Title: A PROCESS FOR PREPARATION OF COBICISTAT

Abstract: The present invention provides novel intermediates of cobicistat or a pharmaceutically acceptable salt thereof and a process for its preparation. The present invention also provides for the preparation of cobicistat or a pharmaceutically acceptable salt thereof using the intermediates.
"A PROCESS FOR PREPARATION OF COBICISTAT"

PRIORITY

This application claims the benefit under Indian Provisional Application No. 619/CHE/2015 filed on 09 Feb, 2015 entitled "A process for preparation of cobicistat", the contents of each of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention generally relates to a novel process for the preparation of cobicistat or a pharmaceutically acceptable salt thereof using novel intermediates.

BACKGROUND OF THE INVENTION

Cobicistat, also known as 1,3-thiazol-5-ylmethyl [(2R,5R)-5-[(2S)2-[(methyl[[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl]carbamoyl]-amino]-4-(morpholine-4yl)-butanoyl] amino]-1,6-diphenylhexan-2-yl]carbamate of Formula I:

![Formula I](image)

Cobicistat is marketed by Gilead Sciences under the trade name Stribild® and also known as "Quad Pill", which is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve. Cobicistat is also approved alone and marketed as Tybost®, which is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection.

U.S. Patent No. 8,148,374 ("the ‘374 patent") discloses cobicistat and process for preparation thereof. The ‘374 patent discloses three different routes for the preparation of cobicistat, which are schematically represented as follows:
U.S. Patent No. 8,497,396 ("the ‘396 patent") discloses a process for the preparation of cobicistat by involving novel intermediates. The process disclosed in the ‘396 patent is schematically represented as follows:


Formula VII
There is a need in the art to develop a novel process for the preparation of cobicistat, which is readily amenable to large scale production.

Hence, present inventors focused alternative process for the preparation of cobicistat with greater yield, and higher purity by using novel intermediates.

**SUMMARY OF THE INVENTION**

In accordance with one embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof:

![Formula I](image)

comprising:

a) reacting a compound of formula IV with morpholine to obtain a compound of Formula V,

![Formula IV](image)

![Formula V](image)

wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C<sub>1-8</sub> alkyl,

b) reacting the compound of Formula V with a suitable base to obtain a compound of Formula VI or a salt thereof; wherein ‘PG’ is defined as above,

![Formula VI](image)
c) coupling the compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIII; wherein ‘PG’ is defined as above,

Formula VII

Formula VIII

d) reacting the compound of Formula VIII with a suitable acid to obtain a compound of Formula IX or a salt thereof, and

Formula IX

e) reacting the compound of Formula IX with a compound of Formula X or a salt thereof to obtain cobicistat of Formula I.

Formula X

In accordance with one embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) coupling a compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIII; wherein ‘PG’ represents a suitable amine protecting group.

b) reacting the compound of Formula VIII with a suitable acid to obtain a compound of Formula IX or a salt thereof, and

c) converting the compound of Formula IX in to cobicistat of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof, comprising:
a) reacting a compound of formula IV with morpholine to obtain a compound of Formula V, wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C_{1-8} alky1,

b) reacting the compound of Formula V with a suitable base to obtain a compound of Formula VI or a salt thereof; wherein ‘PG’ is defined as above,

c) coupling the compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIII; wherein ‘PG’ is defined as above, and

d) converting the compound of Formula VIII into cobicistat of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of formula IV with morpholine to obtain a compound of Formula V, wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C_{1-8} alky1,

b) reacting the compound of Formula V with a suitable base to obtain a compound of Formula VI or a salt thereof; wherein ‘PG’ is defined as above, and

c) converting the compound of Formula VI into cobicistat of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of formula IV with morpholine to obtain a compound of Formula V, wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C_{1-8} alky1, and

b) converting the compound of Formula V into cobicistat of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting L-homoserine lactone of Formula III or a salt thereof with trimethylsilyl halide in presence of an alcohol to obtain a compound of Formula IV; wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C_{1-8} alky1; and
b) converting the compound of Formula IV into cobicistat of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof:

![Formula I](image)

Formulas I

comprising:

a) reacting L-homoserine lactone of Formula II or a salt thereof with pivaloyl chloride to obtain a compound of Formula III,

![Formula II](image)

Formula II

![Formula IIIa](image)

Formulas IIIa

b) reacting the compound of Formula IIIa with trimethylsilyl halide in presence of an alcohol to obtain a compound of Formula IVa; wherein ‘X’ represents halo group, ‘R’ represents C₁-₈ alkyl,

![Formula IVa](image)

Formulas IVa

c) reacting the compound of Formula IVa with morpholine to obtain a compound of Formula Va; wherein ‘X’ and ‘R’ are defined as above,

![Formula Va](image)

Formulas Va

d) reacting the compound of Formula Va with a suitable base to obtain a compound of Formula VIa or a salt thereof,
e) coupling the compound of Formula VIa or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIIIa,

f) reacting the compound of Formula VIIIa with a suitable acid to obtain a compound of Formula IX or a salt thereof, and

g) reacting the compound of Formula IX with a compound of Formula X or a salt thereof to obtain cobicistat of Formula I.

In accordance with another embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) coupling a compound of Formula VIa or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIIIa, and

b) converting the compound of Formula VIIIa into cobicistat of Formula I.
In accordance with another embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) coupling the compound of Formula VIa or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIIIa,

b) reacting the compound of Formula VIIIa with a suitable acid to obtain a compound of Formula IX or a salt thereof, and
c) reacting the compound of Formula IX with a compound of Formula X or a salt thereof to obtain cobicistat of Formula I.

In accordance with another embodiment, the present invention provides a compound of Formula IV or a pharmaceutically acceptable salt thereof,

\[
\text{PG-N} \text{OR} \\
\text{O}
\]

\text{Formula IV}

wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C\textsubscript{1-8} alkyl.

In accordance with another embodiment, the present invention provides a compound of Formula IV or a pharmaceutically acceptable salt thereof,

\[
\text{PG-N} \text{OR} \\
\text{O}
\]

\text{Formula IV}

wherein the “PG” is a suitable amine protecting group. The suitable amine protecting group is selected from the group consisting of carbonates such as carboxy benzoyl (Cbz), fluorenylmethoxy carbonyl (Fmoc), allyloxy carbonyl (alloc), methyl and ethyl carbamates; cyclic imide derivatives such as phthalimide; amides such as formyl; acetyl, pivaloyl; trityl, substituted or unsubstituted aryls such as benzyl benzoyl, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB) and trialkyl silyl groups such as trimethylsilyl (TMS), tert-butyldiphenyldimethylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDS), triisopropylsilyl (TIPS) and the like; wherein the ‘X’ represents halo group such as chloro, bromo, iodo and fluoro; wherein the C\textsubscript{1-8} alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like.
In accordance with another embodiment, the present invention provides a compound of Formula IVa or Formula IVb.

