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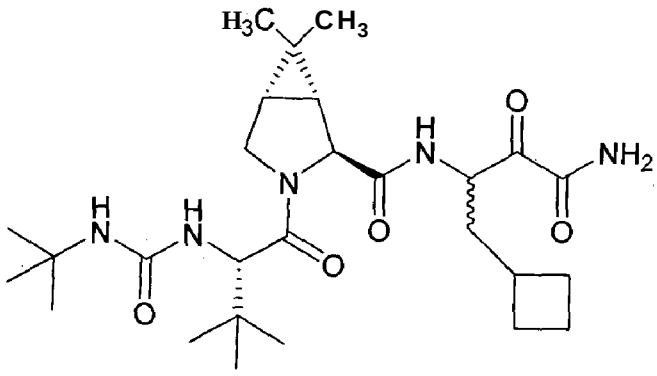
(54) Title: PROCESS FOR PREPARATION OF BOCEPREVIR AND INTERMEDIATES THEREOF



Formula- 1

(57) Abstract: THE PRESENT INVENTION RELATES TO AN IMPROVED PROCESS FOR THE PREPARATION OF (1R,5S)-N-[3-AMINO-l -(CYCLOBUTYLMETHYL)-2,3-DIOXOPROPYL]-3-[2(S)-[[[(l ,1-DIMETHYLETHYL)AMINO]CARBONYL] AMINO] -3,3 -DIMETHYL- 1-OXOBUTYL]-6,6-DIMETHYL-3-AZABICYCLO[3. 1.0]HEXAN-2(S)-CARBOXAMIDE AND ITS INTERMEDIATES

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PROCESS FOR PREPARATION OF BOCEPREVIR AND INTERMEDIATES THEREOF

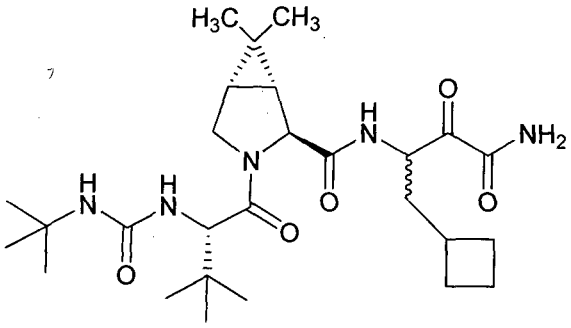
Related Applications:

This application claims the benefit of priority of our Indian patent application numbers 4346/CHE/2012 filed on 18th Oct. 2012, 3308/CHE/2013 filed on 24th July. 2013 and 3691/CHE/2013 filed on 21st Aug. 2013 which are incorporated herein by reference.

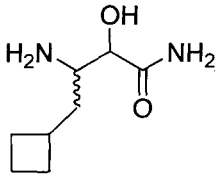
Field of the invention:

The present invention relates to an improved process for the preparation of (lR,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(l ,1-dimethylethyl)amino]carbonyl] amino]-3,3-dimethyl-l-oxobutyl]-6,6-dimethyl-3-azabicyclo[3. 1.0]hexan-2(S)-carboxamide represented by the structural formula-1 and its intermediates.

The present invention also provides a novel process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide represented by the structural formula-2, which is an useful intermediate in the synthesis of compound of formula-1.



Formula-1



Formula-2

Back ground of invention:

(1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethyl ethyl)amino]carbonyl]amino]-3,3-dimethyl-l-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide is commonly known as "Boceprevir". It is a hepatitis C protease inhibitor used

in the treatment of hepatitis C and related disorders. Specifically, the compound of formula-1 is an inhibitor of the HCV NS3/NS4a serine protease. It was developed by Schering-plough, but is now being developed by Merck. It was approved by both FDA and EMEA and marketed under the brand name "Victrelis".

Boceprevir as a compound was first reported in USRE43298. Several processes for preparation of Boceprevir were disclosed in USRE43298, US7326795, US7528263 and US8163937.

Boceprevir is useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis. In view of the importance of Boceprevir, new, novel methods of making such compound is always preferable.

USRE43298 discloses the process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2, which involves the usage of toxic and costly reagents like BOP, and also involves the chromatographic purification of its intermediate compound.

There is a need for developing an improved process for various substances utilized in the synthesis of drug substances which will lead to greater purity, yield and to avoid the toxic reagents.

Brief description of the invention:

The first aspect of the present invention is to provide a novel process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt.

The second aspect of the present invention is to provide an improved process for the preparation of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27.

The third aspect of the present invention relates to a-halo ketone compound of general formula-7 and α,α-dihalo ketone compound of general formula-8, which are useful intermediates in the synthesis of 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid addition salt, which in-turn useful in the synthesis of Boceprevir. Further the third aspect of the present invention also provides a process for the preparation of compound of general formula-7 & compound of general formula-8.

The fourth aspect of the present invention is to provide a process for the preparation of alkyl 2-(benzyloxycarbonylamino)-3-cyclobutylpropanoate compound of general formula-5A.

The fifth aspect of the present invention is to provide a process for the preparation of N-protected β-amino-a-hydroxy acid compound of general formula-10.

The sixth aspect of the present invention is to provide a process for the preparation of N-protected β-amino-a-hydroxy amide compound of general formula-11.

The seventh aspect of the present invention is to provide a process for the preparation of Boceprevir compound of formula-1.

The eighth aspect of the present invention is to provide a process for diastereomeric resolution of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylic acid compound of formula-37 with chiral amine in a suitable solvent, followed by treating with an acid to provide (lR,2S,5S)-3-((S)-2-(3-t-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0] hexane-2-carboxylic acid compound of formula-29.

The ninth aspect of the present invention is to provide novel intermediate compounds of general formula-7 and compound of general formula-8, which are useful in the synthesis of Boceprevir.

The tenth aspect of the present invention is to provide a process for the preparation of 1-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35.

The eleventh aspect of the present invention is to provide a process for the preparation of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-37.

The twelfth aspect of the present invention is to provide a process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxamide compound of formula-30.

The thirteenth aspect of the present invention is to provide an alternative process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30.

The fourteenth aspect of the present invention is to provide an improved process for the preparation of methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride compound of formula-48a.

The fifteenth aspect of the present invention is to provide an improved process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride salt compound of formula-2a.

The sixteenth aspect of the present invention provides a crystalline solid of 2-(tert-butoxy carbonylamino)-3-cyclobutylpropanoic acid compound of formula-49 and its process for preparation.

The seventeenth aspect of the present invention is to provide a process for the preparation of Boceprevir compound of formula- 1.

Brief description of figures:

Figure-1: Illustrates the PXRD pattern of crystalline form-M of 2-(tert-butoxycarbonyl amino)-3-cyclobutylpropanoic acid compound of formula-49.

Figure-2: Illustrates the PXRD pattern of Boceprevir compound of formula- 1.

Detailed description of invention:

The term "suitable solvent" used in the present invention until unless specified is selected from, but not limited to "ester solvents" such as ethyl acetate, methyl acetate, isopropyl acetate, n-butyl acetate and the like; "ether solvents" such as tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, dimethoxy ethane and the like; "hydrocarbon solvents" such as toluene, hexane, heptane, pet.ether, benzene, xylene and cyclohexane and the like; "polar aprotic solvents" such as dimethyl acetamide, dimethyl sulfoxide, dimethyl formamide, N-methyl-2-pyrrolidone and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone and the like;

"alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol and the like; "chloro solvents" such as dichloromethane, chloroform, dichloroethane, carbon tetrachloride and the like; "nitrile solvents" such as acetonitrile, butyronitrile, isobutyronitrile and the like; polar solvents such as water and also mixtures thereof.

The term "suitable base" used herein the present invention until unless specified is selected from inorganic bases like "alkali metal hydroxides" such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; ammonia; and organic bases such as triethyl amine, tribenzylamine, isopropyl amine, diisopropylamine, diisopropylethylamine, N-methylmorpholine, N-ethylmorpholine, piperidine, dimethylaminopyridine, morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methylimidazole, 1,2,4-triazole and/or mixtures thereof.

As used herein the present invention the term "amine protecting group" wherever if necessary is selected from, but not limited to tert-butoxy carbonyl (BOC), benzyloxy carbonyl(CBz), acetyl (Ac), triflouoroacetyl (TFA), benzyl (Bn), dibenzyl, phthalimido, tosyl (Ts), p-methoxybenzylcarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), carbamate, p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP) and benzoyl (Bz).

The "suitable amine protecting agent" is selected such that it is capable of protecting the nitrogen atom with any of the above mentioned amine protecting groups.

The "suitable amine protecting agent" is selected from, but not limited to di-tert.butyl dicarbonate (DIBOC), benzyl chloroformate, fluorenylmethyloxy carbonyl chloride (FMOC chloride), acetyl chloride, acetic anhydride, benzoyl halides, benzyl halides, alkyl or aryl sulfonyl halides or anhydrides such as mesyl halides, mesyl anhydride, tosyl halides, tosyl anhydrides, alkyl trifluoroacetates such as methyl trifluoroacetate, ethyl trifluoroacetate, isopropyl trifluoroacetate, vinyl trifluoroacetate, trifluoroacetic acid, trifluoroacetyl chloride and the like.

The suitable deprotecting agent is selected based on the protecting group employed. The "suitable deprotecting agent" is selected from acids like hydrochloric acid, isopropanolic hydrochloric acid, ethyl acetate-hydrochloric acid, ether-hydrochloric acid, hydrobromic acid, sulfuric acid, periodic acid, formic acid, trichloroisocyanuric acid, phosphoric acid, acetic acid, p-toluene sulfonic acid and trifluoroacetic acid; hydrogenating agents such as palladium, palladium on carbon and rhodium on carbon under hydrogen pressure; bases like piperidine, ammonia and methylamine; ammonium cerium (IV) nitrate; sodium in liquid ammonia; sodium naphthalenide, tetrabutyl ammonium fluoride and the like.

As used herein the present invention the term "suitable halogenating agent" wherever if necessary is selected from, but not limited to phosphorous trichloride, phosphorous penta chloride, phosphorous tribromide, phosphorous penta bromide, N-bromo succinamide, N-chloro succinamide, chlorine, bromine, sulfuryl chloride, copper (II) chloride, copper (II) bromide, ferric chloride, ferric bromide and the like.

The term "suitable condensing agent" used herein the present invention is selected from alkyl (or) aryl chloroformates such as methyl chloroformate, ethyl chloroformate, isobutyl chloroformate, isopropenyl chloroformate, phenyl chloroformate, benzyl chloroformate, p-nitrophenyl chloroformate and the like; alkyl or aryl sulfonyl halides and anhydrides such as methane sulfonyl chloride, ethane sulfonyl chloride, benzene sulfonyl chloride, 4-chlorobenzensulfonyl chloride, toluene sulfonyl chloride, p-toluene sulfonyl halide, methane sulfonic anhydride and the like; carbonyldiimidazole (CDI); carbonyl ditriazole; carbodiimides such as dicyclohexylcarbodiimide (DCC), l-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (EDC-hydrochloride), diisopropyl carbodiimide and the like; (benzotriazol-1-yloxy)tris(dimethyl amino)phosphonium hexafluorophosphate (BOP); 0-(7-azabenzotriazol-l-y^-*N*,*N*,*I*V,iV-tetramethyl uronium hexafluoro phosphate (HATU); (benzotriazol-l-yloxy) tripyrrolidino phosphonium hexafluoro phosphate (PyBOP); oxalyl chloride; di phenylphosphoroazidate (DPPA); P_2O_5; and thoinyl chloride.

The condensing agents may be utilized optionally in presence of catalyst selected from triazole, benzotriazole and substituted benzotriazole such as hydroxy benzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), l-hydroxy-lH-l,2,3-triazole-4-carboxylate (HOCt), N-hydroxy succinamide (HOSu), and (2-(lH-benzotriazol-l-yl) -1,1,3,3-tetra methyl uronium tetrafluoro borate (TBTU) and the like.

The term "oxidizing agent" is selected from dess-martin periodinane (DMP), trichloroisocyanuric acid, pyridinium chlorochromate, potassium dichrormate, manganese dioxide, chromium trioxide, manganese dioxide, pyridinium dichromate, aluminium triisopropoxide in acetone, oxalyl chloride in combination with dimethylsulfoxide and a suitable base; quaternary ammonium salt-TEMPO-oxone, N-chloro succinamide in combination with dimethylsulfide and a suitable base, EDC-dichloroacetic acid and the like.

The term "cyanating agent" is selected from hydrogen cyanide, acetone cyanohydrin, trimethyl silyl cyanide, metal cyanides of formula MCN (where M=Li, Na, and K).

The term "alkyl" as used herein the present invention refers to a saturated straight or branched hydrocarbon chain comprising *Ci-C^* carbon atoms, for example methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl and the like.

