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(54) Title: PROCESSES FOR PREPARATION OF CABOTEGRAVIR OR ITS PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) Abstract: The present invention generally relates to processes for preparation and purification of cabotegravir and its intermediate thereof. The present invention further relates to a process for preparation of polymorphic form of cabotegravir and its sodium salt and pharmaceutical composition thereof.



5 **PROCESSES FOR PREPARATION OF CABOTEGRAVIR OR ITS
PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF**

PRIORITY:

10 This application claims the benefit under Indian Provisional Application No.(S)
202141045988 filed on 08 Oct, 2021 entitled “Process for preparation of polymorphic
form of cabotegravir sodium”; 202241001602 filed on 11 Jan, 2022 entitled “A process
for purification of polycyclic-pyridone compounds”; and 202241032531 filed on 07
Jun, 2022 entitled “Process for purification of cabotegravir” the contents of each of
15 which are incorporated by reference herein.

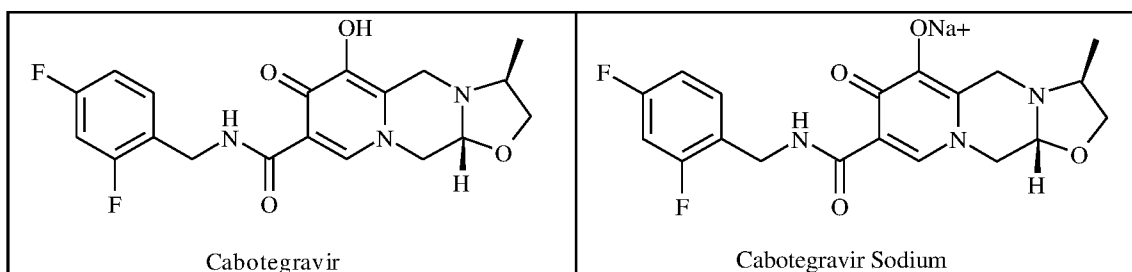
FIELD OF THE INVENTION

The present invention relates to processes for preparation and purification of
20 cabotegravir and its intermediate thereof. The present invention further relates to a
process for preparation of polymorphic form of cabotegravir and its sodium salt and
pharmaceutical composition thereof.

BACKGROUND OF THE INVENTION

25 Cabotegravir is a class of polycyclic carbamoyl pyridone compounds and is chemically
known as (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-
2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide, and
is approved as free acid and its sodium salt, it has the following structure:

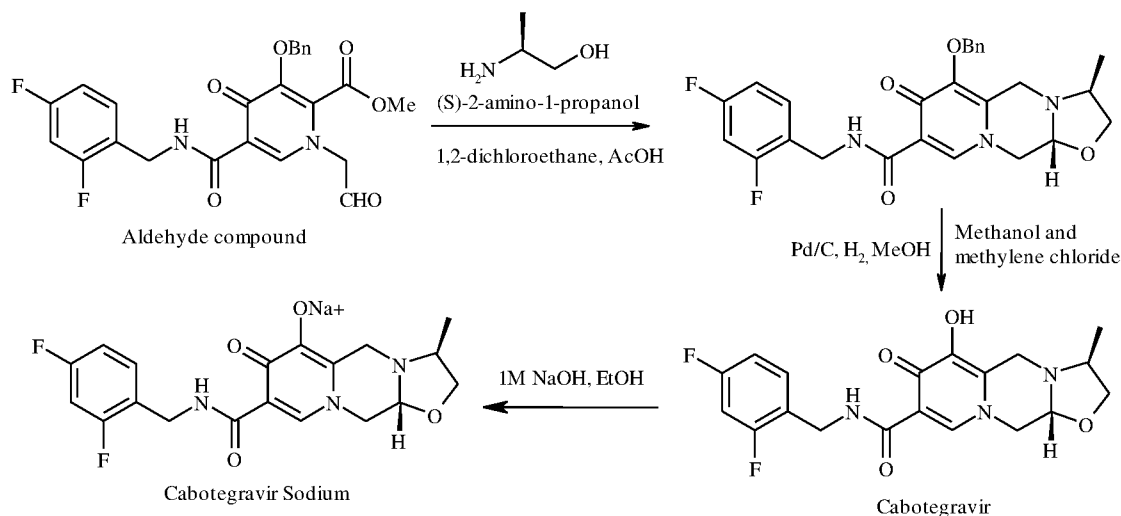
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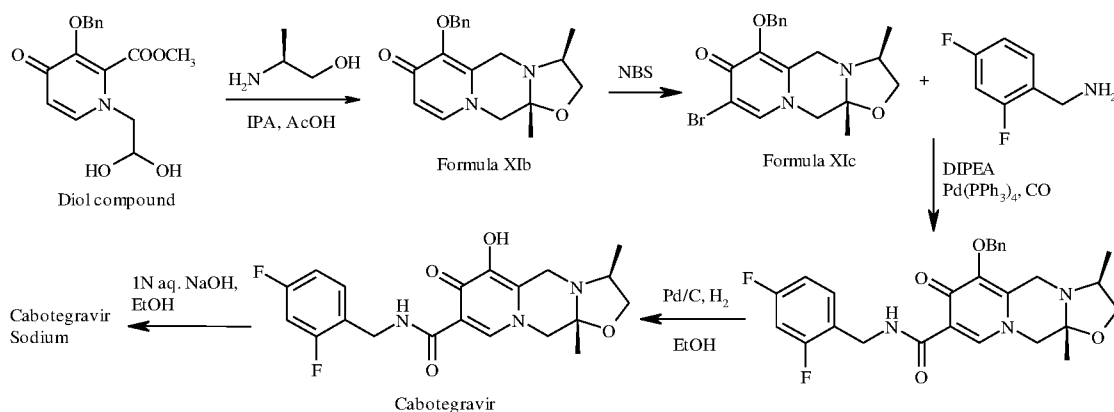
Cabotegravir was approved as its free acid and its sodium salt and sold under the brand
name Vocabria® (Cabotegravir Sodium (Tablet; Oral)) & Cabenuva® KIT (combination
co-pack of Cabotegravir and Rilpivirine (Suspension, Extended Release;
35 Intramuscular)) for treatment of human immunodeficiency virus type 1 (HIV-1)
infection. Further, on December 20, 2021, U.S. FDA approved Cabotegravir free acid

- 5 under the brand name Apretude[®] (Cabotegravir extended-release injectable suspension) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

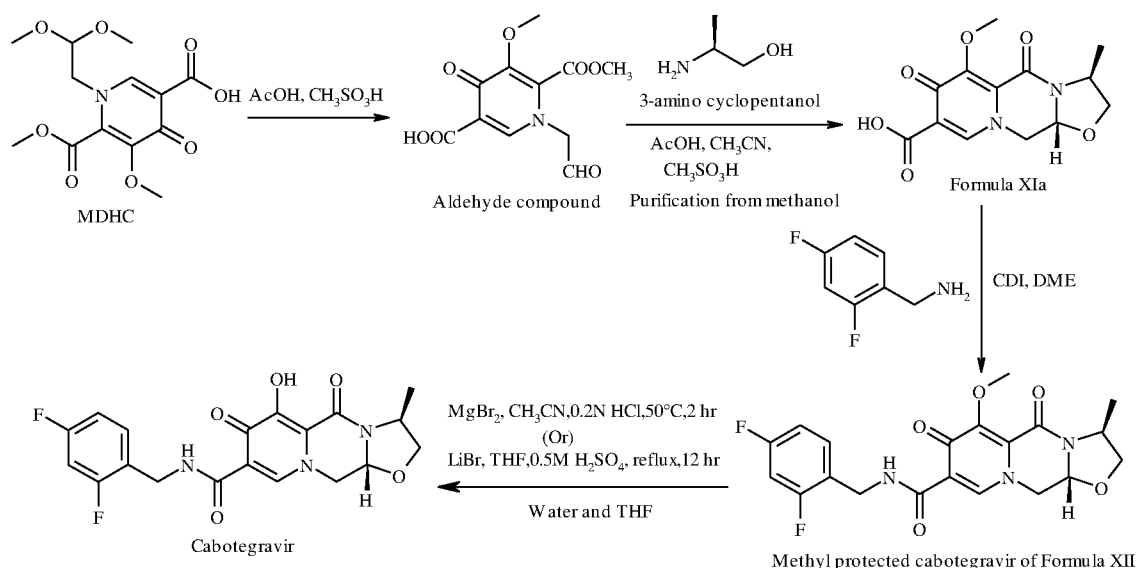
PCT application Number: 2006/116764 (“the ‘764 publication”) discloses a process for preparation of cabotegravir and the process involves isolation of cabotegravir from a mixture of methanol and methylene chloride and converting the obtained cabotegravir in to cabotegravir sodium using ethanol and 1.0 M sodium hydroxide. The ‘764 publication disclosed process is as follows:



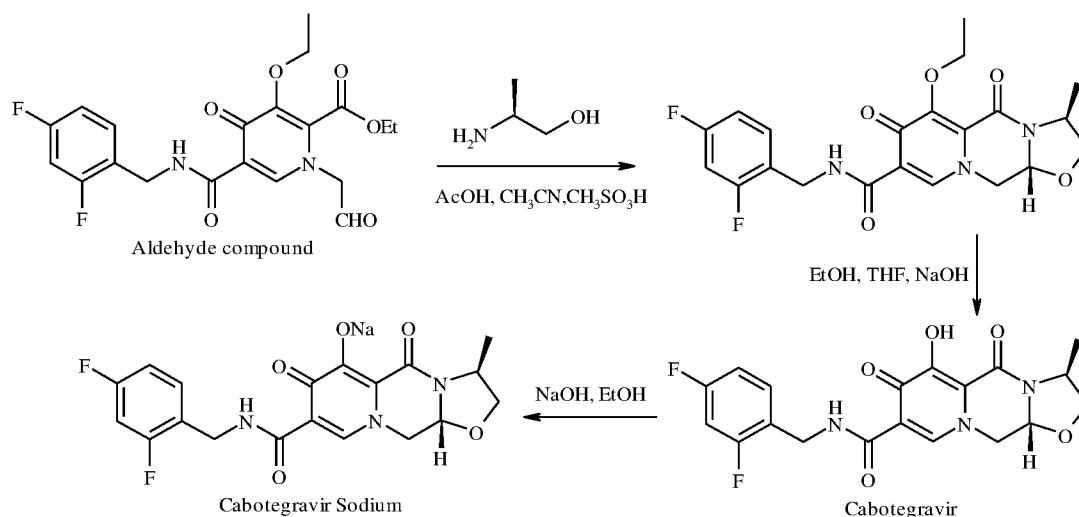
- 15 PCT application Number: 2010/068253 (“the ‘253 publication”) discloses a process for preparation of cabotegravir and the process involves preparation of cabotegravir by formation of Formula XIb (Y = -Obenzyl and R' = hydrogen) and Formula XIc (Y = -Obenzyl and R' = Br) as an intermediates. Further, the ‘253 application disclosed process involves isolation of cabotegravir from ethanol solvent and converting the obtained cabotegravir in to cabotegravir sodium using a mixture of ethanol: water and 1N sodium hydroxide. The ‘253 publication disclosed process is as follows:



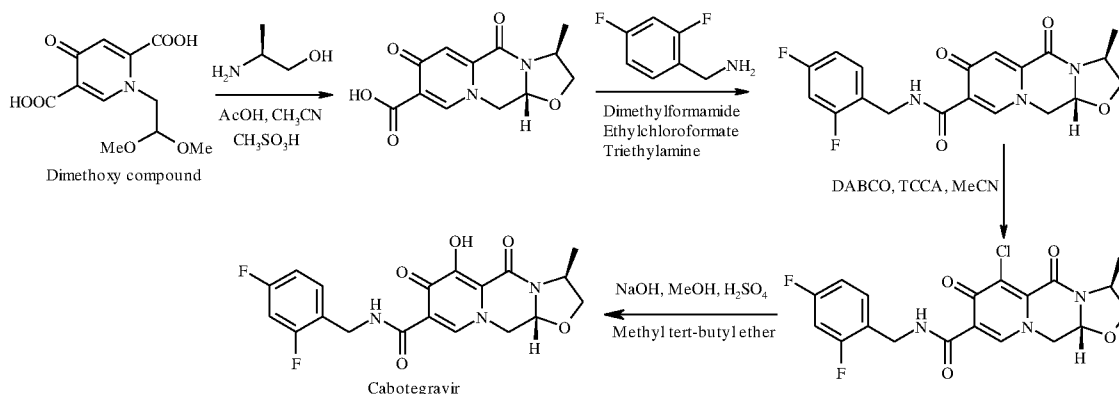
- 5 PCT application Number: 2011/119566 (“the ‘566 publication”) discloses a process for preparation of cabotegravir and the process involves preparation of cabotegravir starting from MDHC compound by formation of Formula XIa (Y= -OMe and R’= -COOH) and methyl protected cabotegravir as an intermediates. Further, the ‘566 application disclosed process involves isolation of cabotegravir from a mixture of water and tetrahydrofuran. The ‘566 publication disclosed process is as follows:



- 15 PCT application Number: 2015/177537 (“the ‘537 publication”) discloses a process for preparation of cabotegravir and the process involves isolation of cabotegravir from a mixture of water and tetrahydrofuran and converting the obtained cabotegravir in to cabotegravir sodium using ethanol and 2 N sodium hydroxide. The ‘537 publication disclosed process is as follows:



- 5 PCT application Number: 2016/113372 (“the ‘372 publication”) discloses a process for preparation of Cabotegravir and the process involves isolation of cabotegravir from methyl tert-butyl ether. The ‘372 application disclosed process is as follows:



10

Further other known literatures for ex: *Organic Letters* 2015, 17(3), 564-567 and CN113527332A discloses a process for preparation of cabotegravir by formation of key acid intermediate of Formula XIa followed by purification of the same from methanol by following the same process disclosed in the ‘566 application.

15

PCT application Number: 2018/109786 (“the ‘786 publication”) discloses crystalline cabotegravir Form C-I and cabotegravir Form C-II; crystalline cabotegravir sodium Form N-I, Form N-II; and crystalline forms of cabotegravir potassium Form K-I, Form K-II, Form K-III and its processes.

20

PCT application Number: 2018/149608 (“the ‘608 publication”) discloses crystalline cabotegravir sodium Form A, Form B, Form C and its processes. According to this publication, cabotegravir sodium Form A was resulted according to the process disclosed under WO2006/116764 and WO2010/068253.

25

Cabotegravir or its pharmaceutically acceptable salts is one of the important approved carbamoylpyridone HIV integrase inhibitors drug available in the market for the treatment of (HIV)-1 infection. Cabotegravir and its intermediates prepared according to the reported methods always involves contamination with unreacted starting materials, by-products generated from the coupling agents used, and process impurities and all these must be controlled at the source level itself otherwise the same may carry forward to further stage of the synthesis and leads to burden at final stage of the process as the purification to remove these impurities at final stage is always compromise the valuable product yield. Further, the reported methods for preparation of crystalline cabotegravir

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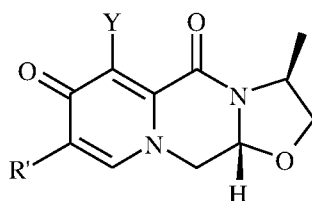
5 sodium are not consistently producing single crystalline form instead producing mixture of one or more other crystalline forms.

Hence, there exists a need in the art to develop a process for preparation and purification of cabotegravir API consistently, which is readily amenable to large scale production and free from its starting material and impurities. Further, there exists a need in the art to develop a process to produce crystalline form of cabotegravir and its sodium salt consistently without contamination of one or more of other polymorphs. Thus, the main objective of the present invention is to provide an improved and effective process for preparation of cabotegravir and its sodium salt and its intermediates, which is commercially feasible on large scale production with greater yield and with higher purity.

SUMMARY OF THE INVENTION

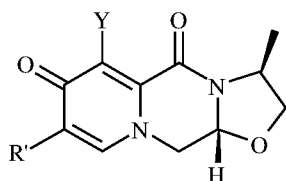
20 The present invention encompasses a process for preparation and purification of cabotegravir and its intermediates thereof. Further, the present invention encompasses a process for preparation of crystalline cabotegravir and its sodium salt and its pharmaceutical composition thereof.

25 In accordance with one another embodiment, the present invention provides process for purification of compound of Formula XI, comprising:

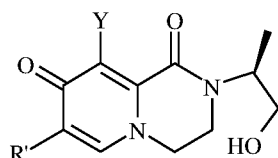


Formula XI

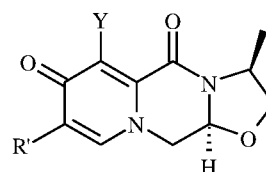
30 a) suspending or dissolving a compound of Formula XI in a suitable solvent at a suitable temperature; wherein the compound of Formula XI having more than 0.15% by HPLC of a compound of Formula XIA and/or Formula XIB, and wherein "Y" represents hydrogen, chloro or -OR; "R' " represents hydrogen, -COOH, -COOR, -CONH₂, -CHO, -CN or halogen; and "R" represents alkyl, aryl or aralkyl; and



Formula XI



Formula XIA



Formula XIB

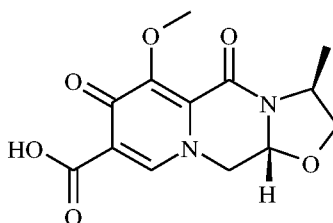
b) isolating the pure compound of Formula XI.

10 In accordance with another embodiment, the present invention provides process for purification of compound of Formula XI, comprising:

a) suspending or dissolving a compound of Formula XI in a suitable solvent at a suitable temperature; wherein the compound of Formula XI having more than 0.15% by HPLC of a compound of Formula XIA and/or Formula XIB, and wherein "Y" represents hydrogen, chloro or -OR; "R'" represents hydrogen, -COOH, -COOR, -CONH₂, -CHO, -CN or halogen; and "R" represents alkyl, aryl or aralkyl; and

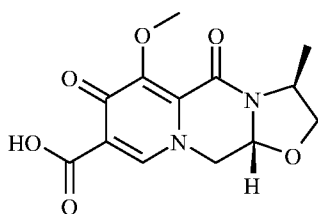
b) isolating the pure compound of Formula XI; wherein the suitable solvent is selected from the group comprising alcohols, halogenated hydrocarbons, ketones, nitriles, water or mixture thereof.