![Formula IVa](image1)

![Formula IVb](image2)

In accordance with another embodiment, the present invention provides a compound of Formula Va or a pharmaceutically acceptable salt thereof,

![Formula Va](image3)

wherein ‘R’ represents C_{1-8} alkyl.

In accordance with another embodiment, the present invention provides a compound of Formula Va or a pharmaceutically acceptable salt thereof.

![Formula Va](image4)

In accordance with another embodiment, the present invention provides a compound of Formula VIa or a pharmaceutically acceptable salt thereof.

![Formula VIa](image5)

In accordance with another embodiment, the present invention provides a compound of Formula VIII or a pharmaceutically acceptable salt thereof,
wherein the “PG” is a suitable amine protecting group. The suitable amine protecting group is selected from the group consisting of carboxy benzyol (Cbz), fluorenylmethyloxycarbonyl (Fmoc), allyloxycarbonyl (alloc), methyl and ethyl carbamates; cyclic imide derivatives such as phthalimide; amides such as formyl; acetyl, pivaloyl; trityl, substituted or unsubstituted aryls such as benzyl benzyol, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB) and trialkyl silyl groups such as trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDDS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS) and the like.

In accordance with another embodiment, the present invention provides a compound of Formula VIIIa or a pharmaceutically acceptable salt thereof.

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

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides a process for the preparation of cobicistat using novel intermediates.

In accordance with one embodiment, the present invention provides a process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof:
comprising:

a) reacting a compound of Formula IV with morpholine to obtain a compound of Formula V,

\[
\begin{align*}
\text{Formula IV} & \quad \text{PG} - N - \begin{array}{c}
\text{OR} \\
X
\end{array} \\
\text{Formula V} & \quad \text{PG} - N - \begin{array}{c}
\text{OR} \\
O
\end{array}
\end{align*}
\]

wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C1-8 alkyl,

b) reacting the compound of Formula V with a suitable base to obtain a compound of Formula VI or a salt thereof; wherein ‘PG’ is defined as above,

\[
\begin{align*}
\text{Formula VI} & \quad \text{PG} - N - \begin{array}{c}
\text{OH} \\
O
\end{array}
\end{align*}
\]


c) coupling the compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIII, wherein ‘PG’ is defined as above,
d) reacting the compound of Formula VIII with a suitable acid to obtain a compound of Formula IX or a salt thereof, and

![Formula IX](image)

Formula IX

e) reacting the compound of Formula IX with a compound of Formula X or a salt thereof to obtain cobicistat of Formula I.

![Formula X](image)

Formula X

Unless otherwise specified the term ‘PG’ represents a suitable amine protecting group.

The suitable amine protecting used herein are selected from carbonates such as carboxy benzoyl (Cbz), fluorenylmethyloxycarbonyl (Fmoc), allyloxycarbonyl (alloc), methyl and ethyl carbamates; cyclic imide derivatives such as phthalimide; amides such as formyl; acetyl, pivaloyl; trityl, substituted or unsubstituted aryls such as benzyl, benzoyl, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB); and trialkyl silyl groups such as trimethylsilyl (TMS), tert-butylidiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS) and the like.

Unless otherwise specified the term ‘X’ represents a halo group, which is selected from chloro, bromo, iodo or fluoro.

Unless otherwise specified the term ‘R’ represents a C_{1-8} alkyl and is selected from but not limited to methyl, ethyl, propyl, butyl and the like.

The starting compound of Formula IV of the present invention may be prepared from the compound of formula III by cleaving the lactone moiety as process described in the following embodiment.

In another embodiment, the present invention provides a process for the preparation of compound of Formula IV, comprising: reacting L-homoserine lactone of Formula III or a salt thereof with trimethylsilyl halide in presence of an alcohol to obtain a compound of Formula IV; wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C_{1-8} alkyl.
In a preferred embodiment the compound of Formula III and Formula IV can be represented as follows:

In an embodiment of the present invention, the L-homoserine lactone of Formula III; preferably Formula IIIa, can be prepared by protecting L-homoserine lactone of Formula II or a salt thereof with a suitable amine protecting group, preferably pivaloyl protecting group in presence of a suitable base to obtain a compound of Formula III or a salt thereof by the processes known in the art.

Exemplary bases used herein for the step of protecting L-homoserine lactone of Formula II with a suitable amine protecting group, preferably pivaloyl protecting group, includes but are not limited to sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like and mixtures thereof; preferably triethylamine.

The protected L-homoserine lactone of Formula III; preferably Formula IIIa, may be converted in to a compound of Formula IV by reacting L-homoserine lactone of Formula III or a salt thereof with trimethylsilyl halide in presence of an alcohol to obtain a compound of Formula IV; wherein ‘PG’ represents a suitable amine protecting group; preferably pivaloyl, ‘X’ represents halo group; preferably bromo or iodo, and ‘R’ represents C_{1,8} alkyl; preferably ethyl.
The trimethylsilyl halide used herein is selected from trimethylsilyl iodide or trimethylsilyl bromide.

The alcohol solvent used for the reaction of Formula III; preferably Formula IIIa, with trimethylsilyl halide is selected from the group consisting of methanol, ethanol, propanol, butanol and the like; preferably ethanol.

The reaction of Formula III with trimethylsilyl halide is carried out at a temperature of about 0°C to reflux temperature; preferably at about 25°C to 35°C.

The resultant compound of Formula IV, preferably a compound of Formula IVa or Formula IVb obtained by the processes described above can be used for the preparation of cobicistat of the invention.

The step a) of the aforementioned process involves reaction of compound of Formula IV, preferably a compound of Formula IVa or Formula IVb with morpholine to obtain a compound of Formula V; wherein ‘PG’, ‘X’ and ‘R’ are defined as above, in a suitable solvent.

