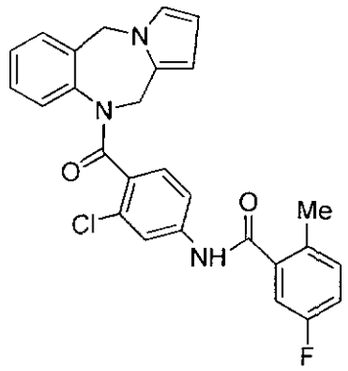
ABSTRACT

The invention relates to an improved process for the preparation of lixivaptan and intermediates thereof. In particular, the invention relates to an improved process for the preparation of 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoic acid (IIIA) or its acid chloride (IIA) and 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V).

E 101/2477/2014.

We Claim:

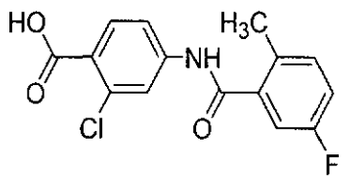
1. A process for the preparation of cyrstalline form of lixivaptan of Formula (I),



(I)

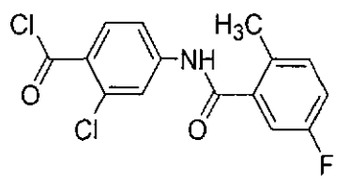
the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA);



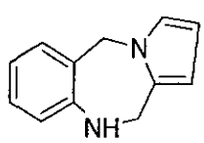
(IIIA)

(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA);



(IIA)

(c) reacting 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA) with 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of (V)



(V)

in one or more suitable solvent to obtain lixivaptan of Formula (I); and

(d) crystallizing lixivaptan from suitable solvent to obtain crystalline form of lixivaptan (I).

2. The process as claimed in claim 1, wherein suitable solvent comprises methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethyl- acetamide, dimethylsulfoxide, N-methylpyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyl- tetrahydrofuran, 1,4-dioxane, water, or mixtures thereof.

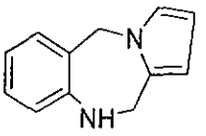
3. The process as claimed in 1, wherein suitable chlorinating agent comprises one or more of thionyl chloride, phosphorus oxychloride, phosphorous trichloride, phosphorus pentachloride, oxaloyl chloride, sulfuryl chloride.

4. The process as claimed in claim 1, wherein the reaction of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA) with 10,11-dihydro-5H-benzo[e]pyrrolo-[1,2-a][1,4]diazepine of (V) is alternatively performed in presence of suitable base comprises of inorganic or organic base.

5. The process as claimed in claim 4, wherein the suitable base comprises sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide, triethylamine, diisopropyl ethyl amine, diethylamine, pyridine, piperidine, DBU.

6. A crystalline lixivaptan characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 8.7°, 11.7°, 15.5°, 17.0°, 23.7°, 25.2°±0.2° 2θ.

7. An improved process for the preparation of crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I),



(V)

the process comprising:

(a) formylation of pyrrole with suitable reagent to obtain 1H-pyrrole-2-carbaldehyde;

(b) reacting 1H-pyrrole-2-carbaldedhye with 2-nitrobenzyl bromide (VIII) in presence of base in one or more of suitable solvent to obtain 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII);

(c) reductive cyclization of 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII) in presence of suitable reducing agent to obtain 10,11-dihydro-5H-benzo[e]- pyrrolo[1,2-a][1,4]diazepine (V); and

(d) isolating crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I) by slurrying in suitable solvent.

8. The process as claimed in claim 7, wherein suitable reagent is Vilsmeier reagent like phosphorus oxychloride in dimethylformamide.

9. The process as claimed in claim 7, wherein the base comprises sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide.

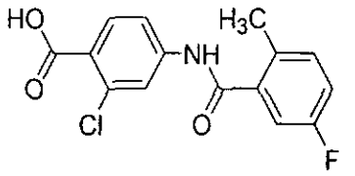
10. The process as claimed in claim 7, wherein the suitable solvent comprises one or more of methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, water, or mixtures thereof.

11. The process as claimed in claim 7, wherein suitable reducing agent comprises of Pd/C, Pt/C, Raney Nickel, Fe/HCl, Sn/HCl, Na2Sx.

12. The process as claimed in claim 7, wherein slurrying solvent comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate.

13. A crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V), an intermediate for lixivaptan (I) characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 8.6°, 12.2°, 14.3°, 19.2°, 20.7°, 22.9°, 24.5°, 28.8°±0.2° 2θ.

14. An improved process for the preparation of crystalline form of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) an intermediate of lixivaptan,

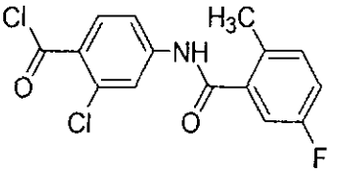


(IIIA)

the process comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA), wherein the improvement comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in dimethylacetamide as solvent in absence of base.

15. A crystalline 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 7.2°, 10.0°, 13.5°, 15.8°, 20.0°, 22.8°, 25.5°±0.2° 2θ.

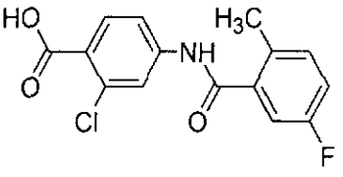
16. An improved process for the preparation of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA),



(IIA)

the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA); and



(IIIA)

(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA), wherein the improvement comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in dimethylacetamide as solvent in absence of base.

17. A crystalline form of (4-amino-2-chloro-phenyl)-(5H,11H-benzo[e]pyrrolo- [1,2-a][1,4]diazepin-10-yl)-methanone Formula (II), which is characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 11.5°, 15.9°, 19.2°, 22.0°, 25.5°, 31.3°±0.2° 2θ.

18. A process for purification of lixivaptan comprises crystallizing lixivaptan from ethyl acetate, isopropyl acetate, butyl acetate.