In accordance with another embodiment, the present invention provides process for purification of compound of Formula XIa, comprising:

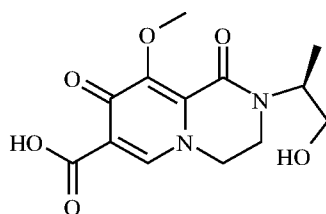


Formula XIa

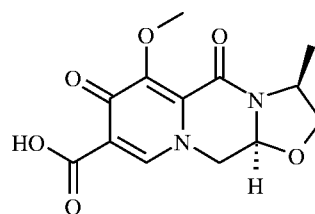
a) suspending or dissolving a compound of Formula XIa in a suitable solvent at a suitable temperature; wherein the compound of Formula XIa having more than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB', and



Formula XIa



Formula XIA'



Formula XIB'

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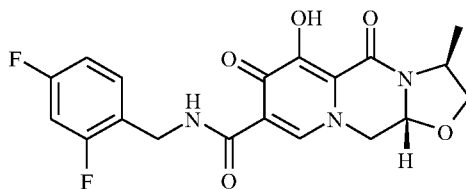
b) isolating the pure compound of Formula XIa.

In accordance with another embodiment, the present invention provides process for purification of compound of Formula XIa, comprising:

- 10 a) suspending or dissolving a compound of Formula XIa in a suitable solvent at room temperature to about reflux; wherein the compound of Formula XIa having more than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB',
- b) optionally, cooling the step a) reaction mass to below 25°C, and
- 15 c) isolating the pure compound of Formula XIa; wherein the pure compound of Formula XIa having less than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB'; wherein the suitable solvent is selected from the group comprising alcohols, halogenated hydrocarbons, ketones, nitriles, water or mixture thereof.

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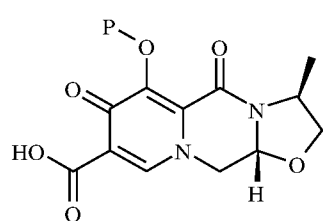
In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:



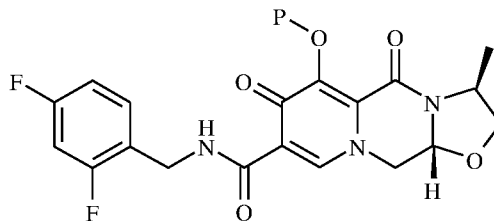
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Formula I

- a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of Formula XII'; wherein the "P" represents an alkyl, aryl or aralkyl, and



Formula XI'



Formula XII'

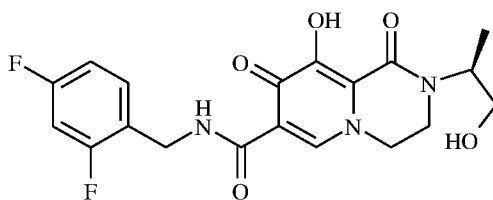
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- b) deprotecting the compound of Formula XII' in presence of a suitable deprotecting agent to obtain cabotegravir; wherein the step a) and/or step b) comprises use of an acid prior to isolation of the corresponding product.

5 In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

- a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of
10 Formula XII'; wherein the "P" represents an alkyl, aryl or aralkyl, and
b) deprotecting the compound of Formula XII' in presence of a suitable deprotecting agent to obtain cabotegravir;

wherein the step a) comprises use of an acid to obtain a compound of Formula XII' contain less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine and by-products of coupling agent; and/or wherein the step b) comprises use of
15 an acid to obtain cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir.



Open chain impurity of cabotegravir

20

In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

- a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of
25 Formula XII'; wherein the "P" represents an alkyl, aryl or aralkyl, and
b) deprotecting the compound of Formula XII' in presence of a suitable deprotecting agent to obtain cabotegravir;

wherein the step a) comprises use of an acid to obtain a compound of Formula XII' contain less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine and by-products of coupling agent; and/or wherein the step b) comprises use of
30 an acid to obtain cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir;

wherein the acid is either organic acid or inorganic acid with the proviso that
35 wherein said organic acid or inorganic acid excludes hydrochloric acid and sulfuric acid.

5 In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

- 10 a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent; wherein the "P" represents an alkyl, aryl or aralkyl,
- b) treating the step a) reaction mass with an acid,
- c) isolating the compound of Formula XII' contain less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine and by-products of coupling agent,
- 15 d) deprotecting the compound of Formula XII' obtained in step c) in presence of a suitable deprotecting agent,
- e) treating the step d) reaction mass with an acid, and
- f) isolating the cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir.

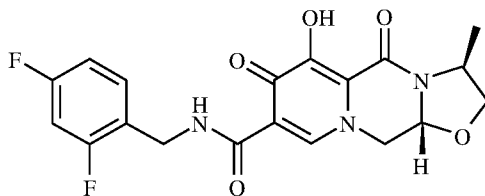
20 In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

- 25 a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent; wherein the "P" represents an alkyl, aryl or aralkyl,
- b) treating the step a) reaction mass with an acid,
- c) isolating the compound of Formula XII' contain less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine and by-products of coupling agent, and
- 30 d) converting the compound of Formula XII' in to cabotegravir or its pharmaceutically acceptable salts thereof.

In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

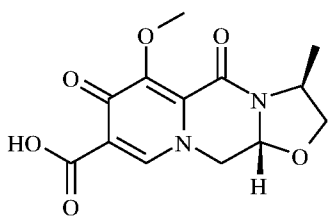
- 35 a) deprotecting a compound of Formula XII', wherein the "P" represents an alkyl, aryl or aralkyl, in presence of a suitable deprotecting agent,
- b) treating the step a) reaction mass with an acid, and
- c) isolating the cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir.

- 5 In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

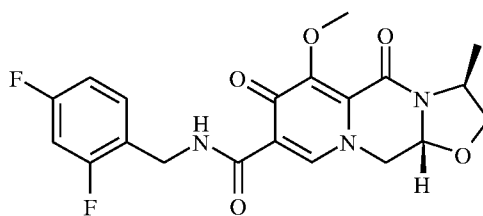


Formula I

- 10 a) reacting a compound of Formula XIa with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of Formula XII, and



Formula XIa



Formula XII

- 15 b) deprotecting the compound of Formula XII in presence of a suitable deprotecting agent to provide cabotegravir;
 wherein the step a) comprises use of an acid to obtain a compound of Formula XII contain less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine and by-products of coupling agent; and/or wherein the step b) comprises use of
 20 an acid to obtain cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir.

In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof,
 25 comprising:

- a) reacting a compound of Formula XIa with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of Formula XII, and
 b) deprotecting the compound of Formula XII in presence of a suitable
 30 deprotecting agent to provide cabotegravir;
 wherein the step a) comprises use of an acid to obtain a compound of Formula XII contain less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine

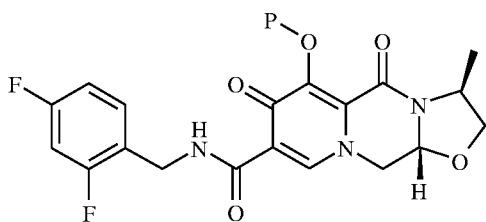
- 5 and by-products of coupling agent; and/or wherein the step b) comprises use of an acid to obtain cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir;
- wherein the acid is either organic acid or inorganic acid with the proviso that wherein said organic acid or inorganic acid excludes hydrochloric acid and
- 10 sulfuric acid.

In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

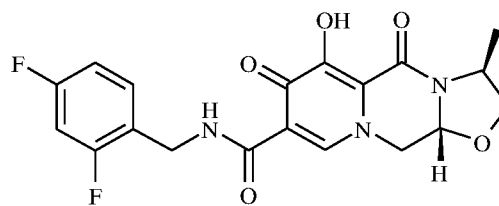
- 15 a) reacting a compound of Formula XIa with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of Formula XII,
- b) treating the step a) reaction mass with an acid,
- c) isolating the compound of Formula XII contain less than 0.5% by HPLC of at
- 20 least one of 2,4-difluorobenzylamine and by-products of coupling agent,
- d) deprotecting the compound of Formula XII in presence of a suitable deprotecting agent,
- e) treating the step d) reaction mass with an acid, and
- f) isolating the cabotegravir contain less than 0.5% by HPLC of an open chain
- 25 impurity of cabotegravir.

In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising: deprotecting a compound of Formula XII' in presence of magnesium

30 chloride in a suitable solvent to provide cabotegravir; wherein the "P" represents an alkyl, aryl or aralkyl.



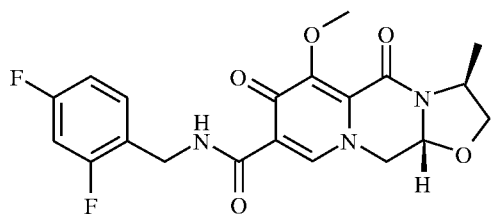
Formula XII'



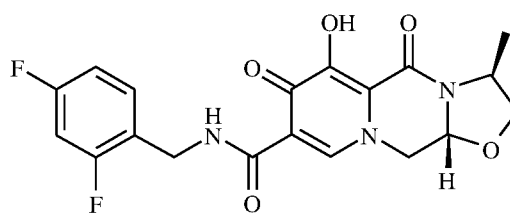
Formula I

- 35 In accordance with another embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof,

- 5 comprising: deprotecting a compound of Formula XII in presence of magnesium chloride in a suitable solvent to provide a cabotegravir of Formula I.

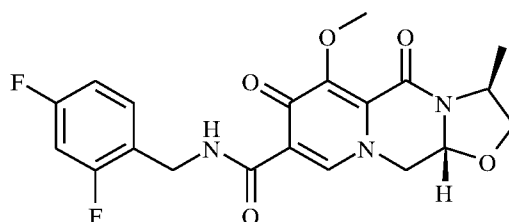


Formula XII



Formula I

- 10 In another embodiment, the present invention provides crystalline compound of Formula XII.



Formula XII

- 15 In another embodiment, the present invention provides crystalline compound of Formula XII characterized by a powder X-ray diffraction (PXRD) pattern substantially in accordance with Figure 3.

In another embodiment, the present invention provides a crystalline compound of
 20 Formula XII characterized by X-Ray diffraction (XRD) pattern having one or more peaks at about 5.5, 6.1, 9.7, 11.4, 12.1, 13.3, 13.7, 15.1, 15.6, 15.9, 16.3, 16.9, 17.2, 17.4, 18.2, 19.2, 19.5, 19.8, 20.3, 20.4, 20.7, 22.3, 22.8, 23.0, 23.1, 23.5, 23.8, 23.9, 24.1, 24.4, 24.5, 25.4, 25.5, 26.2, 26.9, 27.0, 27.6, 28.5, 28.9, 29.1, 29.6, 29.7, 30.6, 30.7, 31.2, 31.5, 32.1, 32.6, 32.9, 33.4, 34.5 and $35.1 \pm 0.2^\circ 2\theta$.

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In another embodiment, the present invention provides a crystalline compound of Formula XII characterized by X-Ray diffraction (XRD) pattern having peaks at about 6.1, 12.1, 13.7, 15.1, 15.6, 17.2, 17.4, 18.2, 19.5, 20.7, 25.4, $30.6 \pm 0.2^\circ 2\theta$.

- 30 In accordance with another embodiment, the present invention provides a process for purification of cabotegravir of Formula I, comprising:

a) suspending or dissolving cabotegravir in a suitable solvent at ambient temperature to reflux,

- 5 b) adding step a) reaction mass to an anti-solvent (or) adding an anti-solvent to step
 a) reaction mass at a suitable temperature,
 c) optionally, cooling the step b) reaction mass to below 25°C, and
 d) isolating the pure cabotegravir.
- 10 In accordance with another embodiment, the present invention provides a process for
 purification of cabotegravir of Formula I, comprising:
 a) suspending or dissolving cabotegravir in a suitable solvent at ambient
 temperature to reflux,
 b) adding step a) reaction mass to an anti-solvent (or) adding an anti-solvent to step
15 a) reaction mass at a suitable temperature,
 c) optionally, cooling the step b) reaction mass to below 25°C, and
 d) isolating the pure cabotegravir; wherein the suitable solvent is selected from the
 group comprising alcohols, amides, sulfoxides, nitriles, halogenated solvents,
 sulfolane, acetic acid and the like and mixtures thereof; and wherein the anti-
20 solvent is selected from the group comprising alcohols, ethers, esters, ketones,
 aromatic hydrocarbons and the like and water and mixtures thereof.

- In accordance with another embodiment, the present invention provides process for
 preparation of pure cabotegravir of Formula I or its pharmaceutically acceptable salts
25 thereof, comprising:
 a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in
 presence of a suitable coupling agent in a suitable solvent; wherein the "P"
 represents an alkyl, aryl or aralkyl,
 b) treating the step a) reaction mass with an acid,
30 c) isolating the compound of Formula XII' contain less than 0.5% by HPLC of at
 least one of 2,4-difluorobenzylamine and by-products of coupling agent,
 d) deprotecting the compound of Formula XII' obtained in step c) in presence of
 a suitable deprotecting agent,
 e) treating the step d) reaction mass with an acid,
35 f) isolating the cabotegravir contain less than 0.5% by HPLC of an open chain
 impurity of cabotegravir,
 g) suspending or dissolving cabotegravir in a suitable solvent at ambient
 temperature to reflux,

- 5 h) adding step g) reaction mass to an anti-solvent (or) adding an anti-solvent to step g) reaction mass at a suitable temperature,
 i) optionally, cooling the step h) reaction mass to below 25°C, and
 j) isolating the pure cabotegravir.
- 10 In accordance with another embodiment, the present invention provides process for preparation of pure cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:
- a) deprotecting a compound of Formula XII' in presence of a suitable deprotecting agent,
15 b) treating the step a) reaction mass with an acid,
 c) isolating the cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir,
 d) suspending or dissolving cabotegravir in a suitable solvent at ambient temperature to reflux,
20 e) adding step d) reaction mass to an anti-solvent (or) adding an anti-solvent to step d) reaction mass at a suitable temperature,
 f) optionally, cooling the step e) reaction mass to below 25°C, and
 g) isolating the pure cabotegravir.
- 25 In accordance with another embodiment, the present invention provides a process for preparation of crystalline cabotegravir sodium Form A, comprising:
- a) suspending or dissolving cabotegravir in an organic solvent,
 b) adding sodium source to step a) reaction mass (or) adding step a) reaction mass to sodium source, and
30 c) isolating cabotegravir sodium Form A; wherein the organic solvent is selected from the group comprising of alcohols, ketones, sulfoxides, nitriles, ethers and the like and mixtures thereof.

- In accordance with another embodiment, the present invention provides a process for
35 preparation of crystalline cabotegravir sodium Form A, comprising:
- a) suspending or dissolving cabotegravir in an organic solvent,
 b) adding sodium source to step a) reaction mass (or) adding step a) reaction mass to sodium source, and

- 5 c) isolating cabotegravir sodium Form A; wherein the organic solvent is selected from the group comprising alcohols include but are not limited to methanol, ethanol, butanol, isobutanol, *tert*-butanol, propanol, isopropanol, pentanol, glycerol and the like; ketones include, but are not limited to acetone, methylisobutylketone, methylethylketone and the like; sulfoxides include, but
10 are not limited to dimethyl sulfoxide, diethyl sulfoxide and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, methyl tertiary butyl ether and the like and mixture thereof.
- 15 In accordance with another embodiment, the present invention provides a process for preparation of crystalline cabotegravir sodium Form A, comprising:
- a) suspending or dissolving cabotegravir in an organic solvent,
 - b) adding sodium source to step a) reaction mass (or) adding step a) reaction mass to sodium source, and
- 20 c) isolating cabotegravir sodium Form A; wherein the organic solvent is selected from trifluoroethanol, dimethyl sulfoxide, methanol, ethanol, n-butanol, n-pentanol, acetone, acetonitrile, tetrahydrofuran and mixture thereof.

In accordance with another embodiment, the present invention provides a process for
25 preparation of crystalline cabotegravir sodium Form A, characterized by a powder X-ray diffraction (PXRD) pattern peaks having peaks selected from at about: 5.4, 9.5, 11.0, 12.7, 13.1, 14.0, 14.6, 15.4, 15.7, 16.1, 19.0, 21.5, 22.1, 23.2, 23.8, 24.4, 25.4, 26.2, 27.1, 28.0, 28.9, 29.9, 32.6 and $34.5 \pm 0.2^\circ 2\theta$.

- 30 In accordance with one embodiment, the present invention provides a process for preparation of crystalline cabotegravir sodium Form A, comprising:
- a) suspending or dissolving cabotegravir in an organic solvent,
 - b) adding sodium source to step a) reaction mass (or) adding step a) reaction mass to sodium source, and
- 35 c) isolating cabotegravir sodium Form A; wherein the organic solvent is selected from the group comprising alcohols, ketones, sulfoxides, nitriles, ethers and the like or mixtures thereof; wherein the crystalline cabotegravir sodium Form A, characterized by: a powder X-ray diffraction (PXRD) pattern having at least one peak selected from: 5.4, 9.5, 11.0, 12.7, 13.1, 14.0, 14.6, 15.4, 15.7, 16.1, 19.0,

5 21.5, 22.1, 23.2, 23.8, 24.4, 25.4, 26.2, 27.1, 28.0, 28.9, 29.9, 32.6 and 34.5
±0.2° 2θ and does not have a peak at about 6.2 and/or 6.8±0.2° 2θ.

In accordance with another embodiment, the present invention provides substantially
pure crystalline cabotegravir sodium Form A, characterized by: a powder X-ray
10 diffraction (PXRD) pattern having at least one peak selected from: 5.4, 9.5, 11.0, 12.7,
13.1, 14.0, 14.6, 15.4, 15.7, 16.1, 19.0, 21.5, 22.1, 23.2, 23.8, 24.4, 25.4, 26.2, 27.1,
28.0, 28.9, 29.9, 32.6 and 34.5 ±0.2° 2θ and does not have a peak at about 6.2 and/or
6.8±0.2° 2θ.

15 In accordance with another embodiment, the present invention provides at least about
95% by weight of the solid crystalline cabotegravir sodium is Form A of cabotegravir
sodium.

In accordance with another embodiment, the present invention provides at least about
20 99% by weight of the solid crystalline cabotegravir sodium is Form A of cabotegravir
sodium.

In accordance with another embodiment, the present invention provides a
pharmaceutical composition, comprising cabotegravir or its pharmaceutically acceptable
25 salts thereof prepared by the processes of the present invention and at least one
pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

30 The accompanying drawings, which are incorporated in and constitute a part of this
specification, illustrate several embodiments of the invention and together with the
description, serve to explain the principles of the invention.