In another embodiment, the compound of Formula V specifically represented as follows:

![Formula Va](image)

The suitable solvent for reaction of compound of Formula IV with morpholine include but is not limited to amides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The amides include, but are not limited to dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone 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 and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably dimethyl formamide, acetonitrile or methylene chloride; more preferably methylene chloride.
The reaction of Formula IV with morpholine is advantageously carried out at a temperature of about 0°C to reflux temperature; preferably at about 10°C to 80°C; more preferably at about 25°C to 35°C.

The step b) of the aforementioned process involves hydrolysis of the ester group using a suitable base to obtain a compound of Formula VI or a salt thereof; wherein ‘PG’ is defined as above.

In another embodiment, the compound of Formula VI specifically represented as following Formula VIa or a salt thereof:

![Formula VIa]

The suitable base used herein for step b) include but is not limited to inorganic bases selected from alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like and mixtures thereof; preferably potassium hydroxide.

The reaction of compound of Formula V with a suitable base is carried out in a suitable organic solvent. The suitable organic solvent includes but is not limited to ketones, nitriles, ethers, halogenated hydrocarbons and mixtures thereof. The ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone 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 and the like and mixtures thereof; preferably methyl isobutyl ketone, tetrahydrofuran or methylene chloride; more preferably methylene chloride.

The reaction of compound of Formula V with a suitable base is carried out at a temperature of about 0°C to reflux temperature; preferably at about 25°C to 35°C.

In another embodiment, the compound of Formula VI thus obtained may be isolated as its salt form, preferably base salt, which may be formed using suitable base in the hydrolysis reaction. More preferably the compound of Formula VI can be isolated as its potassium salt.
The step c) of the aforementioned process involves coupling the compound of Formula VI or a salt thereof, preferably potassium salt of the formula VI with a compound of Formula VII or a salt thereof in presence of a suitable coupling agent to obtain a compound of Formula VIII; wherein ‘PG’ is defined as above, preferably pivaloyl group.

In another embodiment, the compound of Formula VIII specifically represented as following Formula VIIIa or a salt thereof:

![Formula VIIIa](image)

The suitable coupling agent used herein for coupling of compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof is selected from the group consisting of 1-Hydroxybenzotriazole (HOBT), 1-Hydroxy-7-aza-1H-benzotriazole (HOAT), N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide. Hydrochloride) (EDC. HCl), dicyclohexyl carbodiimide (DCC), 1,1’-Carbonyldiimidazole (CDI), diisopropylcarbodiimide (DCI), benzotriazol-1-ylxy-tris (dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-ylxy-tripyrrolidino-phosphonium hexafluorophosphate) (PyBOP), bromo- tripyrrolidino- phosphonium hexafluorophosphate (PyBrOP), 2-(1H-Benzotriazol-1-yl) - N,N,N’,N’- tetramethylinum tetrafluoroborate/hexafluoro phosphate (TBTU), 2-(7-Aza-1H-benzotriazol-1-y1)-N,N,N’,N’-tetramethylinium hexafluorophosphate) (HATU), Propylphosphonic anhydride (T3P) and the like and mixture thereof; preferably 1-Hydroxybenzotriazole (HOBT) and N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide. Hydrochloride) (EDC. HCl). Optionally an additive such as Imidazole or its salts, preferably imidazole hydrochloride can used along with coupling agent in the coupling reaction.

The coupling of compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof is carried out in a suitable organic solvent. The suitable organic solvent includes but is not limited to esters, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl acetate and the like; nitriles include, but are not limited to acetonitrile, propionitrile, benzonitrile 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 and the like; aromatic hydrocarbons include, but are
not limited to toluene, xylene and the like and mixtures thereof; preferably tetrahydrofuran, methylene chloride or toluene; more preferably methylene chloride.

The coupling of compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof is advantageously carried out at a suitable temperature of about -25°C to about 65°C; preferably at about -5°C to -15°C.

The step d) of the aforementioned process involves deprotection of the compound of Formula VIII; wherein 'PG' is defined as above, with a suitable acid to obtain a compound of Formula IX or a salt thereof.

The suitable acid used herein for step d) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and the like and mixture thereof; preferably hydrochloric acid.

The source of acid may be in the form of an aqueous, anhydrous or gas form, for example aqueous hydrochloric acid or solvent containing hydrochloric acid or hydrochloric acid gas.

The deprotection reaction of compound of Formula VIII with a suitable acid is carried out in a suitable organic solvent. The suitable organic solvent includes but is not limited to alcohols, ketones, nitriles, ethers and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone 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 and mixture thereof; preferably methanol or ethanol.

The deprotection reaction may be carried out at a temperature of about 0°C to reflux temperature; preferably at about 55°C to 65°C.

The step e) of the aforementioned process involves reaction of compound of Formula IX with a compound of Formula X or a salt thereof in presence of a suitable coupling agent and optionally a base to obtain cobicistat.

The suitable coupling agent used herein for reaction of compound of Formula IX with a compound of Formula X or a salt thereof is same as used for step c) as mentioned above; preferably 1,1'-Carbonyldiimidazole (CDI).

The suitable base used herein for coupling of compound of Formula IX with a compound of Formula X include, but is not limited to Imidazole or its salts, 1,8-
Diazabicyclo[5.4.0]undec-7-en (DBU); tertiary amines or its hydro halide salts thereof selected from the group consisting of triethyl amine hydrochloride or diisopropylethyl amine hydrochloride or mixtures thereof; preferably Imidazole hydrochloride and diisopropylethyl amine.

The reaction of compound of Formula IX with a compound of Formula X or a salt thereof is carried out in a suitable organic solvent. The suitable organic solvent includes but is not limited to esters, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl 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 and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably acetonitrile, methylene chloride or toluene; more preferably methylene chloride.

The reaction of compound of Formula IX with a compound of Formula X or a salt thereof is carried out at a temperature of about -10°C to reflux temperature; preferably at about 25°C to 35°C.

The resultant cobicistat can be isolated by conventional techniques such as by distillation under reduced pressure, solvent crystallization, solvent precipitation and the like; preferably by distillation under reduced pressure; wherein distillation of solvent from the reaction mass is carried out at a temperature of less than 40°C to obtain cobicistat as residue, which is optionally adsorbed with a suitable adsorbing materials, for example silica particles to obtain solid cobicistat or formed as a suitable pharmaceutically acceptable salt thereof. Preferably the residue so obtained is adsorbed with silicon dioxide particles.

