 0.15% w/w as determined by HPLC.

[0174] In one embodiment, the present invention provides a process wherein amorphous lifitegrast is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC.

[0175] In another embodiment, the present invention provides a process wherein amorphous lifitegrast is obtained in a chemical purity of at least 99% and wherein the level of one or more compounds of formula F, G, IIIA or VIII is less than 0.15% w/w relative to the amount of lifitegrast as determined by HPLC.

[0176] In one embodiment, the amorphous lifitegrast, the compound of formula I obtained by the process of the present invention is converted to crystalline forms A, B, C, D, and E.

[0177] In one embodiment, the present invention provides a process for the preparation of lifitegrast, a compound of formula I, or its organic amine salt thereof, the process comprising the step of deprotecting a compound of formula III,



wherein R is selected from C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl, and wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl,

wherein the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid.

[0178] In one embodiment, the deprotection is carried out by subjecting the compound of formula III to non-hydrolytic treatment with a Lewis acid.

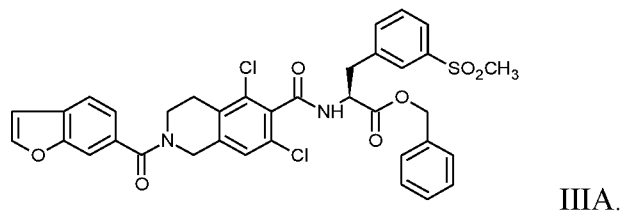
[0179] In one embodiment, the deprotection is carried out by subjecting the compound of formula III to non-hydrolytic cleavage using a Lewis acid.

[0180] The terms “non-hydrolytic” and “non-hydrolytic cleavage” are as discussed supra.

[0181] The deprotection reaction may be carried out in the presence of an aprotic solvent.

[0182] The Lewis acid and the aprotic solvent may be selected as discussed supra.

[0183] In one embodiment, the present invention provides a process for the preparation of crude lifitegrast, comprising deprotecting a compound of formula III, wherein R is benzyl, represented by compound of formula IIIA



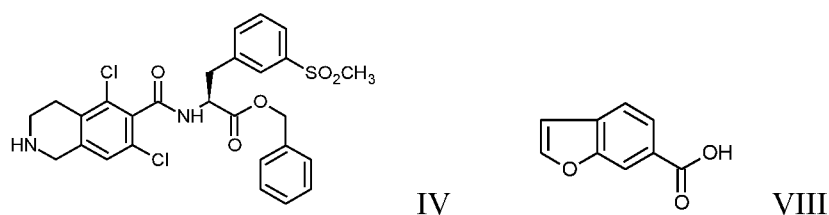
[0184] In one embodiment, the present invention provides a process for lifitegrast, wherein lifitegrast obtained has reduced levels of chemical catalyst as an impurity compared to lifitegrast made using palladium as a catalyst to remove an ester group to yield the carboxylic acid.

[0185] In one embodiment, the present invention provides a process for lifitegrast, wherein the level of chemical catalyst such as palladium, platinum, or nickel is less than 100 ppm.

[0186] In another embodiment, the present invention provides a process for lifitegrast, wherein the level of chemical catalyst such as palladium, platinum, or nickel is less than 50 ppm, preferably less than 10 ppm, more preferably less than 1 ppm.

[0187] In another embodiment, the present invention provides a process for lifitegrast, wherein the lifitegrast obtained is essentially free of chemical catalyst such as palladium, platinum, or nickel.

[0188] In one embodiment, the present invention provides a process for the preparation of compound of formula IIIA, by condensing a compound of formula IV or acid addition salt thereof



with 1-benzofuran-6-carboxylic acid, a compound of formula VIII or an activated derivative thereof.

[0189] In one embodiment, the compound of formula IV is reacted with 1-benzofuran-6-carboxylic acid in the presence of a coupling agent and a solvent to obtain a compound of formula IIIA.

[0190] In one embodiment, the coupling agent may be selected from the group consisting of EDC.HCl [N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, HATU[(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate], T3P@[1-Propanephosphonic anhydride] and CDI(1,1'-carbonyldiimidazole).

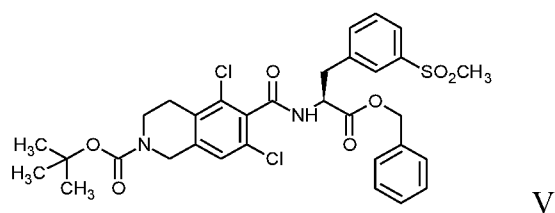
[0191] In one embodiment, the compound of formula IV is reacted with 1-benzofurancarboxylic acid in the presence of a coupling agent, a solvent and optionally a catalyst to obtain a compound of formula IIIA.

[0192] In one embodiment, the catalyst may be selected from the group consisting of HOBT [1-hydroxybenzotriazole], HOAt [1-hydroxyazatriazole], DMAP [4-(N,N-dimethylamino)pyridine], DIPEA [N,N-Diisopropylethylamine] and HOPO [2-hydroxypyridine-N-oxide].

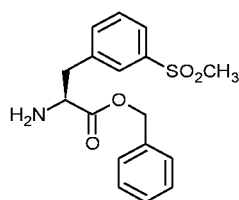
[0193] In one embodiment, the compound of formula IV is reacted with 1-benzofurancarboxylic acid in presence of an agent which promotes carboxamide formation from carboxylic acids such as but not limited to thionyl chloride, oxalyl chloride, sulfuryl chloride, phosphorous pentachloride, an anhydride or a mixed anhydride such as pivalic anhydride, acetic anhydride to obtain a compound of formula III.

[0194] In one embodiment, the solvent is selected from the group consisting of ether such as diethyl ether, diisopropyl ether, methyl tertiary butyl ether, tetrahydrofuran, methyl-tetrahydrofuran and the like; esters such as ethyl acetate, isopropyl acetate and the like; amides such as dimethyl formamide, dimethyl acetamide and the like; ketones such as, N-methyl pyrrolidinone, acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; hydrocarbons such as toluene, xylene, cyclohexane and the like; halogenated hydrocarbons such as methylene dichloride, ethylene dichloride, chloroform and the like; nitrile such as acetonitrile; dimethyl sulfoxide, sulfolane, water or mixture thereof.

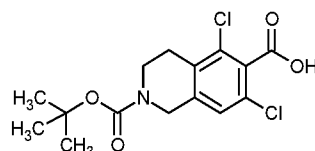
[0195] In one embodiment, the compound of formula IV is obtained by deprotecting a compound of formula V



[0196] In one embodiment, the compound of formula V may be obtained by coupling a compound of formula VI or acid addition salt thereof with a compound of formula VII.



VI



VII

[0197] The coupling reaction may be carried out as discussed supra.

[0198] In one embodiment, the present invention provides a method of assessing the purity of lifitegrast or the pharmaceutical composition containing it, by HPLC comprising the steps of:

- a) providing a standard solution of the compound of formula A, B, C, D, E; and
- b) using the solution of step 'a', as a reference marker to determine the level of the compound of formula A, B, C, D, E.

[0199] The determination of the presence of the compound of formula A to E in the sample of lifitegrast, is effected by comparing the retention of the different components of the sample of lifitegrast, by the chromatographic technique with the retention of the compounds of formula A to E under the same chromatographic conditions.