Figure 1 is the characteristic powder X-ray diffraction (PXRD) pattern of a crystalline
35 cabotegravir.

Figure 2 is the characteristic thermogravimetric analysis (TGA) of a crystalline
cabotegravir.

40 Figure 3 is the characteristic powder X-ray diffraction (PXRD) pattern of a crystalline
compound of Formula XII.

5 Figure 4 is the characteristic powder X-ray diffraction (PXRD) pattern of crystalline cabotegravir sodium Form A.

Figure 5 is the characteristic particle size distribution histogram of crystalline cabotegravir.

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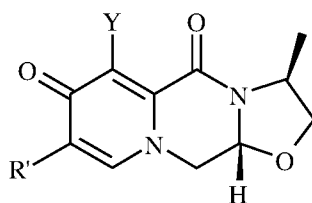
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for preparation of cabotegravir and its intermediates thereof with high product yield and quality substantially lower level of impurities, by-products and unreacted starting materials. The present invention further provides a process for purification of cabotegravir and its pharmaceutical composition thereof. Further, the present invention encompasses a process for preparation of crystalline cabotegravir sodium its pharmaceutical composition thereof.

20 In accordance with one embodiment, the present invention provides a process for purification of compound of Formula XI substantially free of its impurities.

In accordance with another embodiment, the present invention provides a process for purification of compound of Formula XI, which is substantially free of open chain impurity of Formula XIA and/or diastereomer impurity of Formula XIB. The present invention further relates to a process for preparation of pure cabotegravir or its pharmaceutically acceptable salts thereof using the pure compound of Formula XI.

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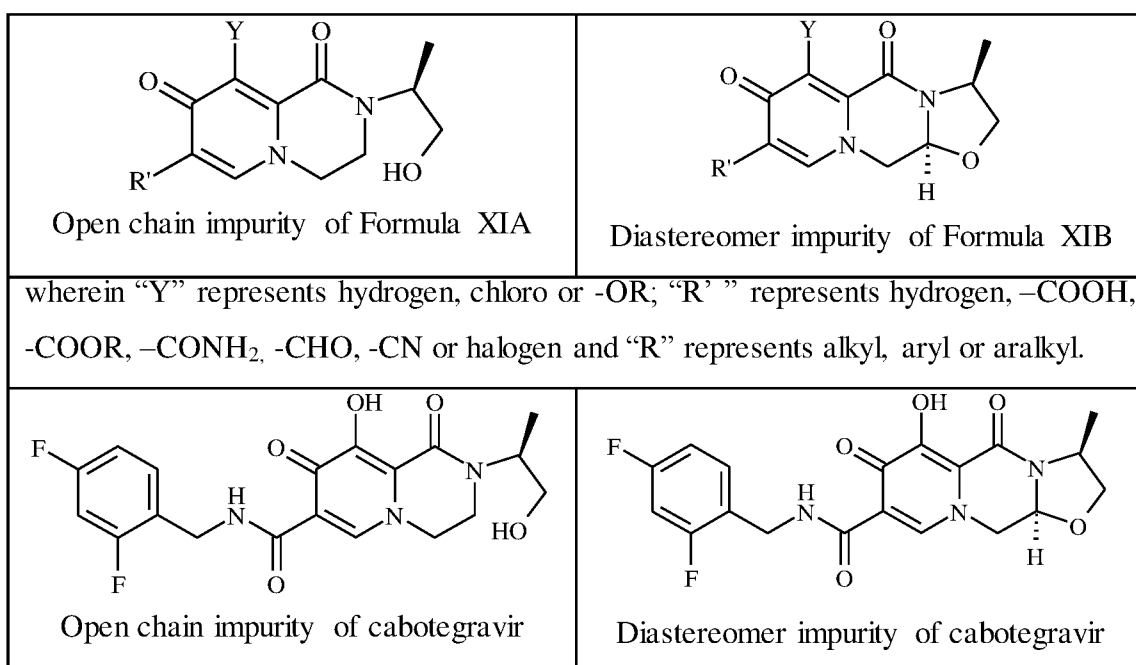
Formula XI

wherein "Y" represents hydrogen, chloro or -OR; "R" represents hydrogen, -COOH, -COOR, -CONH₂, -CHO, -CN or halogen; and "R" represents alkyl, aryl or aralkyl.

The compound of Formula XI is the key intermediate in the preparation of cabotegravir, as it comprises stereomeric centers. The compound of Formula XI prepared according to the process disclosed in the art involves formation of open chain impurity of Formula XIA due to cleavage of oxazole ring and diastereomer impurity of Formula XIB.

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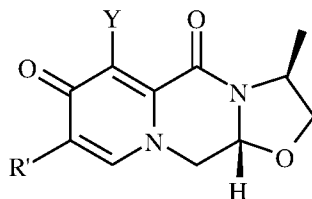
5 Further, these impurities once contaminated with the compound of Formula XI the same may be involved in subsequent stages along with the compound of Formula XI and generates corresponding open chain impurity and diastereomer impurities in the final cabotegravir. Due to less polarity differences, these two impurities cannot be controlled or removed from main product by regular process parameters such as modification trials
 10 or other purification technique. Hence, the purity of the compound of Formula XI is critical parameter in the preparation of cabotegravir as it maintains the same purity level until the final API. If not controlled properly these impurities at the intermediate stage and subsequent purification of cabotegravir to remove these impurities is very difficult as the cabotegravir is a BCS-2 drug substance and having less solubility in most of the
 15 solvents.



Hence, it is an object of the present invention to provide a process for the purification of compound of Formula XI, free from open chain impurity of Formula XIA and/or diastereomer impurity of Formula XIB. The present inventors have surprisingly found
 20 that the open chain and diastereomer impurities can be separated from the product by solvent purification process in accordance with below embodiments.

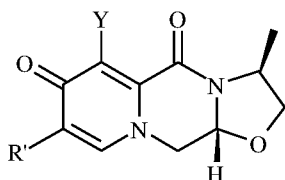
The present invention provides a process for purification of compound of Formula XI, an intermediate for preparation of cabotegravir or its pharmaceutically acceptable salts
 25 thereof.

- 5 In accordance with another embodiment, the present invention provides process for purification of compound of Formula XI, comprising:

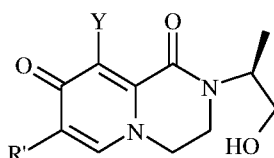


Formula XI

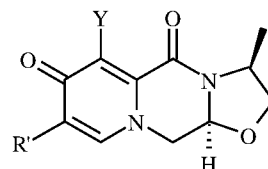
- 10 a) suspending or dissolving a compound of Formula XI in a suitable solvent at a suitable temperature; wherein the compound of Formula XI having more than 0.15% by HPLC of a compound of Formula XIA and/or Formula XIB, and wherein “Y” represents hydrogen, chloro or -OR; “R’ ” represents hydrogen, –COOH, -COOR, -CONH₂, -CHO, -CN or halogen; “R” represents alkyl, aryl or
- 15 aralkyl; and



Formula XI



Formula XIA



Formula XIB

- 20 b) isolating the pure compound of Formula XI.

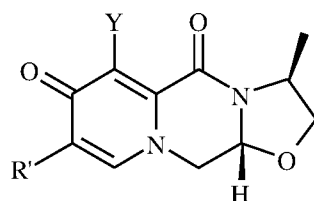
Unless otherwise specified the term “alkyl” used herein is selected from but not limited to methyl, ethyl, isopropyl, butyl, tert-butyl, isoamyl and the like.

- 25 Unless otherwise specified the term “aryl” or “aralkyl” used herein is selected from but not limited to benzyl, benzoyl, para nitro benzyl and the like.

Unless otherwise specified the term “halogen” used herein is selected from fluoro, bromo, chloro and Iodo.

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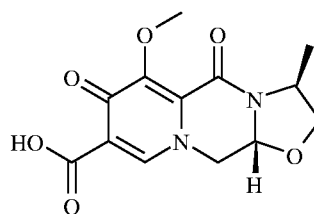
In accordance with a preferred embodiment, the present invention provides process for purification of compound of Formula XI,



Formula XI

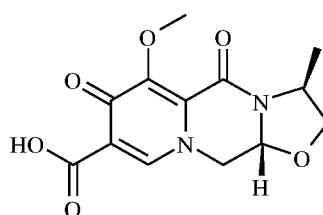
wherein “Y” represents chloro, -OMe or O-benzyl; “R’ ” represents hydrogen or –COOH or halogen.

- 10 In accordance with a specific embodiment, the compound of Formula XI specifically represents as following compound of Formula XIa:



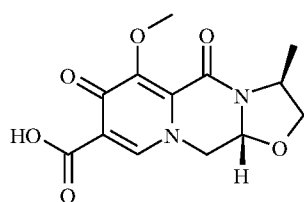
Formula XIa

- 15 In accordance with another preferred embodiment, the present invention provides process for purification of compound of Formula XIa, comprising:

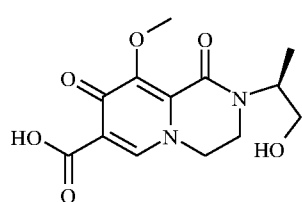


Formula XIa

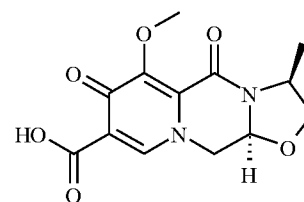
- 20 a) suspending or dissolving a compound of Formula XIa in a suitable solvent at a suitable temperature; wherein the compound of Formula XIa having more than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB', and



Formula XIa



Formula XIA'



Formula XIB'

- b) isolating the pure compound of Formula XIa.

5 The compound of Formula XIa, which is used herein as a starting material is known in the art and can be prepared by any known methods. For example, may be prepared as per the process disclosed in WO2011/119566.

10 The starting compound of Formula XIa may contain about 0.15% to about 50% of the compound of Formula XIA' and/or Formula XIB', as an impurity as measured by HPLC. Further the said compound of Formula XIa may be obtained directly from the reaction mass in the form of crude, or a solution comprising mixture of compound of Formula XIa and, Formula XIA' and/or Formula XIB' or may be in the form of semi-solid or solid.

15 The aforementioned step a) process of formation of suspension or solution of compound of Formula XIa with more than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB' in a suitable solvent, wherein the solvent is selected from the group comprising alcohols, halogenated hydrocarbons, ketones, nitriles, water and
20 mixture thereof.

The suitable solvent used herein step a) is selected from the group comprising of but not limited to alcohols, such as methanol, ethanol, propanol, isopropanol, n-butanol, tert-butanol and the like; halogenated hydrocarbons, such as methylene chloride,
25 chloroform, chlorobenzene and the like; ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diethyl ketone and the like; nitriles, such as acetonitrile, propionitrile and the like; water and mixtures thereof; preferably methanol, ethanol, isopropanol, n-butanol, methylene chloride, acetone, acetonitrile, water and mixtures thereof.

30 The step a) reaction may be carried out at a temperature of about room temperature to about reflux temperature of the solvent used; preferably at about 25°C to about 85°C.

Then the reaction mass can be optionally cooled to below 25°C and stirring for a
35 sufficient period of time. Then isolating the compound of Formula XIa substantially free of Formula XIA' and/or Formula XIB' by any conventional techniques, for example filtration or decantation; preferably by filtration and by this solvent purification the unwanted impurities of compound of Formula XIA' and/ or Formula XIB' are separated through filtrate and pure required solid product is obtained.

40

5 The above purification process may be applied once or twice until the required purity of compound of Formula XIa is attained.

In accordance with another embodiment, the compound of Formula XIa obtained by the processes described as above, having purity of at least about 99% as measured by
10 HPLC, preferably at least about 99.5% as measured by HPLC and substantially free of compound of Formula XIA' and/or Formula XIB'; wherein the word "substantially free" refers to compound of Formula XIa having less than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB', preferably less than about 0.1% by HPLC of a compound of Formula XIA' and/or Formula XIB'; more preferably less than
15 about 0.05% by HPLC of a compound of a Formula XIA' and/or Formula XIB'.

In accordance with another embodiment, the present invention provides a compound of Formula XIa having purity of at least about 99% as measured by HPLC, preferably at least about 99.5% as measured by HPLC and substantially free of compound of Formula
20 XIA' and/or Formula XIB'; wherein the word "substantially free" refers to compound of Formula XIa having less than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB', preferably less than about 0.1% by HPLC of a compound of Formula XIA' and/or Formula XIB'; more preferably less than about 0.05% by HPLC of a compound of a Formula XIA' and/or Formula XIB'.

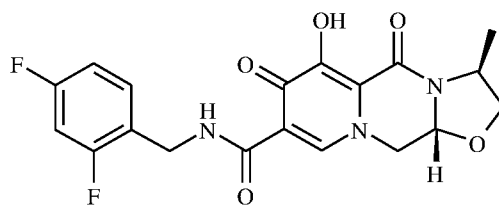
25 The reported processes in art involves formation of open chain impurity of Formula XIA' and diastereomer impurity of Formula XIB' around 3% and 6% respectively by HPLC along with compound of Formula XIa. Due to polarity difference, these impurities are difficult to separate from compound of Formula XIa. Further, these
30 impurities reacted in subsequent stage and carry forward to final stage and forms corresponding open chain impurity and diastereomer impurity of cabotegravir and these are not easily separable from the final product. Hence, the compound of Formula XIa purity is important for preparation of pure cabotegravir API.

35 In contrast, the purification process of the present invention involves purification of compound of Formula XIa by solvent purification. The present process easily separates the undesired open chain impurity of Formula XIA' and/or diastereomer impurity of Formula XIB' along with mother liquors as these impurities are highly soluble in solvents used for the purification and the required product is partially/insoluble in the

5 solvents used for the purification. Hence the purification process of compound of Formula XIa is more economic and easy to scale up to commercial level.

In accordance with another embodiment, the present invention provides an improved process for the preparation of cabotegravir or its pharmaceutically acceptable salts thereof, comprising purifying the compound of Formula XIa as process described above, and converting the compound of Formula XIa having less than 0.15% by HPLC of a compound of Formula XIA' and/or Formula XIB' in to cabotegravir or its pharmaceutically acceptable salts thereof.

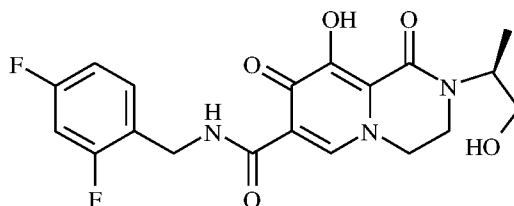
15 In accordance with another embodiment, the present invention provides a process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof.



Formula I

20 Cabotegravir prepared according to the process disclosed under the reported publications have certain drawbacks as it involves:

- a) contamination of unreacted 2,4-difluorobenzylamine and an imidazole, a by-product of coupling agent used in the preparation of compound of Formula XII;
- 25 b) formation of open chain impurity of cabotegravir in the deprotection step. This impurity may be formed under strong acidic conditions at higher temperatures by oxazole ring cleavage, and



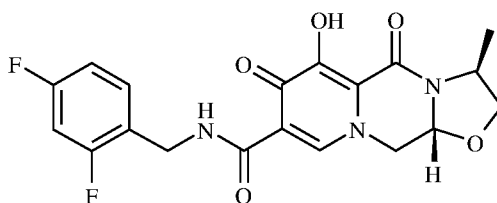
Open chain impurity of cabotegravir

- 30 c) with the use of deprotecting agents as reported in the art there is always possibility of incomplete reaction therefore the unreacted compound of Formula XII is also isolated as an impurity with the resulted cabotegravir.

5 These impurities once formed along with the intermediates and if failure to apply proper removal techniques the same may carry forward through subsequent reactions and may contaminate with the final cabotegravir API. Due to less polarity differences, removal of these impurities at the intermediate stage itself is critical and it requires extensive purification processes at final stage. Purification techniques at final stage are always
 10 compromise the valuable product yield; hence all these impurities and by-products are needs to be controlled at the source level itself.

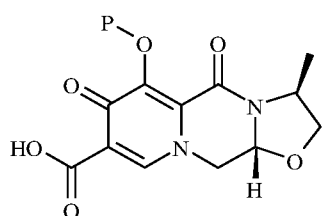
The present inventors have surprisingly found that various strategies to control or removal of these impurities and by-products at prior to isolation of the intermediates
 15 stage and this will reduces the purification burden at intermediate stage or at final stage of the process thereby getting higher yield and high pure product.

In accordance with one embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof,
 20 comprising:

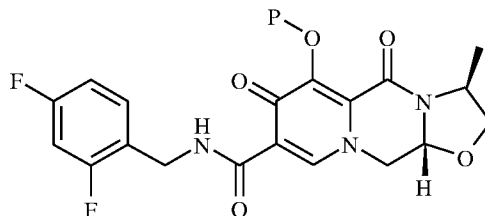


Formula I

- a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of
 25 Formula XII'; wherein the "P" represents an alkyl, aryl or aralkyl, and



Formula XI'



Formula XII'

- b) deprotecting the compound of Formula XII' in presence of a suitable deprotecting agent to obtain cabotegravir; wherein the step a) and/or step b)
 30 comprises use of an acid prior to isolation of the corresponding product.

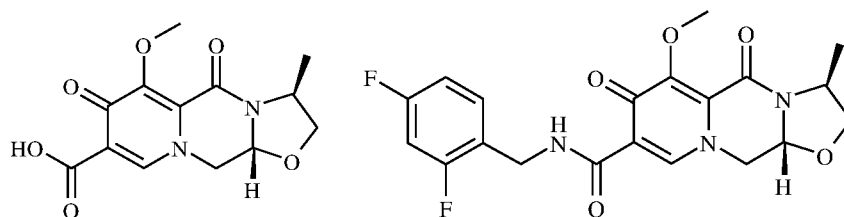
5 As used herein, the terms “comprises,” “comprising,” “includes,” “including,” “has,” “having” or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a composition, process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such composition, process, method, article,
10 or apparatus.

Unless otherwise specified the term “alkyl” used herein is selected from but not limited to methyl, ethyl, isopropyl, butyl, tert-butyl, isoamyl and the like; preferably methyl.

15 Unless otherwise specified the term “aryl” or “aralkyl” used herein is selected from but not limited to benzyl, benzoyl, para nitro benzyl and the like.