The present invention provides a cobicistat or a pharmaceutically acceptable salt thereof obtained by the process described herein, having a purity of at least about 97%, as measured by HPLC, preferably at least about 98% as measured by HPLC, and more preferably at least about 99.5%, as measured by HPLC.

In another embodiment, the present invention provides a compound of Formula IV or a pharmaceutically acceptable salt thereof,
wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C₁₋₈ alkyl.

In another embodiment, the present invention provides a compound of Formula IV or a pharmaceutically acceptable salt thereof,

\[
PG-N\begin{array}{c}
\text{OR} \\
\text{O}
\end{array}
\]

wherein the “PG” is a suitable amine protecting group. The suitable amine protecting group is selected from the group consisting of carbonates such as carboxy benzoyl (Cbz), fluorenylmethyloxy carbonyl (Fmoc), allyloxy carbonyl (Alloc), methyl and ethyl carbamates; cyclic imide derivatives such as phthalamide; amides such as formyl; acetyl, pivaloyl; trityl, substituted or unsubstituted aryls such as benzyl benzoyl, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB) and trialkyl silyl groups such as trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS) and the like; wherein the ‘X’ represents halo group such as chloro, bromo, iodo and fluoro; wherein the C₁₋₈ alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like.

In another embodiment, the present invention provides a compound of Formula IVa or Formula IVb.

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{H}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}-\text{O}
\end{array}
\]

Formula IVa

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{H}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}-\text{O}
\end{array}
\]

Formula IVb

In another embodiment, the present invention provides a compound of Formula V or a pharmaceutically acceptable salt thereof,

\[
PG-N\begin{array}{c}
\text{OR} \\
\text{O}
\end{array}
\]

wherein “PG” represents a suitable amine protecting group, ‘R’ represents H or C₁₋₈ alkyl.
In another embodiment, the present invention provides a compound of Formula Va or a pharmaceutically acceptable salt thereof,

![Formula Va](image)

wherein ‘R’ represents H or C_{1,8} alkyl.

In another embodiment, the present invention provides a compound of Formula Va or a pharmaceutically acceptable salt thereof,

![Formula Va](image)

In another embodiment, the present invention provides a compound of Formula VIa or a pharmaceutically acceptable salt thereof,

![Formula VIa](image)

In another embodiment, the present invention provides a compound of Formula VIII or a pharmaceutically acceptable salt thereof,

![Formula VIII](image)

wherein the “PG” is a suitable amine protecting group. The suitable amine protecting group is selected from the group comprising: carbonates such as carboxy benzoyl (Cbz),
fluorenylmethyloxycarbonyl (Fmoc), allyloxycarbonyl (alloc), methyl and ethyl carbamates; cyclic imide derivatives such as phthalimide; amides such as formyl; acetyl, pivaloyl; trityl, substituted or unsubstituted aryls such as benzyl benzoyl, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB) and trialkyl silyl groups such as trimethylsilyl (TMS), tert-butylidiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS) and the like.

In another embodiment, the present invention provides a compound of Formula VIIIa or a pharmaceutically acceptable salt thereof.

![Formula VIIIa](image)

In another embodiment, the present invention provides a process for the preparation of cobicistat or a pharmaceutically acceptable salt thereof, wherein the process involves a compound of Formula IV, a compound of Formula V, a compound of Formula VI or a compound of Formula VIII as an intermediate or a starting material.

In another embodiment, the present invention provides use of a compound of Formula IV, a compound of Formula V, a compound of Formula VI or a compound of Formula VIII for the preparation of cobicistat or a pharmaceutically acceptable salt thereof according to process described as above embodiments.

As used herein, the pharmaceutical acceptable salts include acid addition salts formed with inorganic acids or with organic acids. The inorganic acids may be selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, sulfamic acid, and the like; organic acids may be selected from acetic acid, oxalic acid, fumaric acid, citric acid, succinic acid, tartaric acid, salicylic acid, benzoic acid, glycolic acid, methane sulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, lactic acid, maleic acid, malonic acid, malic acid and the like.

In another embodiment, the present invention provides a pharmaceutical composition, comprising cobicistat or a pharmaceutically acceptable salt thereof prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient. Such pharmaceutical composition may be administered to a mammalian patient in any dosage form, e.g., solid, liquid, powder, injectable solution, etc.
5 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.

10 EXAMPLE 1: Preparation of (S)-α-aminobutyrolactone hydrobromide:

To a mixture of (S)-2-amino-4-(methylmercapto)butyric acid (100 g) and water (200 mL), bromoacetic acid (99.7 g) was added at 25-35°C and stirred for 10 min. The reaction mass was heated to 85-95°C and stirred for 18 hr at 85-95°C. After completion of reaction, the reaction mass was cooled to 55-60°C and distilled off completely under vacuum at less than 60°C then cooled to 25-35°C. Isopropyl alcohol (100 mL) was added to the obtained residue and distilled off completely under vacuum at less than 60°C. The obtained residue was cooled to 25-35°C, isopropyl alcohol (250 mL) was added and stirred for 10 min IPA in HCl (88 g, 20%) was added to the reaction mass slowly at 25-35°C. The reaction mass was heated to 55-60°C and stirred for 4 hr. The reaction mass was cooled to 10-15°C and stirred for 2 hr at 10-15°C. The solid obtained was filtered, washed with chilled isopropyl alcohol and dried to get the title compound. Yield: 90 g

25 EXAMPLE 2: Preparation of (S)-N-(2-oxotetrahydrofuran-3-yl)pivalamide of Formula IIIa

A mixture of (S)-α-aminobutyrolactone hydrobromide (100 g) and methylene chloride (1100 mL) was cooled to 0-5°C and triethyl amine (168.7 mL) was added to it at 0-5°C. The reaction mass was stirred for 15 min at 0-5°C and filtered off the un-dissolved salts. The obtained filtrate was cooled to 0-5°C, pivaloyl chloride (74.4 mL) was added to it and stirred for an hour at 0-5°C. The reaction mass temperature was raised to 25-30°C and stirred for 4 hr. After completion of reaction, reaction mass was filtered, sodium chloride solution (obtained by dissolving 100 g of sodium chloride in 500 mL of water) was added to the above obtained filtrate at 25-30°C and stirred for 15 min. The organic and aqueous layers were separated. The aqueous layer was extracted with methylene chloride (100 mL). Organic layers were combined and distilled off the solvent completely under vacuum at less than 40°C to get white coloured solid. The reaction mass was cooled to 25-35°C, n-hexane (500 mL) was added and stirred for 2 hr at 25-35°C. The solid obtained was filtered, washed with n-hexane and dried to get the title compound. Yield: 85 g