19. A pharmaceutical composition that includes a therapeutically effective amount of crystalline lixivaptan (I) and one or more pharmaceutically acceptable carriers, excipients or diluents.

Dated this 20th day of January 2014.

(ASHISH K. SHARMA)
Of SUBRAMANIAM & ASSOCIATES
ATTORNEYS FOR THE APPLICANTS

FIELD OF THE INVENTION

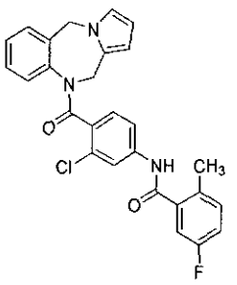
The field of the present invention relates to a process for preparation of pyrrolo-[2,1-c][1,4]benzodiazepin derivative and polymorphs thereof. In particular, the present invention provides a process for the preparation of lixivaptan and polymorphs thereof. More particularly, the invention relates to the polymorphic forms of intermediates of lixivaptan.

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Lixivaptan (CAS 168079-32-1) is a potent, non-peptide, selective vasopressin 2 receptor antagonist. Lixivaptan acts by blocking vasopressin, an anti-diuretic hormone that causes the kidneys to retain water. When the body needs to remain hydrated under certain conditions, vasopressin can have protective effects. But an excess of vasopressin is counterproductive in a body retaining too much fluid. The drug shows promise in treating heart failure in patients with hyponatremia.

Lixivaptan is chemically known as a N-[3-chloro-4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide, with the molecular formula of $C_{27}H_{21}ClFN_3O_2$ and molecular weight of 473.933 g/mol. The structural formula of lixivaptan can be represented by Formula (I)



(I)

U.S. Patent No. 5,516,774 (the US'774) discloses lixivaptan as tricyclic diazepine, which exhibits antagonistic activity towards V_1 and/or V_2 receptors. The US '774 also disclose the process for preparation of lixivaptan in its working example No. 482.

J. Med. Chem. 1998, 41, 2442-2444 discloses the synthesis of lixivaptan and other vasopressin antagonists in particular V_2 receptor antagonists.

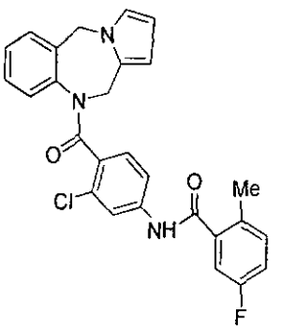
Bioorganic & medicinal chemistry letters 2000, 10, 695-698 also discloses the synthesis of lixivaptan and its analogues.

The prior art cited herein above or any of the prior arts known to the inventors do not disclose the polymorphs of lixivaptan or intermediates thereof. It is desirable to obtain crystalline intermediates of a drug substance so as to have better yields and purity of drug substance.

In view of the above, it is therefore, desirable to provide an efficient, economical and eco-friendly process for the preparation of crystalline form of lixivaptan. In particular, the present inventors have found novel crystalline form of intermediates as Formula (V), Formula (II) and Formula (IIIA) having good physiochemical properties and useful for further processing.

SUMMARY OF THE INVENTION

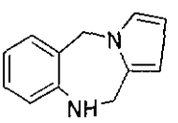
In one general aspect, there is provided a process for the preparation of crystalline form of lixivaptan of Formula (I),



(I)

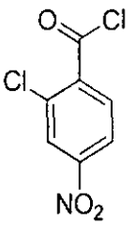
the process comprising:

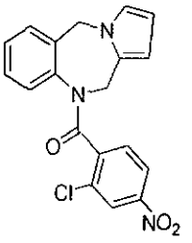
(a) reacting 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of (V)



(V)

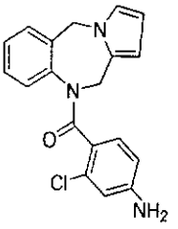
with 2-chloro-4-nitrobenzoyl chloride (VI) in one or more suitable solvent to obtain nitro compound (IV);





(VI) **(IV)**

(b) reducing nitro compound (IV) with suitable reducing agent in one or more of suitable solvent to obtain crystalline form of amino compound (II);

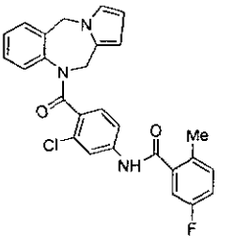


(II)

(c) reacting amino compound (II) with 5-fluoro-2-methylbenzoyl chloride (III) in presence of one or more suitable solvent to obtain lixivaptan (I); and

(d) crystallizing lixivaptan from suitable solvent to obtain crystalline form of lixivaptan (I).

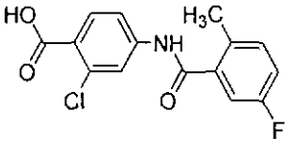
In another general aspect, there is provided a process for the preparation of cyrstalline form of lixivaptan of Formula (I),



(I)

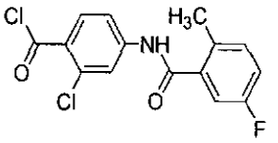
the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA);



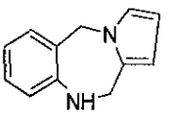
(IIIA)

(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA);



(IIA)

(c) reacting 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA) with 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of (V)

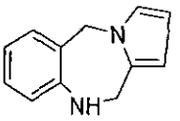


(V)

in one or more suitable solvent to obtain lixivaptan of Formula (I); and

(d) crystallizing lixivaptan from suitable solvent to obtain crystalline form of lixivaptan (I).

In another general aspect, there is provided an improved process for the preparation of crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I).