In a specific embodiment, wherein the “P” represents an alkyl preferably methyl or an aryl preferably benzyl.

20 In accordance with a specific embodiment, the compound of Formula XI' and Formula XII' specifically represents as following compound of Formula XIa and Formula XII:

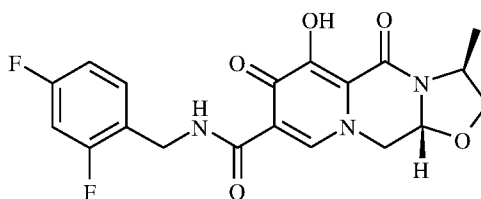


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Formula XIa

Formula XII

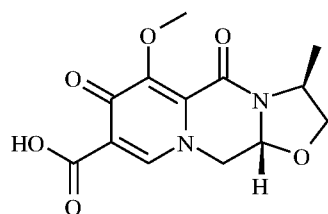
In a specific embodiment, the present invention provides process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:



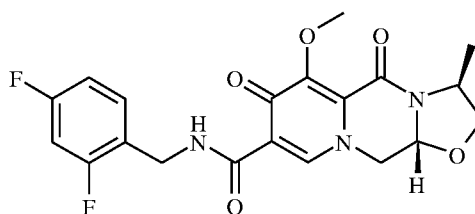
30

Formula I

- a) reacting a compound of Formula XIa with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of Formula XII, and



Formula XIa



Formula XII

b) deprotecting the compound of Formula XII in presence of a suitable deprotecting agent to obtain cabotegravir;

wherein the step a) comprises use of an acid to obtain the compound of Formula XII contain less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine and by-products of coupling agent; and/or wherein the step b) comprises use of an acid to obtain the cabotegravir contain less than 0.5% by HPLC of an open chain impurity of cabotegravir.

The compound of Formula XIa, which is used herein as a starting material is known in the art and can be prepared by any known methods or by following the process described in the present specification.

The suitable coupling agent used in reaction of a compound of Formula XIa with 2,4-difluorobenzylamine is selected from the group comprising of but not limited to 2-chloro-4,6-dimethoxy-1,3,5-triazine, carbonyldiimidazole (CDI), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), 1-Hhydroxy benzotriazole (HOBt), 3-[bis(dimethylamino)methylumyl]-3H-benzotriazol-1-oxide hexafluorophosphate (HBTU), O-(1H-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HCTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), propylphosphonic anhydride (T₃P), dicyclohexylcarbodiimide (DCC), 3-hydroxytriazolo[4,5-b]pyridine (HOAT), thionyl chloride (SOCl₂), oxalyl chloride (COCl₂), phosphorus oxychloride (POCl₃), pivaloyl chloride (PivCl), acetic anhydride (Ac₂O), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEQD), Methanesulfonyl chloride (MsCl), p-toluenesulfonyl chloride (TsCl) and the like and mixture thereof; preferably carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1-Hhydroxy benzotriazole and mixture thereof; more preferably carbonyldiimidazole.

The suitable solvent used in reaction of a compound of Formula XIa with 2,4-difluorobenzylamine is selected from the group comprising but not limited to ketones,

5 esters, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons, polar aprotic solvent, water and mixtures thereof. The ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; esters include, but are not limited to ethyl acetate, isopropyl acetate, butyl acetate and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; polar aprotic solvent include, but are not limited to dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone and the like and mixtures thereof; preferably acetonitrile, tetrahydrofuran, methylene chloride, dimethylformamide and mixtures thereof; more preferably methylene chloride.

20 The reaction of a compound of Formula XIa with 2,4-difluorobenzylamine is carried out at a temperature of about 0°C to about reflux temperature; preferably at about 25°C to about 50°C.

25 The reaction of a compound of Formula XIa with 2,4-difluorobenzylamine in the presence of coupling agent is always possibility to contamination of unreacted starting material, 2,4-difluorobenzylamine and by-products of coupling agent such as imidazole with the product. The process disclosed under the '566 publication involves adding water to the reaction mass after completion of the coupling reaction, which process fails to eliminate unreacted 2,4-difluorobenzylamine and imidazole by-product completely. Hence, the product isolated from the reaction mass contains more than 0.5% by HPLC of at least one of unreacted 2,4-difluorobenzylamine and imidazole by-product.

35 The present inventors surprisingly found that the unreacted 2,4-difluorobenzylamine and the imidazole formed as a by-product from the coupling agent are completely removed from the reaction mass by simply treating the reaction mass which is obtained after the coupling reaction with an acid. The acid used in the process of the invention advantageously forms acid salt with the unreacted 2,4-difluorobenzylamine and the imidazole and these acid salts can easily be dissolved in the aqueous phase thereby it can easily be separated from the reaction mass by simple layer separation and the pure

5 product can be isolated from the organic phase by the conventional techniques for example solvent crystallization.

After performing the coupling reaction, the reaction mass may be diluted with aqueous acid solution at a temperature of about 0°C to about reflux temperature, preferably at
10 about 25°C to about 50°C, so that the reaction mass split into organic phase and aqueous phase. Then the product containing organic phase may be separated from the aqueous phase and isolated the product from the organic phase. The unwanted starting material and the byproducts formed if any are separated through aqueous phase.

15 The acid used for treating the step a) reaction mass is either organic acid or inorganic acid. The organic acid is selected from the group comprising of but not limited to acetic acid, formic acid, citric acid, oxalic acid, tartaric acid, maleic acid, malic acid, mandelic acid, malonic acid, succinic acid, glutaric acid, adipic acid and the like and mixture thereof. The inorganic acid is selected from the group comprising of but not limited to
20 sulfurous acid, phosphoric acid, nitrous acid and the like and mixture thereof; preferably citric acid, oxalic acid and mixture thereof; more preferably citric acid.

In a preferred embodiment, the acid is either organic acid or inorganic acid with the proviso that wherein the said organic acid or inorganic acid excludes both hydrochloric
25 acid and sulfuric acid.

In a preferred embodiment, wherein the acid used in the process of step a) is citric acid.

In accordance with another embodiment, the present invention provides a process for
30 preparation of compound of Formula XII by crystallization from a suitable solvent such as alcohol solvent selected from methanol, ethanol, isopropanol and the like and mixture thereof; preferably methanol, to obtain crystalline compound of Formula XII.

The compound of Formula XII obtained by the processes described as above, having
35 purity of at least about 99% as measured by HPLC, preferably at least about 99.5% as measured by HPLC and substantially free of unreacted 2,4-difluorobenzylamine and byproducts of coupling agent such as imidazole; wherein the word "substantially free" refers to compound of Formula XII having less than 0.5% of unreacted 2,4-difluorobenzylamine or by-products of coupling agent or both as measured by HPLC,

5 preferably less than about 0.3%; more preferably less than about 0.1% as measured by HPLC.

In accordance with another embodiment, the present invention provides compound of Formula XII having less than 0.5% by HPLC of 2,4-difluorobenzylamine and/or by-
10 products of coupling agent.

In accordance with another embodiment, the present invention provides crystalline compound of Formula XII.

15 In accordance with another embodiment, the present invention provides crystalline compound of Formula XII characterized by a powder X-ray diffraction (PXRD) pattern substantially in accordance with Figure 3.

In accordance with another embodiment, the present invention provides a crystalline
20 compound of Formula XII characterized by X-Ray diffraction (XRD) pattern having one or more peaks at about 5.5, 6.1, 9.7, 11.4, 12.1, 13.3, 13.7, 15.1, 15.6, 15.9, 16.3, 16.9, 17.2, 17.4, 18.2, 19.2, 19.5, 19.8, 20.3, 20.4, 20.7, 22.3, 22.8, 23.0, 23.1, 23.5, 23.8, 23.9, 24.1, 24.4, 24.5, 25.4, 25.5, 26.2, 26.9, 27.0, 27.6, 28.5, 28.9, 29.1, 29.6, 29.7, 30.6, 30.7, 31.2, 31.5, 32.1, 32.6, 32.9, 33.4, 34.5 and $35.1 \pm 0.2^\circ 2\theta$.

25 In accordance with another embodiment, the present invention provides a crystalline compound of Formula XII characterized by X-Ray diffraction (XRD) pattern having one or more peaks at about 6.1, 12.1, 13.7, 15.1, 15.6, 17.2, 17.4, 18.2, 19.5, 20.7, 25.4, $30.6 \pm 0.2^\circ 2\theta$.

30 In accordance with another embodiment, the present invention provides preparation of cabotegravir from the compound of Formula XII of the invention, comprises: deprotecting a compound of Formula XII, in presence of a suitable deprotecting agent, treating the reaction mass with an acid, and isolating the cabotegravir.

35 The suitable deprotecting agent used for the process of the above embodiments is selected from the group comprising but not limited to magnesium chloride, magnesium iodide, magnesium hydroxide, lithium chloride, lithium iodide, lithium hydroxide, lithium trisiamyl borohydride, lithium triethyl borohydride, tri-sec-butyl borohydride,
40 boron tribromide, aluminium chloride, aluminium chloride-triethylamine complex,

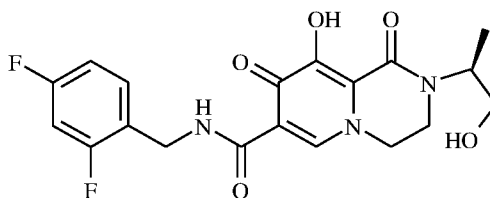
5 aluminium chloride-N,N-dimethyl aniline complex and the like and mixture thereof; preferably magnesium chloride, lithium chloride, aluminium chloride and mixture thereof; more preferably magnesium chloride.

10 In one preferred embodiment, the deprotection of the compound of Formula XII is carried out in presence of magnesium chloride as a deprotecting agent, it is advantage over known deprotecting agents such as magnesium bromide and lithium bromide, as the commercial availability of these compounds are very limited and highly expensive. The deprotecting agent used for the present invention specifically magnesium chloride is cheaper and commercially available when compared to known deprotecting agents.

15 The deprotection of the compound of Formula XII in presence of a suitable deprotecting agent may be advantageously carried out in a suitable solvent. The suitable solvent includes but is not limited to polar aprotic solvents and polar protic solvents and the like and mixture thereof. The polar aprotic solvents include, but are not limited to methylene
20 chloride, N-methylpyrrolidone, tetrahydrofuran, dimethylformamide, acetonitrile, dimethylsulfoxide and the like and mixtures thereof. The polar protic solvents include, but are not limited to methanol, ethanol, formic acid, acetic acid and the like and mixtures thereof; preferably acetonitrile.

25 The deprotection of the compound of Formula XII in presence of a suitable deprotecting agent is carried out at a temperature of about 25°C to reflux temperature; preferably at about 50°C to 80°C.

Deprotection process disclosed under the reported literatures involves use of a strong
30 acids like HCl or H₂SO₄ at higher temperature this will hydrolyzes the magnesium complex formed during the reaction, however with using these strong acids at higher temperature there always high possibility to formation of an open chain impurity of cabotegravir (as shown below) and this may be due to ring cleavage of the oxazole ring. The open chain impurity once formed during the deprotection step, the same may be
35 difficult to remove from the final product under normal purification techniques as both are having close polarity characteristics and thereby necessary to perform multiple solvent purifications, which process makes commercially unviable due to loss of valuable product at each stage of the purification.



Open chain impurity of cabotegravir

The present inventors surprisingly found that the formation of open chain impurity of cabotegravir is either minimized to acceptable levels or completely avoided by the use of an acid (as listed below) of the present invention at ambient temperatures and this process advantageously circumvent the necessary purification steps at final stage thereby getting product with improved yields.

The acid used for treating the reaction mass is either organic acid or inorganic acid with the proviso that wherein said organic acid or inorganic acid. The organic acid is selected from the group comprising of but not limited to acetic acid, formic acid, citric acid, oxalic acid, tartaric acid, maleic acid, malic acid, mandelic acid, malonic acid, succinic acid, glutaric acid, adipic acid and the like and mixture thereof. The inorganic acid is selected from the group comprising of but not limited to sulfurous acid, phosphoric acid, nitrous acid and the like and mixture thereof; preferably citric acid, oxalic acid and mixture thereof; more preferably citric acid.

In accordance with a preferred embodiment, the acid is either organic acid or inorganic acid with the proviso that wherein said organic acid or inorganic acid excludes both hydrochloric acid and sulfuric acid.

In accordance with a preferred embodiment, wherein the acid used in the deprotection step is citric acid.

In accordance with a preferred embodiment, after the deprotection step the acid may be added to the reaction mass obtained after the deprotection step at a temperature of about 0°C to about reflux temperature, preferably at about 25°C to about 50°C. The acid may be advantageously used for the process of the invention is an aqueous solution. Then the product may be isolated from the reaction mass by known techniques for example, when an aqueous solution of an acid is added to the reaction mas the product may get precipitated slowly and the product may be separated by filtration.

5 Cabotegravir obtained by the processes described as above, having purity of at least about 99% as measured by HPLC, preferably at least about 99.5% as measured by HPLC and substantially free of open chain impurity of cabotegravir; wherein the word "substantially free" refers to cabotegravir having less than 0.5% of open chain impurity of cabotegravir as measured by HPLC, preferably less than about 0.3% of open chain
10 impurity of cabotegravir as measured by HPLC; more preferably less than about 0.1% of open chain impurity of cabotegravir as measured by HPLC.

Preparation of cabotegravir reported in the known literatures involves deprotection of protected cabotegravir of Formula XII' (compound of Formula XII, when protection
15 with methyl) using various deprotecting agents but complete cleavage of the protecting group is always a challengeable task and possible to retain protected starting material and this will isolate along with the product as an impurity. Due to close polarity differences the unreacted starting material is difficult to separable from cabotegravir under normal solvent purifications as the both cabotegravir and protected cabotegravir
20 having less solubility in most of the solvents for solvent purification. The present inventors have surprisingly found an effective purification to remove unwanted protected cabotegravir without losing the valuable final product with the purification.

In another embodiment, the present invention provides a process for purification of
25 cabotegravir of Formula I using solvent purification.

In accordance with another embodiment, the present invention provides a process for purification of cabotegravir of Formula I by suspending or dissolving cabotegravir in a suitable solvent and precipitating pure cabotegravir by addition of anti-solvent or vice
30 versa.

In accordance with another embodiment, the present invention provides a process for purification of cabotegravir of Formula I, comprising:

- a) suspending or dissolving cabotegravir in a suitable solvent at an ambient
35 temperature to reflux,
- b) adding step a) reaction mass to an anti-solvent (or) adding an anti-solvent to step a) reaction mass at a suitable temperature,
- c) optionally, cooling the step b) reaction mass to below 25°C, and
- d) isolating the pure cabotegravir.

5 As used herein in this specification, unless otherwise specified, cabotegravir, which is used as a starting material is known in the art and can be prepared by any processes disclosed in art, for example cabotegravir may be synthesized according to the present process described in above embodiments. The starting cabotegravir may be in any form such as crude obtained directly from the reaction mass, crystalline, amorphous or other
10 forms of cabotegravir, including various solvates and hydrates known in the art. Further the starting cabotegravir may contain protected cabotegravir of Formula XII' more than 0.5% by HPLC and the present invention capable of removing the protected cabotegravir from the final cabotegravir to less than 0.5% by HPLC preferably less than 0.3% more preferably less than 0.1% by HPLC.

15 The aforementioned formation of suspension or dissolution of cabotegravir of Formula I in a suitable solvent selected from the group comprising alcohols, amides, sulfoxides, nitriles, halogenated solvents, sulfolane, acetic acid and the like and mixtures thereof. The alcohols include, but are not limited to 2,2,2-trifluoromethanol, 2-mercaptoethanol,
20 2,2,2-trifluoroethanol, glycerol, hexafluoro-2-propanol, ethylene glycol, propylene glycol and the like; amides include, but are not limited to dimethylacetamide, dimethylformamide, N-methyl pyrrolidone and the like; sulfoxides include, but are not limited to dimethyl sulfoxide, diethyl sulfoxide and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; halogenated solvents include, but are
25 not limited to methylene chloride, ethylene chloride, chloroform, chlorobenzene, and the like; acetic acid and mixtures thereof; preferably 2,2,2-trifluoroethanol.

The temperature for suspending or dissolving cabotegravir of Formula I in a suitable solvent and the step of adding reaction mass to an anti-solvent (or) adding an anti-
30 solvent to reaction mass is advantageously carried out at a temperature of about 25°C to about reflux; preferably at about 40°C to 80°C.

The anti-solvent may be selected but are not limited to alcohols, ethers, esters, ketones, aromatic hydrocarbons and the like and water and mixtures thereof. The alcohols
35 include, but are not limited to methanol, ethanol, Isopropyl alcohol, n-propanol, n-butanol, t-butanol, 1-pentanol and the like; ethers include, but are not limited to tetrahydrofuran, methyl tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; esters include, but are not limited to ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate and the like; ketones include, but

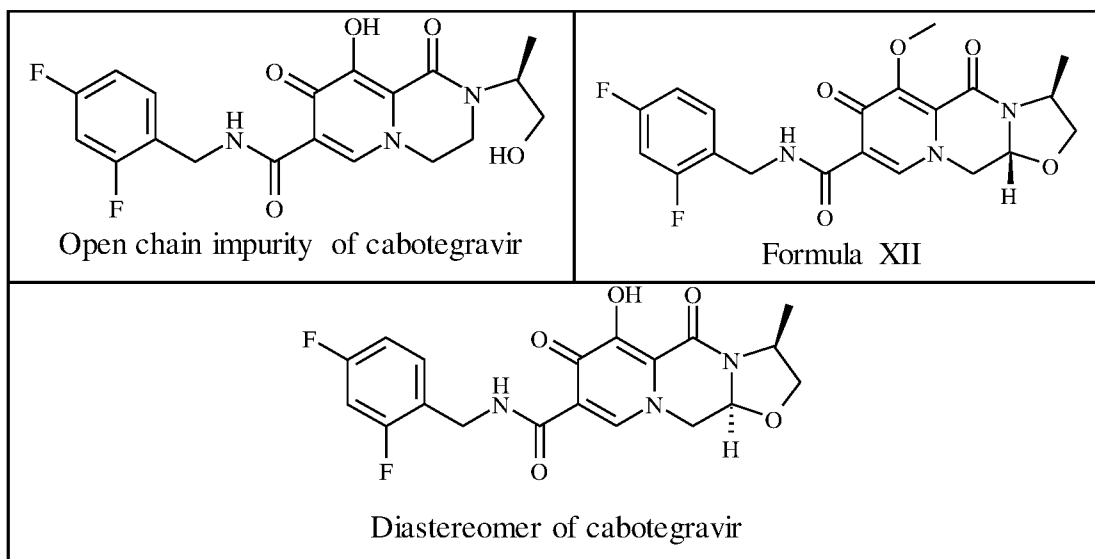
5 are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; aromatic hydrocarbons include, but are not limited to toluene and the like; and water and mixture thereof; preferably methanol, ethanol, Isopropyl alcohol, n-butanol, t-butanol, 1-pentanol, water and mixture thereof.

