The present invention relates to a process for the preparation of Darunavir or a solvate thereof of Formula (I) using a novel intermediate (3R,3aS,6aR)-hexahydro-1-phenylbutan-2-ylcarbamate compound of formula (II): The present invention also relates to the process for the preparation of novel intermediates (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3R)-4-(4-(1,3-dioxoisindolin-2-yl)-N-isobutylphenylsulphonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate compound of formula (II), Darunavir or its solvate of formula (I) are useful therapeutic agent and used in treatment of antiviral diseases.
A NOVEL PROCESS FOR THE PREPARATION OF HIV PROTEASE INHIBITOR AND INTERMEDIATES THEREOF

FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of HIV protease inhibitor compound and intermediates thereof.

More, particularly the present invention relates to a novel process for the preparation of Darunavir or a solvate thereof.

The present invention also to the process for the preparation of novel intermediates (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3R)-4-(4-(1,3-dioxoisoindolin-2-yl)-N-isobutylphenylsulfonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate Compound of formula (II) of Darunavir or a solvate thereof.

BACKGROUND OF THE INVENTION

Darunavir is a new generation of non-peptide protease inhibitor that exhibits potent antiviral activity with low toxicity in vitro and in vivo. The agent retains activity against resistant strains and has lower probability for the development of resistance. Darunavir was approved by the FDA under the name PREZISTA™, and is administered in combination with a low-dose of ritonavir and other active anti-HIV agents.

It is chemically described as [(lS,2R)-3-[[4-Aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester (here after referred by its generic name Darunavir or a solvate thereof) and is represented by structural Formula I.

As indicated by the structure above, Darunavir or a solvate thereof (Approved solvate is ethanolate solvate) exhibits stereoisomerism due to the presence of a chiral...
center. Hence, during the manufacturing process of Darunavir or a solvate thereof and related compounds, there is a possibility that mixture of isomers may be obtained.

Vazquez et. al. in U.S. patent 5,843,946 discloses generically Darunavir and specifically disclosed in US patent 6,248,775.

Vermeersch et. al. in US patent 7,700,645 disclosed darunavir solvate as specifically ethanolate solvate compound.

Vazquez et. al. in patent US 6,248,775 B2 does not provide any enabling disclosure for preparation of Darunavir or solvate thereof, however a related process disclosed for compound IIa is illustrated by below Scheme I

\[
\text{CBz} \quad \underset{\text{TFA}}{\overset{\text{Cl}}{\longrightarrow}} \quad \text{CBz} \quad \overset{\text{Pd/C}}{\longrightarrow} \quad \text{IIa}
\]

**Scheme I**

The process involves simultaneous reduction of nitro moiety and CBz dcprotcction in the intermediate nitro compound results in various unwanted side reactions leading to poor product selectivity.

A few references directed towards synthesis of Darunavir which are different from the process of according to the present invention are located and summarized herein below.

A.K.Ghosh et al., Bioorganic Medicinal Chemistry Letters 1998, 8(6): 687 which discloses the process for the preparation of Darunavir as schematically illustrated below Scheme II:
Scheme II

The process disclosed is not suitable for large scale production because it involves hazardous azide compounds.

Nicolaas Martha Felix Goyvaerts et. al. in U.S. Patent 7,772,411B2 (also referred as "411") discloses a process for the preparation of Darunavir using boc-epoxide which is illustrated by below Scheme III:

Scheme III
The process disclosed suffer difficulty to operate on commercial scale as it involves multistage synthesis, hence the overall yield is limited to about 50% or less.

PCT Publication No. WO 201/05 1978 (also referred as "978") discloses an alternative process of darunavir by introducing furanyl compound before the nitro group reduction. This publication mention that the synthesis of darunavir by coupling of Formula II with hexahydrofuro [2,3-b] furan-3-yl derivative very likely leads to formation of impurities, viz., Impurity A and Impurity B.

![Impurity A and Impurity B](image_url)

Darunavir synthetic procedures as described in the art contained relatively large amounts of impurities, for example, when replicating the processes of the '411, '978 patent resulted in the elevation of impurities such as bisfuranyl impurities. Extensive purification procedures are required in order to limit the impurities to meet the requirements as per regulatory guidelines and this may results low product yield thereby making the process quite expensive. Hence there remains a need for an improved process to prepare darunavir, particularly amorphous form of darunavir, which is cost effective, industrially viable, and provide darunavir substantially free of impurities.