35 EXAMPLE 3: Preparation of (S)-ethyl-4-morpholino-2-pivalamidobutanoate of Formula Va

To a solution of (S)-N-(2-oxotetrahydrofuran-3-yl)pivalamide (100 g) in methylene chloride (500 mL), ethanol (100 mL) was added at 25-30°C. The reaction mass was stirred
for 10 min at 25-30°C and then cooled to 0-5°C. Trimethylsilyl iodide (268.7 mL) was added slowly to the reaction mass over 60 min at 0-5°C and stirred for 30 min. The reaction mass temperature was raised to 25-30°C and stirred for 6 hr at the same temperature. After completion of reaction, the reaction mass was cooled to 0-5°C and hypo solution (obtained by dissolving 50 g of sodium thiosulphate in 500 mL of water) was added and stirred for 10 min at 0-5°C. The reaction mass temperature was raised to 25-30°C, stirred for 15 min, and then organic and aqueous layers were separated. The separated organic layer was washed with sodium bicarbonate solution (obtained by dissolving 40 g of sodium bicarbonate in 500 mL of water) followed by water (2×500 mL). The organic layer was distilled off completely under vacuum at less than 40°C. The obtained white solid material was cooled to 25-30°C and dissolved in methylene chloride (1000 mL). The reaction mass was cooled to 0-5°C, morpholine (141.7 mL) was added slowly over 30 min at 0-5°C and stirred for 15 min. The reaction mass temperature was raised to 25-30°C and stirred for 12 hr at the same temperature. After completion of reaction, an un-dissolved salt from the reaction mass was separated by filtration. Water (1000 mL) was added to the above obtained filtrate at 25-35°C and stirred for 15 min. The organic and aqueous layers were separated and then the organic layer was again washed with water (1000 mL). Organic layer was distilled off completely under vacuum at less than 40°C to get the title compound. Yield: 110 g

**EXAMPLE 4:** Preparation of thiazol-5-ylmethyl(2R,5R)-5-((S)-4-morpholino-2-pivalamido butanamido)-1,6-diphenylhexan-2-yl) carbamate of Formula VIIIa.

(S)-ethyl-4-morpholino-2-pivalamidobutanoate (100 g) was dissolved in methylene chloride (1000 mL) at 25-30°C then cooled to 0-5°C. Potassium hydroxide solution (obtained by dissolving 37.4 g of KOH in 16.8 mL of water) was slowly added to the reaction mass over 30 min at 0-5°C and stirred for 15 min. The reaction mass temperature was raised to 25-30°C and stirred for 18 hr. After completion of reaction, the reaction mass was distilled completely under vacuum at less than 40°C, then the obtained residue was cooled to 25-30°C and methylene chloride (3×500 mL) was added. The solvent from the reaction mass was distilled off completely under vacuum at less than 40°C to obtain reddish coloured compound of Formula VI. The obtained compound of Formula VI was dissolved in methylene chloride (1000 mL) at 25-35°C, sodium sulphate (100 g) was added, stirred for 15 min and then filtered. The obtained filtrate was cooled to -5 to -10°C under nitrogen atmosphere. (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino-1,6-diphenylhexane hydrochloride (101.7 g) was added to the above filtrate at -5°C to -10°C and stirred for an hour under nitrogen atmosphere. 1-hydroxybenzotriazole (33.4 g) was added to the reaction mass at -5 to -10°C and stirred for an hour under nitrogen atmosphere. EDC. HCl (103.1 g) was added to the reaction mass at -5 to -10°C and stirred for 12 hr at -5 to -10°C under nitrogen atmosphere. After completion of reaction, the reaction mass temperature was raised to 0-5°C, citric acid
solution (obtained by dissolving 100 g of citric acid in 1000 mL of water) was added and stirred for 15 min at 0-5°C. The reaction mass temperature was raised to 25-35°C, stirred for 30 min and the organic and aqueous layers were separated. Potassium carbonate solution (2 X 1000 ml, obtained by dissolving 300 g of potassium carbonate in 2000 mL of water) was added to the organic layer at 25-30°C, stirred for 30 min and then organic and aqueous layers were separated. Then separated organic layer was washed with water (1000 mL). The solvent from the organic layer was distilled off completely under vacuum at less than 40°C. The solid obtained was cooled to 25-35°C, isopropyl ether (1000 mL) was added and distilled off the same completely under vacuum at less than 45°C. Isopropyl ether (1000 mL) was added to the obtained white solid at 25-35°C and stirred for an hour. The solid obtained was filtered, washed with isopropyl ether and dried to get the title compound. Yield 135 g.

**EXAMPLE 5:** Preparation of thiazol-5-ylmethyl ((2R,5R)-5-((S)-2-amino-4-morpholino butanamido)-1,6-diphenylhexan-2-yl)carbamate of Formula IXa.

A mixture of thiazol-5-ylmethyl ((2R,5R)-5-((S)-4-morpholino-2-pivalamidobutanamido)-1,6-diphenylhexan-2-yl) carbamate (100 g) and methanolic HCl (1000 mL) was heated to reflux (63-65°C) and stirred for 2 hr at reflux. After completion of reaction, reaction mass was distilled completely under vacuum at less than 50°C and the obtained residue was cooled to 25-30°C, methylene chloride (1000 mL) and water (500 mL) was added and stirred for 15 min at 25-30°C. The pH of the reaction mass was adjusted to 7.5-8 with sodium carbonate solution at 25-30°C and stirred for 15 min. The organic and aqueous layers were separated then aqueous layer was extracted with methylene chloride (200 mL). The solvent from the organic layer was distilled off completely under vacuum at less than 40°C to get the title compound. Yield: 85 g