10 Then the reaction mass may be optionally cooled to below 25°C and stirring for a sufficient period of time. Then isolating the pure cabotegravir of Formula I by any conventional techniques, for example filtration or decantation; preferably by filtration and drying at a suitable temperature for sufficient period of time.

15 In accordance with another embodiment, cabotegravir obtained by the processes described as above, having purity of at least about 99% as measured by HPLC, preferably at least about 99.5% as measured by HPLC and substantially free of protected cabotegravir of Formula XII'; wherein the word "substantially free" refers to cabotegravir having less than 0.5% of protected cabotegravir of Formula XII' as
20 measured by HPLC, preferably less than about 0.3%, more preferably less than about 0.1%.

In accordance with another embodiment, cabotegravir prepared by the processes described as above, having purity of at least about 99% as measured by HPLC,
25 preferably at least about 99.5% as measured by HPLC and substantially free of at least one of 2,4-difluorobenzylamine, by-products of coupling agent, open chain impurity of cabotegravir and protected cabotegravir of Formula XII' as measured by HPLC; wherein the word "substantially free" refers to cabotegravir having less than 0.5% of at least one of 2,4-difluorobenzylamine, by-products of coupling agent, open chain
30 impurity of cabotegravir and protected cabotegravir of Formula XII' as measured by HPLC, preferably less than 0.3%, more preferably less than 0.1%.

In accordance with another embodiment, the present invention provides cabotegravir or a salt thereof having less than 0.5% by HPLC of at least one of 2,4-
35 difluorobenzylamine, imidazole by-product, open chain impurity of cabotegravir, compound of Formula XII and Diastereomer of cabotegravir; preferably less than 0.3% by HPLC; more preferably less than 0.1% by HPLC.



5

In accordance with another embodiment, the present invention provides cabotegravir of Formula I purified by the process described by above embodiment, is a crystalline cabotegravir.

10 In accordance with another embodiment, the present invention provides cabotegravir of Formula I purified by the process described by above embodiment, is a crystalline cabotegravir and is characterized by a powder X-ray diffraction (PXRD) pattern substantially in accordance with Figure 1.

15 In accordance with another embodiment, the present invention provides cabotegravir of Formula I purified by the process described by above embodiment, is a crystalline cabotegravir and is characterized by X-Ray diffraction (XRD) pattern having one or more peaks at about 5.5, 10.9, 12.2, 12.4, 13.1, 13.3, 14.5, 14.7, 16.4, 17.0, 17.3, 17.9, 18.2, 18.9, 20.3, 21.9, 22.8, 24.2, 24.4, 24.6, 25.0, 25.8, 26.8, 27.4, 27.7, 28.2, 28.5,
20 29.5, 30.1, 31.1, 31.7, 32.7, 33.1, 33.5, 35.0 and $35.3 \pm 0.2^\circ 2\theta$.

In accordance with another embodiment, the present invention provides cabotegravir of Formula I purified by the process described by above embodiment, is a crystalline cabotegravir and is characterized by X-Ray diffraction (XRD) pattern having peaks at
25 about 5.5, 12.2, 16.4, 17.3, 17.9, 24.2, 24.6 and $27.7 \pm 0.2^\circ 2\theta$.

In accordance with another embodiment, the present invention provides cabotegravir of Formula I purified by the process described by above embodiment, is a crystalline cabotegravir and is characterized by a thermogravimetric analysis (TGA) substantially
30 in accordance with Figure 2.

5 In accordance with another embodiment, the present invention involves a process for preparation of crystalline cabotegravir sodium Form A and its pharmaceutical composition comprising thereof.

10 As used herein in this specification, unless otherwise specified, cabotegravir, which is used as a starting material is known in the art and can be prepared by the process disclosed in art, for example cabotegravir or its sodium may be synthesized as disclosed in the '764 publication. The starting cabotegravir may be in any form such as crude obtained directly from the reaction mass, crystalline, amorphous or other forms of cabotegravir, including various solvates and hydrates known in the art.

15 The crystalline cabotegravir sodium Form A prepared according to the discourse of the '764 or '253 publications fails to provide same crystalline form consistently instead resulted a mixture of cabotegravir sodium Form A with either Form B (or) Form C. Therefore, the reported methods for crystalline cabotegravir sodium Form A is not
20 suitable on commercial scale manufacturing as it does not produce pure Form A at all times. Hence it is important to have a consistent process for preparation of pure crystalline cabotegravir sodium Form A in a reproducible manner.

In accordance with another embodiment, the present invention provides a process for
25 preparation of crystalline cabotegravir sodium Form A, comprising:

- a) suspending or dissolving cabotegravir in an organic solvent,
- b) adding sodium source to step a) reaction mass (or) adding step a) reaction mass to sodium source, and
- c) isolating cabotegravir sodium Form A; wherein the one or more solvents are
30 selected from the group comprising alcohols, ketones, sulfoxides, nitriles, ethers and the like and mixtures thereof.

The aforementioned process of step a) involves suspending or dissolving cabotegravir in one or more solvents at about 25°C to reflux temperature; preferably at about 25°C to
35 about 80°C. Then, the resultant reaction mass may be optionally cool to below 25°C.

The organic solvent used herein step a) include, but are not limited to alcohols, ketones, sulfoxides, nitriles, ethers and the like and mixtures thereof. The alcohols include but are not limited to methanol, ethanol, butanol, isobutanol, *tert*-butanol, propanol,
40 isopropanol, pentanol, glycerol and the like; ketones include, but are not limited to

5 acetone, methylisobutylketone, methylethylketone and the like; sulfoxides include, but are not limited to dimethyl sulfoxide, diethyl sulfoxide and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, methyl tertiary butyl ether and the like and mixture thereof; preferably trifluoroethanol, dimethyl sulfoxide, methanol, ethanol, n-butanol, n-
10 pentanol, acetone, acetonitrile, tetrahydrofuran and mixture thereof.

The step b) of the aforementioned process involves, adding sodium source to step a) reaction mass or adding step a) reaction mass to sodium source at below 30°C.

15 The sodium source used herein for preparing cabotegravir sodium Form A is used directly as a solid or as a solution i.e. pre-dissolving the sodium source either in water, in a suitable solvent or a mixture thereof. The sodium source used herein is selected from the group comprising sodium hydroxide, sodium formate, sodium acetate and sodium alkoxide such as sodium methoxide, sodium ethoxide, sodium butoxide, sodium
20 pentoxide and the like and mixtures thereof; preferably sodium hydroxide, sodium methoxide.

The solvent used to pre-dissolve sodium source is may be the same as the solvent used in step a) or may be different one include, but are not limited to alcohols, ketones,
25 sulfoxides, nitriles, ethers, esters, amides and the like and water and mixtures thereof. The alcohols include but are not limited to methanol, ethanol, butanol, isobutanol, *tert*-butanol, propanol, isopropanol, pentanol, glycerol and the like; ketones include, but are not limited to acetone, methylisobutylketone, methylethylketone and the like; sulfoxides include, but are not limited to dimethyl sulfoxide, diethyl sulfoxide and the
30 like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, methyl tertiary butyl ether and the like; esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl acetate and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone and the like and water and mixture thereof;
35 preferably methanol, ethanol, water and mixture thereof; more preferably methanol, water and mixture thereof.

5 Then the precipitated cabotegravir sodium Form A can be recovered by any conventional techniques, for example decantation, filtration; preferably by filtration. The resultant product may be further dried at suitable temperatures.

10 In accordance with another embodiment, the process of the present invention produces pure crystalline cabotegravir sodium Form A without contamination of any polymorph and is stable during storage. This property is important and advantageous for the desired use of cabotegravir in pharmaceutical product formulation.

15 In accordance with another embodiment, the present invention provides a process for preparation of crystalline cabotegravir sodium Form A, characterized by a powder X-ray diffraction (PXRD) pattern peaks having peaks selected from at about: 5.4, 9.5, 11.0, 12.7, 13.1, 14.0, 14.6, 15.4, 15.7, 16.1, 19.0, 21.5, 22.1, 23.2, 23.8, 24.4, 25.4, 26.2, 27.1, 28.0, 28.9, 29.9, 32.6 and $34.5 \pm 0.2^\circ 2\theta$.

20 In accordance with another embodiment, the present invention provides substantially pure crystalline cabotegravir sodium Form A, characterized by: a powder X-ray diffraction (PXRD) pattern having at least one peak selected from: 5.4, 9.5, 11.0, 12.7, 13.1, 14.0, 14.6, 15.4, 15.7, 16.1, 19.0, 21.5, 22.1, 23.2, 23.8, 24.4, 25.4, 26.2, 27.1, 28.0, 28.9, 29.9, 32.6 and $34.5 \pm 0.2^\circ 2\theta$ and does not have a peak at about 6.2 and/or
25 $6.8 \pm 0.2^\circ 2\theta$.

In accordance with another embodiment, the present invention provides at least about 95% by weight of the solid crystalline cabotegravir sodium is Form A of cabotegravir sodium.

30 In accordance with another embodiment, the present invention provides at least about 99% by weight of the solid crystalline cabotegravir sodium is Form A of cabotegravir sodium.

35 The compounds obtained by the process of the present invention are characterized by X-ray powder diffraction (XRPD) pattern, thermo gravimetric analysis (TGA) and/or particle size distribution.

40 Another aspect of the present invention is directed to a pharmaceutical composition containing cabotegravir or pharmaceutically acceptable salt disclosed herein and at least

5 one pharmaceutically acceptable excipient. Such pharmaceutical compositions may be administered to a mammalian patient in any dosage form, e.g., tablet, liquid, powder, elixir, injectable solution, etc.

10 In another embodiment, the cabotegravir or pharmaceutically acceptable salt thereof disclosed herein for use in the pharmaceutical compositions of the present invention can have a D50 and D90 particle size of less than about 30 microns, preferably less than about 10 microns, more preferably less than about 5 microns. The particle sizes of the cabotegravir or pharmaceutically acceptable salt thereof prepared according to the present invention can be obtained by any milling, grinding micronizing or other particle
15 size reduction method known in the art to bring the solid state cabotegravir or pharmaceutically acceptable salt thereof into any of the foregoing desired particle size range.

The X-Ray powder diffraction data reported herein may be analyzed using PANalytical
20 X'pert³pro X-ray powder Diffractometer equipped with a Cu-anode ($[\lambda] = 1.54$ Angstrom), X-ray source operated at 45kV, 40 mA. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=3-45°2 θ ; step size=0.01°; and Time per step=50 sec.

25 Thermogravimetric analysis (TGA) data in the present invention was acquired using TA instruments TGA Q500 thermogravimetric analyzer with universal Analysis 2000 software using the following conditions; Heating rate: 10°C/min; Temperature range: 28±2°C - 250°C; Nitrogen flow: 60mL/minute.

30 Particle size distribution data in the present invention was acquired using Malvern Instruments analyzer with Analysis Model: Emulated MS2000 /MS2000E using Particle Refractive Index 1.6, Particle Absorption Index 0.08 and Laser Obscuration 4.2%.

35 In accordance with another embodiment, the present invention provides a pharmaceutical composition, comprising cabotegravir or its pharmaceutically acceptable salts thereof prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient.

- 5 The present invention provides process for preparation of cabotegravir or its pharmaceutically acceptable salts and its intermediates, obtained by the above processes, as analyzed using the high performance liquid chromatography with Zorbax C8 or C18 column and buffer, acetonitrile and water as mobile phase with flow rate of about 0.8 mL/min to 1.0 mL/minute.

10

EXAMPLES

The following non limiting examples illustrate specific embodiments of the present invention. They are not intended to be limiting the scope of the present invention in any way.

15

COMPARATIVE EXAMPLE-1: Preparation of Formula XII

- Compound of Formula XIa (10 g) and carbonyldiimidazole (2.47 g) was charged in 1,2-dimethoxyethane (102.0 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 80°C for 1 hr. The resulting solution was cooled to 20-25°C and 2,4-difluorobenzyl amine (4.8 mL) was added and stirred the reaction mass for 1 hr at same temperature. After completion of the reaction, water (100 mL) was added and dimethoxyethane was concentrated under vacuum. Then the product was filtration and dried at 50°C in hot air oven. Wt: 10.7 g; Purity: 97.5% by HPLC; 2,4-difluorobenzylamine: 1.2% by HPLC; Imidazole: 0.5% by HPLC.

25

COMPARATIVE EXAMPLE-2: Preparation of Formula XII

Variant-A (HCl)

30

Compound of Formula XIa (10 g), dichloromethane (120 mL) and carbonyldiimidazole (2.47 g) were added in to a round bottom flask at 25-35°C and stirred for 2-3 hr. To the reaction mass 2,4-difluorobenzyl amine (4.8 mL) was added and allowed to stir the reaction mass for 1-2 hr at 20-25°C. After completion of the reaction, to the reaction mass water (100 mL) was added and organic and aqueous layers were separated. To the organic layer dil. HCl (50 ml) was added at 25-35°C and stirred for 36 hr at same temperature. Then the organic layer was monitored by HPLC.

35

Formula XII by HPLC	2,4-difluorobenzylamine	Imidazole	Open chain impurity
92.6%	0.99%	0.84%	1.05%

5 **Variant-B (Citric acid)**

Compound of Formula XIa (10 g), dichloromethane (120 mL) and carbonyldiimidazole (2.47 g) were added in to a round bottom flask at 25-35°C and stirred for 2-3 hr. To the reaction mass 2,4-difluorobenzyl amine (4.8 mL) was added and allowed to stir the reaction mass for 1-2 hr at 20-25°C. After completion of the reaction, to the reaction mass water (100 mL) was added and organic and aqueous layers were separated. To the organic layer was added aqueous citric acid solution (15.6 g citric acid dissolved in 81.2 mL of water) at 25-35°C and allowed to stir for 36 hr at same temperature. Then the organic layer was monitored by HPLC.

Formula XII by HPLC	2,4-difluorobenzylamine	Imidazole	Open chain impurity
95.1%	Not detected by HPLC	0.03%	Not detected by HPLC

COMPARATIVE EXAMPLE-3: Preparation of Cabotegravir

Compound of Formula XII (100 g), magnesium bromide (131.6 g) and acetonitrile (1.2 lit) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 50-55°C and allowed to stir for 4 hr at same temperature. After completion of the reaction, reaction mass was cooled to 25-35°C and diluted with a mixture of methylene chloride (500 mL) and water (500 mL). Adjusted the reaction mass pH to 1.0- 2.0 with dil. HCl solution and temperature shoot up was observed and was allowed to cool and stirred for 1-2 hr at 25-35°C, filtered and dried at 60°C for 12 hrs. Wt: 85 g; Purity: 97.5% by HPLC; compound of Formula XII: 0.8% by HPLC; Open chain impurity of cabotegravir: 1.1% by HPLC.

COMPARATIVE EXAMPLE-4: Preparation of compound of Formula XIa according to the '566 publication

MDHC (22.5 gm) in acetonitrile (220 mL) and acetic acid (20 mL), methanesulfonic acid (1.4 mL) were added in to a round bottom flask at 25-30°C and was heated to 57-65°C and stirred for 19.5 hrs at same temperature. To the reaction mass was added a solution of (S)-(+)-2-amino-1-propanol (7.51 gm dissolved in 15 mL) and stirred for 18.5 hrs at 65°C. The mixture was concentrated, and the residue was dissolved in methylene chloride (170 mL) and 1N HCl (170 mL) and stirred for 10-15 min. Then the product containing organic layer was separated and concentrated under

5 vacuum. Methanol (50 mL) was added and the resultant mixture was again concentrated to obtain title compound.

Purification A:

10 A). To the above crude compound (Purity: 84.12% by HPLC; Formula XIA'- 0.5% by HPLC; and Formula XIB'- 2.5% by HPLC) was added methanol (80 mL) and was heated at reflux for 4 h. Reaction mass was allowed to cool to 20°C and stirred at for 15 h at same temperature. The product was collected by filtration and dried under vacuum at 60°C for 12hr. Wt: 13.1 gm.

15 Purification B:

B). To the above crude compound (10 gm; Purity: 97.15% by HPLC; Formula XIA': 0.3% by HPLC; and Formula XIB': 2.5% by HPLC) was added methanol (80 mL) and was heated at reflux for 4 h. Reaction mass was allowed to cool to 20°C and stirred at for 15 h at same temperature. The product was collected by filtration and dried under vacuum at 60°C for 12hr. Wt: 5.8 gm.

COMPARATIVE EXAMPLE-5:

Purification of compound of Formula XIa (from methanol)

25 Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC) and methanol (40 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 45°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 5.9 gm

COMPARATIVE EXAMPLE-6:

35 Purification of compound of Formula XIa (from ethanol)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC) and ethanol (40 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 45°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the

- 5 wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.1 gm

Analytical data for Comparative Examples 4-6 is as follows (Table – 1)

	Purity (% by HPLC)	Formula XIA' (% by HPLC)	Formula XIB' (% by HPLC)
Comp Example-4	84.12	0.5	2.5
Purification A	97.15	0.3	2.5
Purification B	97.4	0.1	2.4
Comp Example-5	95.1	1.5	2.4
Comp Example-6	94.9	1.4	2.3

10 **EXAMPLE-1:** Preparation of Formula XII

Compound of Formula XIa (100 g), methylene chloride (975 mL) and carbonyldiimidazole (66.1 g) were added in to a round bottom flask at 25-35°C and allowed to stir for 2-3 hr at same temperature. Reaction mass was allowed to cool to 12-18°C and 2,4-difluorobenzylamine (53.5 g) was added at same temperature. Reaction mass was heated to 25-30°C and stirred for 2-3 hr at same temperature. After completion of the reaction, to the reaction mass water was added (500 mL) and organic and aqueous layers were separated. Then to the organic layer aq citric acid solution (156 g citric acid dissolved in 812 mL water) was added and organic and aqueous layers were separated followed by washing the organic layer with sodium bicarbonate solution. The organic layer was concentrated under vacuum at below 50°C to obtain solid compound. Then the solid compound was dissolved in methanol (400 mL) at 60-65°C and stir for 45 min at same temperature. Reaction mass was allowed to cool to 2-8°C and stir for 1 min at same temperature. Filtered the solid, suck dried and washed with methanol (100 mL) and dried the wet material under vacuum at 55-65°C for about 10 hr to obtain the titled compound. Wt: 135 g; Purity: 99.1% by HPLC; PXRD: Fig.: 3; 2,4-difluorobenzylamine: not detected by HPLC; Imidazole: not detected by HPLC.