The term "aryl" as used herein the present invention refers to a carbocyclic ring system containing 6 to 10 carbon atoms forming one or more rings, and wherein the ring may be aromatic or non-aromatic in nature, for example phenyl, naphthyl. The aryl may be substituted with halo, nitro, alkoxy and hydroxy.

The term "alkoxy" used herein the present invention refers to alkyl group as defined above, which is attached via an oxygen atom.

The term "halo" herein the present invention refers to halogen such as chlorine and bromine. The term "acid" wherever necessary is selected from hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid and sulfuric acid.

The first aspect of the present invention provides a novel process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt, comprising of:

a) Reacting ketimide compound of general formula-3 with (halomethyl)cyclobutane in a suitable solvent in presence of a base, followed by treating with an acid to provide amino acid ester compound of general formula-4,

b) protecting the amine group of general formula-4 with a suitable amine protecting agent in a suitable solvent, optionally in presence of a base to provide N-protected amino acid ester compound of general formula-5,

c) reacting the compound of general formula-5 with a-halo acetic acid salt compound of general formula-6 in a suitable solvent, in presence of alkyl magnesium halide and a base, followed by decarboxylation to provide a-halo ketone compound of general formula-7,

d) halogenating the compound of general formula-7 with a suitable halogenating agent in a suitable solvent, optionally in presence of a catalyst to provide α,α-dihalo ketone compound of general formula-8,

e) treating the compound of general formula-8 with alkali metal hydroxide in a suitable solvent to provide β-amino-a-hydroxy acid compound of formula-9,

f) protecting the amine group of formula-9 with a suitable amine protecting agent in a suitable solvent, optionally in presence of a base to provide N-protected β-amino-a-hydroxy acid compound of general formula- 10,

g) reacting the compound of general formula- 10 with ammonium chloride in a suitable solvent, in presence of carbonyl diimidazole and a base to provide N-protected β-amino-a-hydroxy amide compound of general formula- 11,

h) deprotecting the compound of general formula- 11 with a suitable deprotecting agent in a suitable solvent to provide 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2. or its acid-addition salt.

Wherein,

in step-a) the base is inorganic base, preferably potassium tert-butoxide; acid is inorganic acid selected from hydrochloric acid, hydrobromic acid and sulfuric acid;

in step-b) & step-f) the base is selected from inorganic bases and organic bases, preferably inorganic base such as sodium bicarbonate and sodium hydroxide;

in step-c) the alkyl magnesium halide is tert-butyl magnesium chloride, tert-butyl magnesium bromide and the like; the base is organic base, preferably triethylamine; the a-halo acetic acid salt is preferably alkali metal salt, such as lithium, sodium and potassium salt of a-halo acetic acid;

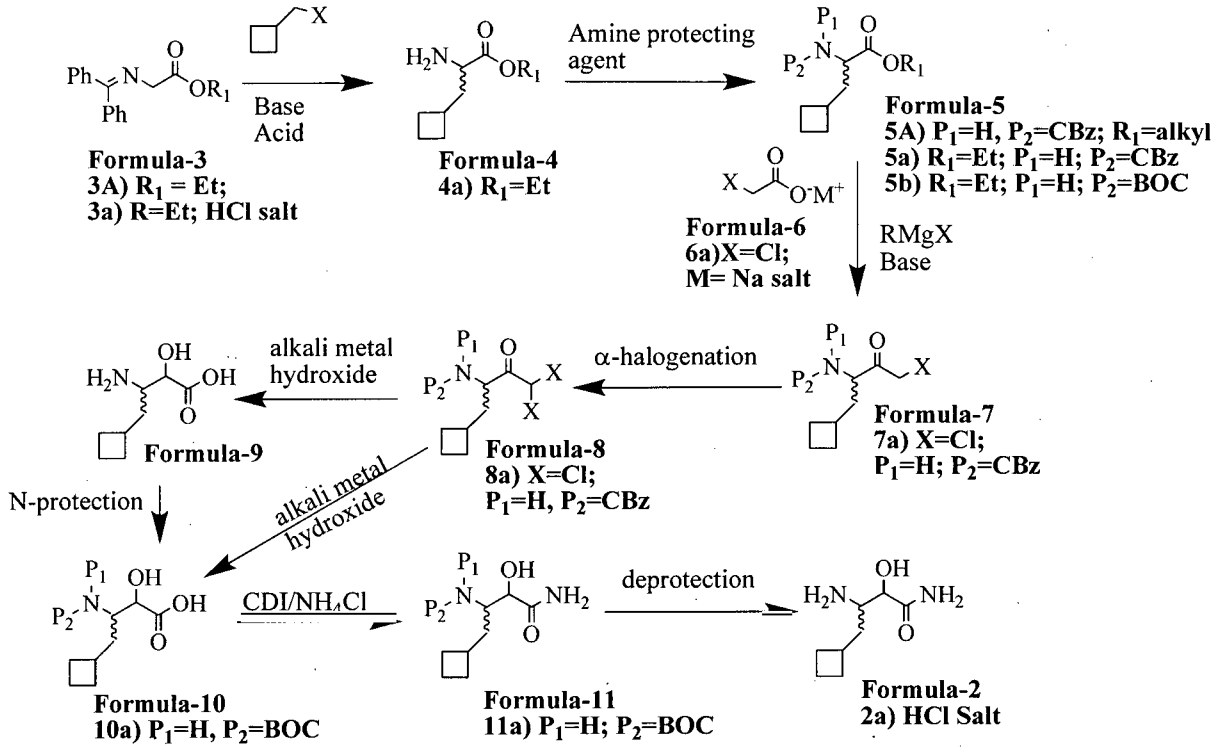
in step-d) the catalyst is p-toluene sulfonyl chloride;

in step-e) alkali metal hydroxide is selected from sodium hydroxide, potassium hydroxide and lithium hydroxide;

in step-g) the suitable base is inorganic base or organic base, preferably diisopropyl ethylamine;

Further, the first aspect of the present invention is represented schematically as shown below:

Scheme-I:



Wherein, P_1 and P_2 both are same or different and independently selected from hydrogen and amine protecting group; R_1 is alkyl; X is halogen; and M is an alkali metal such as sodium, potassium and lithium.

In the above aspect, the compound of formula-2 can also be converted into its hydrochloride salt by treating it with hydrochloric acid.

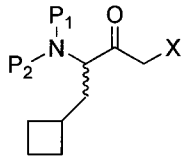
The a-halo acetic acid salt compound of general formula-6 used herein the present invention is converted into its corresponding metal enolate before its reaction with compound of general formula-5. The metal enolate of a-halo acetic acid salt is preferably magnesium enolate. The magnesium enolate of a-halo acetic acid salt can be prepared by reacting a-halo acetic acid salt with magnesium compounds like magnesium amide such as chloromagnesium diisopropylamide; Grignard reagent such as alkyl magnesium halide in presence of an amine such as secondary and tertiary amine.

In the above aspect, the stereospecific products are formed by taking stereospecific starting material as inputs.

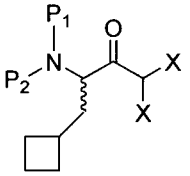
The second aspect of the present invention provides a process for the preparation of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27, comprising of reacting (S)-2-amino-3,3-dimethylbutanoic acid compound of formula-25 or its ester with 2-methylpropan-2-amine compound of formula-26 or its acid-addition salt in a suitable solvent in presence of a suitable condensing agent, optionally in presence of a base and/or a catalyst to provide compound of formula-27. Wherein, the base is selected from inorganic bases or organic bases; and the catalyst is selected from triazole, benzotriazole and substituted benzotriazole such as hydroxy benzotriazole (HOBt), l-hydroxy-7-azabenzotriazole (HOAt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt), N-hydroxy succinamide (HOSu) and the like;

A preferred embodiment of the present invention provides a process for the preparation of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27, comprising of reacting the (S)-trimethylsilyl 2-amino-3,3-dimethylbutanoate compound of formula-25a with 2-methylpropan-2-amine hydrochloride compound of formula-26a in presence of N,N-carbonyl diimidazole in tetrahydrofuran provides (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27.

The third aspect of the present invention provides a-halo ketone compound of general formula-7 and α,α-dihalo ketone compound of general formula-8



Formula-7



Formula-8

wherein, P_1, P_2 and X are same as defined above.

which are useful intermediates in the synthesis of 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2, which in-turn useful in the synthesis of Boceprevir.

In the present invention, the compound of formula-7 and compound of formula-8 may be either a racemic mixture or its individual enantiomers.

Further, the third aspect of the present invention provides a process for the preparation of a-halo ketone compound of general formula-7, comprising of reacting the N-protected amino

acid ester compound of general formula-5 with a-halo acetic acid salt compound of general formula-6 in a suitable solvent, in presence of alkyl magnesium halide and a base, followed by decarboxylation to provide a-halo ketone compound of general formula-7.

Wherein, the base is same as defined in step-(c) of the first aspect.

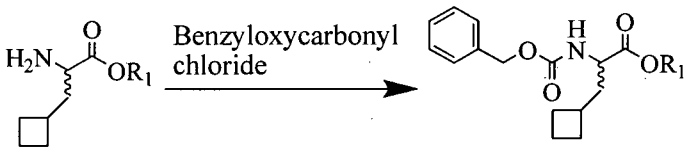
Further, the third aspect of the present invention also provides a process for the preparation of α,α-dihalo ketone compound of general formula-8, comprising of halogenating the a-halo ketone compound of general formula-7 with a suitable halogenating agent in a suitable solvent, optionally in presence of a catalyst to provide α,α-dihalo ketone compound of general formula-8.

Wherein, the suitable halogenating agent is same as defined in step-(d) of the first aspect.

In the above aspect, the stereo specific products can also be obtained by taking the stereospecific starting material instead of their racemates as inputs.

A preferred embodiment of the present invention provides benzyl 4-chloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate compound of formula-7a and benzyl 4,4-dichloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate compound of formula-8a.

The fourth aspect of the present invention provides a process for the preparation of alkyl 2-(benzyloxycarbonylamino)-3-cyclobutylpropanoate compound of general formula-5A, comprising of protecting the amine group of amino acid ester compound of general formula-4 with benzyloxy carbonyl chloride, optionally in presence of a base in a suitable solvent to provide compound of general formula-5A.



Formula-4 **Formula-5A**

Wherein, R_1 is alkyl.

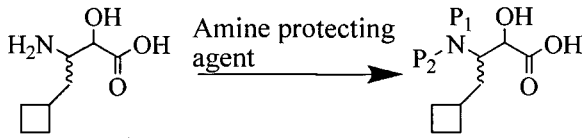
Wherein, the base is selected from inorganic bases and organic base, preferably inorganic base such as sodium bicarbonate.

In the above aspect, the stereo specific enantiomers of compound of formula-5A can be prepared by taking stereo specific starting material i.e. R or S enantiomer of compound of general formula-4 instead of its racemate.

The fifth aspect of the present invention provides a process for the preparation of N-protected β-amino-a-hydroxy acid compound of general formula-10, comprising of:

a) Treating α,α-dihalo ketone compound of general formula-8 with alkali metal hydroxide in a suitable solvent to provide β-amino-a-hydroxy acid compound of formula-9,

b) reacting the compound of formula-9 in-situ with a suitable amine protecting agent in a suitable solvent, optionally in presence of a base to provide compound of general formula-10.

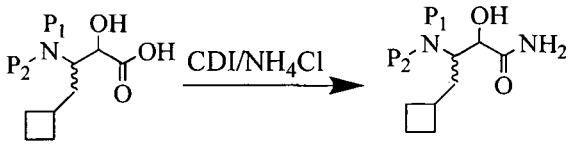


Formula-9 **Formula-10**

wherein, P_1 and P_2 are same as defined above; and the base is selected from inorganic or organic base.

In the above aspect, the stereo specific enantiomer of compound of general formula-10 can be prepared from stereo specific starting material i.e. R or S enantiomer of compound of formula-9 instead of its racemate.

The sixth aspect of the present invention provides a process for the preparation of N-protected β-amino-a-hydroxy amide compound of general formula-11, comprising of reacting N-protected β-amino-a-hydroxy acid compound of general formula-10 with ammonium chloride in a suitable solvent, in presence of carbonyldiimidazole and/or a base to provide compound of general formula-11.



Formula-10 **Formula-11**

Wherein, P_i and P_2 are same as defined above.

In the above aspect, the stereo specific enantiomer of compound of formula-11 can be prepared from stereo specific starting material i.e. R or S enantiomer of compound of formula-10 instead of its racemate.