**Example 6:** Preparation of cobicistat

Thiazol-5-ylmethyl ((2R,5R)-5-((S)-2-amino-4-morpholinobutanamido)-1,6-diphenyl hexan-2-yl) carbamate (100 g) was dissolved in methylene chloride (1000 mL) at 25-30°C under nitrogen atmosphere and cooled to 0-5°C. To this, 1,1-carbonyldiimidazole (28 g), imidazole hydrochloride (4 g) followed by N,N-Diisopropylethylamine (36 mL) was added at 0-5°C under nitrogen atmosphere and stirred for 2 hr at 0-3°C. A solution of 2-isopropyl-4-(methylaminomethyl)thiazole dihydrochloride (obtained by dissolving 46 g of 2-isopropyl-4-(methylaminomethyl)thiazole dihydrochloride in 300 ml of methylene chloride and 54 ml of DIPEA at 0-5°C under nitrogen atmosphere) was slowly added to the above reaction mass over 60 min at 0-5°C under nitrogen atmosphere and stirred for 30 min. Then the reaction mass temperature was raised to 25-30°C and stirred for 6 hr under nitrogen atmosphere. After reaction completion, water (500 mL) added to the reaction mass and stirred for 15 min at 25-35°C. The organic and aqueous layers were separated,
and aqueous layer was extracted with methylene chloride. Organic layers were combined, citric acid solution (obtained by dissolving 100 g of citric acid in 1000 mL of water) was added to it and stirred for 15 min at 25-30°C. The organic and aqueous layers were separated. Sodium bicarbonate solution (obtained by dissolving 80 g of sodium bicarbonate in 1000 mL of water) was added to the separated organic layer at 25-35°C, stirred for 15 min and then organic and aqueous layers were separated. The separated organic layer washed with sodium chloride solution (obtained by dissolving 100 g of sodium chloride in 1000 mL of water) at 25-30°C. Sodium sulphate (100 g) was added to the organic layer, stirred for 15 min and then filtered. The obtained filtrate was distilled off completely under vacuum at less than 40°C to get the title compound as an off white solid (110 g). The solid obtained was dissolved in methylene chloride (500 mL) at 25-30°C under nitrogen atmosphere. Aeroperl 300 pharma silicon dioxide was added to the above reaction mass at 25-30°C and stirred for 15 min. n-Heptane (3000 mL) was added to the reaction mass slowly over 60 min at 25-30°C under nitrogen atmosphere and stirred for 90 min. The reaction mass filtered, washed with n-heptane and then dried at 25-35°C under vacuum to get the cobicistat silicon dioxide. Yield: 190 g; Purity by HPLC: 97%.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed 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 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.
WE CLAIM

Claim 1: A process for preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof:

![Formula I](image)

comprising:

a) reacting a compound of formula IV with morpholine to obtain a compound of Formula V,

![Formula IV](image) ![Formula V](image)

wherein ‘PG’ represents a suitable amine protecting group, ‘X’ represents halo group and ‘R’ represents C$_{1-8}$ alkyl,

b) reacting the compound of Formula V with a suitable base in a suitable organic solvent to obtain a compound of Formula VI or a salt thereof; wherein ‘PG’ is defined as above,

![Formula VI](image)

c) coupling the compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIII; wherein ‘PG’ is defined as above,
d) reacting the compound of Formula VIII with a suitable acid in a suitable organic solvent to obtain a compound of Formula IX or a salt thereof, and

e) reacting the compound of Formula IX with a compound of Formula X or a salt thereof to obtain cobicistat of Formula I.

Claim 2: The process of claim 1, wherein the suitable amine protecting group is selected from the group consisting of carboxy benzoyl (Cbz), fluorenlymethyloxycarbonyl (Fmoc), allyloxycarbonyl (alloc), methyl and ethyl carbamates, phthalimide, formyl, acetyl, pivaloyl, trityl, substituted or unsubstituted aryls such as benzyl benzoyl, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB), trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS) and triisopropylsilyl (TIPS).

Claim 3: The process of claim 1, wherein the halo group is selected from the group consisting of chloro, bromo, iodo and fluoro.

Claim 4: The process of claim 1, wherein the C_{1-8} alkyl is selected from the group consisting of methyl, ethyl, propyl and butyl.

Claim 5: The process of claim 1, wherein the ‘‘PG’’ is pivaloyl; ‘X’ is bromo or iodo; and ‘R’ is ethyl.
Claim 6: The process of claim 1, wherein the step a) is carried out in a suitable solvent, wherein the solvent is selected from the group consisting of dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone, acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, toluene, xylene and mixtures thereof.

Claim 7: The process of claim 6, wherein the suitable solvent is methylene chloride.

Claim 8: The process of claim 1, wherein the suitable base of step b) is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and mixtures thereof.

Claim 9: The process of claim 1, wherein the suitable organic solvent of step b) is selected from the group consisting of acetone, methyl isobutyl ketone, methyl ethyl ketone, acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride and mixtures thereof.

Claim 10: The process of claim 1, wherein the suitable organic solvent of step b) is methylene chloride and suitable base of step b) is potassium hydroxide.

Claim 11: The process of claim 1, wherein the step c) is carried out in presence of a suitable coupling agent and a suitable organic solvent.

Claim 12: The process of claim 11, wherein the suitable coupling agent is selected from the group consisting of 1-Hydroxybenzotriazole, 1-Hydroxy-7-aza-1H-benzotriazole, N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide, dicyclohexyl carbodiimide, 1,1’-Carbonyldimidazole, diisopropylcarbodiimide, benzotriazol-1-yl oxy-tris (dimethylamino) phosphonium hexafluorophosphate, benzotriazol-1-yl oxy-tripyrrolidino-phosphonium hexafluorophosphate, bromo- tripyrrolidino- phosphonium hexafluorophosphate, 2-(1H-Benzotriazol-1-yl) - N,N,N’,N’- tetramethylinum tetrafluoroborate/hexa fluoro phosphate, 2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N’,N’-tetramethylaminium hexafluorophosphate, Propylphosphonic anhydride and mixture thereof.

Claim 13: The process of claim 11, wherein the suitable organic solvent is selected from the group consisting of methyl acetate, ethyl acetate, isopropyl acetate, acetonitrile, propionitrile, benzonitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, toluene, xylene and mixtures thereof.
Claim 14: The process of claim 11, wherein the coupling agent is 1-Hydroxybenzotriazole and N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide and suitable organic solvent is methylene chloride.

Claim 15: The process of claim 1, wherein the suitable acid of step d) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and mixture thereof.

Claim 16: The process of claim 1, wherein the suitable organic solvent of step d) is selected from the group consisting of methanol, ethanol, isopropanol, acetone, methyl isobutyl ketone, methyl ethyl ketone, acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and mixture thereof.

Claim 17: The process of claim 1, wherein the suitable acid of step d) is hydrochloric acid and the suitable organic solvent of step d) is methanol or ethanol.