**SUMMARY OF THE INVENTION**

Aspects of the present invention relates to the commercially viable process for the preparation of Darunavir and its intermediates.

Particular aspects of the present invention, it relates to process for the preparation of Darunavir or a solvate thereof of Formula I comprising the steps of:

a. reacting the compound of Formula VI or a salt thereof with a compound of Formula VII in an organic solvent to afford the compound of Formula V and treating the compound of Formula V or a salt thereof with acid to get the compound of Formula IV or a salt thereof;
b. reacting the compound of Formula IV or a salt thereof with a compound of Formula IIIA optionally in presence of base in an organic solvent to give the compound of Formula II:

c. treating the compound of Formula II with base in an organic solvent to get the Darunavir compound of Formula I or a solvate thereof.

In another particular aspect, the present invention relates a novel intermediate compound of formula (II):
useful in the preparation of Darunavir of formula (I).

In yet still particular aspect of the present invention relates to a process for the preparation of compound of formula II, wherein the process comprising the steps of:

a. reacting the compound of Formula VI or a salt thereof with a compound of Formula VII in an organic solvent afford the compound of Formula V and treating the compound of Formula V or a salt thereof with acid selected from hydrochloric acid, gaseous hydrochloric acid to get the compound of Formula IV or a salt thereof;

b. reacting the compound of Formula IV or a salt thereof with a compound of Formula IIIA optionally in presence of base in an organic solvent to give the compound of Formula II;
**DETAILED DESCRIPTION OF THE INVENTION**

As set forth herein, embodiments of the present invention provide a process for the preparation of Darunavir or a solvate thereof of Formula I comprising the steps of:

a. reacting the compound of Formula VI or a salt thereof with a compound of Formula VII in an organic solvent to afford the compound of Formula V and treating the compound of Formula V or a salt thereof with acid to get the compound of Formula IV or a salt thereof;

b. reacting the compound of Formula IV or a salt thereof with a compound of Formula IIIA optionally in presence of base in an organic solvent to give the compound of Formula II:
c. treating the compound of Formula I with base in an organic solvent to get the
compound of Formula I or a solvate thereof.

In reaction step a, the compounds having Formula (V) is generally synthesized
under alkaline conditions. Suitable alkaline conditions include inorganic or organic
bases and/or acid scavengers. Conventional inorganic or organic bases include
hydroxides, carbonates, or hydrogen carbonates of alkaline earth Metals; metal amides,
such as sodium amide, potassium amide, lithium diisopropylamide or potassium
hexamethyldisilazide, and sodium hydroxide, potassium hydroxide, ammonium
hydroxide, sodium acetate, potassium acetate, calcium acetate, ammonium acetate,
sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate,
cesium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, or
ammonium carbonate, and also basic organic nitrogen compounds such as,
trialkylamines, like triethylamine, tributylamine, N.N-diisopropylethylamine, pyridine,
1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN), or
1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), Dimethylaminopyridine, DMF or any
other catalyst or an excess of an appropriate piperidine compound may be used.
Preferably triethylamine is used.

In a preferred embodiment, the step a is carried out in the presence of a solvent
which is selected from solvent used in the present invention is selected from water or
"alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and
tert-butanol and the like or "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or "esters solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or "ether solvents" such as di-tert-butylether, dimethylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 2-methoxyethanol and dimethoxyethane, or "Amide solvents" such as formamide, DMF, DMAC, N-methyl-2-pyrrolidone, N-methylformamide, 2-pyrrolidone, 1-ethenyl-2-pyrrolidone, haloalkanes such as dichloromethane, 1,2-dichloroethane and chloroform and/or mixtures thereof.

In another embodiment of the present invention, reaction usually performed at from 0°C to a boiling point of an organic solvent used for the reaction for about 30 minutes to 15 hours.

In another embodiment of the present invention, wherein process of step a involves the isolation of the compound of formula V optionally as a solid material.

In another embodiment of the present invention, process for the preparation of Darunavir or a solvate thereof of Formula I, wherein the process step n involves reaction of substantially pure compound of Formula VI with a compound of Formula VII to in an organic solvent to give the compound of Formula V.