The seventh aspect of the present invention provides a process for the preparation of Boceprevir compound of formula-1, which comprises of:

a) Cyanating the 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33 in presence of a suitable cyanating agent in a suitable solvent, optionally in presence of an acid or a base to provide 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34, optionally isolating the compound of formula-34 as an acid-addition salt,

b) condensing the compound of formula-34 or its acid-addition salt with (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo [3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35,

c) reacting the compound of formula-35 with an alcohol of formula R-OH in presence of a catalyst provides compound of general formula-36, wherein R represents C_{1-4} alkyl group,

d) hydrolyzing the compound of general formula-36 in a suitable solvent in presence of an acid or a base provides compound of formula-37,

e) treating the diastereomeric mixture of compound of formula-37 with an organic amine to provide compound of general formula-38, optionally isolating the compound of general formula-38,

f) treating the compound of general formula-38 with an acid to provide (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0]hexane-2-carboxylic acid compound of formula-29,

g) condensing the compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]

hexane-2-carboxamide compound of formula-30,

h) oxidizing the compound of formula-30 with a suitable oxidizing agent in a suitable solvent, optionally in presence of a catalyst to provide Boceprevir of formula-1.

Wherein,

in step-a) the acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; the base is selected from inorganic bases and organic bases;

in step-b) & step-g) the base is selected from inorganic bases such as alkali metal hydroxides, carbonates, bicarbonates; and organic bases; the catalyst is selected from triazole, benzotriazole and substituted benzotriazole such as hydroxy benzotriazole (HOBt), l-hydroxy-7-azabenzotriazole (HOAt), l-hydroxy-lH-l,2,3-triazole-4-carboxylate (HOCt), N-hydroxy succinamide (HOSu) and the like;

in step-c) the catalyst is selected from dry HC1 gas, HC1 solution, thionyl chloride, tri alkyl silyl halide such as trimethyl silyl chloride, triethyl silyl chloride, tert-butyl dimethyl silyl chloride and the like, triaryl silyl halide such as triphenyl silyl chloride and the like;

in step-d) the base is selected from alkali metal hydroxides, carbonates and bicarbonates; the acid is inorganic acid selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and the like;

in step-e) the organic amine may be chiral or achiral. The organic amine is selected from, but not limited to 1,2,3,4-tetrahydronaphthalene-l -amine, 2-phenyl glycinol, (S)-l,2,3,4-tetrahydro naphthalene- 1-amine, (R)-l,2,3,4-tetrahdyro naphthalene- 1-amine, (R)-2-phenyl glycinol, (S)-2-phenyl glycinol and the like;

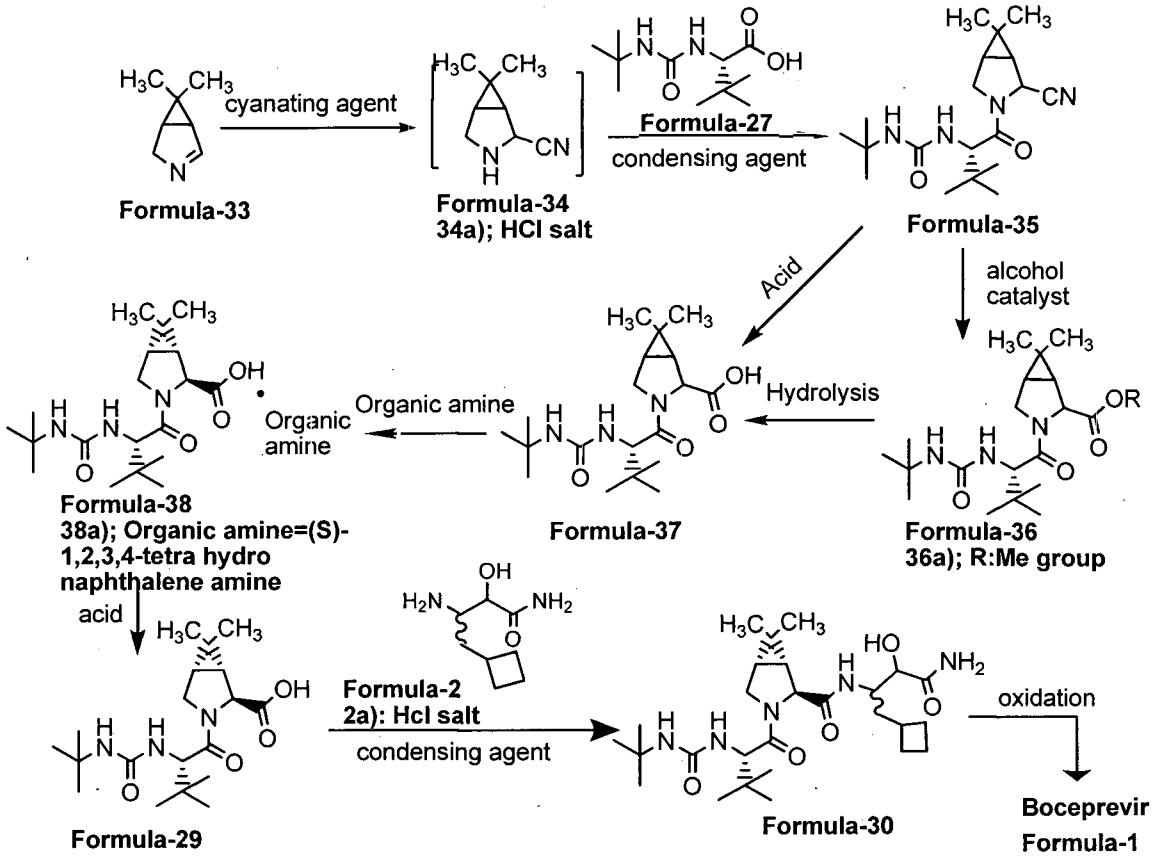
in step-f) the acid is inorganic acid selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like;

in step-h) the catalyst is selected from is selected from TEMPO, 4-methoxy TEMPO, 4-amino TEMPO and the like;

in step-a) to step-h) the suitable solvent is selected from ester solvents, ether solvents, hydrocarbon solvent, polar aprotic solvent, ketone solvents, alcoholic solvents, chloro solvents, nitrile solvents, polar solvent and/or mixtures thereof.

The seventh aspect of the present invention is schematically represented as follows:

Scheme-II:

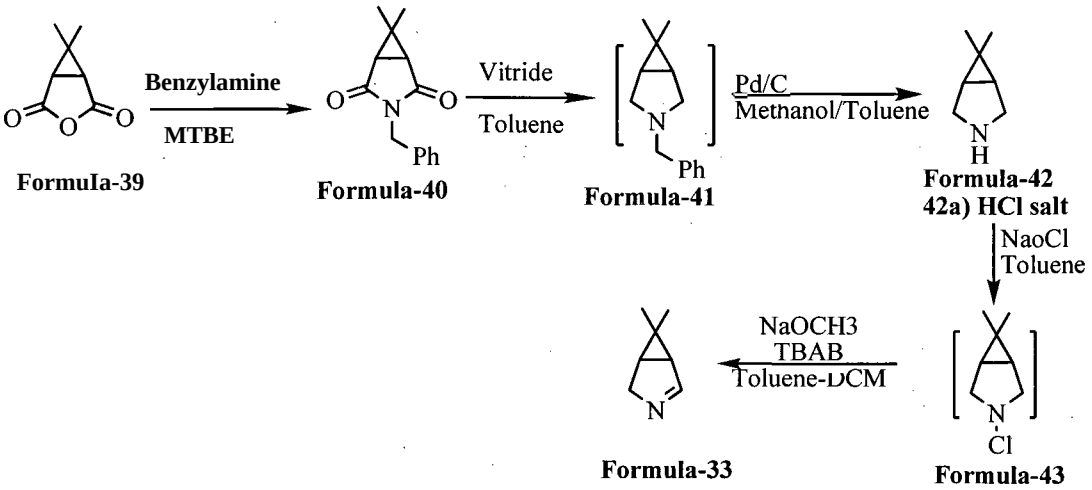


In the above aspect, the compound of formula-37 can be prepared from compound of formula-35 by hydrolyzing it in presence of an acid or a base in a suitable solvent.

Wherein, the acid is inorganic acid selected from hydrochloric acid, hydrobromic acid, nitric acid and sulfuric acid. The base is selected from alkali metal hydroxide, carbonates and bicarbonates.

The compound of formula-33 used in the present invention can be prepared by the process represented in the following scheme-Ill:

Scheme-Ill:

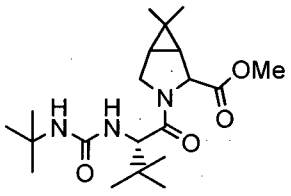


The specific embodiment of the present invention provides a process for the preparation of Boceprevir compound of formula-1, comprising of:

a) Cyanating the 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33 in toluene, in presence of acetone cyanohydrin and triethylamine provides 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34,

b) condensing the compound of formula-34 in-situ with (S)-2-(3-tert-butylureido)-3,3-dimethyl butanoic acid compound of formula-27 in toluene in presence of 1-(3-dimethyl aminopropyl)-3-ethyl carbodimide hydrochloride (EDC-HC1) and 2,6-lutidine to provide l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo [3.1.0] hexan-3-yl)-3,3-dimethyl- 1-oxobutan-2-yl) urea compound of formula-35,

c) reacting the compound of formula-35 with methanol in presence of thionyl chloride provides methyl 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylate compound of formula-36a,

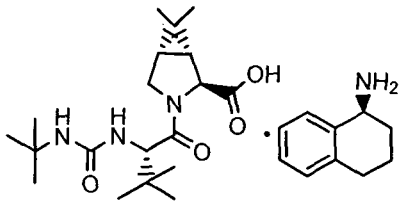


Formula-36a

d) hydrolyzing the compound of formula-36a in tetrahydrofuran in presence of lithium hydroxide in water to provide compound of formula-37,

e) treating the diastereomeric mixture of compound of formula-37 with (S)-1,2,3,4-tetrahydronaphthalene-1-amine in ethyl acetate to provide (S)-l,2,3,4-tetrahydro

naphthane-1-amine salt of (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-38a,



Formula-38a

f) treating the compound of formula-38a in-situ with hydrochloric acid to provide (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-29,

g) condensing the compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxy butanamide hydrochloride salt compound of formula-2a in presence of dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBT) and diisopropyl ethylamine in dichloromethane provides (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30,

h) oxidizing the compound of formula-30 with Dess-martin periodinane (DMP) in dichloromethane provides Boceprevir compound of formula-1.

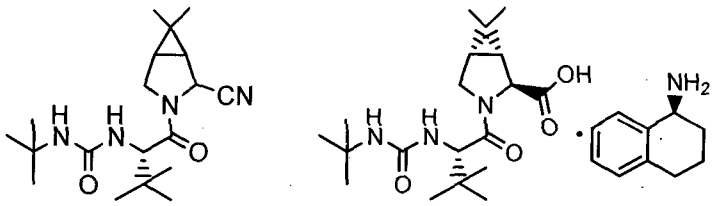
The process of the present invention provides the Boceprevir with a purity of 99.3% by HPLC and controls all the impurities to the level which meets ICH requirements.

The eighth aspect of the present invention provides a process for diastereomeric resolution of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0] hexane-2-carboxylic acid compound of formula-37 with chiral amine in a suitable solvent, followed by treating with an acid to provide (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylic acid compound of formula-29. Wherein, the suitable chiral amine is selected from (S)-l,2,3,4-tertahydronaphthalene-1amine, (R)-1,2,3,4-tertahydronaphthalene-1amine, (R)-2-phenyl glycinol, (S)-2-phenyl glycinol and the like; and the acid is selected from hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid and sulfuric acid.

The specific embodiment of the present invention provides a diastereomeric resolution of (lR,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-37 with (S)- 1,2,3,4-tetrahydronaphthalene-l-amine in ethyl acetate provides (S)-l,2,3,4-tetrahydronaphthalen-l-amine salt of (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-38a, which is in-situ treated with hydrochloric acid provides compound of formula-29.

The resolution of compound of formula-37 with chiral amine provides compound of formula-29 having a high purity which meets the requirement of ICH guidelines.

The ninth aspect of the present invention provides novel intermediate compounds which are useful in the synthesis of Boceprevir. These novel intermediate compounds are represented by the following structural formulae.



and stereo isomers thereof.

The tenth aspect of the present invention provides a process for the preparation of 1-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35, comprising of:

a) Cyanating 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33 in presence of a suitable cyanating agent in a suitable solvent, optionally in presence of an acid or a base to provide 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34, optionally isolating the compound of formula-34 as an acid-addition salt,

b) condensing the compound of formula-34 or its acid-addition salt with (S)-2-(3-tert-butyl ureido)-3,3-dimethylbutanoic acid compound of formula-27 in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide compound of formula-35.

Wherein,

in step-a) the acid and the base are same as defined in step-a) of the seventh aspect;

in step-b) the base and catalyst are same as defined in step-b) of the seventh aspect.

The specific embodiment of the present invention provides a process for the preparation of l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35, comprising of:

a) Cyanating the 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33 in toluene in presence of acetone cyahohydrin and triethylamine to provide 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34,

b) condensing the compound of formula-34 in-situ with (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 in toluene, in presence of l-(3-dimethylamino propyl)-3-ethyl carbodimide hydrochloride (EDC-HCl) and 2,6-lutidine to provide compound of formula-35.