(V)

the process comprising:

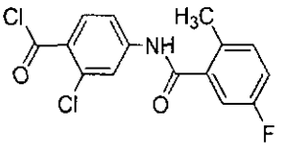
(a) formylation of pyrrole with suitable reagent to obtain 1H-pyrrole-2-carbaldehyde;

(b) reacting 1H-pyrrole-2-carbaldedhye with 2-nitrobenzyl bromide (VIII) in presence of base in one or more of suitable solvent to obtain 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII); and

(c) reductive cyclization of 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII) in presence of suitable reducing agent to obtain 10,11-dihydro-5H-benzo[e]- pyrrolo[1,2-a][1,4]diazepine (V); and

(d) isolating crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I) by slurrying in suitable solvent.

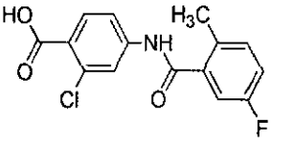
In another general aspect, there is provided an improved process for the preparation of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA),



(IIA)

the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA); and



(IIIA)

(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA),

wherein the improvement comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in dimethylacetamide as solvent in absence of base.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the crystalline lixivaptan (I); and one or more pharmaceutically acceptable carriers, excipients or diluents.

BRIEF DESCRIPTION OF THE ACCOMPNYING DRAWINGS

FIG. 1 discloses the x-ray diffractogram (XRD) of crystalline form of compound 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of Formula (V).

FIG. 2 discloses the DSC of crystalline form of compound 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of Formula (V).

FIG. 3 discloses the x-ray diffractogram (XRD) of crystalline form of (4-Amino-2-chloro-phenyl)-(5H,11H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10-yl)-methanone of Formula (II).

FIG. 4 discloses the x-ray diffractogram (XRD) of crystalline form of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA).

FIG. 5 discloses the x-ray diffractogram (XRD) of crystalline form of lixivaptan of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

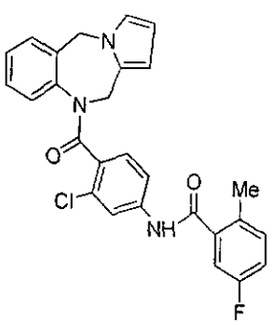
The inventors have discovered that use of polar solvents for the condensation of amino compound (II) and 5-fluoro-2-methylbenzoyl chloride (III) doesn't require use of base for the condensation reaction to obtain lixivaptan. Further, the inventors of the present invention provides an improved process for the preparation of 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I) with purity greater than 99%.

Further, the inventors of the present invention provides crystalline form of 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V), (4-Amino-2-chloro-phenyl)-(5H,11H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10-yl)-methanone of Formula (II), and 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) as well a process of their preparation and use thereof in the preparation of crystalline form of lixivaptan of Formula (I).

As used here in the term "obtaining" may include filtration, filtration under vacuum, centrifugation, and decantation to isolate product. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a hot air oven, tray drier, dried under vacuum and/or in a Fluid Bed Drier.

"Suitable solvent" means a single or a combination of two or more solvents. As used herein, the term "contacting" includes mixing, adding, slurrying, stirring, or a combination thereof.

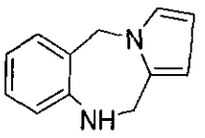
In one general aspect, there is provided a process for the preparation of crystalline form of lixivaptan of Formula (I),



(I)

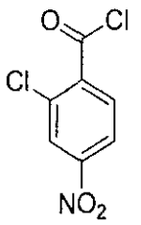
the process comprising:

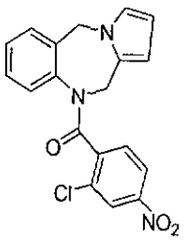
(a) reacting 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of (V)



(V)

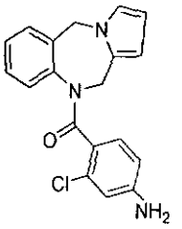
with 2-chloro-4-nitrobenzoyl chloride (VI) in one or more suitable solvent to obtain nitro compound (IV);





(IV) **(VI)**

(b) reducing nitro compound (IV) with suitable reducing agent in one or more of suitable solvent to obtain amino compound (II);



(II)

(c) reacting amino compound (II) with 5-fluoro-2-methylbenzoyl chloride (III) in presence of one or more suitable solvent to obtain lixivaptan (I); and

(d) crystallizing lixivaptan from suitable solvent to obtain crystalline form of lixivaptan (I).

In general, the compound 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of (V) may be reacted with 2-chloro-4-nitrobenzoyl chloride (VI) in one or more suitable solvent comprises methanol, ethanol, isopropanol, butanol, dimethyl- formamide, dimethylacetamide, dimethylsulfoxide, N-methyl pyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyl tetrahydrofuran, 1,4-dioxane, water, or mixtures thereof. In particular, dimethylacetamide may be used as solvent.

The reaction may also by performed alternatively in presence of suitable base comprises of inorganic or organic base. The inorganic base comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide and the like. The organic base

comprises of triethylamine, diisopropyl ethyl amine, diethylamine, pyridine, piperidine, DBU and the like.

The reaction when performed in presence of base, the suitable solvent comprises one or more of methylene dichloride, ethylene dichloride, chloroform, toluene, xylene, ethyl benzene and the like. In particular, methylene dichloride or toluene may be used.

The embodiments of the process further comprises reducing compound (IV) with suitable reducing agent comprises of Pd/C, Pt/C, Raney Nickel, Fe/HCl, Sn/HCl, Na_2Sx and the like. In particular, Raney Nickel or Pd/C may be use. The solvents for the reduction comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, tetrahydrofuran, 2-methyltetrahydrofuran, or mixtures thereof to obtain amino compound (II).

The embodiments of the process further involves preparation of lixivaptan by condensation of amino compound (II) with 5-fluoro-2-methylbenzoyl chloride (III) in one or more of suitable solvents. The suitable solvent comprises one or more of polar solvent like methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrrolidone and the like. In particular dimethyl acetamide may be used.

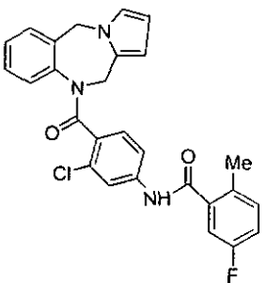
The lixivaptan of Formula (I) may be crystallized in suitable solvent comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrrolidone and the like to obtain crystalline form of lixivaptan. In particular, ethyl acetate may be used.