[0200] The term "reference marker", as used herein, refers to a compound that may be used in qualitative analysis to identify components of a mixture based on their position, and/or in quantitative analysis to determine the concentration of said compound in a mixture by reference to the concentration of a solution comprising a known amount of said component.

[0201] In one embodiment, the present invention provides lifitegrast, salt or solvate thereof obtained by the processes herein described, having D₉₀ particle size of less than about 150 microns, preferably less than about 100 microns, more preferably less than about 50 microns, still more preferably less than about 30 microns, still more preferably less than about 10 microns.

[0202] In one embodiment, the present invention provides lifitegrast, salt or solvate thereof obtained by the processes herein described, having D₅₀ particle size of less than about 150 microns, preferably less than about 100 microns, more preferably less than about 50 microns, still more preferably less than about 30 microns, still more preferably less than about 10 microns.

[0203] The particle size disclosed here can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the

solid state lifitegrast or salt, solvate thereof into any of the foregoing desired particle size range.

[0204] HPLC method

High performance liquid chromatography (HPLC) was performed with the conditions described below for detecting chemical purity:

Column: Inertsil ODS 3V, 250 x 4.6mm, 5 μ , Make: GL-Science, Column temperature: 30°C, Sample cooler temperature: 25°C, Mobile phase: A = Buffer, Buffer: 1.0ml of o-phosphoric acid in 1000ml of water, B = Acetonitrile, Diluent: Water: Methanol (40: 60, v/v); Flow Rate: 1.0 mL/minute, Detection wavelength: UV 210nm, Injection volume: 20 μ L.

Gradient Program:

Time (min)	% Mobile Phase A	% Mobile Phase B
0.01	85	15
45	25	75
70	25	75
72	85	15
80	85	15

High performance liquid chromatography (HPLC) was performed with the conditions described below for detecting stereochemical purity:

Column: Chiralpak AD-H, 250 X 4.6mm, 5 μ , Make: Daicel, Column temperature: 35°C, Sample cooler temperature: 15°C, Mobile phase: n-Hexane: Isopropyl alcohol (500: 500 v/v) add 1.0ml Trifluoroacetic acid and mix well, Diluent: Ethanol: Isopropyl alcohol (100: 900 v/v) add 1.0ml Trifluoroacetic acid and mix well; Flow Rate: 1.0 mL/minute, Detection wavelength: UV 220nm, Injection volume: 20 μ L.

[0205] Instrumental Settings

A. Proton NMR spectra were recorded in CDCl₃ and DMSO-d₆ using NMR instrument- Varian 300 MHZ.

B. XRPD: The measurements were performed on Philips X-Ray Diffractometer model XPERT-PRO (PANalytical) Detector: X'celerator [1] using Cu lamp with type and wavelength of the X-ray radiation: K- α_1 1.54060[Å], K- α_2 1.5444[Å]

[0206] The examples that follow are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

EXAMPLES

[0207] **Example 1: Preparation of compound of formula V**

To a solution of 2-(*tert*-butoxycarbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (compound VII, 100gm) and Benzyl (*S*)-2-amino-3-[3-(methylsulfonyl)phenyl]propionate hydrochloride (compound VI, 112.17gm) in DMF was added EDC.HCl (83gm), HOAt (58.96gm) followed by triethyl amine (87.6gm) under stirring at room temperature. After completion of reaction, the reaction mass was added slowly to water, stirred for 2-3 hours and the precipitated solid was filtered. The solid obtained was washed with water. The wet cake was stirred in 5% aq. potassium carbonate and filtered. The solid was washed with water and dried under vacuum at 40-45°C for 12 hours to afford the title compound

Yield: 170 gm, HPLC Purity: 95.68 %.

[0208] **Example 2: Preparation of compound of formula IV**

Ethyl acetate hydrochloride (990ml) was added slowly to ethyl acetate solution of compound of formula V (165gm) at room temperature and stirred. The reaction mass was stirred for about 20 hours. After completion of reaction, the reaction mass was filtered under nitrogen atmosphere, solid was washed with ethyl acetate and dried under vacuum at about 40-45°C. The crude material was purified by crystallizing from a mixture of dichloromethane and methanol.

Yield: 100 gm; HPLC Purity: 99.20 %.

[0209] **Example 3: Preparation of compound of formula IIIA**

To a methylene dichloride solution of compound of formula IV (100gm) and 1-benzofuran-6-carboxylic acid (28.5gm), EDC.HCl (48.10gm), HOBT (34.0gm) followed by TEA (50.8gm) was added and stirred at room temperature for 12 hours. After completion of reaction, water was added to reaction mass, stirred and the layers were separated. The organic layer was washed with water, separated and concentrated under vacuum to give foamy solid. The solid was stirred in 20% ethyl acetate in cyclohexane and then filtered. The obtained solid was washed with 20% ethyl acetate in cyclohexane and dried in vacuum oven at about 40-45°C for 12 hours.

Yield: 80 gm; HPLC purity: 98.5%.

[0210] Example 4: Preparation of Lifitegrast benzyl amine salt compound of formula IIA

A solution of lithium hydroxide monohydrate (6.2gm) in 240 ml of water was added slowly to an acetone solution of compound IIIA (80gm) at about 0 to -5°C. The reaction mass was maintained at 0 to -5°C for 1 hour. After completion of reaction, the reaction mass was diluted with water and ethyl acetate, stirred and layers were separated. The aqueous layer was extracted with ethyl acetate. Ethyl acetate was added to the aqueous layer, acidified with dilute hydrochloric acid to a pH of about 2 and layers were separated. The aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with water and concentrated under vacuum to give the foamy solid (62gm). The solid was dissolved in ethyl acetate and isopropanol, and heated to 70-75°C and benzyl amine (10.8 gm) was added and stirred at 70-75°C for 1 hour. The reaction mass was then cooled to room temperature, stirred for 5-6 hours and the precipitated solid was filtered. The solid was dried in an air oven to obtain crude benzyl amine salt of lifitegrast (62gm), which was crystallized from 5% aqueous ethanol to obtain pure compound of Formula IIA.

Yield: 45 gm; HPLC purity: 98.5%; chiral purity: 100%

XRD peaks of Lifitegrast benzyl amine salt

Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]
2.25	1.61	17.44	29.27	24.36	34.58	36.35	8.94
8.78	29.38	19.10	100.00	25.26	46.10	38.80	6.12
9.99	29.71	19.80	91.05	26.64	16.65	41.10	3.41
11.03	6.41	20.60	64.03	28.76	23.98	43.35	6.20
14.31	13.44	21.10	79.82	30.51	31.20	44.25	4.41
15.00	56.53	21.97	30.57	32.08	8.93	45.51	4.99
15.63	27.78	22.33	37.12	33.60	19.15	48.59	4.26
16.51	5.58	23.70	93.74	35.55	7.14		

[0211] Example 5: Preparation of amorphous Lifitegrast

The pure benzyl amine salt of lifitegrast of Ex-4 was added to ethyl acetate and water, acidified with dilute hydrochloric acid to a pH of about 2 and stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and was concentrated under vacuum to give a

foamy solid which was stirred in a mixture of ethyl acetate and cyclohexane for a period of about 2 hours. The reaction mixture was filtered and solid dried in an air oven at about 40-45°C.