The eleventh aspect of the present invention provides a process for the preparation of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylic acid compound of formula-37, comprises of:

a) Reacting the l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35 with an alcohol of formula R-OH in presence of a catalyst provides its corresponding alkyl-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate compound of general formula-36, wherein"R" represents an alkyl group containing C_{1-4} carbon atoms,

b) hydrolyzing the compound of general formula-36 in presence of an aqueous acid or aqueous base in a suitable solvent to provide compound of formula-37.

Wherein,

in step-a) the catalyst is selected from dry hydrochloric acid gas, hydrochloric acid soution, thionyl chloride, trialkyl silyl halides, triaryl silyl halides;

in step-b) the acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like; and the base is selected from alkali metal hydroxides, carbonates and bicarbonates.

The preferred embodiment of the present invention provides a process for the preparation of 3-((S)-2-(3-tert-butyl ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylicacid compound of formula-37, comprising of:

a) Reacting l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35 with methanol in presence of thionyl chloride to provide methyl 3-((S)-2-(3-tert-butylureido)-3,3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-36a,

b) hydrolyzing the compound of formula-36a in presence of lithium hydroxide in a mixture of tetrahydrofuran and water provides compound of formula-37.

The twelfth aspect of the present invention provides a process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1 .0]hexane-2-carboxamide compound of formula-30, comprising of condensing the (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt in presence of dicyclohexylcarbodiimide in a suitable solvent, optionally in presence of a base and/or a catalyst provides compound of formula-30.

Wherein, the catalyst and base for the above reaction is same as defined in step-(b) or (g) of the seventh aspect of the present invention. The suitable solvent is selected from ester solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, ketone solvents, alcoholic solvents, chloro solvents, nitrile solvents, polar solvents and/or mixtures thereof.

The above condensation reaction of compound of formula-29 and compound of formula-2 or its acid-addition salt is carried out at a temperature of -20°C to about 80°C, preferably at 10-50°C, more preferably at 20-35°C for about 3-8 hours or until the reaction is completed. The mole ratio of the compound of formula-2 or its acid-addition salt is in the range of 0.8-1.2 molar equivalents per one mole compound of formula-29.

The preferred embodiment of the present invention provides a process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butyl ureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0]hexane-2-carboxamide

compound of formula-30, comprising of condensing the (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0]hexane-2-carboxylic acid compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride compound of formula-2a in presence of dicyclohexyl carbodiimide, 1-hydroxy benzotriazole and diisopropyl ethylamine in dichloromethane provides compound of formula-30.

The thirteenth aspect of the present invention provides a process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30, which comprises of:

a) Condensing the (lR,2S,5S)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-44 with 3-amino-4-cyclobutyl-2-hydroxy butanamide compound of formula-2 or its acid-addition salt in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst provides (1R,2S,5 S)-tert-butyl 2-(4-amino- 1-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamoyl)-6,6-dimethyl-3-azabicyclo[3.1 .0]hexane-3-carboxylate compound of formula-45,

b) deprotecting the compound of formula-45 with a suitable deprotecting agent in a suitable solvent to provide (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-46, optionally converting it into its acid-addition salt,

c) condensing the compound of formula-46 or its acid-addition salt with (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst provides compound of formula-30.

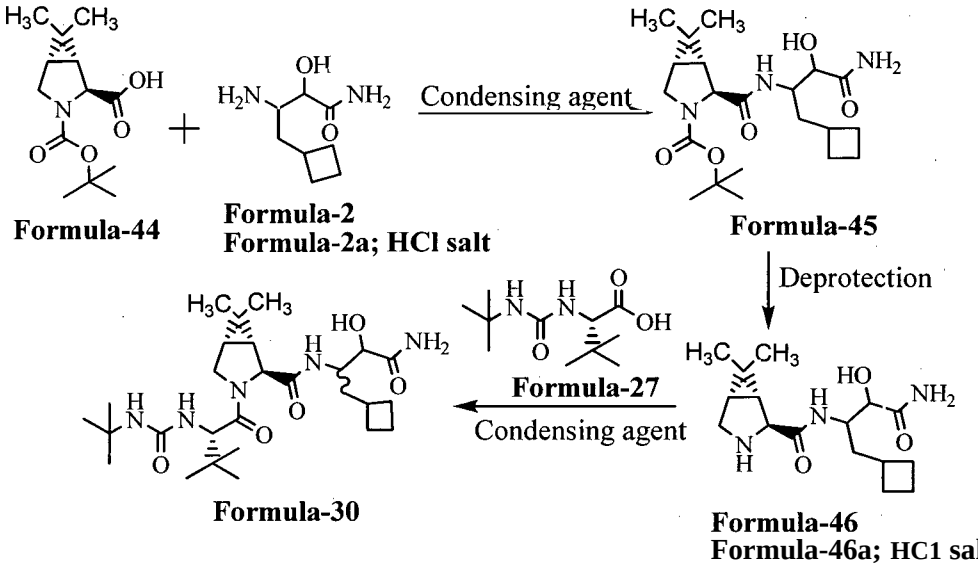
Wherein,

In step-(a) & (c) the base and catalyst are same as defined in step-b) of the seventh aspect of the present invention.

In step-(b) the suitable deprotecting agent is selected from hydrochloric acid, trifluoroacetic acid, tetrabutyl ammonium fluoride, formic acid, aqueous phosphoric acid, BF3-etherate, acetic acid, and p-toluene sulfonic acid.

Further, the thirteenth aspect of the present invention is represented schematically as follows:

Scheme-IV:



Formula-44 **Formula-2** **Formula-2a; HCl salt** **Formula-45** **Formula-27** **Formula-30** **Formula-46** **Formula-46a; HC1 salt**

The compound of formula-44 of the present invention can be prepared by resoluting from its corresponding racemic compound using chiral bases such as (S)-l,2,3,4-tetrahydro naphthalene- 1amine, (R)-l,2,3,4-tetrahydronaphthalene-lamine, (R)-l-phenylethylamine, (S)-l-phenylethyl amine, L-2-phenyl glycinol and D-2-phenyl glycinol.

The specific embodiment of the present invention provides a process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30, comprises of:

a) Condensing the (lR,2S,5S)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-44 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 in presence of l-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (EDC-HC1), 1-hydroxybenzotriazole (HOBT) and diisopropylethylamine in a mixture of dichloromethane and dimethyl formamide provides (lR,2S,5S)-tert-butyl 2-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-3-carboxylate compound of formula-45,

b) deprotecting the compound of formula-45 with isopropanolic-hydrochloride in isopropanol provides (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-

6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide hydrochloride compound of formula-46a,

c) condensing the compound of formula-46a with (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 in presence of 0-(7-azabenzotriazol-l-yl)-*N* ^V,iV,iV-tetramethyluroniumhexafluoro phosphate (HATU) and diisopropylethylamine (DIPEA) in acetonitrile provides compound of formula-30.

The compound of formula-44 of the present invention can be prepared by any of the known methods, for example the process disclosed in Journal of organic chemistry, 1999, 64, 330-331.

The fourteenth aspect of the present invention provides an improved process for the preparation of methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride compound of formula-48a, comprising of,

a) Chlorinating the 6,6-dimethyl-3-azabicyclo[3.1.0]hexane compound of formula-42 or its acid-addition salt with sodium hypochlorite in toluene to provide 3-chloro-6,6-dimethyl-3-azabicyclo [3.1.0]hexane compound of formula-43, which is in-situ treated with sodium methoxide in presence of tetrabutyl ammonium bromide in a mixture of toluene and dichloromethane provides 6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-ene compound of formula-33,

b) cyanating the compound of formula-33 in-situ in presence of acetone cyanohydrin and triethyl amine to provides 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34,

c) treating the compound of formula-34 in-situ with ditert-butyldicarbonate provides tert-butyl 2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate compound of formula-47,

d) reacting the compound of formula-47 in-situ with methanol in presence of catalyst such as trimethylsilyl chloride or thionyl chloride provides methyl 6,6-dimethyl-3-azabicyclo [3.1 .0]hexane-2-carboxylate hydrochloride compound of formula-48a.

In the preferred embodiment of the present invention, the 6,6-dimethyl-3-azabicyclo[3.1.0] hexane which is starting material is used in the form of its hydrochloride salt compound of formula-42a.

The compound of formula-48 or its acid-addition salt prepared by the present invention can be further resoluted with suitable chiral acids to provide compound of formula-53.

Wherein, the chiral acids includes, but not limited to D-tartaric acid, L-tartaric acid, D-di(p-anisoyl)tartaric acid, L-di(p-anisoyl)tartaric acid, D-mandelic acid, L-mandelic acid, L-camphor sulfonic acid and D-camphor sulfonic acid.

The BOC protection of compound of formula-34 and usage of trimethyl silyl chloride instead of hydrochloric acid enhances the yield and purity of the final compound of formula-48a. The BOC protection of compound of formula-34 also avoids the formation of dimer impurity. The following tables shows the quality and yield improvements through the present invention.

Table-1: Yield comparison of compound of formula-48a

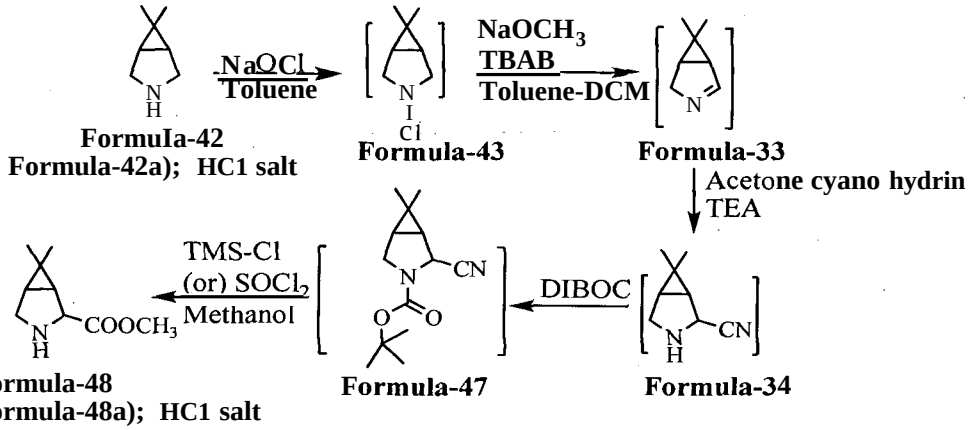
	With BOC protection of compound of formula-34	Without BOC protection compound of formula-34
Yield % of compound-48a	73.00%	29.87%

Table-2: Yield and purity comparison of compound of formula-48a during conversion of compound of formula-47 to compound of formula-48a.

	Deprotecting agent	
	TMSCl	HCl
Yield % of compound-48a	73.00%	41.66%
Purity of compound-48a by GC	90.14%	48.32%

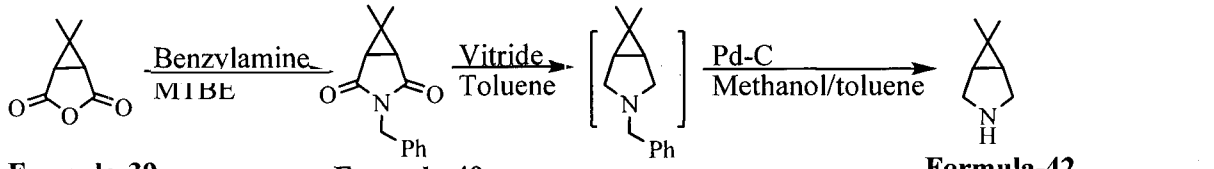
Further the fourteenth aspect of the present invention is schematically represented as follows:

Scheme-V:



The compound of formula-42 can be prepared by any of the known method (or) by the process represented in the below scheme.

Scheme-VI:



Formula-39 **Formula-40** **Formula-41** **Formula-42**
Formula-42a) HCl salt

The obtained compound of formula-42 can be converted into its acid-addition salt by treating it with an acid selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid.