In another embodiment of the present invention, substantially pure compound of Formula VI obtained by treating the compound of Formula VI in a solvent selected from water, isopropyl alcohol, toluene, diisopropyl ether, ethanol, methanol for 1-4 hours. Filtered the compound and washed with solvent and dried to get substantially pure compound of Formula VII.

A substantially pure compound formula VI may have purity exceeding 99.0% (by HPLC).

In another embodiment of the present invention, substantially pure compound of Formula VI is having dibenzyl impurity of formula (VIII) less than 1.00%.
In another particular embodiment of the present invention, substantially pure compound of Formula VI is having dibenzyl impurity of formula (VIII) less than 0.5% (by HPLC).

The mole ratios of reactants and the reagents used therein can be appropriate based on the resultant product and the side products or by products.

In the reaction step of removal of the amino-protecting-group can be achieved using conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like, thus using commonly known acids in suitable solvents.

Examples of acids employed in the removal of the amino-protecting group include inorganic acids such as hydrochloric acid, alcoholic HCl such as Isopropyl alcohol, HCl, methanolic HCl, HCl gas, sulfuric acid and phosphoric acid, organic acids such as acetic acid, trifluoroacetic acid methanesulfonic acid and p-toluenesulfonic acid.

The reaction temperature employed depends upon various factors such as the nature of the starting materials, solvents and acids. However it is usually between 30°C and 150°C, or reflux temperatures of the solvents used and is preferably between 35°C and 100°C, even more preferably at a temperature of reflux. The reaction time employed depends on the reaction temperature and the like. It is typically from 30 minutes to 24 hours.

In one of the particular embodiment of the present invention, removal of boc-protection can be carried using Hydrochloric acid in Isopropyl alcohol at temperature 75-80°C and the reaction carried for 4 - 5 hours.

In the step b reaction of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl derivate (IIIA) with compound of Formula (IV) will be performed optionally in the presence of basic organic nitrogen compounds such as trialkylamines, like triethylamine,
tributylamine, N,N-diisopropylethylamine, pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) may be used.

The step b condensation of Formula IV or its salt with compound of Formula (IIIA) is carried out optionally in the presence of basic organic nitrogen compounds such as, trialkylamines like triethylamine, tributylamine, N,N-diisopropylethylamine, pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), may be used. Preferably triethylamine is used. The reaction can also be carried out using inorganic bases such as sodium carbonate, Sodium bicarbonate, Potassium carbonate, Potassium bicarbonate like.

Solvent/s in the present invention is selected from water or "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and tert-butanol and the like or "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or "esters solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or "ether solvents" such as di-tert-butylether, dimethylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 2-methoxyethanol and dimethoxyethane, or "Amide solvents" such as formamide, DMF, DMAC, N-methyl-2-pyrrolidone, N-methylformamide, 2-pyrrolidone, 1-ethenyl-2-pyrrolidone, haloalkanes such as dichloromethane, 1,2-dichloroethane and chloroform, "Amine solvents" selected from diethylenetriamine, ethylenediamine, morpholine, piperidine, pyridine, quinolinc, tributylamine, diisopropyl amine and/or mixtures thereof.

In one of the particular embodiment of the present invention, step b of coupling of (3R,3aS,6aR)-Hydroxyhexahydrofurano[2,3 -β]furan Succinimidyl Carbonate (IIIA) with compound of Formula (IV), will be performed in the presence of triethylamine in ethyl acetate and water at temperature 25 - 35°C for 1-2 hours.
The suitable agent that can be used for the conversion of compound of Formula II to the compound of Formula I in step c include but are not limited to alkylamines as methyl amine, n-butylamine, isobutylamine, isopropylamine, alkali metal hydroxide as sodium hydroxide, potassium hydroxide and the like; alkali metal carbonate such as sodium carbonate, potassium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, Hydrazine hydrate, phenyl hydrazine and sodium sulphide.

The solvents that can be used in the said conversion include but are not limited to water; alcohols such as methanol, ethanol, propanol, isopropyl alcohol and the like; esters such as ethyl acetate, isopropyl acetate, butyl acetate and the like; water miscible organic solvent such as acetone, tetrahydrofuran, 1,4-dioxan, dimethylsulfoxide and the like; and a mixture of solvents thereof.

In one of the particular embodiment of the present invention, reaction step c is performed in aqueous methylamine at temperature 0 - 15°C for 12 hours.