Yield: 45 gm; HPLC Purity: 99.8%, Chiral purity: 100% (R-isomer Not detected).

[0212] Example 6: Preparation of amorphous Lifitegrast

The pure benzyl amine salt of lifitegrast of Ex-4 was added to ethyl acetate and water. The reaction mass acidified with dilute hydrochloric acid to a pH of about 2 and stirred for 30 minutes. The layers were separated and aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and concentrated under vacuum to give a foamy solid which was dissolved in ethyl acetate. The solution was slowly added to cyclohexane at room temperature and stirred for 2-3 hours. The reaction mass was filtered and solid was dried in air oven at about 40-45°C.

Yield: 45 gm; HPLC Purity: 99.7%; Chiral purity: 100%, (R-isomer Not Detected).

[0213] Example 7: Preparation of Lifitegrast benzyl amine salt IIA

To a solution of IIIA (80gm) in ethyl acetate at room temperature was added 10 % palladium on carbon (8gm) and the reaction mass was kept in hydrogenator at 1-2 kg/cm pressure at 25 to 30° C for 1 hour. After completion of reaction, the reaction mass was filtered through hyflow bed to remove the catalyst. The organic layer was concentrated under vacuum to afford a foamy solid. The solid was dissolved in ethyl acetate and isopropanol, heated to 70-75°C, benzyl amine (10.8gm) was added and stirred at 70-75°C for 1 hour. The reaction mass was then cooled to room temperature, stirred for 5-6 hours and filtered. The solid was dried in an air oven to obtain crude benzyl amine salts of lifitegrast (62gm), which was crystallized from 5% aqueous ethanol.

Yield: 45 gm; HPLC purity: 99.8%; Chiral purity: 100% (R-isomer Not detected).

[0214] Example 8: Preparation of amorphous Lifitegrast

The pure benzyl amine salt of lifitegrast of Ex-7 was added to ethyl acetate and water. The reaction mass was acidified with dilute hydrochloric acid to a pH of about 2 and stirred for 30 minutes. The layers were separated and aqueous layer was extracted with

ethyl acetate. The combined organic layer was washed with water and concentrated under vacuum to give a foamy solid which was dissolved in ethyl acetate. The ethyl acetate solution was slowly added to cyclohexane at room temperature and stirred for 2-3 hours. The reaction mass was filtered and solid was dried in an air oven at about 40-45°C.

Yield: 45 gm; HPLC Purity: 99.5 %; Chiral purity: 100% (R-isomer Not detected).

[0215] Example 9: Preparation of compound IIA (Lifitegrast benzyl amine salt)

Benzyl amine (10.8 gm) was added to the solution of crude lifitegrast (62gm) in ethyl acetate and isopropanol and heated to 70-75°C and stirred at 70-75°C. The reaction mass was then cooled to room temperature, stirred for 5-6 hours and filtered. The solid was dried in an air oven.

Yield: 62 gm; HPLC Purity: 98.0%; Chiral purity: 100% (R-isomer Not detected).

[0216] Example 10: Purification of compound IIA (Lifitegrast benzyl amine salt)

The crude benzyl amine salt of lifitegrast (62 gm) of Ex-11 was dissolved in 5% aqueous ethanol at reflux temperature. The clear solution was cooled to room temperature, stirred for 12 hours and filtered. The solid was dried in an air oven.

Yield: 55 gm; HPLC Purity: 99.7 %; Chiral purity: 100% (R-isomer Not detected).

[0217] Example 11: Preparation of amorphous lifitegrast from benzyl amine salt of (2S)-2-[[2-(1-benzofuran-6-carbonyl)-5,7-dichloro-3,4-dihydro-1H-isoquinoline-6-carbonyl]amino]-3-(3-methylsulfonylphenyl)propanoic acid

The pure benzyl amine salt of lifitegrast (55 gm) of Ex-12 was added to ethyl acetate and water under stirring. The reaction mass was acidified with dilute hydrochloric acid to a pH of about 2 and stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and concentrated under vacuum to give a foamy solid which was dissolved in ethyl acetate. The ethyl acetate solution was slowly added to cyclohexane at room temperature, stirred for 2-3 hours and filtered. The solid was dried in an air oven at about 40-45°C to give amorphous lifitegrast

Yield: 45 gm; HPLC purity: 99.7 %; Chiral purity: 100% (R-isomer Not Detected).

[0218] Comparative Example 1: Preparation of amorphous Lifitegrast

The aq solution of lithium hydroxide monohydrate (6.2gm) was added slowly to acetone solution of compound IIIA (80gm) at about 0 to -5° C. The reaction mass was maintained at 0 to -5°C for 1 hour. After completion of reaction, reaction mass was diluted with water and ethyl acetate, stirred and layers were separated. The aq. layer was extracted with ethyl acetate. Fresh ethyl acetate was added to the aq layer and acidified with dilute hydrochloric acid to a pH of about 2 and stirred. The layers were separated and the aqueous layer was further extracted with ethyl acetate. The combined organic layers was washed with water and concentrated under vacuum to give the foamy solid (62gm). The foamy solid was taken in a mixture of ethyl acetate and cyclohexane, stirred and filtered. The solid was dried in an air oven at about 40-45°C.

Yield: 62 gm (89%); HPLC Purity: 96.0%; Chiral purity: 98.5% (R-isomer around 1.5%).

[0219] Comparative Example 2: Preparation of amorphous Lifitegrast

To a solution of compound IIIA (80gm) in ethyl acetate, 10 % palladium on carbon (8 gm) was added and stirred for 1 hour. The reaction mass was kept in hydrogenator at 1-2 kg/cm pressure at about 25-30°C for 1 hour. After completion of reaction, reaction mass was filtered through hyflow bed to remove the catalyst. The organic layer was concentrated under vacuum to afford a foamy solid (62gm). The solid was added to a mixture of ethyl acetate and cyclohexane, stirred and filtered. The solid was dried in an air oven at about 40-45°C.

Yield: 62 gm (64%); HPLC Purity: 94.0%; Compound of formula A: 1.0%; Chiral purity; 96.5% (R-isomer around 3.5%).

[0220] Example 12: Preparation of benzyl-(2S)-N-[(5,7-dichloro-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-(methylsulfonyl)-L-phenylalaninate hydrochloride

To a solution of 2-(*tert*-butoxycarbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (100g) and benzyl-(*S*)-2-amino-3-[3-(methylsulfonyl)phenyl]propionate hydrochloride (117.49g) in dimethylformamide (1000mL), was added HATU (120.81g)

followed by triethylamine (87.6g) under stirring and the reaction mixture was stirred at about room temperature for about 4h. The reaction mixture was filtered, added slowly in to water and stirred for about 3h. The precipitated solid was filtered, washed with water and suck dried. To the wet solid, was added dichloromethane (500mL) and the mixture was stirred for about 15min. The dichloromethane layer was treated with activated charcoal and washed with water. The dichloromethane layer was diluted with dichloromethane (1300mL) and ethyl acetate/hydrochloric acid (10-12%, 500mL). The reaction mixture was stirred for about 4h at about room temperature, filtered under nitrogen atmosphere, washed with *n*-hexane or cyclohexane and dried under vacuum at about 40°C to about 45°C for about 12h. The crude solid was purified by crystallizing from a mixture of dichloromethane and methanol.