30 **EXAMPLE-2:** Preparation of Cabotegravir

Compound of Formula XII (100 g), magnesium chloride (68.1 g) and acetonitrile (1.1 lit) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 70-75°C and allowed to stir for 5 hr at same temperature. After completion of the reaction,

5 reaction mass was allowed to cool to 25-35°C and dilute citric acid solution (137.4 g citric acid was dissolved in 715 mL water) was added and allowed to stir for 1-2 hr at same temperature. Filtered the solid, suck dried and washed with water (200 mL) and dried the wet material under vacuum at 55-65°C for about 10 hr to obtain the titled compound. Wt: 90 g; Purity: 99.1% by HPLC; compound of Formula XII: 0.5% by
10 HPLC; Open chain impurity of cabotegravir: not detected by HPLC.

EXAMPLE-3: Purification of Cabotegravir

Cabotegravir (100 g; Purity: 99.1 % by HPLC; compound of Formula XII: 0.5 % by
15 HPLC) and 2,2,2-trifluoroethanol (500 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 55-65°C and pre heated ethanol (55-65°C, 1.2 lit) was added for a period of 15-20 min at 55-65°C. Reaction mass was allowed to stir for 30-40 min at 55-65°C and then the reaction mass was allowed to cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried and washed
20 with ethanol (100 mL) and dried the wet material under vacuum at 55-65°C for about 12 hr to obtain the titled compound. Wt: 99.5 g; Purity: 99.9% by HPLC; compound of Formula XII: not detected by HPLC. PXRD: Fig. 1; Particle size distribution histogram: Fig. 5.

25 **EXAMPLE-4:** Purification of Cabotegravir

Cabotegravir (10 g; Purity: 99.1 % by HPLC; compound of Formula XII: 0.5 % by
HPLC) and 2,2,2-trifluoroethanol (50 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 60-65°C and water (20 mL) was added for a period
30 of 15-20 min at 25-35°C. Reaction mass was allowed to stir for 2 hr at 25-35°C. Filtered the solid, suck dried and washed with water (2 mL) and dried the wet material under vacuum at 55-65°C for about 12 hr to obtain the titled compound. Wt: 9.7 g; Purity: 99.89% by HPLC; compound of Formula XII: not detected by HPLC. PXRD: Fig. 1.

35 **EXAMPLE-5:** Purification of Cabotegravir

Cabotegravir (2 g; Purity: 99.1 % by HPLC; compound of Formula XII: 0.5 % by
HPLC) and 2,2,2-trifluoroethanol (10 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 60-65°C and methanol (24 mL) was added for a
40 period of 15-20 min at 60-65°C and allowed to stir for 30 min at same temperature. Then the reaction mass was allowed to cool to 25-35°C and allowed to stir for 1-2 hr at

- 5 same temperature. Filtered the solid, suck dried and washed with methanol (2 mL) and dried the wet material under vacuum at 55-65°C for about 8 hr to obtain the titled compound. Wt: 1.94 g; Purity: 99.9% by HPLC; compound of Formula XII: not detected by HPLC. PXRD: Fig. 1.
- 10 Purification of cabotegravir by following the example-3 process and using different solvent combinations and the results given as below:

Ex	Solvent	Anti-solvent	Output wt	Purity by HPLC	Formula XII by HPLC and open chain impurity
Ex-6	Trifluoroethanol (5 vol)	Ethanol (12 vol)	1.88 g	99.9%	Not detected
Ex-7	Trifluoroethanol (5 vol)	Isopropyl alcohol (12 vol)	1.92 g	99.87%	Not detected
Ex-8	Trifluoroethanol (5 vol)	n-butanol (12 vol)	1.89 g	99.9%	Not detected
Ex-9	Trifluoroethanol (5 vol)	n-propanol (12 vol)	1.91 g	99.9%	Not detected
Ex-10	Trifluoroethanol (5 vol)	t-butanol (12 vol)	1.9 g	99.9%	Not detected
Ex-11	Trifluoroethanol (5 vol)	1-pentanol (12 vol)	1.88 g	99.9%	Not detected
Ex-12	Trifluoroethanol (5 vol)	water (12 vol)	1.94 g	99.9%	Not detected
Ex-13	Dimethylformamide (12 vol)	water (24 vol)	1.82 g	99.87%	Not detected
Ex-14	Dimethylformamide (12 vol)	methanol (24 vol)	1.78 g	99.89%	Not detected
Ex-15	N-Methyl pyrrolidone (10 vol)	water (20 vol)	1.84 g	99.9%	Not detected
Ex-16	Dimethyl sulfoxide (10 vol)	water (24 vol)	1.87 g	99.9%	Not detected

EXAMPLE-17:

15

Preparation of crude compound of Formula XIa

MDHC (150 gm) in acetonitrile (2.8 lit) and acetic acid (150 mL) and methanesulfonic acid (5.5 gm) were added in to a round bottom flask at 25-30°C and

5 was heated to 75-81°C and stirred for 18 hr at same temperature. Reaction mass was allowed to cool to 30°C and was added potassium acetate (7 gm) and stir for 2 hr at same temperature. To the reaction mass was added (S)-(+)-2-amino-1-propanol (72.8 gm) at 30°C and was heated to 75-81°C and stir for 12 hr at same temperature. Reaction mass was concentrated under vacuum to obtain title compound. Wt: 168 gm; HPLC
10 analysis: Product-78%; Formula XIA'- 2.5%; and Formula XIB'- 5.9%.

EXAMPLE-18:

Purification of compound of Formula XIa (from methylene chloride and water)

15 Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), methylene chloride (20 mL) and water (60 mL) were added in to a round bottom flask at about 25°C to 35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet
20 material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.5 gm. HPLC analysis: Product-99.9%; Formula XIA'- Not detected; and Formula XIB'- 0.1%.

EXAMPLE-19:

25 Purification of compound of Formula XIa (from methylene chloride)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), methylene chloride (20 mL) were added in
30 to a round bottom flask and stirred for 1-2 hr at 38°C. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.7 gm; HPLC analysis: Product-99.8%; Formula XIA'- 0.05%; and Formula XIB'- 0.12%.

EXAMPLE-20:

35 Purification of compound of Formula XIa (from acetonitrile)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by
40 HPLC; and Formula XIB'- 5.9% by HPLC), acetonitrile (40 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 45°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the

5 wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.4 gm; HPLC analysis: Product-99.7%; Formula XIA'- 0.1%; and Formula XIB'- not detected

EXAMPLE-21:

10 Purification of compound of Formula XIa (from acetone)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), acetone (40 mL) were added in to a round
15 bottom flask at 25-35°C. Reaction mass was heated to 45°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.5 gm; HPLC analysis: Product-99.8%, Formula XIA'- 0.1% and Formula
20 XIB'- 0.1%

EXAMPLE-22:

25 Purification of compound of Formula XIa (from methylene chloride and methanol)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), methylene chloride (10 mL) and methanol (50 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 55°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to
30 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.7 gm; HPLC analysis: Product-99.9%; Formula XIA'- not detected; and Formula XIB'- 0.05%

35 **EXAMPLE-23:**

Purification of compound of Formula XIa (from methylene chloride and ethanol)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by
40 HPLC; and Formula XIB'- 5.9% by HPLC), methylene chloride (10 mL) and ethanol (50 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 75°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the

5 solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.8 gm; HPLC analysis: Product-99.8% Formula XIA'- 0.03% and Formula XIB'- 0.08%

10 **EXAMPLE-24:**

Purification of compound of Formula XIa (from methylene chloride and n-butanol)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), methylene chloride (10 mL) and n-butanol
15 (50 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 75°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 7 gm; HPLC analysis: Product-99.7%;
20 Formula XIA'- not detected and Formula XIB'- 0.15%.

EXAMPLE-25:

Purification of compound of Formula XIa (from acetonitrile and methanol)

25 Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), acetonitrile (10 mL) and methanol (50 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 75°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-
30 35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 7.2 gm; HPLC analysis: Product-99.9%; Formula XIA'- not detected; and Formula XIB'- 0.05%.

35 **EXAMPLE-26:**

Purification of compound of Formula XIa (from acetonitrile and ethanol)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by
40 HPLC; and Formula XIB'- 5.9% by HPLC), acetonitrile (10 mL) and ethanol (50 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 75°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid

5 for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 7.3 gm; HPLC analysis: Product-99.9%; Formula XIA'- 0.03% and Formula XIB'- 0.07%.

EXAMPLE-27:

10 Purification of compound of Formula XIa (from acetonitrile and n-butanol)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), acetonitrile (10 mL) and n-butanol (50 mL)
15 were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 75°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 7.8 gm; HPLC analysis: Product-99.8%;
20 Formula XIA'- not detected and Formula XIB'- 0.15%.

EXAMPLE-28:

25 Purification of compound of Formula XIa (from acetonitrile and Isopropanol)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by HPLC; and Formula XIB'- 5.9% by HPLC), acetonitrile (10 mL) and Isopropanol (125 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 75°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to
30 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 7.7 gm; HPLC analysis: Product-99.9%; Formula XIA'- 0.04% and Formula XIB'- 0.1%.

35 **EXAMPLE-29:**

Purification of compound of Formula XIa (from acetonitrile and water)

Compound of Formula XIa (10 gm; Purity: 78% by HPLC; Formula XIA'- 2.5% by
40 HPLC; and Formula XIB'- 5.9% by HPLC), acetonitrile (10 mL) and water (150 mL) were added in to a round bottom flask at 25-35°C. Reaction mass was heated to 40°C and stirred for 30-40 min at same temperature. Then the reaction mass was cool to 25-35°C and stirred for 1-2 hr at same temperature. Filtered the solid, suck dried the solid

5 for 15 min and dried the wet material under vacuum at 60°C for about 12 hr to obtain the pure compound of Formula XIa. Wt: 6.5 gm; HPLC analysis: Product-99.8%; Formula XIA'- 0.05% and Formula XIB'- 0.13%.

EXAMPLE-30:

10

Preparation of Cabotegravir Form A

Cabotegravir (2 gm) and 2,2,2-trifluoro ethanol (10 mL) were added in to a round bottom flask at 20-25°C and heated to 58-62°C and stirred for 20-30 min at same temperature. Reaction mass was cooled to 22°C to 26°C. Then the solution was added to a mixture of aqueous sodium hydroxide and methanol (0.21 gm NaOH was dissolved in 2.64 mL water and 32 mL methanol) at 22°C to 26°C over a period of 30 min. To the reaction mass methanol (32 mL) was added at 22°C to 26°C and allowed to stir for 1-2 hours at same temperature. Solid was filtered and washed with methanol (10 mL), suck dried the solid for 15 min and dried the wet material under vacuum at 50-55°C for about 15 hrs to obtain the title compound. Wt: 2.1 gm. The PXRD is set forth in Figure-4.

EXAMPLE-31:

25

Preparation of Cabotegravir Form A

Cabotegravir (2 gm) and 2,2,2-trifluoro ethanol (10 mL) were added in to a round bottom flask at 20-25°C and heated to 58-62°C and stirred for 20-30 min at same temperature. Reaction mass was cooled to 22°C to 26°C. Then the solution was added to a methanol solution of sodium methoxide (0.28 gm sodium methoxide was dissolved in 32 mL methanol) at 22°C to 26°C over a period of 30 min. To the reaction mass methanol (32 mL) was added at 22°C to 26°C and allowed to stirred for 1-2 hours at same temperature. Solid was filtered and washed with methanol (10 mL), suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 15 hrs to obtain the title compound. Wt: 2.05 gm.

EXAMPLE-32:

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Preparation of Cabotegravir Form A

Cabotegravir (0.5 gm) and 2,2,2-trifluoro ethanol (2.5 mL) were added in to a round bottom flask at 20-25°C and heated to 58-62°C and stirred for 20-30 min at same temperature. Reaction mass was cooled to 22°C to 26°C. To the solution methanol

5 solution of sodium hydroxide (0.52 gm sodium hydroxide was dissolved in 2.5 mL methanol) was added at 22°C to 26°C over a period of 15 min. To the reaction mass methanol (5 mL) was added at 22°C to 26°C and allowed to stirred for 1.5 hour at same temperature. Solid was filtered and washed with methanol (1 mL), suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 15 hrs to
10 obtain the title compound. Wt: 0.49 gm.

EXAMPLE-33:

Preparation of Cabotegravir Form A

15 Cabotegravir (2 gm) and dimethyl sulfoxide (36 mL) were added in to a round bottom flask at 20-25°C and heated to 73-77°C and stirred for 20-30 min at same temperature. Reaction mass was cooled to 22°C to 26°C. Then the solution was added to a mixture of aqueous sodium hydroxide and methanol (0.19 gm NaOH was dissolved in 2.48 mL
20 water and 60 mL methanol) at 22°C to 26°C over a period of 20 min and allowed to stirred for 2 hours at same temperature. Solid was filtered and washed with methanol (10 mL), suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 15 hrs to obtain the title compound. Wt: 2.04 gm.

EXAMPLE-34:

Preparation of Cabotegravir Form A

30 Cabotegravir (2 gm) and dimethyl sulfoxide (36 mL) were added in to a round bottom flask at 20-25°C and heated to 73-77°C and stirred for 20-30 min at same temperature. Reaction mass was cooled to 22°C to 26°C. Then the solution was added to aqueous sodium hydroxide (0.19 gm NaOH was dissolved in 2.48 mL water) at 22°C to 26°C over a period of 15 min and allowed to stirred for 2 hours at same temperature. Solid was filtered and washed with methanol (10 mL), suck dried the solid for 15 min and
35 dried the wet material under vacuum at 58-62°C for about 15 hrs to obtain the title compound. Wt: 2.12 gm.

EXAMPLE-35:

40 Preparation of Cabotegravir Form A

Cabotegravir (2 gm) and dimethyl sulfoxide (36 mL) were added in to a round bottom flask at 20-25°C and heated to 73-77°C and stirred for 20-30 min at same temperature.

- 5 Reaction mass was cooled to 22°C to 26°C. Then the solution was added to methanol solution of sodium methoxide (0.28 gm sodium methoxide was dissolved in 60 mL methanol) at 22°C to 26°C over a period of 15 min and allowed to stirred for 2 hours at same temperature. Solid was filtered and suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 15 hrs to obtain the title compound.
- 10 Wt: 2.09 gm.

EXAMPLE-36:

Preparation of Cabotegravir Form A

- 15 Cabotegravir (0.3 gm) and methanol (3 mL) were added in to a round bottom flask at 22-26°C. To the reaction mass methanolic solution of sodium hydroxide (0.32 gm sodium hydroxide was dissolved in 0.6 mL methanol) was added at 22°C to 26°C over a period of 5 min. To the reaction mass methanol (2.1 mL) was added at 22°C to 26°C
- 20 and allowed to stirred for 8 hours at same temperature. Solid was filtered, washed with methanol (0.6 mL) and suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 14 hrs to obtain the title compound. Wt: 0.25 gm.

EXAMPLE-37:

- 25 Preparation of Cabotegravir Form A

- Cabotegravir (0.3 gm) and ethanol (3 mL) were added in to a round bottom flask at 22-26°C. To the reaction mass methanolic solution of sodium hydroxide (0.32 gm sodium
- 30 hydroxide was dissolved in 0.6 mL methanol) was added at 22°C to 26°C over a period of 5 min. To the reaction mass ethanol (3 mL) was added at 22°C to 26°C and allowed to stirred for 8 hours at same temperature. Solid was filtered, washed with ethanol (1 mL) and suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 14 hrs to obtain the title compound. Wt: 0.26 gm.

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EXAMPLE-38:

Preparation of Cabotegravir Form A

- 40 Cabotegravir (0.3 gm) and n-butanol (3 mL) were added in to a round bottom flask at 22-26°C. To the reaction mass methanolic solution of sodium hydroxide (0.32 gm sodium hydroxide was dissolved in 0.6 mL methanol) was added at 22°C to 26°C over a period of 5 min. To the reaction mass n-butanol (5.4 mL) was added at 22°C to 26°C

5 and allowed to stirred for 8 hours at same temperature. Solid was filtered, washed with n-butanol (0.9 mL) and suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 14 hrs to obtain the title compound. Wt: 0.24 gm.

EXAMPLE-39:

10

Preparation of Cabotegravir Form A

Cabotegravir (0.3 gm) and n-pentanol (3 mL) were added in to a round bottom flask at 22-26°C. To the reaction mass methanolic solution of sodium hydroxide (0.32 gm sodium hydroxide was dissolved in 0.6 mL methanol) was added at 22°C to 26°C over a
15 period of 5 min. To the reaction mass n-pentanol (4.2 mL) was added at 22°C to 26°C and allowed to stirred for 8 hours at same temperature. Solid was filtered, washed with n-pentanol (1 mL) and suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 14 hrs to obtain the title compound. Wt: 0.28 gm.

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EXAMPLE-40:

Preparation of Cabotegravir Form A

25 Cabotegravir (0.3 gm) and acetone (3 mL) were added in to a round bottom flask at 22-26°C. To the reaction mass methanolic solution of sodium hydroxide (0.32 gm sodium hydroxide was dissolved in 0.6 mL methanol) was added at 22°C to 26°C over a period of 5 min. To the reaction mass acetone (4.2 mL) was added at 22°C to 26°C and allowed to stir for 8 hours at same temperature. Solid was filtered, washed with acetone
30 (0.6 mL) and suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 14 hrs to obtain the title compound. Wt: 0.27 gm.