The fifteenth aspect of the present invention provides an improved process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride salt compound of formula-2a, which comprises of:

a) Reacting the ethyl 2-(diphenylmethyleneamino)acetate compound of formula-3A or its acid-addition salt with cyclobutylmethylbromide in presence of potassium tert-butoxide in tetrahydrofuran, followed by treating with an aqueous hydrochloric acid to provide ethyl 2-amino-3-cyclobutylpropanoate compound of formula-4a,

b) treating the compound of formula-4a in-situ with ditert-butyl dicarbonate in presence of potassium carbonate to provide ethyl 2-(tert-butoxycarbonylamino)-3-cyclobutyl propanoate compound of formula-5b,

c) hydrolyzing the compound of formula-5b in-situ in presence of lithium hydroxide in water provides 2-(tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid compound of formula-49,

d) isolating the compound of formula-49 as a solid using hydrocarbon solvent such as cyclohexane,

e) condensing the 2-(tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid compound of formula-49 with N-methylhydroxylamine hydrochloride in tetrahydrofuran in presence of carbonyl diimidazole (CDI) and diisopropyl ethylamine provides tert-butyl 3-cyclobutyl-l-(methoxy(methyl) amino)- l-oxopropan-2-ylcarbamate compound of formula-50,

f) reducing the compound of formula-50 with vitride in a mixture of toluene and

dichloromethane provides tert-butyl l-cyclobutyl-3-oxopropan-2-ylcarbamate compound of formula-51,

g) cyanating the compound of formula-51 in-situ in presence of acetone cyanohydrin and triethylamine provides tert-butyl l-cyano-3-cyclobutyl-l-hydroxypropan-2-ylcarbamate compound of formula-52,

h) converting the compound formula-52 to tert-butyl 4-amino-l-cyclobutyl-3-hydroxy-4-oxo butan-2-ylcarbamate compound of formula-11a by treating it with hydrogen peroxide in presence of aqueous sodium hydroxide in dimethylsulfoxide,

i) deprotecting the compound of formula-lla using isopropanolic hydrochloride in isopropanol provides compound of formula-2a.

In the present invention the compound of formula-49 is obtained as a solid, which enhances the purity of the said compound as well as final compound of formula-2a. The purity of compound of formula-2a obtained by the present invention is 99.6% by HPLC.

The reported literature like USRE43298 discloses the purification of compound of formula-50 by column chromatography using ethyl acetate and hexane. As the chromatographic purification process is tedious and hence not suggestible for commercial purposes. The present invention avoids the chromatographic purification and involves the simple purification of compound of formula-50 using cyclohexane to provide the compound with a purity of 99.9% by HPLC.

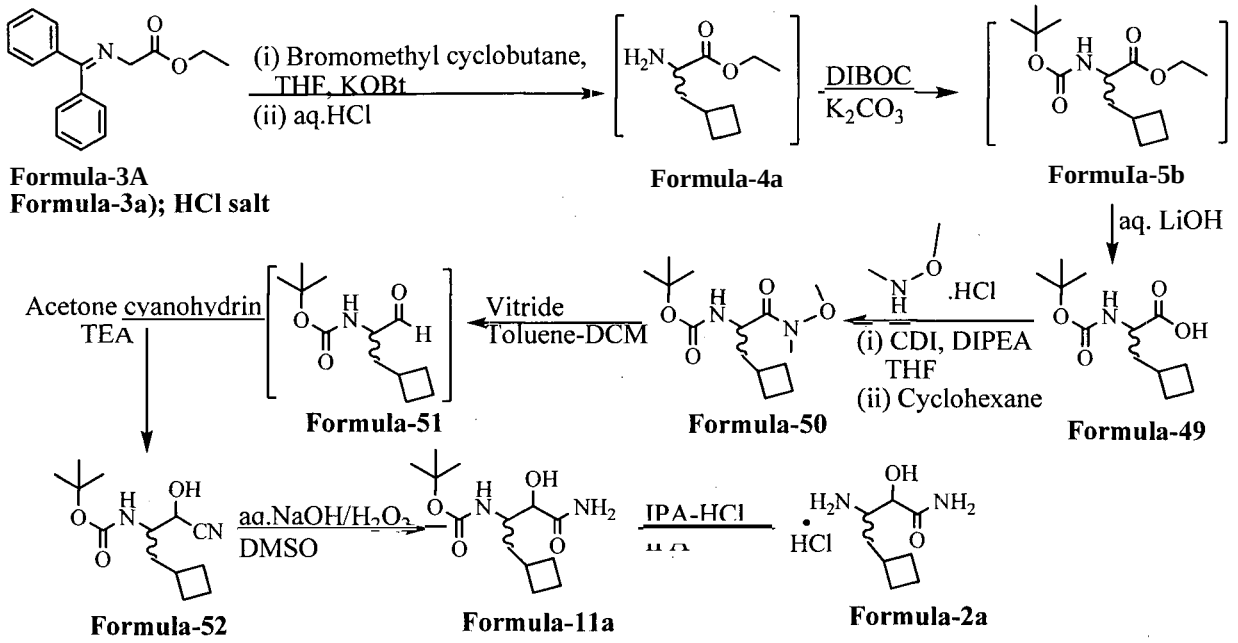
USRE43298 disclosed the use of BOP in condensation reaction of compound of formula-49 with N-methyl hydroxylamine. The HMPA bi-product generated when BOP is used in condensation reaction, is carcinogenic and having respiratory toxicity. Hence use of BOP is limited in condensation reaction in large-scale synthesis. Moreover BOP is costly and not suggestible for commercial scale-up.

In a preferred embodiment of the present invention, ethyl 2-(diphenylmethylene amino)acetate compound of formula-3A, the starting material used in the form of its hydrochloride salt of formula-3a.

The ethyl 2-(diphenylmethyleneamino)acetate hydrochloride compound of formula-3a can be prepared by reacting the ethyl 2-aminoacetate hydrochloride with benzophenone in dichloromethane.

Further, the fifteenth aspect of the present invention is schematically represented as follows:

Scheme-VII:



The sixteenth aspect of the present invention provides a crystalline solid 2-(tert-butoxycarbonyl amino)-3-cyclobutylpropanoic acid compound of formula-49. The crystalline solid herein designated as crystalline form-M. The crystalline form-M is characterized by its powder X-ray diffractogram having peaks at 8.05, 13.7, 13.9, 19.5, 20.4 and 21.3± 0.2 theta. Further the PXRD of crystalline form-M is shown in figure- 1.

The sixteenth aspect also provides a process for the preparation of crystalline form-M of 2-(tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid compound of formula-49, comprises of:

a) Adding a solution of lithium hydroxide in water to a solution of ethyl 2-(tert-butoxycarbonylamino)-3-cyclobutyl propanoate compound of formula-5b in tetrahydrofuran,
b) heating the reaction mixture to 60-70°C,
c) stirring the reaction mixture,
d) filtering the reaction mixture and washing with toluene,
e) separating the organic and aqueous layers from the filtrate,

f) adding dichloromethane to the aqueous layer,
g) acidifying the reaction mixture with orthophosphoric acid solution,
h) separating the organic and aqueous layers,
i) distilling off the solvent from the organic layer,
j) adding cyclohexane to the compound obtained in step-(i),
k) cooling the reaction mixture to 10-15°C,
l) stirring the reaction mixture,
m) filtering the precipitated solid, washing with cyclohexane and then dried to get crystalline form-M of compound of formula-49.

The seventeenth aspect of the present invention provides a process for the preparation of Boceprevir compound of formula-1, comprising of:

a) Condensing (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 with (lR,2S,5S)-methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-53 or its acid-addition salt in dichloromethane, in presence of dicyclohexyl carbodiimide, 1-hydroxy benzotriazole and diisopropyl ethylamine to provide (1R,2S,5S)-methyl 3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylate compound of formula-54,
b) hydrolyzing the compound of formula-54 in a mixture of [tetrahydrofuran and water, in presence of lithium hydroxide to provide (lR,2S,5S)-3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-29,
c) condensing the compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt in presence of dicyclohexylcarbodiimide in a suitable solvent, optionally in presence of a base and/or a catalyst to provide (1R,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30,
d) oxidizing the compound of formula-30 using dess-martin periodinane in dichloromethane to provide Boceprevir compound of formula-1.

Wherein,

in step-c) the suitable base & catalyst are same as defined in step-b) of the seventh aspect

of the present invention; the suitable solvent is selected from ester solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, ketone solvents, alcoholic solvents, chloro solvents, nitrile solvents, polar solvents and/or mixtures thereof. The compound of formula-53 or its hydrochloride salt can be prepared by the process disclosed in Journal of organic chemistry, 1999, 64, 330-331.

Boceprevir compound of formula-1 can be purified by converting it into potassium bisulfate adduct by treating it with bisulfate source includes, but not limited to potassium bisulfate and potassium metabisulfite. Further the obtained compound is isolated/purified by treating with alkaline earth metals salts, hydroxides and acetates. The alkaline earth metals includes, but not limited to calcium and magnesium.

The compounds-30, 48a, and 2a which are prepared by the present invention are useful intermediates in the synthesis of Boceprevir compound of formula- 1.

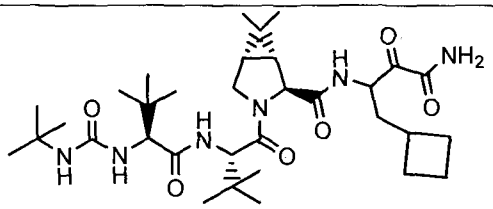
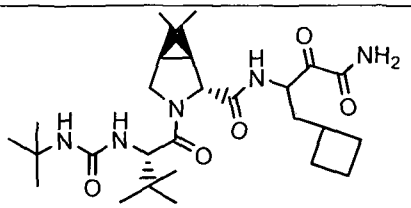
Boceprevir produced by the present invention can be further micronized or milled to get the desired particle size to below 50 microns, preferably less than 20 microns to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball mills, chilled micronization, sieving, roller, hammer mills and jet mills with a pressure 3-8 kg/cm2. Milling or micronization may be performed before drying or after drying of the product.

The particle size of Boceprevir produced by the present invention can also be increased to above 200 microns, preferably more than 250 microns based on the pharmaceutical composition requirements by using conventional techniques includes, but not limited to compaction, slugging and recrystallization.

The following are the abbreviations used through out the specification:

TEMPO: 2,2,6,6-Tetramethylpiperidinyloxy; EDC: l-(3-dimethylamino propyl)-3 -ethyl carbodimide, HOBT: 1-hydroxybenzotriazole; DCC: dicyclohexyl carbodiimide; DIPEA: Diisoporpylethylamine; DCM: dichloromethane; TBAB: tetrabutyl ammonium bromide; DCM: dichloromethane and MTBE: methyl tert-butyl ether.

The impurtities that are formed & controlled during the synthesis of Boceprevir along with their RRT are mentioned in the following table.

Impurity	Structure	RRT
Impurity-I		1.16
Impurity-II		1.08

HPLC method of analysis:

Tert-butyl 3-cyclobutyl-1-(methoxy(methyl)amino)- 1-oxopropan-2-ylcarbamate compound of formula-50 of the present invention is analyzed by HPLC using the following conditions:

Apparatus: A liquid chromatographic system is to be equipped with variable wavelength UV-detector; Column: Cosmicsil Aster XDC18, 100 x 4.6 mm, 3µm or equivalent; Flow rate: 1.0 ml/min; wavelength: 210 nm; column temperature: 30°C; Injection volume; 10 µL; Run time: 38 minutes; Needle wash: diluent; Elution: Gradient; Mobile phase-A: Buffer; Mobile phase-B: acetonitrile:water (90:10 v/v); Buffer: Weigh accurately about 1.36 g of potassium dihydrogen ortho phosphate and 1.0 g of 1-Octane sulphonic acid sodium salt anhydrous in 1000 ml of milli-Q water and filter through 0.22µm nylon membrane filter paper.