Yield: 100g; HPLC purity: 99.83%

[0221] Example 13: Preparation of benzyl amine salt of lifitegrast

To a solution of benzyl-(2*S*)-*N*-[(5,7-dichloro-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-(methylsulfonyl)-L-phenylalaninate hydrochloride (100g) and 1-benzofuran-6-carboxylic acid (28.5g) in dichloromethane (2000mL) was added EDC.HCl (48.1g), HOBT (34g) followed by triethylamine (50.8g) under stirring and the reaction mixture was stirred at about room temperature for about 12h. Water was added to the reaction mixture which was stirred for about 30min. The two layers were separated and the organic layer was concentrated under vacuum to give compound of formula IIIA as foamy solid. To the obtained solid, ethyl acetate (2000mL) and lithium iodide (100g) was added. The reaction mixture was stirred for about 24h at about reflux temperature. Water was added to the reaction mixture and the two layers were separated. The organic layer was concentrated under vacuum to give a foamy solid which was dissolved in ethyl acetate and isopropanol. The reaction mixture was heated to about 70°C to about 75°C and benzyl amine (10.8g) was added to it. The reaction mixture was stirred at about the same temperature for about 1h. The reaction mixture was cooled to about room temperature and was stirred for about 6h. The precipitated solid was filtered and dried to give crude benzyl amine salt of lifitegrast (62g). The crude benzyl amine salt of Lifitegrast was crystallized from 5% aqueous ethanol to give pure benzyl amine salt of lifitegrast (45g).

HPLC purity: 99.88%; Compound of formula A: Not detected; Chiral purity: 100% (R-isomer not detected)

[0222] Example 14: Preparation of benzyl amine salt of lifitegrast

To a solution of benzyl-(2*S*)-*N*-[(5,7-dichloro-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-(methylsulfonyl)-L-phenylalaninate hydrochloride (100g) and 1-benzofuran-6-carboxylic acid (28.5g) in dichloromethane (2000mL) was added EDC.HCl (48.1g), HOBT (34g) followed by triethylamine (50.8g) under stirring and the reaction mixture was stirred at about room temperature for about 12h. Water was added to the reaction mixture which was stirred for about 30min. The two layers were separated and the organic layer was concentrated under vacuum to give compound of formula IIIA as foamy solid. The solid was dissolved in tetrahydrofuran (1000mL) and 10%Pd/C (2g) was added to it. Triethylsilane was added to the reaction mixture at about room temperature. The reaction mixture was stirred for about 1h at about the same temperature. Water was added to the reaction mixture and the two layers were separated. The organic layer was concentrated under vacuum to give a foamy solid which was dissolved in ethyl acetate and isopropanol. The reaction mixture was heated to about 70°C to about 75°C and benzyl amine (10.8g) was added to it. The reaction mixture was stirred at about the same temperature for about 1h. The reaction mixture was cooled to about room temperature and was stirred for about 6h. The precipitated solid was filtered and dried to give crude benzyl amine salt of lifitegrast (62g). The crude benzyl amine salt of Lifitegrast was crystallized from 5% aqueous ethanol to give pure benzyl amine salt of lifitegrast (45g).

HPLC purity: 96.10; Chiral purity: 100% (R-isomer not detected)

[0223] Example 15: Preparation of amorphous lifitegrast from benzyl amine salt of lifitegrast

A mixture of pure benzyl amine salt of lifitegrast (100g) in ethyl acetate (675mL) and water (450mL) was acidified with dilute hydrochloric acid to a pH of about 2 and was stirred for about 30min. The two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and concentrated under vacuum to give a foamy solid which was stirred in cyclohexane

containing 30% ethyl acetate. The solid obtained was filtered and dried at about 40°C to about 45°C to give amorphous lifitegrast (90g) which was milled in jet mill at about 4-5kg pressure under nitrogen to afford ICH quality amorphous lifitegrast.

HPLC purity: 99.8%; Compound of formula A: Not detected; Chiral purity: 100% (R-isomer Not Detected)

[0224] Example 16: Preparation of amorphous lifitegrast from benzyl amine salt of lifitegrast

A mixture of pure benzyl amine salt of lifitegrast (100g) in ethyl acetate (675mL) and water (450mL) was acidified with dilute hydrochloric acid to a pH of about 2 and was stirred for about 30min. The two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and concentrated under vacuum to give a foamy solid. Water was added to the obtained solid followed by addition of aqueous lithium hydroxide. The solution was stirred and filtered. The pH of the filtrate was adjusted to about 3 to about 4 using dilute hydrochloric acid. The precipitated solid was filtered and dried at about 40°C to about 45°C to give amorphous lifitegrast.

Yield: 90g; HPLC purity: 99.85 %; Chiral purity: 99.99% (R-isomer 0.01%)

[0225] Example 17: Preparation of benzyl-(2*S*)-*N*-[(5,7-dichloro-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-(methylsulfonyl)-L-phenylalaninate hydrochloride

To a solution of 2-(*tert*-butoxycarbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (100g) and benzyl-(*S*)-2-amino-3-[3-(methylsulfonyl)phenyl]propionate hydrochloride (112.2g) in dichloromethane (1000mL), was added HATU (120.81g) followed by triethylamine (87.7g) under stirring and the reaction mixture was stirred at reflux temperature for about 24h. The reaction mass was cooled to room temperature and water was added and stirred for about 10min. The layers were separated and organic layer washed with aqueous potassium carbonate solution and then washed with water. The organic layer was washed with 3% aqueous hydrochloric acid and then washed with water. The organic layer was treated with charcoal and filtered through hyflow bed. The organic layer was diluted with dichloromethane and ethyl acetate hydrochloric

acid was added slowly at about room temperature. The reaction mixture was stirred for about 4h at about room temperature. The precipitated solid was filtered under nitrogen atmosphere and washed with dichloromethane followed by cyclohexane. The solid was dried under vacuum at about 40°C to about 45°C for about 12h to afford crude benzyl-(2*S*)-*N*-[(5,7-dichloro-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-(methylsulfonyl)-L-phenylalaninate hydrochloride. The crude solid was taken in mixture of dichloromethane and methanol (9.6:0.4) and the suspension was heated for about 30min at about reflux temperature. The reaction mass was cooled to about 20-25 °C and stirred for about 4h. The solid was filtered under nitrogen atmosphere and washed with dichloromethane followed by cyclohexane. The solid was dried under vacuum at about 40°C to about 45°C for about 12h.