The obtained compound of Formula I (Darunavir or a solvate thereof) is optionally purified by crystallization or slurry using a suitable organic solvent or mixture of solvents, e.g. acetone, ethyl acetate, dichloromethane, acetonitrile, 2-propanol or methanol. Optionally, the obtained Darunavir or a solvate thereof is converted to the corresponding salt by treatment with pharmaceutically acceptable acids.

In a preferred embodiment, compound of Formula Via is prepared by reacting aniline with Phthalic anhydride in solvent and optionally in the presence of a base and a reagent to give 2-phenylisoindoline-1,3-dione which is further reacted with chlorosulphonic acid in solvent and optionally in the presence of a reagent and base to give compound of Formula VII.

In another preferred embodiment, compound of Formula Via is prepared by reacting aniline (Vila) with Phthalic anhydride (Vllb) in the absence of a solvent to give 2-phenylisoindoline-1,3-dione (Vile) which is further reacted with chlorosulphonic acid optionally in solvent and optionally in the presence of a reagent and base to give compound of Formula VII.

In one of the particular embodiment of the present invention, compound of Formula VI is prepared by reacting tert-butyl (S)-l-((S)-oxiran-2-yl)-2-phenylethylcarbamate with isobutylamine in a solvent, optionally in the presence of a
base, wherein the solvent used is selected from alcoholic solvents, esters, dichloromethane, chloroform, DMF, DMSO, tetrahydrofuran, methyl THF, aromatic solvents, water or mixture.

In another particular embodiment of the present invention, compound of Formula VI is prepared by reacting tert-butyl (S)-1-((S)-oxiran-2-yl)-2-phenylethylcarbamate with isobutylamine in the absence of a solvent.

For example, the working-up of reaction mixtures, especially in order to isolate desired compounds, follows customary procedures, known to the organic chemists skilled in the norms of the art and steps, e.g. selected from the group comprising but not limited to extraction, neutralization, crystallization, chromatography, evaporation, drying, filtration, centrifugation and the like.

Advantageously, the process of present invention prevents the carrying of dibenyl impurity of formula (VIII) to other steps of the process by using substantially pure compound of formula (VI).

Advantageously, the process of present invention does not involve additional purification steps intermittently thus provides the final product Darunavir or a solvate thereof (I) with higher yields and purities.

As used herein, the term "HPLC" refers to High-performance liquid chromatography. As used herein, the term "% area by HPLC" refers to the area in an HPLC chromatogram of one or more peaks compared to the total area of all peaks in the HPLC chromatogram expressed in percent of the total area.

In this specification the term "racemic mixture" may include mixtures of enantiomers in ratios other than, as well as, a 50:50 mixture of R:S enantiomers (for example from 99:1 to 1:99). A particular process of the invention begins with a 50:50 mixture of enantiomers. The process may involve differing mixtures of enantiomers at various stages (including, but not limited to 50:50 mixtures). The term "racemization" covers the conversion of an unresolved enantiomer into a mixture containing the enantiomer to be resolved.

The solution obtained is optionally filtered through celite or diatamious earth to separate the extraneous matter present or formed in the solution by using conventional filtration technique known in the art.
The precipitation of solid is achieved but not limited to evaporation, cooling, drying, by adding antisolvent and the like.

The suitable antisolvent is selected from the group consisting of ethers such as diethyl ether, disopropyl ether, 1,4-dioxane and the like; hydrocarbons such as methyl cyclohexane, cyclohexane, n-hexane, n-heptane and the like; optionally water.

In another embodiment, the present invention may provide Darunavir or a solvate thereof of Formula I having purity greater than 99% as measured by chiral HPLC.

In yet another embodiment, the present invention may provide Darunavir or a solvate thereof of Formula I having purity greater than 99.4% as measured by chiral HPLC.

The term "stereoisomeric forms" as used herein defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. Except where specified, all stereoisomeric forms of the compounds employed in the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds mentioned herein, i.e. where a particular stereoisomeric form is specified, are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i.e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%.
Pure stereoisomeric forms of the compounds mentioned herein may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereoselective methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

After completion of the reaction, the desired compounds can be obtained from the reaction mixture by conventional means known in the art. For example, the working-up of reaction mixtures, especially in order to isolate desired compounds, follows customary procedures, known to the organic chemists skilled in the norms of the art and steps, e.g. selected from the group comprising but not limited to extraction, neutralization, crystallization, chromatography, evaporation, drying, filtration, centrifugation and the like.