3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride compound of formula-2a is analyzed by HPLC using the following conditions:

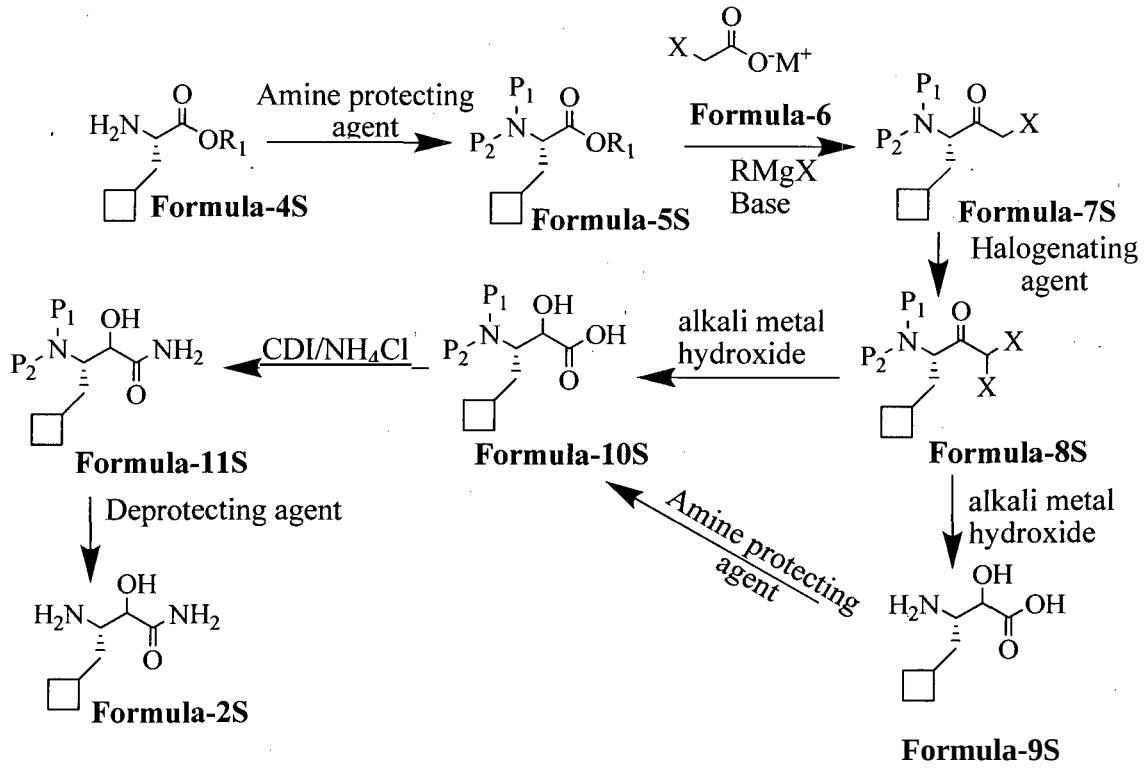
Apparatus: A liquid chromatographic system is to be equipped with variable wavelength UV-detector; Column: Kromasil C18, 250 x 4.6 mm, 5µm or equivalent; Flow rate: 1.0 ml/min; wavelength: 200 nm; column temperature: 25°C; Injection volume: 20 µL; Run time: 45 minutes; Needle wash: watenmethanol (1:1 v/v); Diluent: Mobile phase; Elution: isocratic; Mobile phase: Transfer accurately about 0.5 ml of ortho phosphoric acid and 3.0 g of 1-octane sulphonic acid sodium salt anhydrous in 500 ml of milli-Q water and filter through 0.22µm nylon membrane filter paper.

Methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride compound of formula-48a is analyzed by GC using the following conditions:

Apparatus: A gas chromatographic system is to be equipped with FID (Flame Ionization Detector); Column: Elite capillary column or equivalent with length: 30 mts, ID: 0.53 mm, film thickness: 5.0 µm; Injector temperature: 200°C; Split ratio: 1:10; Detector temperature: 260°C (FID); carrier gas: Heliu,m PSI (Helium); Hydrogen flow: 4. ml/min; air flow: 400ml/ min; make up(N2): 30 ml/min; Diluent: methanol; Injection volume: 1.0 µL; Oven programme: The column temperature is to be programmed according to the following steps: initially keep at 180°C for 10 minutes, then rise to 240°C at the rate of 10°C per minute and hold at 240°C for 18 minutes.

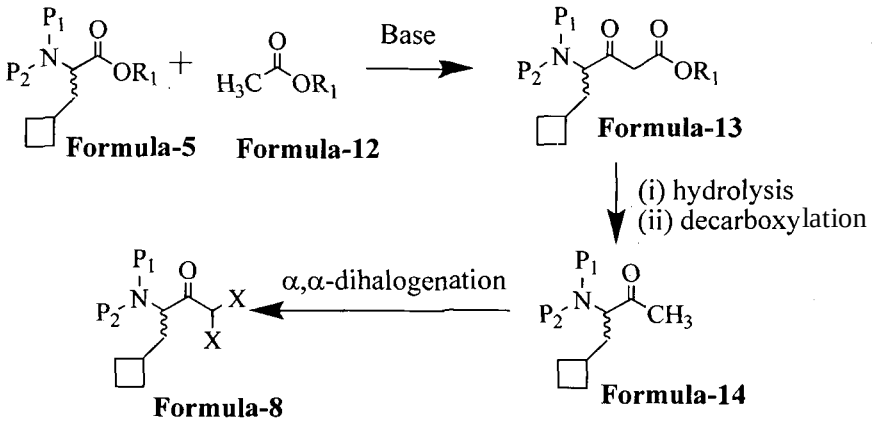
The process of the present invention is schematically represented as below:

Scheme-VIII



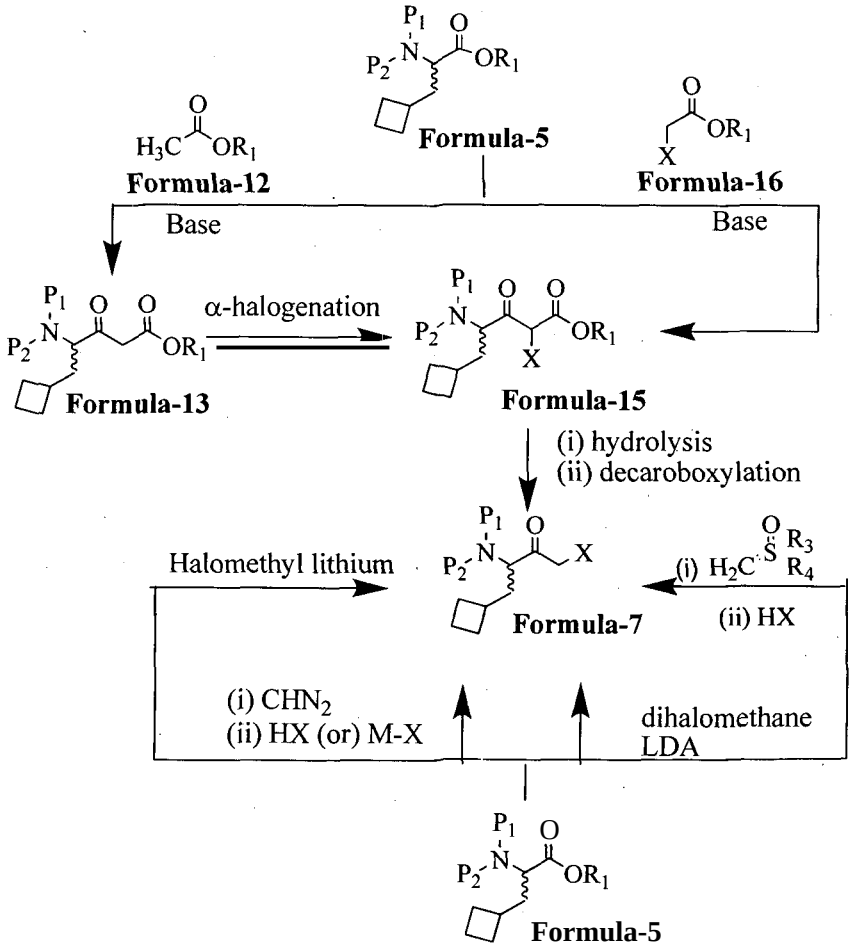
Wherein, P_1, P_2, R_1, M and X are same as defined above.

Scheme-IX



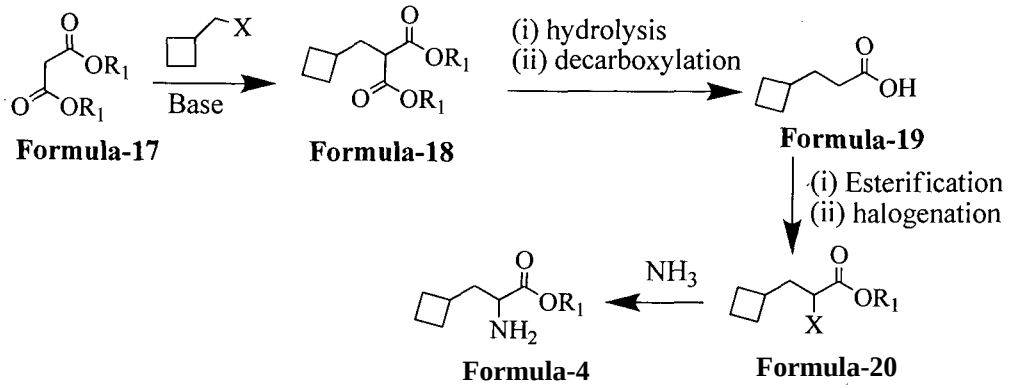
wherein, Pi, P_2, R_1, M and X are same as defined above.

Scheme-X



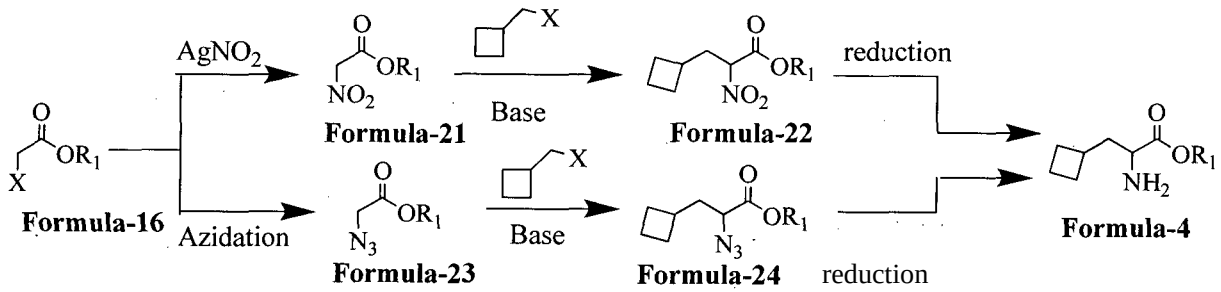
Wherein, Pi, P_2, R_1, M and X are same as defined above; M is an alkali metal.

Schcmc-XI



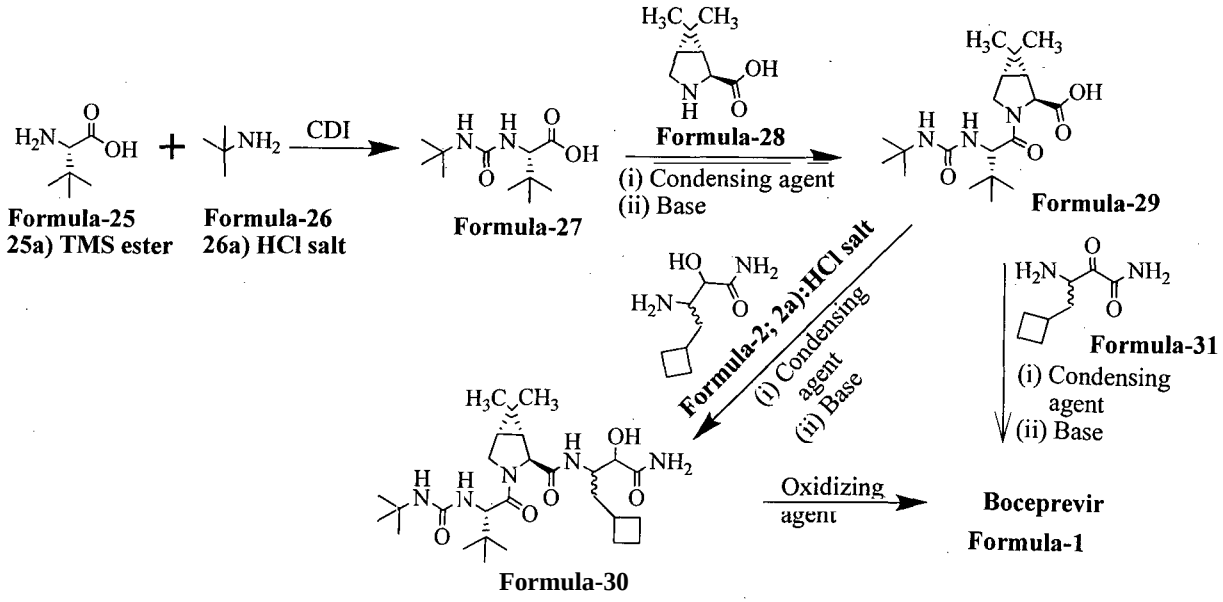
Wherein, $\mathbf{R_1}$ is alkyl; and X is halogen.

Scheme-XII

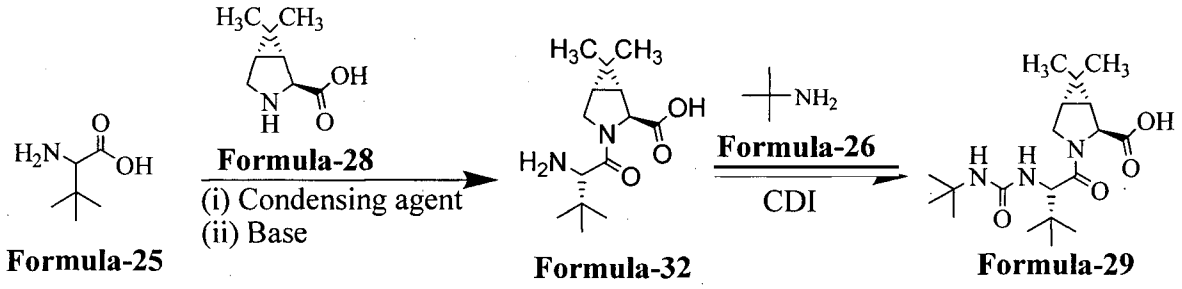


Wherein, $\mathbf{R_1}$ is alkyl; and X is halogen.