Yield: 150g; HPLC purity: 99.83%

[0226] Example 18: Preparation of benzyl amine salt of lifitegrast

To a solution of benzyl-(2*S*)-*N*-[(5,7-dichloro-1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-3-(methylsulfonyl)-L-phenylalaninate hydrochloride (100g) and 1-benzofuran-6-carboxylic acid (28.5g) in dichloromethane (1000mL) was added EDC.HCl (48.1g), HOBT (34g) followed by triethylamine (50.8g) under stirring and the reaction mixture was stirred at room temperature for about 4h. The reaction mass was diluted with dichloromethane, and water was added to the reaction mixture. The reaction mass was stirred for about 15min and the two layers were separated. The organic layer was washed with of 2% aqueous potassium carbonate and then washed with water. The layers were separated and the organic layer was washed with 1% aqueous hydrochloric acid followed by washing with water. The organic layer was treated with charcoal and filtered through hyflow bed. The organic layer was concentrated under vacuum to give compound of formula IIIA as foamy solid (yield: 118g, 100%). 1000 ml ethyl acetate and 110g lithium iodide was added to the concentrated mass. The reaction mixture was stirred for about 24h at about reflux temperature. The reaction mass was cooled to about room temperature and water was added to the reaction mass. The reaction mass was stirred for 15min to get a clear solution. The layers were separated and the aqueous layer was washed with ethyl acetate. Ethyl acetate and tetrahydrofuran were added to the aqueous layer and acidified

with 15% hydrochloric acid. The layers were separated and the aqueous layer was extracted with a mixture of ethyl acetate and tetrahydrofuran followed by extraction with ethyl acetate. The combined organic layer was washed with 4% aqueous sodium metabisulphite solution followed by washing with water. The organic layer was filtered through hyflow bed and concentrated under vacuum to give a foamy solid (yield: 100g, 97%; HPLC purity: 99.0%; R-isomer: 1.2%). The solid was dissolved in ethyl acetate and isopropyl alcohol and benzylamine (21.5g) was added to the reaction mass. The reaction mixture was stirred at ambient temperature for about 8h. The precipitated solid was filtered and dried to give benzylamine salt of lifitegrast (90g). The benzyl amine salt of Lifitegrast was crystallized from aqueous ethanol to give benzylamine salt of lifitegrast (80g).

HPLC purity: 99.88%; Chiral purity: 100% (R-isomer not detected); Compound of formula A: Not detected; Compound of formula B: < 0.05%; Compound of formula C: < 0.01%; Compound of formula D: < 0.03%; Compound of formula D: < 0.03%

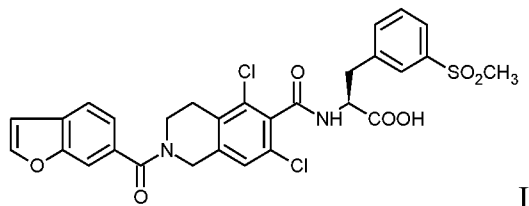
[0227] Example 19: Preparation of amorphous lifitegrast from benzyl amine salt of lifitegrast

A mixture of pure benzyl amine salt of lifitegrast (100g) in dichloromethane (1500mL) and water (1000mL) was acidified with dilute hydrochloric acid to a pH of about 2 and was stirred for about 30min. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water and concentrated under vacuum to give a foamy solid which was stirred in cyclohexane containing ethyl acetate. The solid obtained was filtered and dried at about 40°C to about 45°C to give amorphous lifitegrast (90g) which was milled in jet mill at about 4-5 kg pressure under nitrogen to afford ICH quality amorphous lifitegrast.

HPLC purity: 99.8%; Chiral purity: 100% (R-isomer Not Detected); Compound of formula A: Not detected; Compound of formula B: < 0.05%; Compound of formula C: < 0.01%; Compound of formula D: < 0.03%; Compound of formula D: < 0.03%

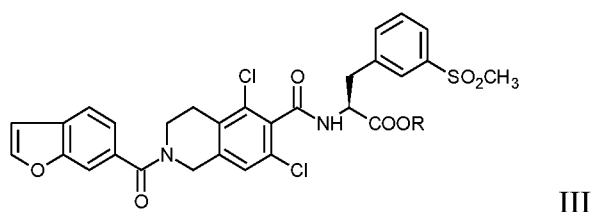
CLAIMS:

- 1] A process for the preparation of lifitegrast, a compound of formula I,



the process comprising:

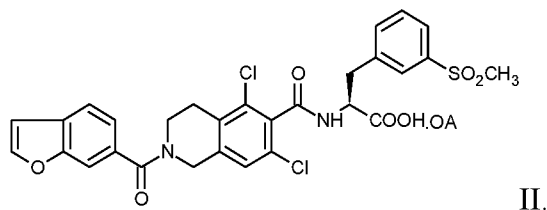
- (a) deprotecting a compound of formula III,



wherein R is selected from C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl, and wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl;

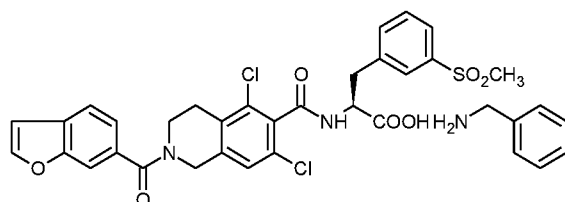
wherein the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid selected from the group consisting of lithium iodide, magnesium iodide, trimethylsilyl iodide, aluminium triiodide, and mixtures thereof, to obtain lifitegrast; and

- (b) optionally, reacting the lifitegrast obtained in step (a) with an organic amine OA to form an organic amine salt thereof, a compound of formula II,



- 2] The process of claim 1, wherein R is selected from C₁-C₆ alkyl optionally substituted with C₆ aryl, and wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl and C₁-C₆ alkyl.

- 3] The process of claim 1, wherein the deprotection is carried out in the presence of an aprotic solvent.
- 4] The process of claim 3, wherein the aprotic solvent is selected from esters such as methyl acetate, ethyl acetate, *n*-propyl acetate, *tert*-butyl acetate; ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dioxane, dimethoxy ethane, 2-methyltetrahydrofuran; nitriles such as acetonitrile; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane; sulfur compounds such as carbon disulfide; tertiary amines such as pyridine; amides such as dimethylformamide; or mixtures thereof.
- 5] The process of claim 1, wherein the deprotection is carried out at room temperature to the reflux temperature of the solvent.
- 6] The process of claim 1, wherein the lifitegrast obtained in step (a) is in-situ and carried forward to step (b).
- 7] The process of claim 1, wherein OA is an organic amine of formula $NR_1R_2R_3$; wherein R_1, R_2, R_3 may be independently selected from the group consisting of H or C_1 - C_6 alkyl optionally substituted with C_6 - C_{18} aryl; wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C_1 - C_6 alkoxy and C_1 - C_6 alkyl.
- 8] The process of claim 7, wherein the compound of formula $NR_1R_2R_3$, wherein R_1 is H, R_2 is H, R_3 is C_1 - C_6 alkyl group substituted with a C_6 aryl group.
- 9] The process of claim 1, wherein compound of formula II is lifitegrast benzylamine salt, a compound of formula IIA,

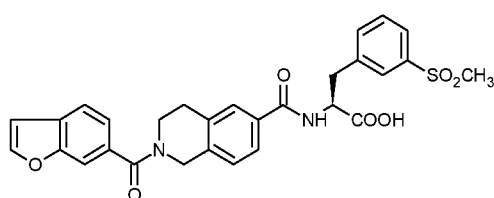


IIA.

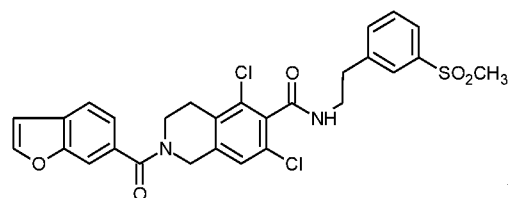
10] The process of claim 1, further comprising reacting the organic amine salt of lifitegrast, the compound of formula II, with an acid to form lifitegrast, the compound of formula I.