Crystallization may include in a single solvent or mixture of solvents to facilitate the precipitation of the compound of Formula-I. The resulting crystals are then recovered by conventional techniques, such as filtration. They may be washed with water or an organic solvent. The crystals are then preferably dried. The temperature may be increased or the pressure reduced to accelerate the drying process. Drying may be carried out at a suitable temperature.

The purity of the Darunavir samples was measured using Chromatography. Chromatography was performed with Waters Alliance HPLC system (MILD, USA) that consists of quaternary pump equipped with a 2695 separation module with inbuilt auto injector and 2996 photodiode array detector. The output signal was monitored and processed using chromelean software version 6.8.

The mass spectrum of sample was measured using Waters SQD-2, Shimadzu-LCMS, Agilent -6120 Quadrupole/LC-MS.

NMR of the sample can be predicted using the instrument JEOL 500 MHz NMR Spectrometer with Royal Probe and auto sampler, JEOL 400 MHz NMR Spectrometer.
with TH5ATFG probe lacility, BRUKER Ascend 400 MHz AVANCE III HD and IR spectroscopy was performed by using Perkin Elmer.

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

EXAMPLES:

EXAMPLE 1: Synthesis of 2-phenylisoindoline-1,3-dione compound of formula (Via):

\[
\begin{align*}
\text{NH}_2 & \quad \text{(Vila)} \\
\text{O} & \quad \text{(Vilb)} \\
\text{O} & \quad \text{(Vile)}
\end{align*}
\]

A solution of aniline (Vila) (50g, 0.537 mol) in acetic acid (500 mL) was added with phthalic anhydride (Vilb)(79.62g, 0.537 mol) at room temperature. The reaction mixture was heated to 110-115°C and stirred at the same temperature for 4-5hrs. After completion of the reaction (monitored by TLC), the reaction mass was cooled to room temperature. The precipitated solid was filtered and washed with water (150.0 ml) to give compound 2-phenylisoindoline-1 J-dione (Vile) as an off white solid.

Yield: 91.39 %,
Purity: 99.97 % (by HPLC)

EXAMPLE 2: Synthesis of 4-(1,3-dioxoisindoline-2-yI)benzene-1-sulfonyI chloride Compound of Formula (VII):

\[
\begin{align*}
\text{O} & \quad \text{(Vile)} \\
\text{PCl}_5 & \quad \text{(Vilb)} \\
\text{Cl} & \quad \text{(VII)}
\end{align*}
\]
Phosphorus pentachloride (9.3 g, 0.0448 mol) was added to the chlorosulfonic acid (9.0 ml) at room temperature. Compound 2-phenylisoindoline-1,3-dione (Via) (10 g) was added to above mixture slowly at room temperature. The reaction mixture was heated to 50-55°C and stirred for 30-45 min. The reaction mass was quenched into water (100 mL) and chloroform (100 mL) at 5-10°C. Separated organic layer and extracted aqueous layer with Chloroform. The combined organic layer was washed with 10% brine (100 mL), dried over Na2SO4 and concentrated under vacuum to give compound 4-(1,3-dioxoisindolin-2-yl)benzene-l-sulfonyl chloride (VII) as a solid.

Yield: 86.98
Purity: 91.99 (by HPLC)

**EXAMPLE 3: Synthesis of tert-Butyl (2S,3R)-3-hydroxy-4-(isobutylamino)-l-phenylbutan-2-ylcarbamate of Compound formula (VI):**

Isobutylamine (111.03 g, 1.519 mol) was charged to (2S,3S)-1,2-Epoxy-3-(Boc-Amino)-4-Phenylbutane (20.0 g, 0.0759 mol) at room temperature. Reaction mass heated to 65-70°C and stirred for 3-4 hours for the completion of reaction. Distilled the reaction mass completely under vacuum. Charged methanol (20.0 ml) and charge water (200.0 ml) at 50-55°C. Cool the reaction mass to 25-35°C and stir for 2-3 hours. Filtered the solid under vacuum and washed with water (40.0 ml). Dried the wet compound at 50-55°C and obtained the compound tert-Butyl (2S,3R)-3-hydroxy-4-(isobutylamino)-l-phenylbutan-2-ylcarbamate.