Claim 18: The process of claim 1, wherein the step e) is carried out in presence of a suitable coupling agent and a suitable organic solvent.

Claim 19: The process of claim 18, wherein the suitable coupling agent is selected from the group consisting of 1-Hydroxybenzotriazole, 1-Hydroxy-7-aza-1H-benzotriazole, N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide, dicyclohexyl carbodiimide, 1,1’-Carbonyldimidazole, diisopropylcarbodiimide, benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorphosphate, benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorphosphate, bromo- tripyrrolidino- phosphonium hexafluorphosphate, 2-(1H-Benzotriazol-1-yl) - N,N,N’,N’-tetramethylaminium tetrafluoroborate/hexa fluoro phosphate, 2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N’,N’-tetramethylaminium hexafluorphosphate, Propylphosphonic anhydride and mixture thereof.

Claim 20: The process of claim 18, wherein the suitable organic solvent is selected from the group consisting of methyl acetate, ethyl acetate, isopropyl acetate, acetonitrile, propionitrile, benzonitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, toluene, xylene and mixtures thereof.

Claim 21: The process of claim 18, wherein the suitable coupling agent is 1,1’-Carbonyldimidazole and the suitable organic solvent is methylene chloride.

Claim 22: A process for preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof:
Formula I

a) coupling a compound of Formula VI or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIII; wherein ‘PG’ represents a suitable amine protecting group,

Formula VI

Formula VII

Formula VIII

b) reacting the compound of Formula VIII with a suitable acid in a suitable organic solvent to obtain a compound of Formula IX or a salt thereof, and

Formula IX

c) converting the compound of Formula IX in to cobicistat of Formula I.
Claim 23: The process of claim 22, wherein the step a) is carried out in presence of a suitable coupling agent and a suitable organic solvent.

Claim 24: The process of claim 23, wherein the suitable coupling agent is selected from the group consisting of 1-Hydroxybenzotriazole, 1-Hydroxy-7-aza-1H-benzotriazole, N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide, dicyclohexyl carbodiimide, 1,1’-Carbonyldimidazole, diisopropylcarbodiimide, benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorophosphate, benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate, bromo- tripyrrolidino- phosphonium hexafluorophosphate, 2-(1H-Benzotriazol-1-yl) - N,N,N’,N’- tetramethylaminium tetrafluoroborate/hexa fluoro phosphate, 2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N’,N’-tetrathemethylaminium hexafluorophosphate, Propylphosphonic anhydride and mixture thereof.

Claim 25: The process of claim 23, wherein the suitable organic solvent is selected from the group consisting of methyl acetate, ethyl acetate, isopropyl acetate, acetonitrile, propionitrile, benzonitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, toluene, xylene and mixtures thereof.

Claim 26: The process of claim 23, wherein the coupling agent is 1-Hydroxybenzotriazole and N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide and suitable organic solvent is methylene chloride.

Claim 27: The process of claim 22, wherein the suitable acid of step b) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and mixture thereof.

Claim 28: The process of claim 22, wherein the suitable organic solvent of step b) is selected from the group consisting of methanol, ethanol, isopropanol, acetone, methyl isobutyl ketone, methyl ethyl ketone, acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and mixture thereof.

Claim 29: The process of claim 22, wherein the suitable acid of step b) is hydrochloric acid and the suitable organic solvent of step b) is methanol or ethanol.

Claim 30: A process for the preparation of cobicistat of Formula I or a pharmaceutically acceptable salt thereof:
comprising:

a) reacting L-homoserine lactone of Formula II or a salt thereof with pivaloyl chloride to obtain a compound of Formula III,

b) reacting the compound of Formula IIIa with trimethylsilyl halide in presence of an alcohol to obtain a compound of Formula IVa; wherein ‘X’ represents halo group, ‘R’ represents C_{1-8} alkyl,

c) reacting the compound of Formula IVa with morpholine to obtain a compound of Formula Va; wherein ‘X’ and ‘R’ are defined as above,

d) reacting the compound of Formula Va with a suitable base in a suitable organic solvent to obtain a compound of Formula VIa or a salt thereof,
e) coupling the compound of Formula VIa or a salt thereof with a compound of Formula VII or a salt thereof to obtain a compound of Formula VIIIa,

f) reacting the compound of Formula VIIIa with a suitable acid in a suitable organic solvent to obtain a compound of Formula IX or a salt thereof, and

g) reacting the compound of Formula IX with a compound of Formula X or a salt thereof to obtain cobicistat of Formula I.

Claim 31: The process of claim 30, wherein the halo group is selected from the group consisting of chloro, bromo, iodo and fluoro.

Claim 32: The process of claim 30, wherein the C_{1-8} alkyl is selected from the group consisting of methyl, ethyl, propyl and butyl.

Claim 33: The process of claim 30, wherein the ‘X’ is bromo or iodo; and ‘R’ is ethyl.
Claim 34: The process of claim 30, wherein the trimethylsilyl halide is selected from the group consisting of trimethylsilyl iodide or trimethylsilyl bromide.

Claim 35: The process of claim 30, wherein the alcohol of step b) is selected from the group consisting of methanol, ethanol, propanol and butanol.

Claim 36: The process of claim 30, wherein the step c) is carried out in a suitable solvent, wherein the solvent is selected from the group consisting of dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone, acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, toluene, xylene and mixtures thereof.

Claim 37: The process of claim 36, wherein the suitable solvent is methylene chloride.

Claim 38: The process of claim 30, wherein the suitable base of step d) is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and mixtures thereof.

Claim 39: The process of claim 30, wherein the suitable organic solvent of step d) is selected from the group consisting of acetone, methyl isobutyl ketone, methyl ethyl ketone, acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride and mixtures thereof.

Claim 40: The process of claim 30, wherein the suitable organic solvent of step d) is methylene chloride and suitable base of step d) is potassium hydroxide.

Claim 41: The process of claim 30, wherein the step e) is carried out in presence of a suitable coupling agent and a suitable organic solvent.