11] The process of claim 10, wherein the lifitegrast is obtained in a chiral purity of at least 99% and wherein the level of *R* isomer of lifitegrast is less than 1% as determined by HPLC.

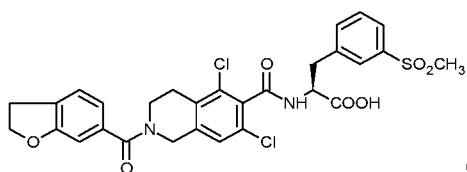
12] The process of claim 10, wherein the lifitegrast is obtained in a chemical purity of at least 99%, and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w, relative to the amount of lifitegrast as determined by HPLC,



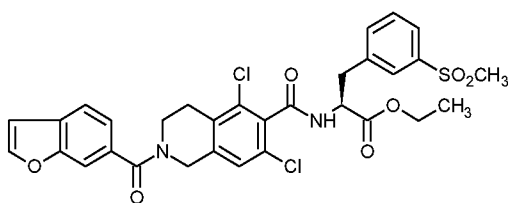
A



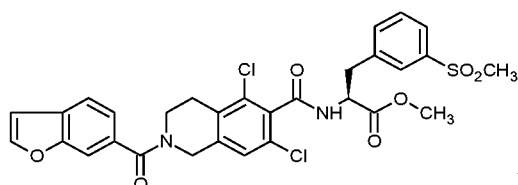
B



C



D



E.

13] The process for the preparation of lifitegrast comprising:

- (a) providing a solution of lifitegrast, prepared by the process of claim 10, in a solvent; and
- (b) isolating lifitegrast by
 - (i) removing the solvent from the solution obtained in (a); or
 - (ii) combining the solution obtained in (a) with an antisolvent followed by optional cooling; or
 - (iii) slurring the compound obtained from (b) (i); or
 - (iv) cooling the solution obtained in (a);wherein the lifitegrast obtained is in amorphous form.

14] The process of claim 13, wherein the removal of solvent in (b)(i) is carried out by solvent distillation, concentration, spray drying, fluid bed drying, lyophilization, flash drying, spin flash drying, or thin-film drying.

15] The process of claim 13, wherein the solvent in (a) is an ester solvent and antisolvent used in b(ii) is an acyclic ether or aliphatic hydrocarbon.

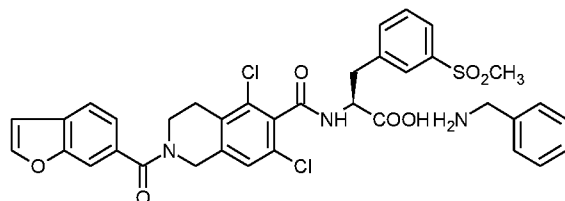
16] The process for the preparation of lifitegrast comprising:

- (a) providing a mixture of lifitegrast, prepared by the process of claim 10, in water, optionally in presence of an organic solvent; and
- (b) isolating lifitegrast by
 - (i) treating the mixture obtained in (a) with a base to give a solution;
 - (ii) treating the solution obtained in (b)(i) with an acid to form lifitegrast; and
 - (iii) filtering the lifitegrast obtained in (b)(ii);wherein the lifitegrast obtained is in amorphous form.

17] The process of claim 16, wherein the base used in (b)(i) is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, sodium bicarbonate and potassium bicarbonate.

18] The process of claim 16, wherein the acid used in (b)(ii) is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, citric acid and phosphoric acid.

19] Lifitegrast benzylamine salt, a compound of formula IIA,



20] The compound of claim 19, characterized by ^1H NMR having peaks at δ 8.11-8.12, 8.04-8.06, 7.71-7.83, 7.62-7.64, 7.43-7.52, 7.3-7.39, 7.05, 4.74, 4.41-4.46, 3.95, 3.62, 3.26-3.30, 3.08-3.16, 2.77-2.80.

21] The compound of claim 19 in crystalline form characterized by XRD having 2 θ peaks at 15.0, 19.1, 19.8, 20.6 and $21.1 \pm 0.2^\circ$.

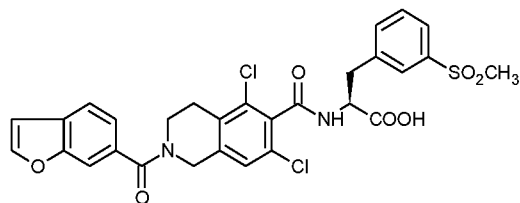
22] A process for the preparation of lifitegrast benzylamine salt, a compound of formula IIA, the process comprising:

- (a) reacting lifitegrast with benzylamine in presence of a solvent to form a reaction mixture;
- (b) obtaining lifitegrast benzylamine salt from the reaction mixture of step (a); and
- (c) isolating the lifitegrast benzylamine salt, the compound of formula IIA.

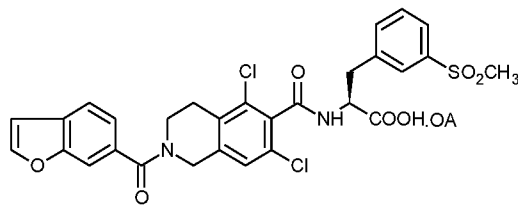
23] The process of claim 22, wherein the step (b) of obtaining lifitegrast benzylamine salt comprises:

- (i) cooling and stirring the mixture obtained in (a); or
- (ii) removing the solvent from the mixture obtained in (a); or
- (iii) treating the mixture of step (a) with an anti-solvent optionally, cooling and stirring the obtained mixture.

24] A process for the preparation of lifitegrast, a compound of formula I comprising:



(a) reacting crude lifitegrast, with an organic amine OA, to form an organic amine salt thereof, a compound of formula II; and

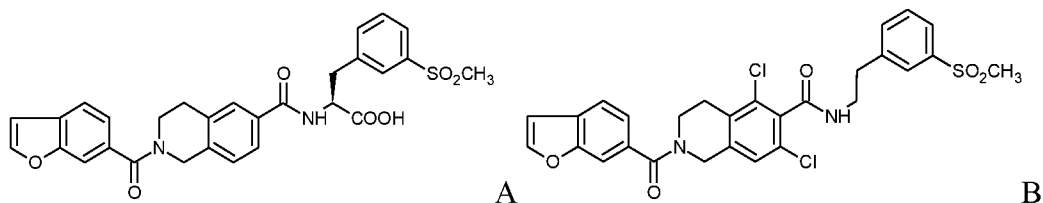


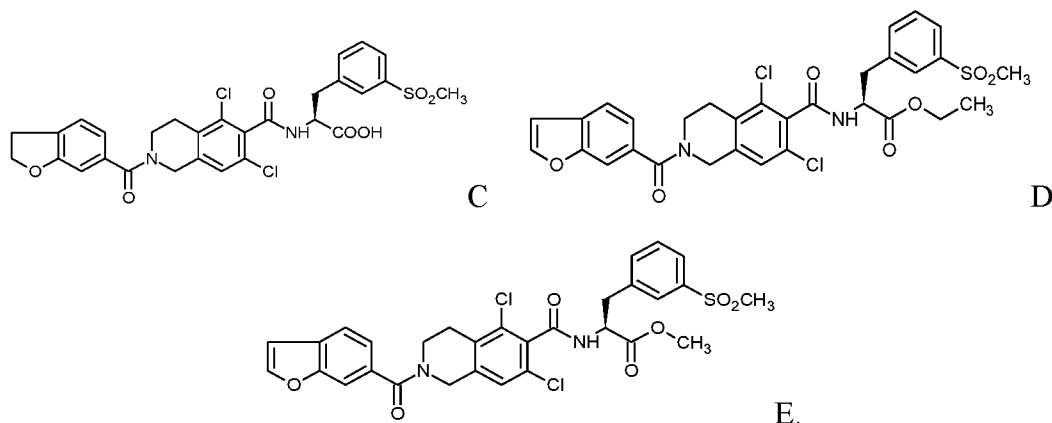
(b) treating the compound of formula II with an acid to form lifitegrast, a compound of formula I, in a chiral purity of at least 99% and wherein the level of R isomer of lifitegrast is less than 1% as determined by HPLC.