Yield: 97.87%
Purity: 98.55% (by HPLC)

**Purification:** tert-Butyl(2S,3R)-3-hydroxy-4-(isobutylamino)-l-phenylbutan-2-yl carbamate compound (VI) (5.0 g) was stirred in Diisopropylether (50 ml) at 65-70°C for
30-60 minutes. Cooled the reaction mass to room temperature and stirred for 30-45 minutes. Filtered the solid under vacuum and washed with Diisopropyl ether (10.0 ml) and dried at 50-55°C.

Yield: 78.0 %

Purity: 99.32 %, Dibenzyl impurity (VIII): 0.51 % (by HPLC)

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EXAMPLE 4: Synthesis of N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-4-(1,3-dioxiisoindolin-2-yl)-N-isobutylbenzenesulfonamide of Compound of formula (IV):

Compound tert-Butyl (2S,3R)-3-hydroxy-4-(isobutylamino)-1-phenylbutan-2-ylcarbamate (VII) - (30.0 g, 0.0892 mol) was added to the dichloromethane (300.0 ml) & Triethylamine (9.95 eq) solution at 25-30°C. Slowly added 4-(1,3-dioxiisoindolin-2-yl)benzene-1-sulfonyl chloride (VI) (1.2 eq, 34.5 g) lot wise at 25-30°C. Reaction mass was maintained for 60-90 minutes at room temperature for the completion of reaction. Reaction mass was washed with water (2×90.0 ml) and distilled organic layer completely under vacuum at below 50°C. Charged Isopropyl alcohol (600.0 ml) and concentrated HCl(15.0 ml) at room temperature. Heated the reaction mass to 75-80°C and stirred for 4-5 hours for the completion of reaction. Cooled the reaction mass to room temperature and stirred for 30-60 minutes. Reaction mass was filtered and washed with Isopropyl alcohol (60.0 ml). The above crude material was slurried in Isopropyl alcohol (100.0 ml) for 60-90 minutes at room temperature. Reaction mass was filtered and washed with Isopropyl alcohol (30.0 ml) and dried at 50-55°C.

Yield: 88.38 %,
Purity: 96.19% (by HPLC)

H NMR (DMSO-d6, 500 MHz): δ 8.02-7.93 (m, 9H), 7.74-7.72 (d, J = 8.8 Hz, 211), 7.39-7.36 (m, 4H), 7.30-7.27 (m, 1H), 5.68-5.67 (d, J = 5.7 Hz, 1H), 4.04-4.03 (m, 1H), 3.51-3.43 (m, 1H), 3.41-3.40 (m, 1H), 3.07-3.02 (m, 2H), 3.02-2.95 (m, 1H), 2.84-2.79 (m, 2H), 1.95-1.90 (m, 1H), 0.86-0.85 (d, J = 6.5 Hz, 3H), 0.79-0.78 (d, J = 6.7 Hz, 3H);

13C NMR (CDCl3, 125 MHz): δ 166.5, 137.6, 136.8, 135.6, 134.9, 131.4, 129.4, 128.5, 127.8, 127.5, 126.8, 123.6, 68.7, 57.0, 55.4, 51.1, 32.7, 26.3, 19.9;

Mass (m/z): 522 [M+H];

Melting range: 255-258°C.

EXAMPLE 5: Synthesis of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3R)-4-(4-(1,3-dioxoisindolin-2-yl)-N-isobutylphenylsulfonamido)-3-hydroxy-l-phenylbutan-2-yI carbamate Compound of formula (II):

Compound N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-4-(1,3-dioxoisindolin-2-yl)-N-isobutylbenzenesulfonamide (IV) (15g, 0.0287 mol), was charged to solution of water (45 mL), ethylacetate (300 mL) and triethylamine (10 mL) at room temperature. (3R,3aS,6aR)-Hydroxyhexahydrofuro[2,3-P]furanyl Succinimidyl Carbonate (III) (7.7 g, 0.028 mol) was added to the above mixture at 25-35°C. The reaction mass was stirred at 25-35°C for 1-2 h. After completion of reaction, filtered the reaction mixture and the obtained solid washed with ethyl acetate (50 mL). The above material was slurried in water at room temperature for 30-60 minutes. Reaction mass was filtered and washed with water (45 ml). The solid was dried at 50-55°C.