The crystalline form of lixivaptan is characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 8.7°, 11.7°, 15.5°, 17.0°, 23.7°, 25.2°±0.2° 2θ. The crystalline form of lixivaptan of Formula (I) may further be characterized by x-ray powder diffraction pattern substantially as depicted in FIG. 5.

In another general aspect, there is provided crystalline form of (4-amino-2-chloro-phenyl)-(5H,11H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10-yl)-methanone Formula (II), which is characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 11.5°, 15.9°, 19.2°, 22.0°, 25.5°, 31.3°±0.2° 2θ. The crystalline form of compound of Formula (II) may further be characterized by x-ray powder diffraction pattern substantially as depicted in FIG. 3.

Though the compound of Formula (II) shows characteristic crystalline peaks, the compound may exist in the mixture of crystalline and amorphous form, which should be considered as the scope of the invention.

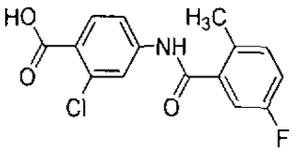
In another general aspect, there is provided a process for the preparation of cyrstalline form of lixivaptan of Formula (I),



(I)

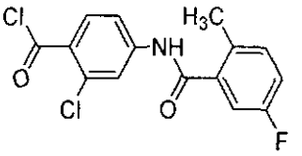
the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA);



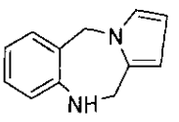
(IIIA)

(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA);



(IIA)

(c) reacting 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA) with 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of (V)



(V)

in one or more suitable solvent to obtain lixivaptan of Formula (I); and crystallizing lixivaptan from suitable solvent to obtain crystalline form of lixivaptan (I).

In general, the compound 4-amino-2-chloro-benzoic acid may be reacted with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable solvents in absence of base. In general, the suitable solvent comprises methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methyl- pyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyl- tetrahydrofuran, 1,4-dioxane, water, or mixtures thereof. In particular, dimethyl- acetamide may be used as solvent.

The compound 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid (IIIA) obtained may be isolated by quenching the reaction mixture in water followed by filtration and drying. The 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid (IIIA) was converted to its acid chloride of Formula (IIA) by reaction with suitable chlorinating agent.

The suitable chlorinating agent comprises one or more of thionyl chloride, phosphorus oxychloride, phosphorous trichloride, phosphorus pentachloride, oxaloyl chloride, sulfuryl chloride and the like. In particular, oxaloyl chloride may be used to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA).

The embodiments of the process involves reacting 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA) with 10,11-dihydro-5H-benzo[e]pyrrolo- [1,2-a][1,4]diazepine of (V) in one or more of suitable solvents to obtain lixivaptan of Formula (I). The reaction may be performed in presence or absence of base. In particular, the reaction was performed in absence of base. The suitable solvent comprises one or more of methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methyl- pyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyl- tetrahydrofuran, 1,4-dioxane, water, or mixtures thereof. In particular dimethyl-acetamide may be used as solvent.

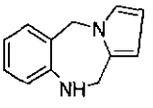
The reaction may also by performed alternatively in presence of suitable base comprises of inorganic or organic base. The inorganic base comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide and the like. The organic base comprises of triethylamine, diisopropyl ethyl amine, diethylamine, pyridine, piperidine, DBU and the like.

The reaction when performed in presence of base, the suitable solvent comprises one or more of methylene dichloride, ethylene dichloride, chloroform, toluene, xylene, ethyl benzene and the like. In particular, methylene dichloride or toluene may be used.

The reaction conditions are like temperature, time and isolation conditions are those disclosed in the examples hereinafter. The conditions may be modified according to the suitability of the reaction in order to achieve higher yields and purity of lixivaptan and intermediates thereof.

The crystalline form of lixivaptan is characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 8.7°, 11.7°, 15.5°, 17.0°, 23.7°, 25.2°±0.2° 2θ. The crystalline form of lixivaptan of Formula (I) may further be characterized by x-ray powder diffraction pattern substantially as depicted in FIG. 5.

In another general aspect, there is provided an improved process for the preparation of crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I),



(V)

the process comprising:

(a) formylation of pyrrole with suitable reagent to obtain 1H-pyrrole-2-carbaldehyde;

(b) reacting 1H-pyrrole-2-carbaldedhye with 2-nitrobenzyl bromide (VIII) in presence of base in one or more of suitable solvent to obtain 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII);

(c) reductive cyclization of 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII) in presence of suitable reducing agent to obtain 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V); and

(d) isolating crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I) by slurrying in suitable solvent.

In general, the formylation of pyrrole may be accomplished by Vilsmeier reagent like Phosphorus oxychloride in dimethylformamide. The other suitable reagents may be selected. The formylation may be performed in one or more of suitable solvent. The suitable solvent comprises one or more methylene dichloride, ethylene dichloride, chloroform, toluene, xylene, ethyl benzene and the like. In particular, methylene dichloride or toluene may be used.

The embodiments of the process further includes reacting 1H-pyrrole-2-carbaldedhye with 2-nitrobenzyl bromide (VIII) in presence of base. The base comprises sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide and the like. The reaction may be done in suitable solvent comprises one or more of methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, water, or mixtures thereof.

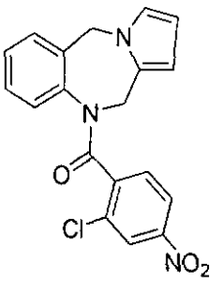
The embodiments of the process further comprises reductive cyclization of compound (VII) with suitable reducing agent comprises of Pd/C, Pt/C, Raney Nickel, Fe/HCl, Sn/HCl, Na_2Sx and the like. In particular, Raney Nickel or Pd/C may be use. The solvents for the reduction comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, tetrahydrofuran, 2-methyltetrahydrofuran, or mixtures thereof to obtain compound (V), intermediate for lixivaptan.