25] The process of claim 24, wherein OA is an organic amine of formula $NR_1R_2R_3$; wherein R_1, R_2, R_3 may be independently selected from the group consisting of H or C_1 - C_6 alkyl optionally substituted with C_6 - C_{18} aryl; wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl and C_1 - C_6 alkyl.

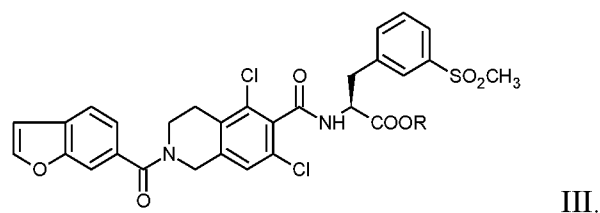
26] The process of claim 25, wherein the compound of formula $NR_1R_2R_3$, wherein R_1 is H, R_2 is H, R_3 is C_1 - C_6 alkyl group substituted with a C_6 aryl group.

27] The process of claim 24, wherein lifitegrast is obtained in a chemical purity of at least 99%, and wherein the level of one or more compounds of formula A, B, C, D or E is less than 0.15% w/w, relative to the amount of lifitegrast as determined by HPLC,





28] The process for the preparation of crude lifitegrast of claim 24, comprising deprotecting a compound of formula III, wherein R is selected from C₁-C₆ alkyl optionally substituted with C₆-C₁₈ aryl, and wherein the aryl group may be optionally substituted with one or more substituents selected from the group consisting of nitro, cyano, amino, halogen, hydroxyl, C₁-C₆ alkoxy and C₁-C₆ alkyl,



29] The process of claim 28, wherein when R is C₁-C₆ alkyl group, the deprotection is carried out by acid or base hydrolysis.

30] The process of claim 28, wherein when R is C₁-C₆ alkyl group, the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid.

31] The process of claim 28, wherein when R is C₁-C₆ alkyl group substituted with C₆-C₁₈ aryl, the deprotection is carried out by acid or base hydrolysis or by hydrogenolysis.

32] The process of claim 28, wherein when R is C₁-C₆ alkyl group substituted with C₆-C₁₈ aryl, the deprotection is carried out by subjecting the compound of formula III to treatment with a Lewis acid.

33] The process for the preparation of lifitegrast comprising:

(a) providing a solution of lifitegrast, prepared by the process of claim 24, in a solvent; and

(b) isolating lifitegrast by

(i) removing the solvent from the solution obtained in (a); or

(ii) combining the solution obtained in (a) with an antisolvent followed by optional cooling; or

(iii) slurring the compound obtained from (b) (i); or

(iv) cooling the solution obtained in (a);

wherein the lifitegrast obtained is in amorphous form.

34] The process of claim 33, wherein the removal of solvent in (b)(i) is carried out by solvent distillation, concentration, spray drying, fluid bed drying, lyophilization, flash drying, spin flash drying, or thin-film drying.

35] The process of claim 33, wherein the solvent in (a) is an ester solvent and antisolvent used in b(ii) is an acyclic ether or aliphatic hydrocarbon.

36] The process for the preparation of lifitegrast comprising:

(a) providing a mixture of lifitegrast, prepared by the process of claim 24, in water, optionally in presence of an organic solvent; and

(b) isolating lifitegrast by

(i) treating the mixture obtained in (a) with a base to give a solution;

(ii) treating the solution obtained in (b)(i) with an acid to form lifitegrast; and

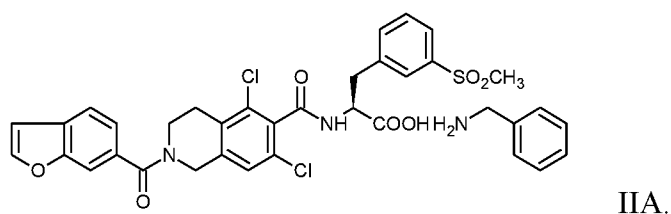
(iii) filtering the lifitegrast obtained in (b)(ii);

wherein the lifitegrast obtained is in amorphous form.

37] The process of claim 36, wherein the base used in (b)(i) is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, sodium bicarbonate and potassium bicarbonate.

38] The process of claim 36, wherein the acid used in (b)(ii) is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, citric acid and phosphoric acid.

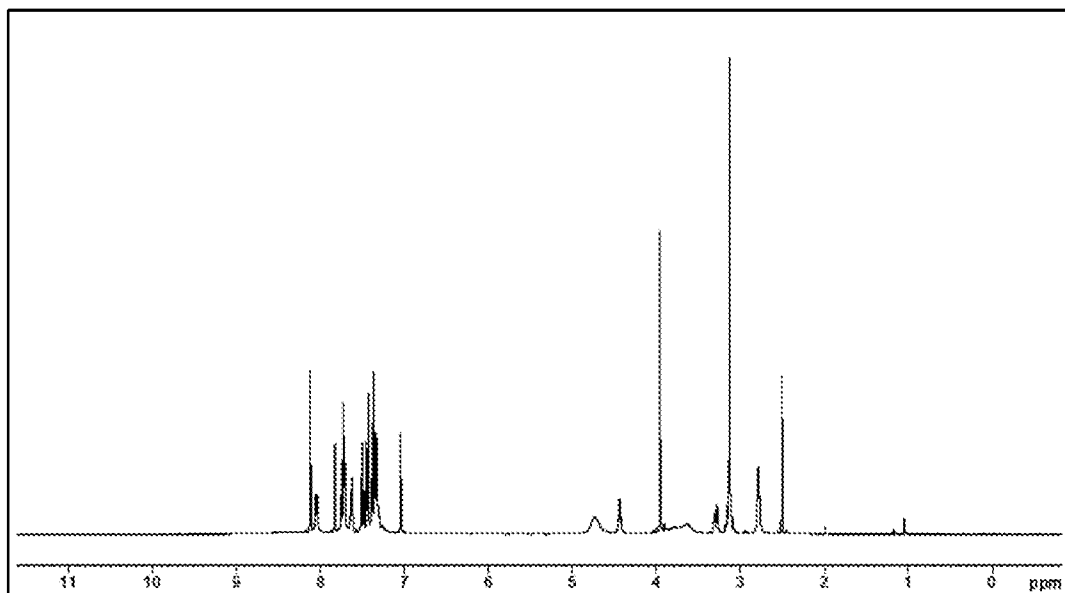
39] The process of claim 24, wherein compound of formula II is lifitegrast benzylamine salt, a compound of formula IIA,



40] The use of lifitegrast benzylamine salt, compound of formula IIA, in the preparation of lifitegrast.