Claim 42: The process of claim 41, wherein the suitable coupling agent is selected from the group consisting of 1-Hydroxybenzotriazole, 1-Hydroxy-7-aza-1H-benzotriazole, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, dicyclohexyl carbodiimide, 1,1'-Carbonyldimidazole, diisopropylcarbodiimide, benzotriazol-1-ylxy-tris (dimethylamino)-phosphonium hexafluorophosphate, benzotriazol-1-ylxy-tripyrrolidino-phosphonium hexafluorophosphate, bromo-tripyrrolidino-phosphonium hexafluorophosphate, 2-(1H-Benzotriazol-1-yl)-N,N,N',N'- tetramethylaminium tetrafluoroborate/hexa fluoro phosphate, 2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate, Propylphosphonic anhydride and mixture thereof.
Claim 43:  The process of claim 41, wherein the suitable organic solvent is selected from the group consisting of methyl acetate, ethyl acetate, isopropyl acetate, acetonitrile, propionitrile, benzonitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, toluene, xylene and mixtures thereof.

Claim 44:  The process of claim 41, wherein the coupling agent is 1-Hydroxybenzotriazole and N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide and suitable organic solvent is methylene chloride.

Claim 45:  The process of claim 30, wherein the suitable acid of step f) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and mixture thereof.

Claim 46:  The process of claim 30, wherein the suitable organic solvent of step f) is selected from the group consisting of methanol, ethanol, isopropanol, acetone, methyl isobutyl ketone, methyl ethyl ketone, acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and mixture thereof.

Claim 47:  The process of claim 30, wherein the suitable acid of step f) is hydrochloric acid and the suitable organic solvent of step f) is methanol or ethanol.

Claim 48:  The process of claim 30, wherein the step g) is carried out in presence of a suitable coupling agent and a suitable organic solvent.

Claim 49:  The process of claim 48, wherein the suitable coupling agent is selected from the group consisting of 1-Hydroxybenzotriazole, 1-Hydroxy-7-aza-1H-benzotriazole, N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide, dicyclohexyl carbodiimide, 1,1’-Carbonyldimidazole, diisopropylcarbodiimide, benzotriazol-1-yloxy-tris (dimethylamino)-phosphonium hexafluorophosphate, benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate, bromo- tripyrrolidino- phosphonium hexafluorophosphate, 2-(1H-Benzotriazol-1-yl) - N,N,N’,N’- tetramethylammonium tetrafluoroborate/hexa fluoro phosphate, 2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N’,N’-tetramethylammonium hexafluorophosphate, Propylphosphonic anhydride and mixture thereof.

Claim 50:  The process of claim 48, wherein the suitable organic solvent is selected from the group consisting of methyl acetate, ethyl acetate, isopropyl acetate, acetonitrile, propionitrile, benzonitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, toluene, xylene and mixtures thereof.
Claim 51: The process of claim 48, wherein the suitable coupling agent is 1,1'-Carbonyldimidazole and the suitable organic solvent is methylene chloride.

Claim 52: A compound of Formula IV or a pharmaceutically acceptable salt thereof,

\[ \text{Formula IV} \]

wherein ‘PG’ represents a suitable amine protecting group selected from the group consisting carbonates such as carboxy benzoyl (Cbz), fluorenylmethyloxycarbonyl (Fmoc), allyloxycarbonyl (alloc), methyl and ethyl carbamates; cyclic imide derivatives such as phthalimide; amides such as formyl; acetyl, pivaloyl; trityl, substituted or unsubstituted aryls such as benzyl benzoyl, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB) and trialkyl silyl groups such as trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS); ‘X’ represents halo group such as chloro, bromo, iodo or fluoro and ‘R’ represents C\textsubscript{1-8} alkyl selected from the group consisting of methyl, ethyl, propyl and butyl.

Claim 53: The compound of claim 52, wherein ‘PG’ is pivaloyl group, ‘X’ bromo or iodo and ‘R’ is ethyl.

Claim 54: A compound of Formula Va or a pharmaceutically acceptable salt thereof,

\[ \text{Formula Va} \]

wherein ‘R’ represents C\textsubscript{1-8} alkyl.

Claim 55: The compound of claim 54, wherein ‘R’ represents ethyl.

Claim 56: A compound of Formula VIa or a pharmaceutically acceptable salt thereof.
Claim 57: A compound of Formula VIII or a pharmaceutically acceptable salt thereof,

wherein ‘PG’ represents a suitable amine protecting group selected from the group consisting carbonates such as carboxy benzoyl (Cbz), fluorenlymethyloxycarbonyl (Fmoc), allyloxycarbonyl (alloc), methyl and ethyl carbamates; cyclic imide derivatives such as phthalimide; amides such as formyl; acetyl, pivaloyl; trityl, substituted or unsubstituted aryls such as benzyl benzoyl, p-nitrobenzoyl (PNB), p-phenyl benzyl (PPB) and trialkyl silyl groups such as trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyltrimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS).

Claim 58: The compound of claim 57, wherein the ‘PG’ represents pivaloyl.

Claim 59: A pharmaceutical composition comprising cobicistat or a pharmaceutically acceptable salt thereof according to claim 1-58 and at least one pharmaceutically acceptable excipient.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/427,C07C307/06,C07C203/24 Version=2016.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K,C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>A</td>
<td>WO2014057498 A2 (MYLAN LAB LTD[IN]) 17 APRIL 2014 (17/04/2014). The whole document</td>
<td>1-29,52-53,57-58</td>
</tr>
</tbody>
</table>

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

* Special categories of cited documents:
“X” document defining the general state of the art which is not considered to be of particular relevance
“L” earlier application or patent but published on or after the international filing date
“O” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
“P” document referred to in oral proceedings. Use, exhibition or other means

“T” document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“V” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search 27-06-2016

Date of mailing of the international search report 27-06-2016

Name and mailing address of the ISA/Indian Patent Office Plot No.32, Sector 14, Dwarka, New Delhi-110075 Facsimile No. Authorized officer K Janardana Telephone No. +91-112530200

Form PCT/ISA/210 (second sheet) (January 2015)
**INTERNATIONAL SEARCH REPORT**

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

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

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

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:

**Lack of unity of invention:**

Invention 1: Claims (1-29, 52-53 and 57-58)

An invention relating to a process for the preparation of Formula I via intermediate (VIII), intermediate compounds of Formula (IV) and (VIII).

Invention 2: Claims (30-51 and 54-56)

An invention relating to a process for the preparation of Formula I

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-29, 52-53 and 57-58

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
Continuation of Observations where unity of invention is lacking (Box III) via intermediate (VIIIa), intermediate compounds of Formula (Va) and (VIa).

The process steps for the preparation of cobisistat in the above said methods are entirely different and not falling under single inventive concept.
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<td>WO 2010115000 A2</td>
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