The compound (V) may be slurried in suitable solvent comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate and the like to isolate in crystalline form. In particular, methanol may be used.

The crystalline form of compound of Formula (V) is characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 8.6°, 12.2°, 14.3°, 19.2°, 20.7°, 22.9°, 24.5°, 28.8°±0.2° 2θ. The crystalline form of compound of Formula (V) may further be characterized by x-ray powder diffraction pattern substantially as depicted in FIG. 1.

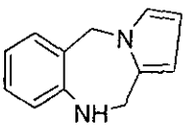
The crystalline form of compound of Formula (V) is further characterized by differential scanning calorimeter having endothermic peak at about 151°C. The differential scanning calorimetric is substantially as depicted in FIG.2.

In another general aspect, there is provided an improved process for the preparation of (5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-yl)(2-chloro-4-nitrophenyl)methanone (IV) an intermediate for lixivaptan,



(IV)

the process comprising reacting 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]- diazepine of (V)



(V)

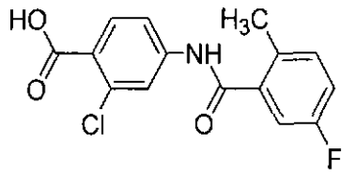
with 2-chloro-4-nitrobenzoyl chloride (VI) in dimethyl acetamide as solvent in absence of base and obtaining 5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-yl)(2-chloro-4-nitrophenyl) methanone (IV).

In general, the reaction of compound (V) with 2-chloro-4-nitrobenzoyl chloride may be performed in dimethyl acetamide. The reaction may be performed at room temperature to the reflux temperature of solvent. When dimethyl acetamide was used as the solvent, the reaction was performed in absence of base. When the condensation was performed in presence of base, the solvent dimethylacetamide may be replaced with suitable other solvents.

The suitable other solvent comprises one or more of methylene dichloride, ethylene dichloride, chloroform, toluene, xylene, ethyl benzene and the like. In particular, methylene dichloride or toluene may be used.

In another general aspect, there is provided an improved process for the preparation of lixivaptan (I) comprising reacting amino compound (II) with 5-fluoro-2-methylbenzoyl chloride (III) in dimethyl acetamide as solvent in absence of base and obtaining lixivaptan (I).

In another general aspect, there is provided an improved process for the preparation of crystalline form of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) an intermediate of lixivaptan,



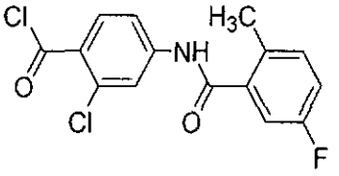
(IIIA)

the process comprises:

reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA), wherein the improvement comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in dimethylacetamide as solvent in absence of base.

In another general aspect of the present invention comprises crystalline form of compound of Formula (IIIA), which is characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 7.2°, 10.0°, 13.5°, 15.8°, 20.0°, 22.8°, 25.5°±0.2° 2θ. The crystalline form of compound of Formula (IIIA) may further be characterized by x-ray powder diffraction pattern substantially as depicted in FIG. 4.

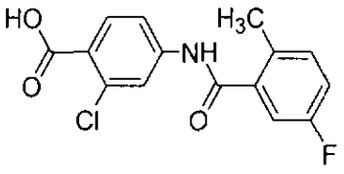
In another general aspect, there is provided an improved process for the preparation of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA),



(IIA)

the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA); and



(IIIA)

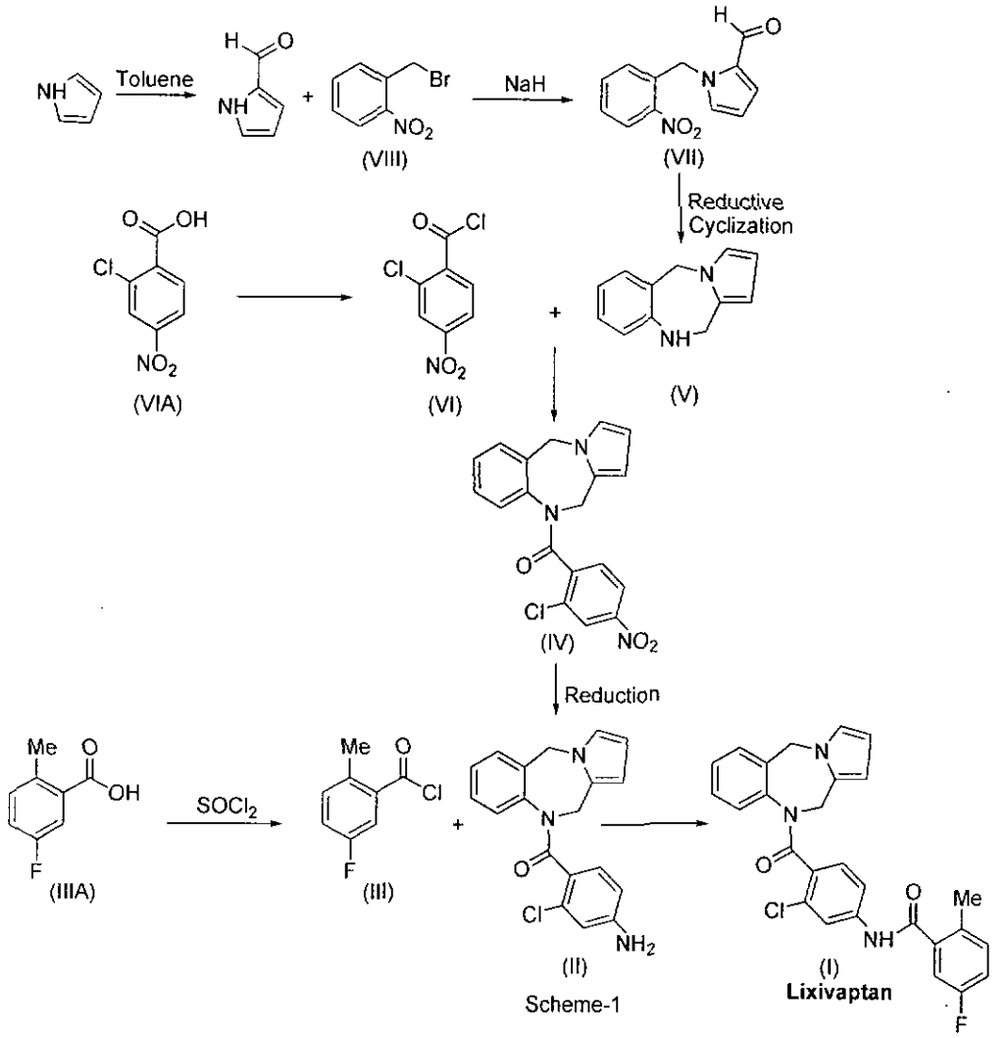
(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA),