EXAMPLE-41:

35 Preparation of Cabotegravir Form A

Cabotegravir (0.3 gm) and acetonitrile (3 mL) were added in to a round bottom flask at 22-26°C. To the reaction mass was added a methanolic solution of sodium hydroxide (0.32 gm sodium hydroxide was dissolved in 0.6 mL methanol) at 22°C to 26°C over a
40 period of 5 min. To the reaction mass was added acetonitrile (4.2 mL) at 22°C to 26°C and allowed to stir for 8 hours at same temperature. Solid was filtered, washed with acetonitrile (0.6 mL) and suck dried the solid for 15 min and dried the wet material under vacuum at 58-62°C for about 14 hrs to obtain the title compound. Wt: 0.2 gm.

5 **EXAMPLE-42:**

Preparation of Cabotegravir Form A

Cabotegravir (0.3 gm) and tetrahydrofuran (3 mL) were added in to a round bottom
10 flask at 22-26°C. To the reaction mass was added a methanolic solution of sodium
hydroxide (0.32 gm sodium hydroxide was dissolved in 0.6 mL methanol) at 22°C to
26°C over a period of 5 min. To the reaction mass was added tetrahydrofuran (4.2 mL)
at 22°C to 26°C and allowed to stir for 8 hours at same temperature. Solid was filtered,
washed with tetrahydrofuran (0.6 mL) and suck dried the solid for 15 min and dried the
15 wet material under vacuum at 58-62°C for about 14 hrs to obtain the title compound.
Wt: 0.25 gm.

EXAMPLE-43:

20 Stability of Cabotegravir sodium Form A

a) Stability in aq medium (water)

Cabotegravir sodium Form A (200 mg) was suspended in water (2 mL) and stirred the
mixture at room temperature for 1 hour, then heated to 50°C for 2 hours. A portion of
25 the suspension was filtered at end of the each slurry step processed at room temperature
and at 50°C to examine the stability of Form A. At both these conditions no change in
polymorph nature indicating that Form A is stable in water even at 50°C.

b) Stability of Cabotegravir sodium Form A under humid air:

30 Cabotegravir sodium Form A (200 mg) was placed at 85% RH at room temperature for
24 hours. Wt: 199.9 mg. PXRD: Form A.

c) Stability of Cabotegravir sodium Form A under heating:

35 Cabotegravir sodium Form A (201.1 mg) was dried at 90±2°C in air tray dryer for 8
hours. Wt: 164.4 mg. PXRD: Form A.

All the above conditions Form A was retained and no change in polymorphic nature.

40 It will be understood that various modifications may be made to the embodiments
disclosed herein. Therefore the above description should not be constructed as limiting,
but merely as exemplifications of preferred embodiments. For example, the functions
described above and implemented as the best mode for operating the present invention

5 are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the specification appended hereto.

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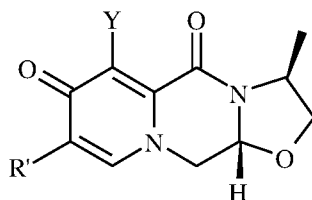
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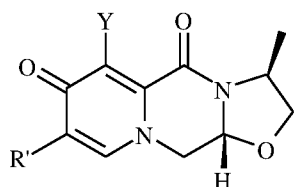
5 **We Claim:**

1. A process for purification of compound of Formula XI, comprising:

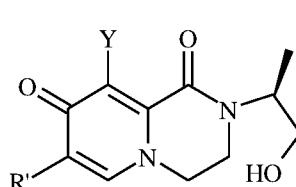


10 Formula XI

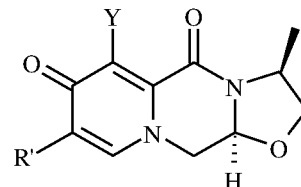
- a) suspending or dissolving a compound of Formula XI in a suitable solvent at a suitable temperature; wherein the compound of Formula XI having more than 0.15% by HPLC of a compound of Formula XIA and/or Formula XIB, and wherein “Y” represents hydrogen, chloro or -OR; “R” represents alkyl, aryl or aralkyl; and “R' ” represents hydrogen, -COOH, -COOR, -CONH₂, -CHO, -CN or halogen; and



Formula XI



Formula XIA

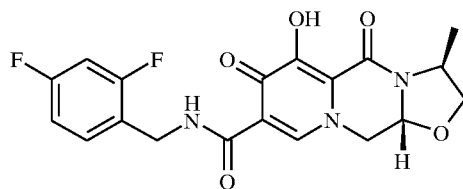


Formula XIB

- b) isolating the pure compound of Formula XI having less than 0.15% by HPLC of a compound of Formula XIA and/or Formula XIB; wherein the suitable solvent is selected from the group comprising alcohols, halogenated hydrocarbons, ketones, nitriles, water and mixture thereof.

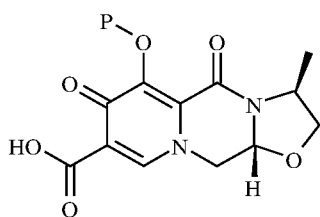
2. The process as claimed in claim 1, wherein the “Y” represents -OR and wherein the “R' ” represents -COOH and wherein the “R” represents methyl or ethyl.
3. The process as claimed in claim 1, wherein the suitable solvent is selected from the group comprising methanol, ethanol, propanol, isopropanol, n-butanol, tert-butanol, methylene chloride, chloroform, chlorobenzene, acetone, methyl ethyl ketone, methyl isobutyl ketone, diethyl ketone, acetonitrile, propionitrile, water and mixtures thereof.

4. The process as claimed in claim 3, wherein the suitable solvent is selected from the group comprising methanol, ethanol, isopropanol, n-butanol, methylene chloride, acetone, acetonitrile, water and mixtures thereof.
5. The process as claimed in claim 1, wherein the step a) is carried out at a temperature of about 25°C to about 85°C.
6. A process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising:

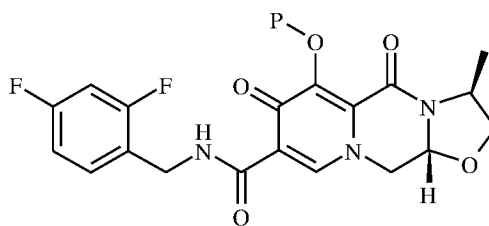


Formula I

- a) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence of a suitable coupling agent in a suitable solvent to obtain a compound of Formula XII'; wherein the "P" represents an alkyl, aryl or aralkyl, and



Formula XI'



Formula XII'

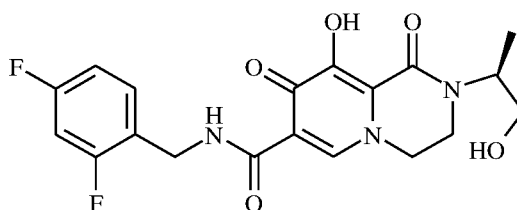
- b) deprotecting the compound of Formula XII' in presence of a suitable deprotecting agent in a suitable solvent to obtain cabotegravir; wherein the step a) and/or step b) comprises use of an acid prior to isolation of the corresponding product.
7. The process as claimed in claim 6, wherein the "P" represents methyl, ethyl or benzyl.
8. The process as claimed in claim 6, wherein the "P" represents methyl.
9. The process as claimed in claim 6, wherein the step a) comprises:

- 5 i) reacting a compound of Formula XI' with 2,4-difluorobenzylamine in presence
 of a suitable coupling agent in a suitable solvent,
 ii) treating the step i) reaction mass with an acid at a temperature of about 25°C to
 about 50°C, and
 iii) isolating the compound of Formula XII' contain less than 0.5% by HPLC of at
10 least one of 2,4-difluorobenzylamine and by-products of coupling agent.
10. The process as claimed in claim 9, wherein the suitable coupling agent is selected
from the group comprising 2-chloro-4,6-dimethoxy-1,3,5-triazine,
carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
15 hydrochloride, 1-Hhydroxy benzotriazole, 3-[bis(dimethylamino)methylumyl]-3H-
benzotriazol-1-oxide hexafluorophosphate, O-(1H-6-Chlorobenzotriazole-1-yl)-
1,1,3,3-tetramethyluronium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-
tetramethyluronium tetrafluoroborate, propylphosphonic anhydride,
dicyclohexylcarbodiimide, 3-hydroxytriazolo[4,5-b]pyridine, thionyl chloride,
20 oxalyl chloride, phosphorus oxychloride, pivaloyl chloride, acetic anhydride, N-
ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, Methanesulfonyl chloride, p-
toluenesulfonyl chloride and mixture thereof.
11. The process as claimed in claim 10, wherein the suitable coupling agent is
25 carbonyldiimidazole.
12. The process as claimed in claim 9, wherein the suitable solvent is selected from the
group comprising methanol, ethanol, formic acid, acetic acid, acetone, methyl
isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate,
30 acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl
tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, chloroform,
toluene, xylene, dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-
methylpyrrolidone and mixtures thereof.
13. The process as claimed in claim 12, wherein the suitable solvent is methylene
35 chloride.
14. The process as claimed in claim 9, wherein the by-products of coupling agent is
imidazole.

5 15. The process as claimed in claim 9, wherein the step i) is carried out at a temperature of about 25°C to about 50°C.

16. The process as claimed in claim 6, wherein the step b) comprises:

- 10 i) deprotecting the compound of Formula XII' with a suitable deprotecting agent in a suitable solvent,
- ii) treating the step i) reaction mass with an acid at a temperature of about 25°C to about 50°C, and
- iii) isolating the cabotegravir contain less than 0.5% by HPLC of open chain impurity of cabotegravir



Open chain impurity of cabotegravir

17. The process as claimed in claim 16, wherein the suitable deprotecting agent is selected from the group comprising magnesium chloride, magnesium iodide, magnesium hydroxide, lithium chloride, lithium iodide, lithium hydroxide, lithium trisiamyl borohydride, lithium triethyl borohydride, tri-sec-butyl borohydride, boron tribromide, aluminium chloride, aluminium chloride-triethylamine complex, aluminium chloride-N,N-dimethyl aniline complex and mixture thereof.

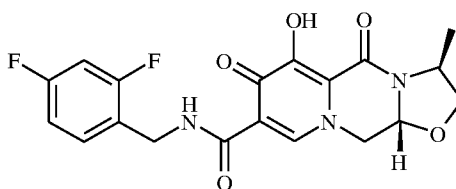
25 18. The process as claimed in claim 17, wherein the suitable deprotecting agent is magnesium chloride.

19. The process as claimed in claim 16, wherein the suitable solvent is selected from the group comprising methylene chloride, N-methylpyrrolidone, tetrahydrofuran, dimethylformamide, acetonitrile, dimethylsulfoxide, methanol, ethanol, formic acid, acetic acid and mixtures thereof.

20. The process as claimed in claim 19, wherein the suitable solvent is acetonitrile.

35 21. The process as claimed in claim 16, wherein the step i) is carried out at a temperature of about 50°C to about 80°C.

- 5 22. The process as claimed in claim 6, wherein the acid is either organic acid or inorganic acid with the proviso that wherein said organic acid or inorganic acid excludes hydrochloric acid and sulfuric acid.
- 10 23. The process as claimed in claim 22, wherein the acid is selected from the group comprising acetic acid, formic acid, citric acid, oxalic acid, tartaric acid, maleic acid, malic acid, mandelic acid, malonic acid, succinic acid, glutaric acid, adipic acid, sulfurous acid, phosphoric acid, nitrous acid and mixture thereof.
- 15 24. The process as claimed in claim 23, wherein the acid is citric acid.
25. A process for purification of cabotegravir of Formula I, comprising:



Formula I

- 20 a) suspending or dissolving cabotegravir in a suitable solvent at ambient temperature to reflux,
- b) adding step a) reaction mass to an anti-solvent (or) adding an anti-solvent to step a) reaction mass at a suitable temperature,
- c) optionally, cooling the step b) reaction mass to below 25°C, and
- d) isolating the pure cabotegravir.
- 25 26. The process as claimed in claim 25, wherein the suitable solvent is selected from the group comprising 2,2,2-trifluoromethanol, 2-mercaptoethanol, 2,2,2-trifluoroethanol, glycerol, hexafluoro-2-propanol, ethylene glycol, propylene glycol, dimethylacetamide, dimethylformamide, N-methyl pyrrolidone, dimethyl sulfoxide, diethyl sulfoxide, acetonitrile, propionitrile, methylene chloride, ethylene chloride, chloroform, chlorobenzene, acetic acid and mixtures thereof.
- 30 27. The process as claimed in claim 26, wherein the suitable solvent is 2,2,2-trifluoroethanol.
- 35 28. The process as claimed in claim 25, wherein the anti-solvent is selected from the group comprising methanol, ethanol, Isopropyl alcohol, n-propanol, n-butanol, t-butanol, 1-pentanol, tetrahydrofuran, methyl tetrahydrofuran, dimethyl ether,

5 diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, acetone, methyl isobutyl ketone, methyl ethyl ketone, toluene, water and mixture thereof.

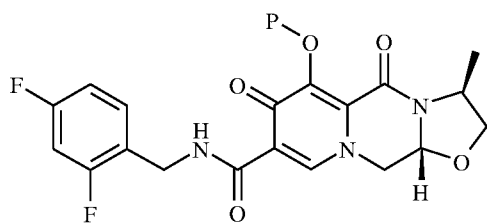
29. The process as claimed in claim 28, wherein in the anti-solvent is selected from the
10 group comprising methanol, ethanol, Isopropyl alcohol, n-butanol, t-butanol, 1-pentanol, water and mixture thereof.

30. The process as claimed in claim 25, wherein the step a) and step b) are carried out at about 40°C to 80°C.

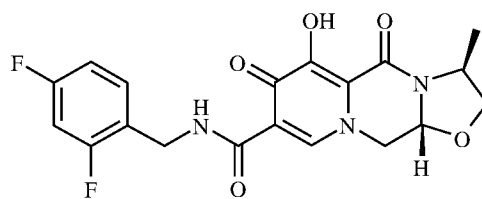
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31. A process for preparation of cabotegravir of Formula I or its pharmaceutically acceptable salts thereof, comprising: deprotecting a compound of Formula XII' in presence of magnesium chloride in a suitable solvent to provide cabotegravir; wherein the "P" represents an alkyl, aryl or aralkyl.

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Formula XII'



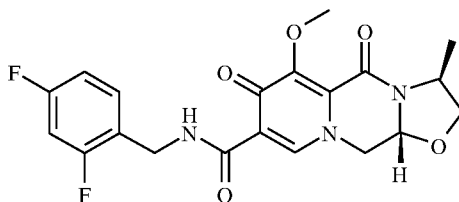
Formula I

32. The process as claimed in claim 31, wherein the "P" represents methyl or ethyl.

25 33. The process as claimed in claim 31, wherein the suitable solvent is selected from the group comprising methylene chloride, N-methylpyrrolidone, tetrahydrofuran, dimethylformamide, acetonitrile, dimethylsulfoxide, methanol, ethanol, formic acid, acetic acid and mixtures thereof.

30 34. The process as claimed in claim 31, wherein the deprotection is carried out at a temperature of about 50°C to about 80°C.

35. Crystalline compound of Formula XII

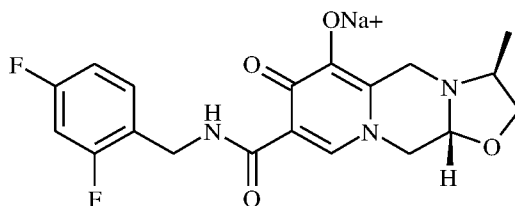


Formula XII

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36. The compound as claimed in claim 35, wherein the crystalline compound of Formula XII characterized by X-Ray diffraction (XRD) pattern having one or more peaks at about 6.1, 12.1, 13.7, 15.1, 15.6, 17.2, 17.4, 18.2, 19.5, 20.7, 25.4, 30.6 $\pm 0.2^\circ 2\theta$.

37. A process for preparation of crystalline cabotegravir sodium Form A, comprising:

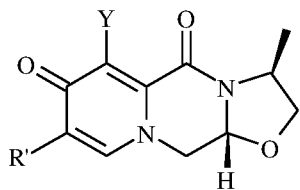


Cabotegravir Sodium

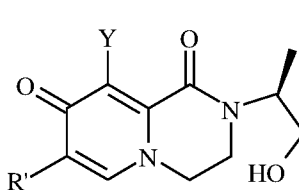
- a) suspending or dissolving cabotegravir in an organic solvent,
 - b) adding sodium source to step a) reaction mass (or) adding step a) reaction mass to sodium source at below 30°C , and
 - c) isolating the crystalline cabotegravir sodium Form A; wherein the organic solvent is selected from the group comprising alcohols, ketones, sulfoxides, nitriles, ethers and the like or mixtures thereof; wherein the crystalline cabotegravir sodium Form A characterized by a powder X-ray diffraction (PXRD) pattern having at least one peak selected from: 5.4, 9.5, 11.0, 12.7, 13.1, 14.0, 14.6, 15.4, 15.7, 16.1, 19.0, 21.5, 22.1, 23.2, 23.8, 24.4, 25.4, 26.2, 27.1, 28.0, 28.9, 29.9, 32.6 and $34.5 \pm 0.2^\circ 2\theta$ and does not have a peak at about 6.2 and/or $6.8 \pm 0.2^\circ 2\theta$.
38. The process as claimed in claim 37, wherein the organic solvent is selected from the group comprising methanol, ethanol, butanol, isobutanol, tert-butanol, propanol, isopropanol, pentanol, glycerol, acetone, methylisobutylketone, methylethylketone, dimethyl sulfoxide, diethyl sulfoxide, acetonitrile, propionitrile, tetrahydrofuran, methyl tertiary butyl ether and mixture thereof; where in the sodium source is selected from the group comprising sodium hydroxide, sodium formate, sodium acetate, sodium methoxide, sodium ethoxide, sodium butoxide, sodium pentoxide and mixtures thereof.
39. The process as claimed in claim 38, wherein the organic solvent is trifluoroethanol, dimethyl sulfoxide, methanol, ethanol, n-butanol, n-pentanol, acetone, acetonitrile

5 or tetrahydrofuran; and wherein the sodium source is sodium hydroxide or sodium methoxide.

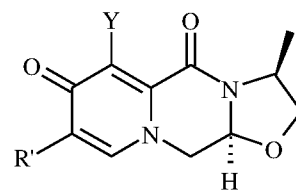
40. A compound of Formula XI having less than 0.15% by HPLC of a compound of Formula XIA and/or Formula XIB.