Yield: 73.19 %

Purity: 97.91 % (by HPLC)

H NMR (DMSO-d6, 500 MHz): δ 8.01-7.96 (m, 2H), 7.94-7.91 (m, 4H), 7.73-7.70 (m, 2H), 7.34-7.32 (d, J = 9.3 Hz, 1H), 7.25-7.19 (m, 4H), 7.15-7.12 (m, 1H), 5.50-5.49 (d, J = 5.2 Hz, 1H), 5.14-5.12 (d, J = 6.7 Hz, 1H), 4.89-4.85 (m, 1H), 3.85-3.84 (dd, J = 9.6, 5.9 Hz, 1H), 3.72 (td, J = 8.2, 1.7 Hz, 1H), 3.61-3.58 (m, 4H), 3.44-3.41 (dd, J = 14.8, 2.6 Hz, 1H), 3.11-3.09 (dd, J = 13.4, 8.8 Hz, 1H), 3.06-3.03 (dd, J = 13.6, 2.9 Hz, 1H), 2.91-2.83 (m, 4H), 2.04-1.98 (m, 1H), 1.41-1.36 (m, 1H), 1.24-1.11 (dd, J = 13.1, 5.5 Hz, 2H), 0.90-0.85 (d, J = 6.5 Hz, 3H), 0.83-0.81 (d, J = 6.7 Hz, 3H);
**EXAMPLE 6: Synthesis of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl(2S,3R)-4-(4-amino-N-isobutylphenylsulphonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate Compound of formula (I)**

Added (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (2S,3R)-4-(4-(1,3-dioxoisooxindolin-2-yl)-N-isobutylphenylsulphonamido)-3-hydroxy-1-phenylbutan-2-ylcarbamate (II) (5.0 g, 0.00738 mol) to the 40% Aqueous methylamine solution (50.0 ml) at 10-15°C. Reaction mass was stirred at 10-15°C for completion of reaction (-12 hours). Reaction mass was filtered and washed with water (25 ml), above compound was dissolved in dichloromethane (100 ml) and washed with 5% citric acid solution (3*50 ml). Organic layer was washed with water (25ml) and 20% sodium hydroxide solution (4*50 ml). Organic layer was washed with water (2*25ml) and with 5% sodium chloride solution (2*50 ml). Neat organic layer was distilled under vacuum at below 50°C to give the Darunavir (I) as solid.

Yield: 84.36 %;
Purity: 99.53 % (by HPLC).

While the foregoing pages provide a detailed description of the preferred embodiments of the invention, it is to be understood that the summary, description and examples are illustrative only of the core of the invention and non-limiting in this scope. Furthermore, as many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein shall be interpreted as illustrative of the invention and not in a limiting sense.
We Claim:
1. A process for the preparation of Darunavir or a solvate thereof of Formula I comprising the steps of:
   a. reacting the compound of Formula VII or a salt thereof with a compound of Formula VI in an organic solvent to afford the compound of Formula V and treating the compound of Formula V or a salt thereof with acid to get the compound of Formula IV or a salt thereof;
   
   ![Chemical Structure](image1)

   b. reacting the compound of Formula IV or a salt thereof with a compound of Formula IIIA optionally in presence of base in an organic solvent to give the compound of Formula II:
   
   ![Chemical Structure](image2)

   c. treating the compound of Formula II with base in an organic solvent to get the Darunavir compound of Formula I or a solvate thereof.
2. The process for the preparation of Darunavir or a solvate thereof of Formula I according to claim 1, wherein the process comprising the steps of:

a. reacting the substantially pure compound of Formula VI with a compound of Formula VII in an organic solvent afford the compound of Formula V and treating the compound of Formula V with hydrochloric acid to afford the compound of Formula IV;

b. reacting the compound of Formula IV or a salt thereof with a compound of Formula IIIA optionally in presence of base in an organic solvent to afford the compound of Formula II;
c. treating the compound of Formula I with aqueous methylamine in an organic solvent to afford the Darunavir compound of Formula I or a solvate thereof.

3. The process for the preparation of Darunavir or a solvate thereof of Formula I according to claim 2, wherein substantially pure compound of Formula VI is having dibenzyl impurity of formula (VIII) less than 1.00% and purity of compound of formula (I) more than 99% (Area % by HPLC).