wherein the improvement comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in dimethylacetamide as solvent in absence of base.

In another general aspect, there is provided a process for purification of lixivaptan comprises crystallizing lixivaptan from ethyl acetate, isopropyl acetate, butyl acetate.

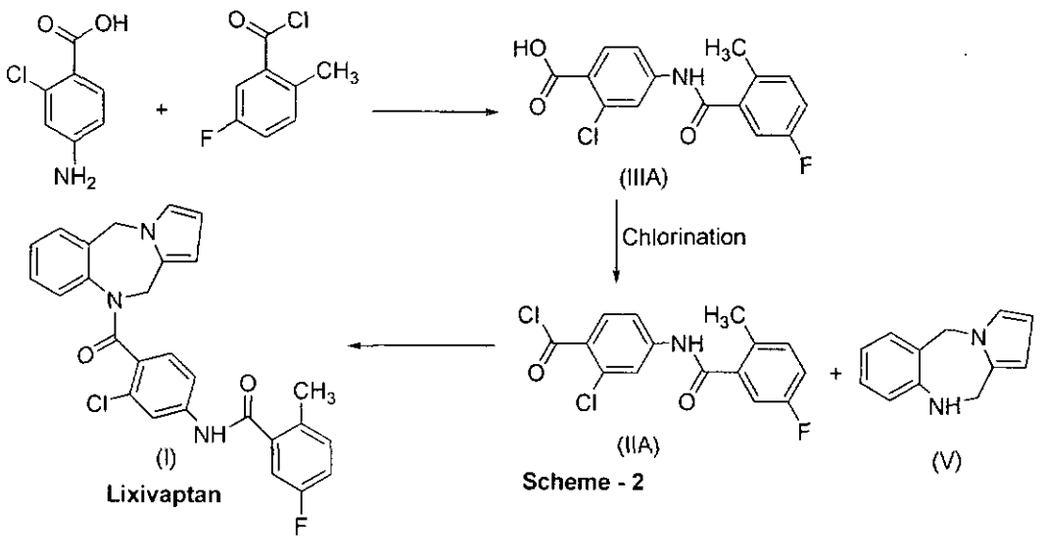
In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the crystalline lixivaptan (I); and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect scheme 1 discloses use of compounds of Formula (II) and Formula (V) as intermediates for the preparation of lixivaptan as shown below:



Scheme-1

In another general aspect scheme 2 discloses use of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) as an intermediate for the preparation of lixivaptan as shown below:



Scheme - 2

The present invention is further illustrated by the following example which is provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modification and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Examples

Example-1: Preparation of 1H-pyrrole-2-carbaldehyde

In a 500-mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, dimethylformamide (13.1 g), and phosphorusoxychloride (25 g) was added slowly at 10 to 20°C. The solution was maintained for 30 minutes. Toluene (100 mL) was added and reaction mixture was cooled to 0-5°C. Pyrrole (10 g) was added in 30 minutes, stirred the mass for 30 min. Reflux for 15 minutes, quenched into sodium acetate solution, and refluxed for 15 minutes again. The reaction mass was cooled to room temperature (25-35°C) and organic layer was separated. The organic layer was washed with sodium carbonate solution and water, aqueous layers were collected and the product was extracted with methylene dichloride under vacuum, to collect as solid mass 12.3 g of product obtained. (Yield: 86.80%).

Example-2: Preparation of 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII)

In a 3L R. B. Flask equipped with mechanical stirrer, thermometer pocket and an addition funnel N,N-Dimethylformamide (200 mL), and Sodium hydride (21.03 g) was added. The mass is maintained for 15 minutes. 1H-pyrrole-2-carbaldehyde (50 g) as obtained in example 1 was dissolved in DMF (100 mL) and added at 0-5°C, stirred the mass for 30 minutes and solution of 2-Nitro benzyl bromide (113.6 g) in DMF (100 mL)

was slowly added in 1 hour and reaction mass was stirred for next 1 hour at 5-10°C. The reaction mixture was quenched into water (2L) at 5-10°C and stirred for 1 hour. The solid obtained was filtered and washed with water. The product was dried under vacuum at 60°C to obtain 118.2 g (Yield: 96.29%) titled compound.

Example-3: Preparation of 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4] diazepine (V)

In a 2L Hydrogenator, equipped with mechanical stirrer, thermometer sensor, methanol (920 mL), ethyl acetate (920 mL), 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (115 g) obtained in example 2 and Raney Ni (57.5 g) were added. The solution was hydrogenated for 14 hours. The reaction mixture was filtered through Hyflow bed. The filtrate was concentrated in vacuum and slurried with methanol (345 mL). The solid was filtered solid and dried under vacuum to obtain 80.85 g (Yield: 87.88 %) titled compound. XRD (FIG.1) and DSC (FIG.2).