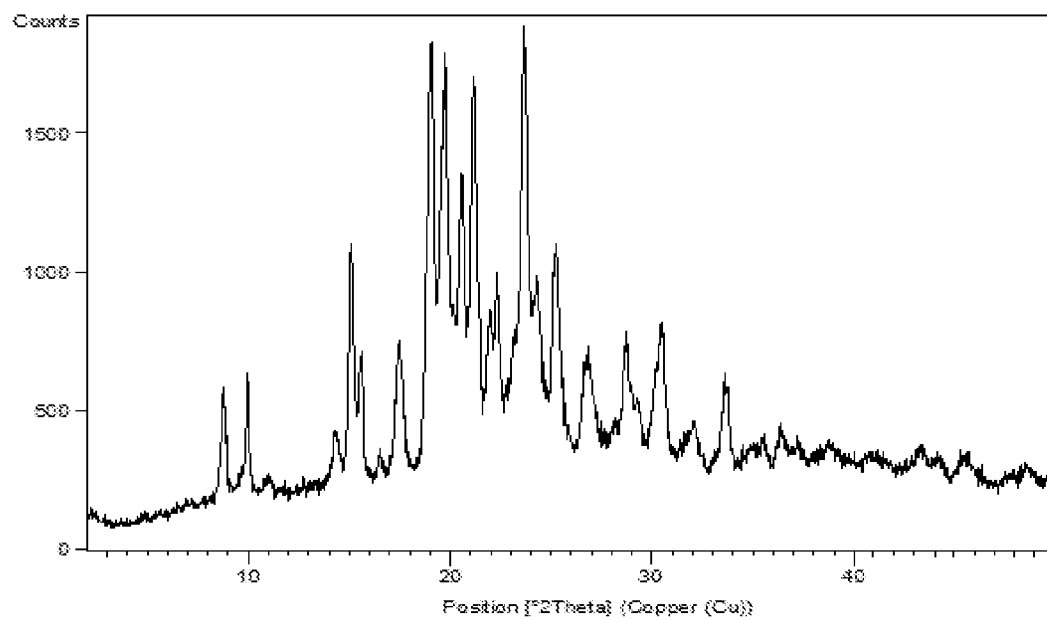
Glenmark Pharmaceuticals Limited

Figure 1



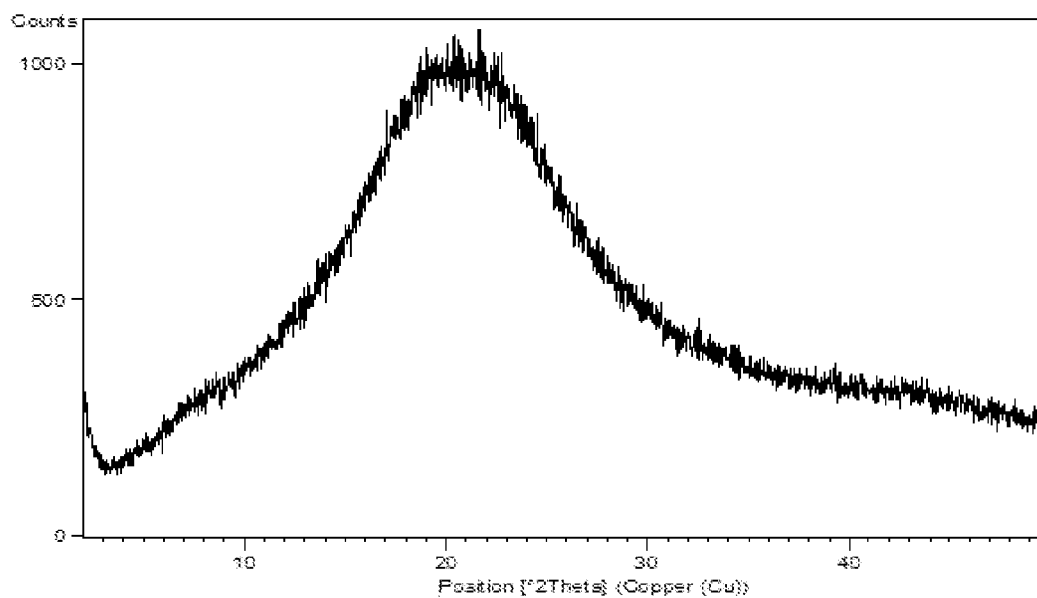
Glenmark Pharmaceuticals Limited

Figure 2



Glenmark Pharmaceuticals Limited

Figure 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/056959

A. CLASSIFICATION OF SUBJECT MATTER
C07D217/06, C07D405/06 Version=2018.01

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, A61K, C07C, A61P

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2014018748 A1 (SARCODE BIOSCIENCE INC.) 30 January 2014 (30/01/2014). abstract, claims 1, 23;	1-6
Y	WO2009139817 A2, (SARCODE CORPORATION) 19 November 2009 (19/11/2009). abstract, claims 1, 15-16;	1-23
Y	WO2011050175 A1, (SARCODE CORPORATION) 28 April 2011 (28/04/2011). abstract, claims 1;	1-6
Y	Marcantoni E., et al, Selective Deprotection of N-Boc-Protected tert-Butyl Ester Amino Acids by the CeCl ₃ •7H ₂ O/NaI System in Acetonitrile, J. Org. Chem. 2001, 66, 12, 4430-4432, DOI: 10.1021/jo010010y abstract, table 2;	1-6
Y	Berge S M. et al, Pharmaceutical salts, J. Pharm. Sci. (1977) 66(1): pages 1-19. whole document;	7-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search

26-12-2018

Date of mailing of the international search report

26-12-2018

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/056959

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Group I: claims 1-23, deals with the preparation of lifitegrast from its ester form by deprotection (of compound of formula II) and further deals with the preparation of its organic amine salt.
Group II: claims 24-40, deals with preparation of the lifitegrast from its organic amine salt.
Multiple inventions listed above do not come under single inventive concept because there is no common technical feature/special feature that connecting above described group of inventions. The technical feature of the Group I is that the synthesis of lifitegrast from its ester form is carried out by hydrolysis using Lewis acids. The

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-23

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking(Box III)

technical feature of the Group II is that the synthesis of lifitegrast from its organic amine form is carried out either by hydrolysis using acids or bases or by hydrogenolysis. The same process could be used for these two different set of inventions. Since the special technical features are not common between the groups of inventions as mentioned above, claims 1-40 of the present application lacks unity and does not meet the requirement of PCT Rule 13.1.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2018/056959

Citation	Pub.Date	Family	Pub.Date
WO 2014018748 A1	30-01-2014	CA 2879982 A1	30-01-2014
		EP 2877465 A1	03-06-2015
		JP 2015523398 A	13-08-2015
		US 20140031387 A1	30-01-2014
WO 2009139817 A2	19-11-2009	US 20090298869 A1	03-12-2011
WO 2011050175 A1	28-04-2011	US 20110092707 A1	21-04-2011