Formula XI



Formula XIA



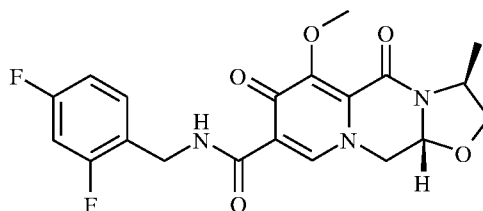
Formula XIB

wherein “Y” represents hydrogen, chloro or -OR; “R” represents alkyl, aryl or aralkyl; and “R’ ” represents hydrogen, -COOH, -COOR, -CONH₂, -CHO, -CN or halogen.

41. The compound as claimed in claim 40, wherein the “Y” represents -OR and wherein the “R’ ” represents -COOH and wherein the “R” represents methyl or ethyl.

42. The compound as claimed in claim 41, wherein the “Y” represents -OMethyl and “R’ ” represents -COOH.

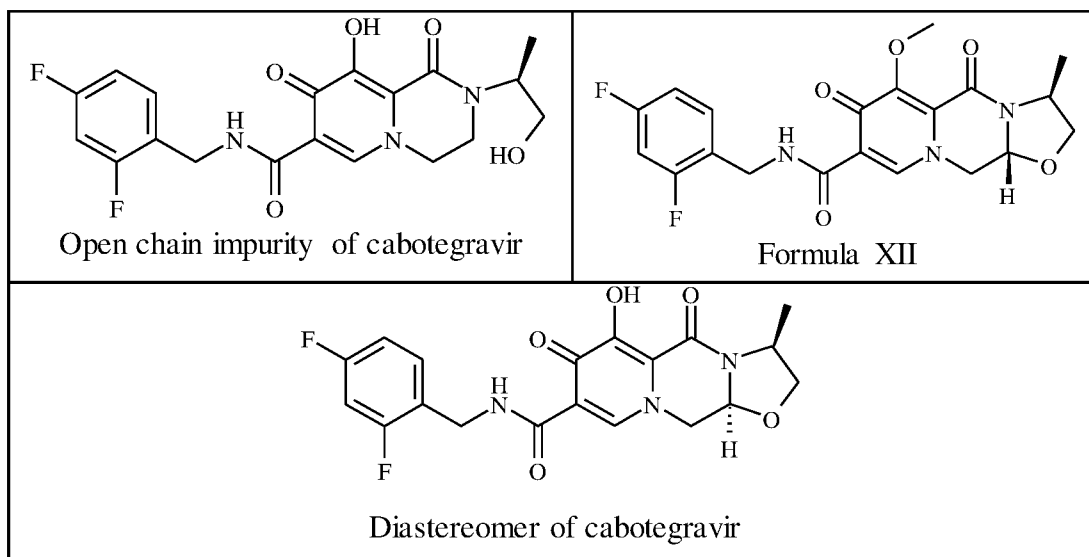
43. A compound of Formula XII having less than 0.5% by HPLC of 2,4-difluorobenzylamine and/or by-products of coupling agent.



Formula XII

44. The compound as claimed in claim 43, wherein the by-products of coupling agent is imidazole.

45. Cabotegravir or a salt thereof having less than 0.5% by HPLC of at least one of 2,4-difluorobenzylamine, imidazole by-product, open chain impurity of cabotegravir, compound of Formula XII and Diastereomer of cabotegravir.



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46. A pharmaceutical composition comprising cabotegravir or a salt thereof according to claims 1-45 and at least one pharmaceutically acceptable excipient.

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FIGURE 1

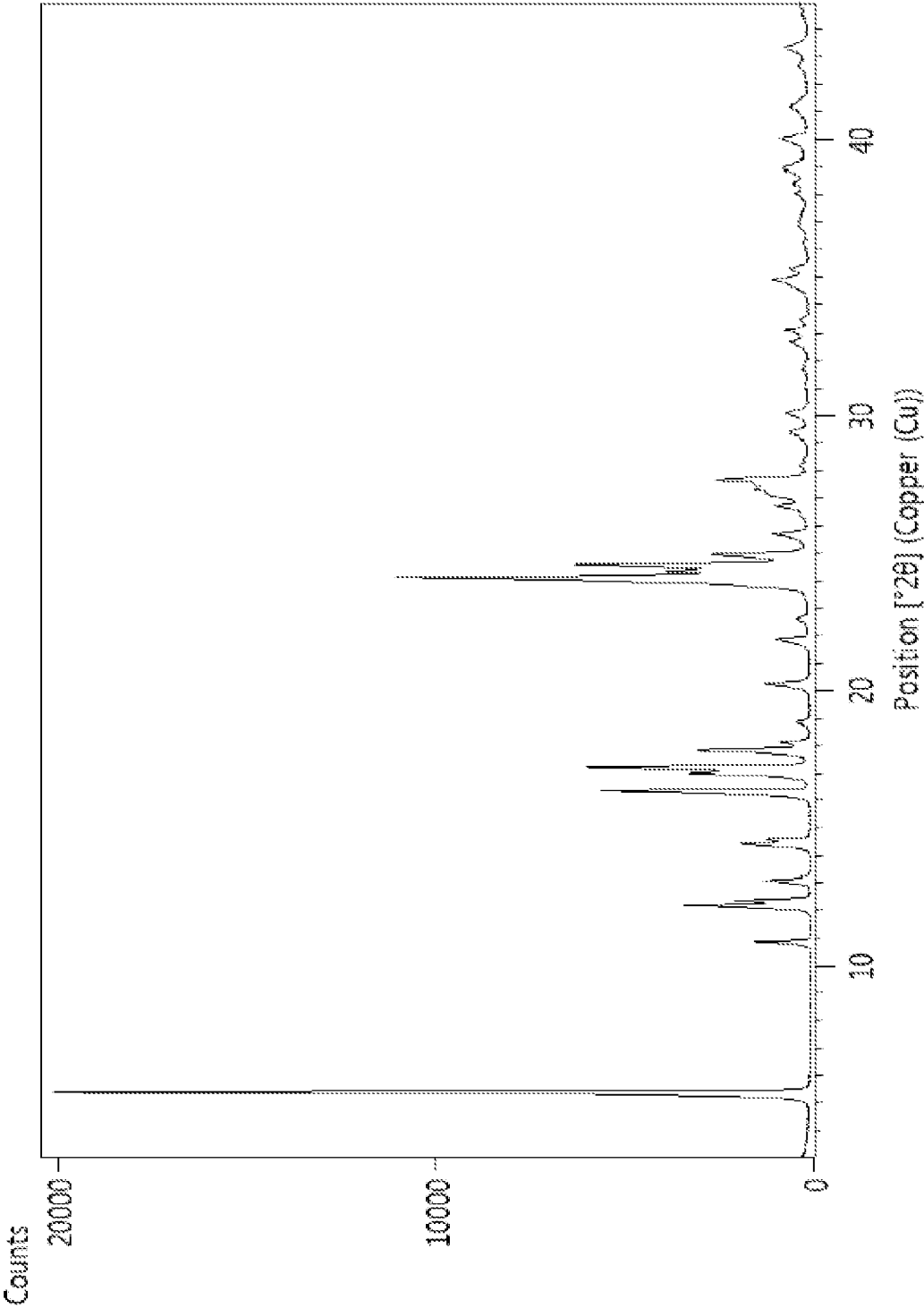


FIGURE 2

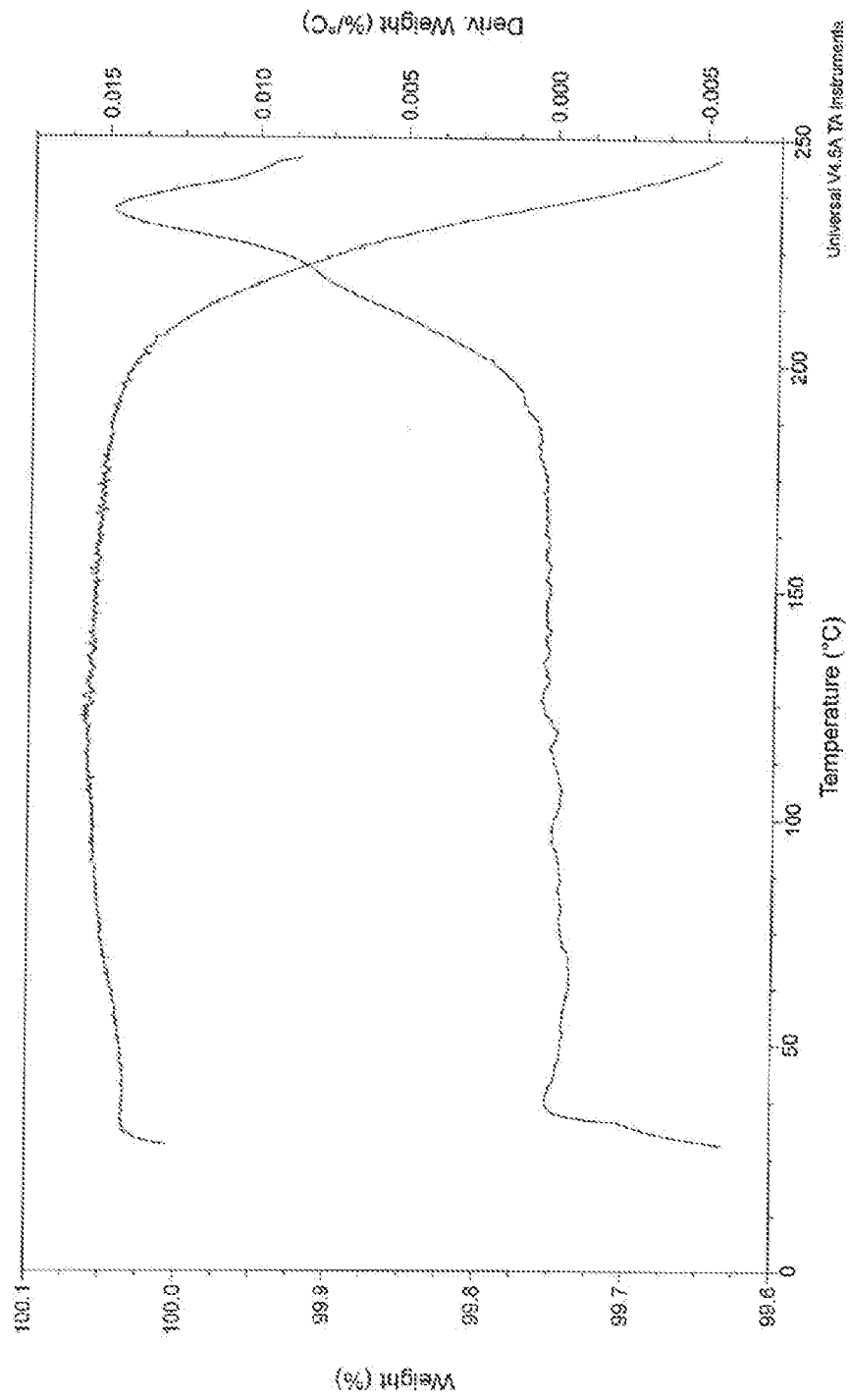


FIGURE 3

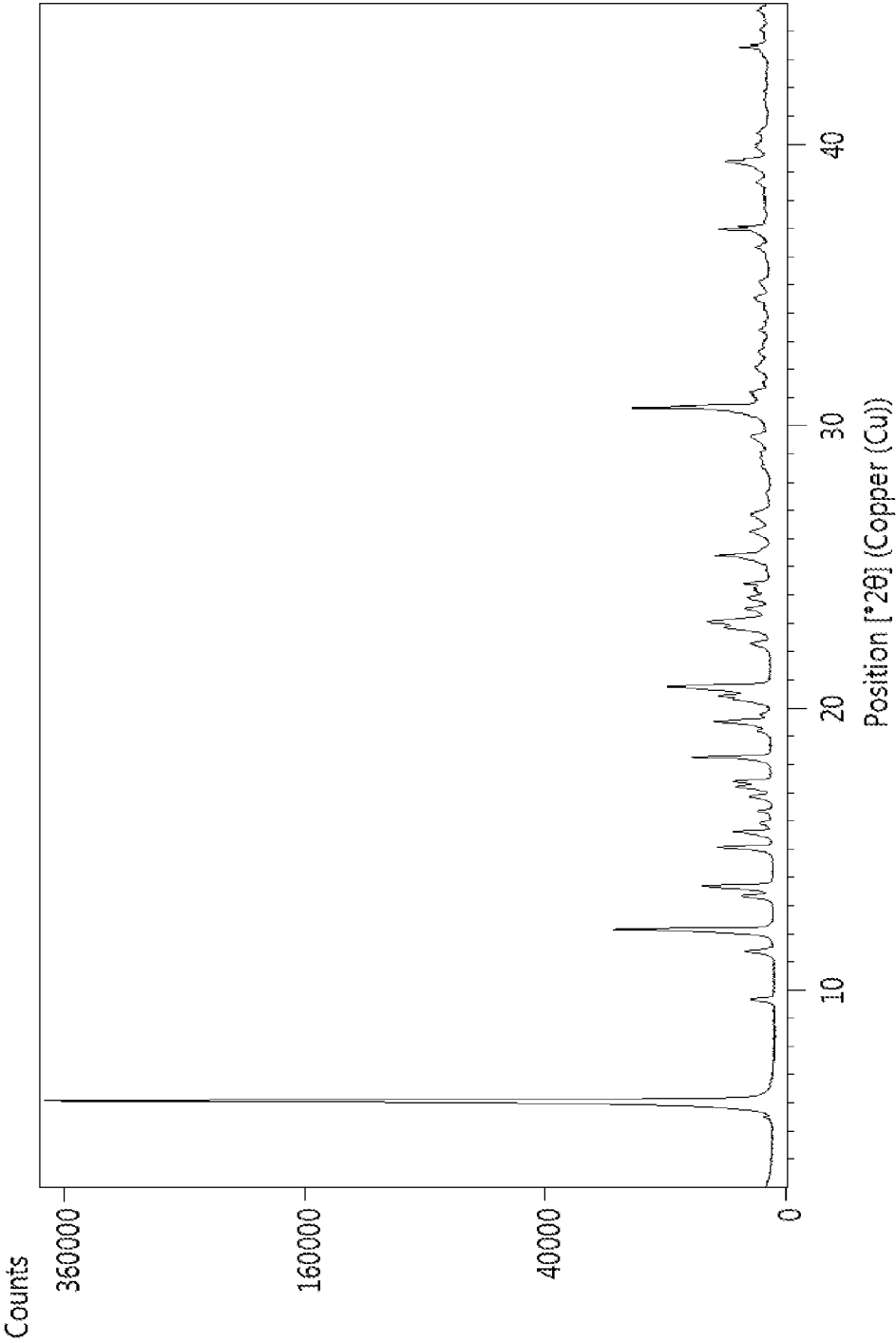


FIGURE 4

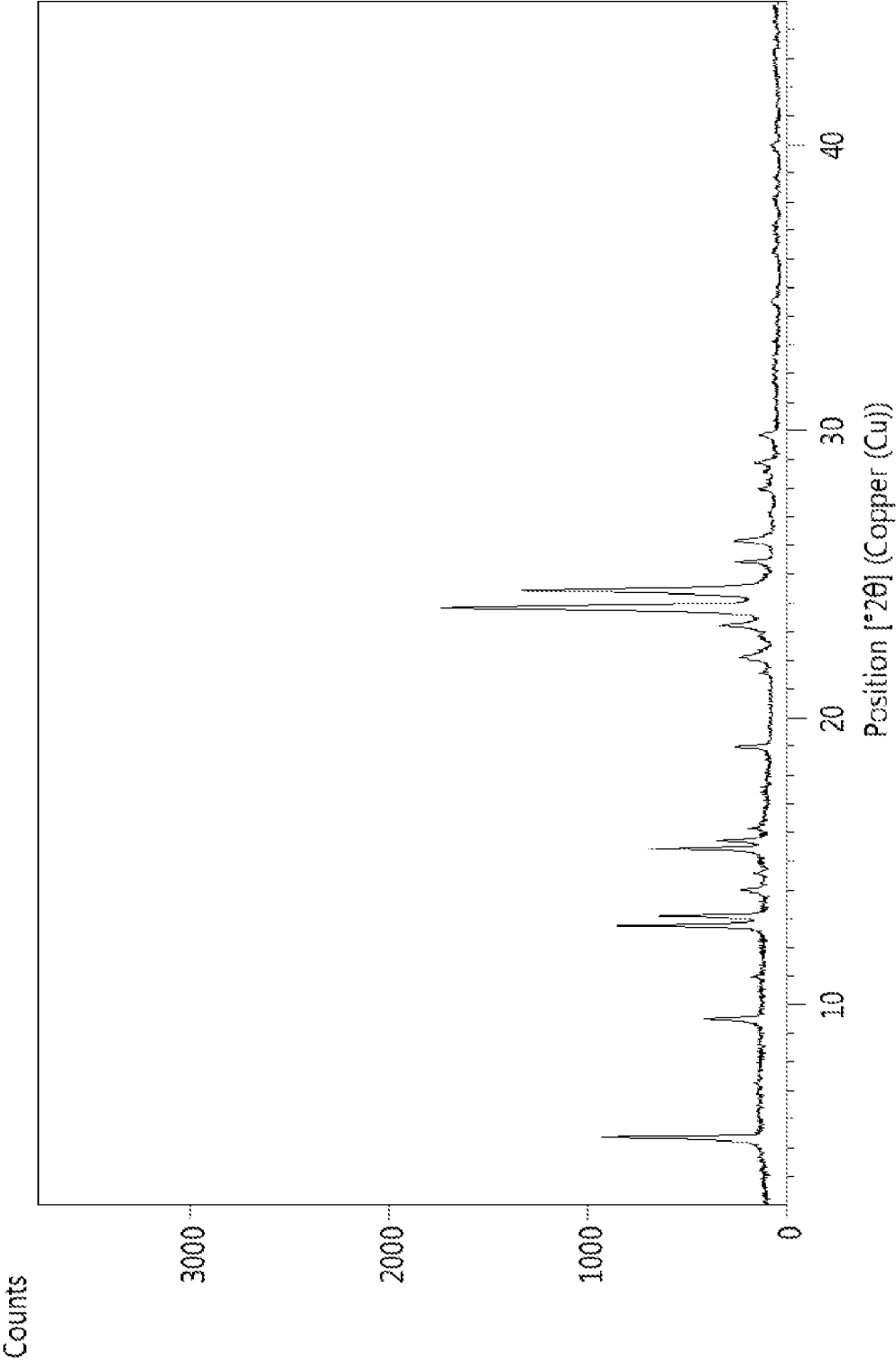


FIGURE 5