Example-4: Preparation of 2-chloro-4-nitrobenzoyl chloride

In a 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Toluene (50 mL), 2-chloro-4-nitrobenzoic acid (5 g), DMF (0.2 mL), Thionyl chloride (3.54 g) were charged, The reaction mixture was heated at 90-100°C next 2 hours. The toluene was distilled under vacuum below 65°C to get oily product 5.25 g (Yield: 95.23 %).

Example-5: Preparation of (5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-yl)(2-chloro-4-nitrophenyl)methanone (IV)

In a 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, dimethyl acetamide (15 mL) and 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (3 g) as obtained in example 3 were added. 2-chloro-4-nitrobenzoyl chloride (4.29 g) as obtained in example 4 was slowly added at 25-35°C in 15 to 30 minutes. The reaction mixture was stirred for 30 minutes, quenched into chilled water and stirred for 1 hour again. The reaction mixture was filtered, washed with water and dried under vacuum at 50°C to get 4.8 g of dried product. (Yield: 80.40 %).

Example-6: Preparation of (4-amino-2-chlorophenyl)(5H-benzo[e]pyrrolo- [1,2-a][1,4] diazepin-10(11H)-yl)methanone (II)

In a 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, methanol (12 mL), ethyl acetate (12 mL), (5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-yl)(2-chloro-4-nitrophenyl) methanone (1.5 g) as obtained in example 5 and Raney Ni (1.5 g) were added. The solution was hydrogenated for 24 hrs. The reaction mixture was filtered through hyflow bed. The filtrate was concentrated in vacuum and slurried with diisopropyl ether. The solid obtained was filtered and dried to obtain 1.0 g (Yield: 73.26 %) of titled compound. (Yield: 73.26 %). XRD (FIG.3)

Example-7: Preparation of 5-fluoro-2-methylbenzoyl chloride (III)

In a 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Toluene (50 mL), 5-fluoro-2-methyl-benzoic acid (5 g), dimethylformamide (0.2 mL), thionyl chloride (4.63 g) were added and the reaction mixture was heated at 90-100°C for 2 hours. The reaction mixture was distilled to remove toluene under vacuum below 65°C to get oily product 5 g (Yield: 89.36 %).

Example-8: Preparation of lixivaptan (I)

In a 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, dimethyl acetamide (3 mL) and (4-amino-2-chlorophenyl)(5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-10(11H)-yl)methanone (0.5 g) as obtained in example 6, were added. 5-fluoro-2-methylbenzoyl chloride (0.28 g) as obtained in example 7 slowly added at 0-10°C in 15 to 30 minutes. The reaction mass was stirred for 30 minutes, quenched into chilled water and stirred for 1 hr. again. The resultant mixture was filtered and solid product was washed with water. The resultant product was dried under vacuum at 50°C. Wt. 0.4 g (Yield: 71.42 %).

Example-9: Preparation of 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoic acid (IIIA)

In a 100 mL R. B. Flask equipped with mechanical stirrer and thermometer pocket, condenser, dimethylacetamide (10 mL), 4-amino-2-chloro-benzoic acid (2 g), were charged, 5-fluoro-2-methylbenzoyl chloride (2.41 g) was slowly added at 0-10°C in 15 min. The reaction mixture was stirred at 0-10°C for 1 hour and quenched in water. The reaction mixture was stirred for 1 hr and filtered. The solid product was washed with water

and dried under vacuum at 60°C to obtain 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoic acid. Wt. 3.4 g (Yield: 94.97%). XRD (FIG.4).

Example-10: Preparation of 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoyl chloride (IIA)

In a 100 mL R. B. Flask equipped with mechanical stirrer and thermometer pocket, condenser, methylene dichloride (20 mL), 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoic acid (2 g) and dimethylformamide (0.05 mL) were heated at 35 to 40°C, solution of oxaloyl chloride (1 g) and methylene dichloride (5 mL) were slowly added at 35-40°C in 15 to 30 min. The reaction mixture was maintained at 35-40°C for 2 hours and distilled to remove methylene dichloride at 40°C under vacuum to obtain 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoyl chloride. Wt. 1.8 g (Yield: 85.30%).

Example-11: Preparation of Lixivaptan (I)

In a 100 mL R. B. Flask equipped with mechanical stirrer and thermometer pocket, condenser, dimethylacetamide (10 mL), 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (1 g), and 2-chloro-4-(5-fluoro-2-methylbenzamido)benzoyl chloride were stirred at 20-25°C for 30 min. The reaction mixture was quenched in water and stirred for 1 hr. The product was filtered and wet-cake was washed with water and dried to obtain lixivaptan of Formula (I). Wt. 2.1 g (Yield: 81.71%).

Example-12: Purification of Lixivaptan (I)

In a 25 mL R. B. Flask equipped with mechanical stirrer and thermometer pocket, ethyl acetate (5 mL) and lixivaptan as obtained in example 8 and 11 were added and dissolved. The reaction mixture was stirred at 0 to 5°C for 6 hours and filtered. The wet-cake was dried under vacuum at 50°C for 3 hours. The resulting solid product was obtained as crystalline lixivaptan of Formula (1). Wt. 0.45 g (Yield: 45%). XRD (FIG.5).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

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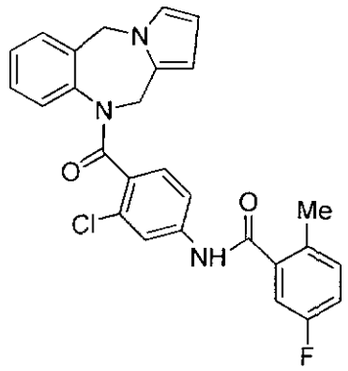
We Claim:

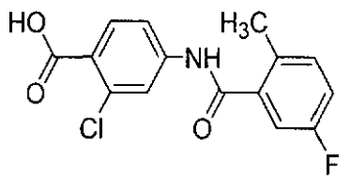
1. A process for the preparation of cyrstalline form of lixivaptan of Formula (I),



(I)

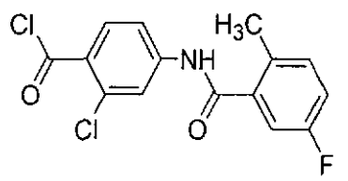
the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA);



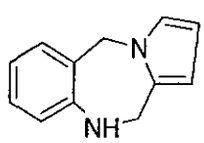
(IIIA)

(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA);



(IIA)

(c) reacting 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA) with 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine of (V)



(V)

in one or more suitable solvent to obtain lixivaptan of Formula (I); and

(d) crystallizing lixivaptan from suitable solvent to obtain crystalline form of lixivaptan (I).