4. The process for the preparation of Darunavir or a solvate thereof of Formula I according to claim 1, wherein the organic solvent used in step a, in step b or in step c are selected from ester solvents as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate, or dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide, or acetone or acetonitrile or alcohol solvents as methanol, ethanol, ethylene glycol, isopropyl alcohol, 2-methoxy ethanol, tert-butanol, 2-butanol, n-butanol halogenated hydrocarbon solvents as dichloromethane, chloroform hydrocarbon...
solvents as toluene, xylene, ortho-xylene, n-heptane, n-hexane, cyclohexane, methylcyclohexane ether solvents as Diisopropyl ether, tetrahydrofuran (THF), methyl tetrahydrofuran or water and mixtures thereof.

5. The process for the preparation of Darunavir or a solvate thereof of Formula I according to claim 1. wherein the acid used in step a is selected from hydrochloric acid, gaseous hydrochloric acid, trifluoroacetic acid, triflic acid, methanesulfonic acid.

6. The process for the preparation of Darunavir or a solvate thereof of Formula I according to claim 1, wherein the base used in step c is selected methyl amine, n-butylamine, isobutylamine, isopropylamine, hydrazine hydrate, phenyl hydrazine, sodium hydroxide, sodium sulphide, triethylamine (TEA).

7. A novel intermediate compound of formula (II):

![Chemical Structure](image)

useful in the preparation of compound of formula (I).

8. A process for the preparation of compound of formula II, wherein the process comprising the steps of:

   a. reacting the compound of Formula VI or a salt thereof with a compound of Formula VII in an organic solvent afford the compound of Formula V and treating the compound of Formula V or a salt thereof with acid selected from hydrochloric acid, gaseous hydrochloric acid to get the compound of Formula IV or a salt thereof;
b. reacting the compound of Formula IV or a salt thereof with a compound of Formula IIIA optionally in presence of base in an organic solvent to give the compound of Formula II;  

9. The process for the preparation of compound of formula II, according to claim 8, wherein step b comprising the steps of:
   i. N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-4-(1,3-dioxoisindolin-2-yl)-N-iso butylbenzenesLilfonamide compound of formula (IV) condensed with (3R,3aS,6aR)-HydroxyhexahydrofuiO[2,3-p]furanyl Succinimidyl Carbonate compound of formula (IIIA) in a organic solvent and reaction is maintained at temperature 20-50°C for 1-2 hours;
   ii. isolating the compound of fonnula II.

10. The process for the preparation of compound of fonnula II, according to claim 9, wherein organic solvents used in step a and step b are selected from ester solvents as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate, or dimethylsulfoxide
(DMSO) or N,N-dimethylformamide (DMF) or N,N-dimethylacetamide, or acetone or acetonitrile or alcohol solvents as methanol, ethanol, ethylene glycol, isopropyl alcohol, 2-methoxy ethanol, tert-butanol, 2-butanol, n-butanol halogenated hydrocarbon solvents as dichloromethane, chloroform hydrocarbon solvents as toluene, xylene, ortho-xylene, n-heptane, n-hexane, cyclohexane, methylcyclohexane ether solvents as Diisopropyl ether, tetrahydrofuran (THF), methyl tetrahydrofuran or water and mixtures thereof to get the compound of Formula I or a solvate thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
C07D493/04 Version=2017.01
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)
C07D493/04

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<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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<tr>
<td>Y</td>
<td>WO2011048604 (MATRIX LABORATORIES LIMITED) 28-04-2011 (28 April 2011); Claim 1 and Scheme C</td>
<td>1-10</td>
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<tr>
<td>Y</td>
<td>SYNTHESES, CHARACTERIZATION AND ANTIBACTERIAL SCREENING OF NEW SCHIFF BASES LINKED TO PHTHALIMIDE; Ahlam Marouf Al-Azzawi et al.; IJRPC 2013, 3(3); Abstract</td>
<td>1-10</td>
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<tr>
<td>Y</td>
<td>Solid-phase synthesis and chemical properties of 2-(2-amino/hydroxyethyl)-1-aryl-3, 4-dihydropyrazino [1, 2-b] indazol-2-iums; Jan Ko i and Viktor Krch ak* J Comb Chem. 2010 Jan-Feb; 12(1): 168-175; Scheme 1 and 2</td>
<td>1-10</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 13-10-2017
Date of mailing of the international search report 13-10-2017

Authorized officer Latika Dawara
Telephone No. +91-1125300200

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