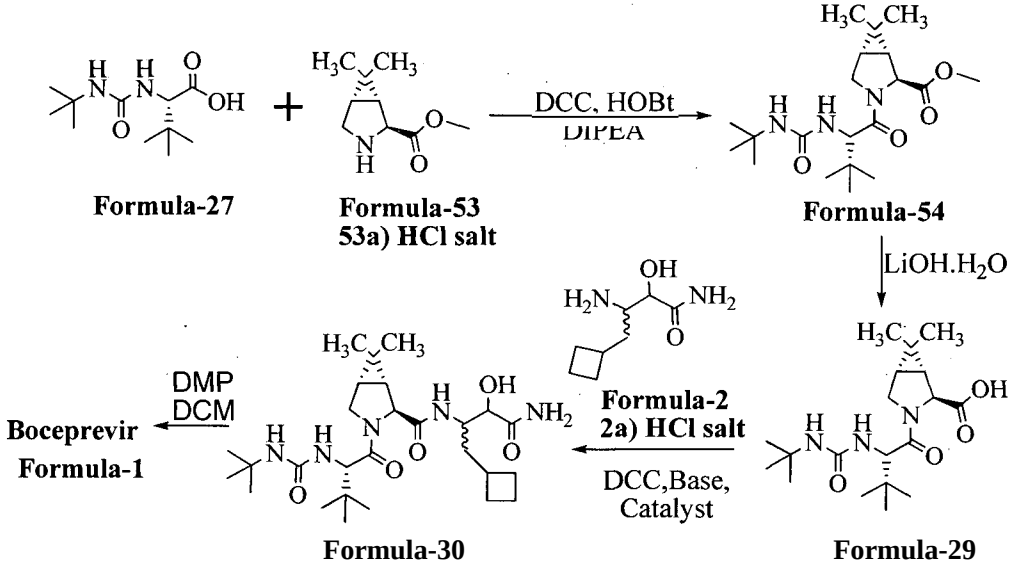
Scheme-XIII



Scheme-XIV



Scheme-XV:



The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Example-1: Preparation of ethyl 2-amino-3-cyclobutylpropanoate (formula-4a)

A mixture of ethyl 2-(diphenylmethyleneamino)acetate compound of formula-3A (250 gms) and tetrahydrofuran (2000 ml) was cooled to 0-5°C. Potassium tert-butoxide (157.4 gms) was slowly added to the reaction mixture at a temperature below 10°C and stirred for 1 hour at 0-5°C. Cyclobutylmethyl bromide (185 g) was added slowly to the reaction mixture for a period of 30 minutes at 0-5°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 30 hours. After completion of the reaction, 2N hydrochloric acid was added to the reaction mixture and stirred for 6 hours. Dichloromethane was added to the reaction mixture and stirred for 15 minutes. Both the organic and aqueous layers were separated and the aqueous layer was washed with dichloromethane. Dichloromethane was added to the aqueous layer and cooled to 0-5°C. pH of the reaction mixture was adjusted to 12.5 by using 50% sodium hydroxide and stirred for 10 minutes. Both the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane at 0-5°C. The organic layers were combined, dried with sodium sulfate and the solvent from organic layer was distilled off completely under reduced pressure to get title compound. Yield: 45 gms.

Example-2: Preparation of ethyl 2-(benzyloxycarbonylamino)-3-cyclobutylpropanoate (Formula-5a)

A mixture of ethyl 2-amino-3-cyclobutylpropanoate compound of formula-4a (10 g), acetonitrile (30 ml) and water (50 ml) was cooled to 5-10°C. Sodium bicarbonate (9.8 g) was added to the reaction mixture at 5-10°C and stirred for 1 hour at the same temperature. 50%Benzyl chloroformate (20.9 ml) was slowly added to the reaction mixture over a period of 1 hour and stirred for 4 hours at 5-10°C. After completion of the reaction, both the organic and aqueous layers were separated and the aqueous layer was extracted with toluene. Both the organic layers were combined and washed with sodium chloride solution. The organic layer was dried with sodium sulfate and then distilled under reduced pressure to get title compound.
Yield: 12 gms.

Example-3: Preparation of benzyl 4-chloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate (Formula-7a)

A mixture of magnesium turnings (4.7 g), iodine (0.02 g) and tetrahydrofuran (15 ml)

was taken into a clean RBF at 25-30°C under nitrogen atmosphere and heated to the reaction mixture 55-60°C. A solution of t-butyl chloride (1.51 g) in tetrahydrofuran (2.5 ml), followed by a solution of ethyl bromide (0.1 ml) in tetrahydrofuran (0.5 ml) were added to the reaction mixture and the reaction mixture was stirred for 15 minutes at 55-60°C. Again a solution of t-butyl chloride (13.59 g) in tetrahydrofuran (22.5 ml) was added slowly to the reaction mixture and stirred for 30 minutes to form t-butylmagnesium chloride. The reaction mixture containing t-butylmagnesium chloride was cooled to 25-30°C and stored under nitrogen atmosphere. A mixture of ethyl 2-(benzyloxycarbonylamino)-3-cyclobutyl propanoate compound of formula-5a (5 g), sodium mono chloroacetate compound of formula-6a (2.8 g) and toluene (25 ml) was cooled to 0-5°C and triethylamine (3.5 ml) was added to reaction mixture under nitrogen atmosphere. The above t-butyl magnesium chloride solution was added to the reaction mixture at 0-5°C and stirred for 2 hours at the same temperature. After completion of the reaction, the reaction mixture was added to a pre-cooled dilute hydrochloric acid solution at 0-5°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 15 minutes. Both the organic and aqueous layers were separated, the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with aqueous sodium bicarbonate solution, followed by aqueous sodium chloride solution. The organic layer was dried with sodium sulfate and then distilled off the solvent under reduced pressure to get title compound. Yield: 4.8 gms; MS (MH^+): 310.2; IR: 1746.88

Example-4: Preparation of benzyl 4,4-dichloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate (Formula-8a)

Sulfuryl chloride (3.7 ml) was added to a mixture of benzyl 4-chloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate compound of formula-7a (4.8 g) and ethyl acetate (48 ml) at 25-30°C for a period of 30 minutes under nitrogen atmosphere. P-toluene sulfonyl chloride (0.29) was added to the reaction mixture and the reaction mixture was heated to 45-50°C and stirred for 40 hours at 45-50°C. After completion of the reaction, the reaction mixture was cooled to 0-5°C and water was added to the reaction mixture. pH of the reaction mixture was adjusted to 3.5 using aqueous sodium hydroxide solution and stirred the reaction mixture for 15 minutes at 0-5°C. Both the organic and aqueous layers were separated, the aqueous layer was extracted with ethyl acetate. Both the organic layers were combined and washed with aqueous sodium chloride solution. The organic layer was dried with sodium sulfate and then distilled under reduced

pressure to get title compound. Yield: 4 gms; MS (MH^+): 344.2; IR: 1714.5

Example-5: Preparation of 3-(tert-butoxycarbonylamino)-4-cyclobutyl-2-hydroxybutanoic acid (Formula-lOa)

A solution of sodium hydroxide (2 g) in water (20 ml) was added to a mixture of benzyl 4,4-dichloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate compound of formula-8a (4 g) and toluene (32 ml). The reaction mixture was heated to 45-50°C and stirred for 9 hours. After completion of the reaction, the reaction mixture was cooled to 25-30°C. Both the organic and aqueous layers were separated; the aqueous layer was washed with ethyl acetate. 1,4-dioxane (20 ml) was added to the aqueous layer containing 3-amino-4-cyclobutyl-2-hydroxybutanoic acid compound of formula-9 and the resulting mixture was cooled to 0-5°C. Di-tert-butyl carbonate (2.52 g) was added to the reaction mixture at 0-5°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 12 hours. After completion of the reaction, ethyl acetate was added to the reaction mixture and stirred for 15 minutes. Both the organic and aqueous layers were separated, the aqueous layer was cooled to 0-5°C and dichloromethane was added to it. pH of the reaction mixture was adjusted to 2.5 using aqueous hydrochloric acid and the reaction mixture was stirred for 15 minutes. Both the organic and aqueous layers were separated, the aqueous layer was extracted with dichloromethane. Both the organic layers were combined, washed with aqueous sodium chloride solution, dried with sodium sulfate and then distilled under reduced pressure to get title compound. Yield: 2.1 gms.

Example-6: Preparation of tert-butyl 4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamate (Formula-lla)

N,N-carbonyl dimidazole (0.44 g) was added to a mixture of 3-(tert-butoxycarbonyl amino)-4-cyclobutyl-2-hydroxybutanoic acid compound of formula-10a (0.5 g), diisopropyl ethylamine (0.5 ml) and dimethylformamide (10 ml) and stirred for 1 hour at 25-30°C. Ammonium chloride (0.3 g) was added to the reaction mixture and stirred for 12 hours at 25-30°C. After completion of the reaction, water followed by ethyl acetate were added to the reaction mixture and stirred for 10 minutes. Both the organic and aqueous layers were separated, the aqueous layer was extracted with ethyl acetate. Both the organic layers were combined, washed with 10% sodium bicarbonate solution, followed by 10% sodium chloride solution, dried with sodium sulfate and then distilled off to get title compound. Yield: 0.3 gms.

Example-7: Preparation of 3-amino-4-cycIobutyI-2-hydroxybutanamide hydrochloride

(Formula-2a)

A mixture of compound of formula-11a (5 g), isopropanol (15 ml) and isopropanolic hydrochloric acid (10 ml) was heated to 60-65°C and stirred for 4 hours at the same temperature. After completion of the reaction, the reaction mixture was cooled to 25-30°C. Filtered the precipitated solid, washed with isopropanol and then dried to get tile compound. Yield: 3.2 gms.

Example-8: Preparation of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid (Formula-27)

Trimethyl silyl chloride (5.0 g) was slowly added to a mixture of (S)-2-amino-3,3-dimethylbutanoic acid compound of formula-25 (5 g), triethylamine (6.42 ml) and dichloromethane (35 ml) at 25-30°C for a period of 30 minutes. The reaction mixture was heated to 40-45°C and stirred for 3 hours. The reaction mixture containing (S)-trimethylsilyl 2-amino-3,3-dimethylbutanoate compound of formula-25a was cooled to 25-30°C. N,N-carbonyl diimidazole (6.8 g) was added to a mixture of 2-methylpropan-2-amine hydrochloride compound of formula-26a (7.5 g) and tetrahydrofuran (15 ml) at 25-30°C and stirred for 3 hours at 25-30°C. This reaction mixture was slowly added to the reaction mixture containing compound of formula-26a at 25-30°C for a period of 30 minutes and stirred for 10 hours at 25-30°C. After completion of the reaction, water followed by dichloromethane were added to the reaction mixture and pH of the reaction mixture was adjusted to 2.5 using 6N hydrochloric acid. The reaction mixture stirred for 15 minutes. Both the organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane. Both the organic layers were combined, washed with 10% sodium chloride solution, dried with sodium sulfate and then distilled under reduced pressure to get title compound. Yield: 6 gms.

Example-9: Preparation of 6,6-dimethyI-3-azabicyclo[3.1.0]hexane-2-carbonitrile (Formula-34)

A solution of 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33 (25 g) in toluene (150 ml) was cooled to 0-5°C and triethylamine (47.0 ml) was added to it at 0-5°C. Acetone cyanohydrin (38.6 ml) was slowly added to the reaction mixture at 0-5°C and stirred for 6 hours at the same temperature. Water was added to the reaction mixture and stirred for 10 minutes at 0-5°C. Both the organic and aqueous layers were separated, the aqueous layer was extracted with toluene (25.0 ml). The organic layers were combined and washed with water. The organic layer was dried with sodium sulfate and taken to the next step without isolating the title

compound from the recation mixture.

Example-10: Preparation of l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo [3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea (ForniuIa-35)

The organic layer containing 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34 which is obtained in example-9 was cooled to 0-5°C. (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 (40 g) followed by l-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (39.8 g), 2,6-lutidine (40.5 ml) were added to the reaction mixture at 0-5°C. The temperature of the reaction mixture was raised to 30-35°C and stirred for 5 hours at 30-35°C. The reaction mixture was cooled to 0-5°C and treating it with 2N hydrochloric acid followed by 10% sodium bicarbonate and 10% sodium chloride solution. Distilled off the solvent completely from the reaction mixture under reduced pressure to provide title compound as a residue. The obtained compound is purified by column chromatography using cyclohexane:ethyl acetate (8:2) to get title compound as a solid.

Yield: 30 gms; Melting range: 140-150°C; DIP-MS (APCI +) m/z = 349.4.