2. The process as claimed in claim 1, wherein suitable solvent comprises methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethyl- acetamide, dimethylsulfoxide, N-methylpyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyl- tetrahydrofuran, 1,4-dioxane, water, or mixtures thereof.

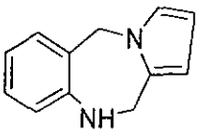
3. The process as claimed in 1, wherein suitable chlorinating agent comprises one or more of thionyl chloride, phosphorus oxychloride, phosphorous trichloride, phosphorus pentachloride, oxaloyl chloride, sulfuryl chloride.

4. The process as claimed in claim 1, wherein the reaction of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA) with 10,11-dihydro-5H-benzo[e]pyrrolo-[1,2-a][1,4]diazepine of (V) is alternatively performed in presence of suitable base comprises of inorganic or organic base.

5. The process as claimed in claim 4, wherein the suitable base comprises sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide, triethylamine, diisopropyl ethyl amine, diethylamine, pyridine, piperidine, DBU.

6. A crystalline lixivaptan characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 8.7°, 11.7°, 15.5°, 17.0°, 23.7°, 25.2°±0.2° 2θ.

7. An improved process for the preparation of crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I),



(V)

the process comprising:

(a) formylation of pyrrole with suitable reagent to obtain 1H-pyrrole-2-carbaldehyde;

(b) reacting 1H-pyrrole-2-carbaldedhye with 2-nitrobenzyl bromide (VIII) in presence of base in one or more of suitable solvent to obtain 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII);

(c) reductive cyclization of 1-(2-nitrobenzyl)-1H-pyrrole-2-carbaldehyde (VII) in presence of suitable reducing agent to obtain 10,11-dihydro-5H-benzo[e]- pyrrolo[1,2-a][1,4]diazepine (V); and

(d) isolating crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V) an intermediate for lixivaptan (I) by slurrying in suitable solvent.

8. The process as claimed in claim 7, wherein suitable reagent is Vilsmeier reagent like phosphorus oxychloride in dimethylformamide.

9. The process as claimed in claim 7, wherein the base comprises sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide.

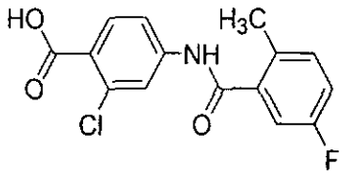
10. The process as claimed in claim 7, wherein the suitable solvent comprises one or more of methanol, ethanol, isopropanol, butanol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrrolidone, methyl ethyl ketone, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, water, or mixtures thereof.

11. The process as claimed in claim 7, wherein suitable reducing agent comprises of Pd/C, Pt/C, Raney Nickel, Fe/HCl, Sn/HCl, Na2Sx.

12. The process as claimed in claim 7, wherein slurrying solvent comprises one or more of methanol, ethanol, isopropanol, butanol, acetone, methyl isobutyl ketone, ethyl acetate, butyl acetate, isopropyl acetate.

13. A crystalline 10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (V), an intermediate for lixivaptan (I) characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 8.6°, 12.2°, 14.3°, 19.2°, 20.7°, 22.9°, 24.5°, 28.8°±0.2° 2θ.

14. An improved process for the preparation of crystalline form of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) an intermediate of lixivaptan,

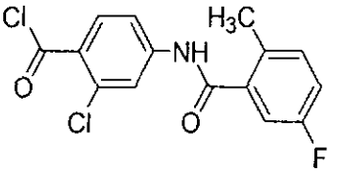


(IIIA)

the process comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA), wherein the improvement comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in dimethylacetamide as solvent in absence of base.

15. A crystalline 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 7.2°, 10.0°, 13.5°, 15.8°, 20.0°, 22.8°, 25.5°±0.2° 2θ.

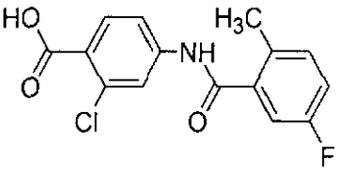
16. An improved process for the preparation of 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA),



(IIA)

the process comprising:

(a) reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in one or more of suitable organic solvent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA); and



(IIIA)

(b) chlorinating 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoic acid of Formula (IIIA) with suitable chlorinating agent to obtain 2-chloro-4-(5-fluoro-2-methyl-benzoylamino)-benzoyl chloride (IIA), wherein the improvement comprises reacting 4-amino-2-chloro-benzoic acid with 5-fluoro-2-methyl-benzoyl chloride in dimethylacetamide as solvent in absence of base.

17. A crystalline form of (4-amino-2-chloro-phenyl)-(5H,11H-benzo[e]pyrrolo- [1,2-a][1,4]diazepin-10-yl)-methanone Formula (II), which is characterized by the x-ray diffraction pattern that exhibits the characteristic peaks at 11.5°, 15.9°, 19.2°, 22.0°, 25.5°, 31.3°±0.2° 2θ.

18. A process for purification of lixivaptan comprises crystallizing lixivaptan from ethyl acetate, isopropyl acetate, butyl acetate.

19. A pharmaceutical composition that includes a therapeutically effective amount of crystalline lixivaptan (I) and one or more pharmaceutically acceptable carriers, excipients or diluents.

Dated this 20th day of January 2014.

(ASHISH K. SHARMA)
Of SUBRAMANIAM & ASSOCIATES
ATTORNEYS FOR THE APPLICANTS