Example-ll: Preparation of methyl 3-((S)-2-(3-tert-butyIureido)-3,3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (Formula-36a)

A mixture of l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo [3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35 (10 g) and methanol (100 ml) was cooled to 0-5°C. Thionyl chloride (12.4 ml) was slowly added to the reaction mixture at 0-5°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 5 hours. After completion of the reaction, the reaction mixture was cooled to 0-5°C and water was added to it. Both the organic and aqueous layers were separated, organic layer was washed with water and the solvent from the organic layer was distilled off completely to get title compound as a solid.

Yield: 10 gms; Melting range: 135-140°C; purity by HPLC: 97.5%.

Example-12: Preparation of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (Formula-37)

Water (70 ml) followed by lithium hydroxide mono hydrate (1.15 gm) was added to a mixture of methyl 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylate compound of formula-36a (7 g) and tetrahydrofuran (70 ml) and stirred for 6 hours at 25-30°C. After completion of the reaction, water followed by ethyl acetate were added to the reaction mixture and stirred for 15 minutes. Both the organic and

aqueous layers were separated; the aqueous layer was acidified with cone. Hydrochloric acid. The aqueous layer was extracted twice with dichloromethane, and then washed with sodium chloride solution. Distilled off the solvent from the organic layer to get the title compound as a solid. Yield: 6.0 gms; purity by HPLC: 50.38%; SRSR isomer impurity: 46.25%.

Example-13: Preparation of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (Formula-37)

A mixture of l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35 (20 g) and conc.hydrochloric acid (160 ml) was stirred for 10 hours at 25-30°C. Water followed by dichloromethane were added to the reaction mixture. Both the organic and aqueous layers were separated; the organic layer was washed with water and then distilled off the solvent completely to get title compound as a residue. Yield: 19 gms.

Example-14: Preparation of (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (Formula-29)

(S)-l, 2,3,4-tetrahydronaphthal en- 1-amine (23.2 g) was added to a mixture of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0]hexane-2-carboxylic acid compound of formula-37 (58 g) and ethyl acetate (290 ml) at 25-30°C and stirred for 30 hours at the same temperature. Filtered the unwanted isomer as a solid, 2N hydrochloric acid (116 ml) was added to the obtained filtrate at 25-30°C and stirred for 20 minutes. Separated the organic and aqueous layers and the organic layer was washed with aquoeus sodium chloride solution. Distilled off the solvent from the organic layer to get title compound as a solid.

Yield: 27 gms; Melting range: 130- 150°C; Purity by HPLC: 98.62%; SRSR isomer impurity: 0.02%.

Example-15: Preparation of (S)-l,2,3,4-tetrahydronaphthalen-l-amine salt of (1R,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethyIbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0] hexane-2-carboxylate (Formula-38a)

(S)-l,2,3,4-tetrahydronaphthalen-l-amine (23.2 g) was added to a mixture of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0]hexane-2-carboxylic acid compound of formula-37 (58 g) and ethyl acetate (290 ml) at 25-30°C and stirred for 30 hours at the same temperature. After completion of the reaction, filtered the reaction mixture, distilled off the solvent from the filtrate to get title compound. Yield: 54 gms.

Example-16: Preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxamide (Formula-30)

1-Hydroxybenzotriazole (1.83 g) followed by 3-amino-4-cyclobutyl-2-hydroxy butanamide hydrochloride salt compound of formula-2a (6.24 g) and diisopropylethylamine (5.68 ml) was added to a pre-cooled mixture of (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-29 (10 g) and dichloromethane (100 ml) at 0-5°C. A solution of N,N'-dicyclohexylcarbodiimide (6.16 g) in dichloromethane (30 ml) was slowly added to the reaction mixture at 0-5°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 5 hours. After completion of the reaction, filtered the reaction mixture through hyflow bed and washed the bed with dichloromethane. Further the organic layer was washed with dilute hydrochloric acid followed by aqueous sodiumbicarbonate solution and then with sodium chloride solution. Distilled off the solvent from the organic layer to get title compound as a solid. Yield: 13 gms.; Melting range: 125-145°C; Purity by HPLC: 99.10%.

Example-17: Preparation of Boceprevir (Formula-1)

A mixture of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30 (10 g) and dichloromethane (200 ml) was cooled to 0-5°C. Dess-martin periodinane (10.56 g) was added to the reaction mixture at 0-5°C; the temperature of the reaction mixture was raised to 25-30°C and stirred for 2 hours at 25-30°C. After completion of the reaction, filtered the reaction mixture through hyflow bed and washed the bed with dichloromethane. The filtrate was cooled to 0-5°C, a solution of sodium thio sulfate (5 g), sodium bicarbonate (5 g) in water (100 ml) was added to the filtrate and stirred for 30 minutes. Both the organic and aqueous layers were separated, sodium bicarbonate solution was added to organic layer. The organic and aqueous layers were separated, washed the organic layer with sodium chloride solution and distilled off the solvent from the organic layer completely under reduced pressure to get title compound as a solid.

Yield: 8.8 gms; Melting range: 130-140°C; purity by HPLC: 99.3%.

Example-18: Preparation of (lR,2S,5S)-tert-butyl2-(4-amino-l-cyclobutyl-3-hydroxy-4-oxo butan-2-ylcarbamoyl)-6,6-dimethyI-3-azabicyclo[3.1.0]hexane-3-carboxylate (Formula-45)

A mixture of (lR,2S,5S)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-44 (6 g), dichloromethane (90 ml) and dimethylformamide (90 ml) was cooled to 0-5°C. 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 (4.9 g) followed by 1-hydroxybenzotriazole (4.7 g), l-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (6.7 g) and diisopropylethylamine (12.2 ml) were added to the reaction mixture. The temperature of the reaction mixture was raised to 25-30°C and stirred for 6 hours. Water followed dichloromethane was added to the reaction mixture. Both the organic and aqueous layers were separated; the organic layer was washed with hydrochloric acid solution followed by sodium bicarbonate solution and sodium chloride solution. Distilled off the solvent from the organic layer under reduced pressure to get the title compound. Yield: 8 gms.

Example-19: Preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide hydrochloride (Formula-46a)

Isopropanolic hydrochloride (12 ml) was added to a mixture of (lR,2S,5S)-tert-butyl 2-(4-amino-1-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0] hexane-3-carboxylate compound of formula-45 (6 g) and isopropanol (30 ml). The reaction mixture was heated to 60-65°C and stirred for 6 hours at the same temperature. After completion of the reaction, the reaction mixture was concentrated to get title compound. Yield: 4. 9 gms.

Example-20: Preparation of (lR,2S,5S)-N-(4-amino-l-cycIobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butyIureido)-3,3-dimethyIbutanoyl)-6,6-dimethyl-3-azabicycIo[3.1.0] hexane-2-carboxamide (Formula-30)

(S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 (2 g), followed by 6>-(7-azabenzotriazol-l-yl)-*N*,*N*,*N'*,*N'*-tetramethyluroniumhexafluorophosphate (3.92 g) and diisopropyl ethylamine (4.5 ml) were added to a mixture of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-6,6-dimethyl-3-azabicyclo[3 .1.0]hexane-2-carboxamide hydrochloride compound of formula-46a (3 g) and acetonitrile (60 ml) at 25-30°C and stirred for 5 hours. After completion of the reaction, water followed by ethyl acetate were added to the reaction mixture at 25-30°C and stirred for 10 minutes. Both the organic and aqueous layers were separated; the organic layer was washed with sodium bicarbonate solution followed by sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get residue. Co-distillation of the obtained residue with cyclohexane to get title

compound. Yield: 4.5 gms.

Example-21: Preparation of 3-benzyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (Formula-40)

Benzyl amine (229.5 g) was slowly added to a mixture of caronic anhydride compound of formula-39 (250 g) and methyl tert-butyl ether (500 ml) at 25-30°C and stirred for 45 minutes at the same temperature. After completion of the reaction, the solvent from the reaction mixture was distilled off at a temperature below 70°C. Further the reaction mixture was heated to 135-140°C and stirred for 6 hours under distillation mode. The reaction mixture was cooled to 55-60°C and 5% aqueous isopropanol was added to it, further the reaction mixture was cooled to 0-5°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid, washed with isopropanol and then dried to get title compound. Yield: 330 gms; Melting range: 80-90°C.

ExampIe-22: Preparation of 3-benzyl-6,6-dimethyI-3-azabicyclo[3.1.0]hexane (Formula-41)

A solution of 3-benzyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione compound of formula-40 (200 g) and toluene (600 ml) was added to a mixture of vitride (1133 g) and toluene (800 ml) at 25-30°C over a period of 3 hours and stirred the reaction mixture for 3 hours. After completion of the reaction, the reaction mixture was cooled to 0-5°C and quenched with a pre-cooled solution of sodium potassium tartarate (424 g) in water (1640 ml) at a temperature below 20°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 60 minutes. Separated both the organic & aqueous layer. Toluene (200 ml) was added to the below two layers. Again separated the upper organic layers. The two separated upper organic layers were combined and taken to the next step without isolation.

Example-23: Preparation of 6,6-dimethyl-3-azabicyclo[3.1.0]hexane hydrochloride (Formula-42a)

Methanol (850 ml) followed by Pd-C (20 g) was added to the organic layer containing 3-benzyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane compound of formula-41 obtained in example-22 under nitrogen atmosphere. Hydrogen gas was passed through the reaction mixture with a pressure of 4.0 kg/cm^2. The reaction mixture was heated to 40-45°C and stirred for 10 hours. The reaction mixture was cooled to 5-10°C, and filtered through hyflow bed. Hydrochloric acid (200 ml) was added to the filtrate at 25-30°C and stirred for 15 minutes. Distilled off the solvent completely from the reaction mixture under reduced pressure. The reaction mixture was co-distilled with methyl tertiary butyl ether. Isopropanol (100 ml) was added to the reaction mixture

at 55-60°C and stirred for 15 minutes. The reaction mixture was cooled to 25-30°C, methyl tertiary butyl ether (700 ml) was slowly added to it and stirred for 1 hour at 25-30°C. Filtered the precipitated solid, washed with methyl tert-butyl ether and then dried to get title compound. Yield: 92 gms; Melting range: 147-157°C.

Example-24: Preparation of 3-chloro-6,6-dimethyl-3-azabicyclo [3.1.0] hexane (Formula-43)

Sodium hypochlorite solution (120 ml) was slowly added to a mixture of 6,6-dimethyl-3-azabicyclo[3.1.0]hexane hydrochloride compound of formula-42a (25 g) and toluene (125 ml) at 30-35°C and stirred for 45 minutes at the same temperature. After completion of the reaction, both the organic and aqueous layers were separated and the aqueous layer was extracted with toluene (25 ml). Both the organic layers were combined, washed with 10% sodium thiosulfate solution followed by sodium chloride solution. This organic layer containing the title product can be used to next step without isolation.

Example-25: Preparation of 6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-ene (Formula-33)

Sodium methoxide (19.0 g) was added to the organic layer obtained in example-24. A solution of tert-butyl ammonium bromide (0.54 g) in dichloromethane (12.5 ml) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 40-45°C and stirred for 8 hours. Cooled the reaction mixture to 25-30°C and the reaction mixture was quenched with water. Both the organic and aqueous layers were separated; the aqueous layer was extracted with toluene. Both the organic layers were combined and washed with water followed by sodium chloride solution. This organic layer containing the title compound can be used to next step without isolation. Purity by GC: 96.9%

Example-26: Preparation of 6,6-dimethyI-3-azabicyclo[3.1.0]hexane-2-carbonitrile (Formula-34)

The organic layer containing compound of formula-33 obtained in example-25 was cooled to 0-5°C and triethylamine (47.0 ml) was added to it at 0-5°C. Acetone cyanohydrin (38.6 ml) was slowly added to the reaction mixture at 0-5°C and stirred for 6 hours at the same temperature. After completion of the reaction, water was added to the reaction mixture and stirred for 10 minutes at 0-5°C. Both the organic and aqueous layers were separated, the aqueous layer was extracted with toluene (25.0 ml). The organic layers were combined and washed with water. This organic layer containing the title compound was taken to the next step without isolation.

Example-27: Preparation of tert-butyl 2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (Formula-47)

Di tert-butyl dicarbonate (37.0 g) was added to the organic layer containing compound of formula-34 obtained in example-26 at 0-5°C. The temperature of the reaction mixture was raised to 30-35°C and stirred for 5 hours at 30-35°C. After completion of the reaction, water was added to the reaction mixture. Both the organic and aqueous layers were separated, washed the organic layer with sodium chloride solution and distilled off the solvent from reaction mixture under reduced pressure to provide title compound as a residue. This residue is taken to the next step without isolation. Purity by GC: 83.18%

Example-28: Preparation of methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (Formula-48a)

Trimethyl silyl chloride (198 g) was slowly added to a solution of tert-butyl 2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate compound of formula-47 obtained in example-27 in methanol (540 ml) at 20-25°C. The reaction mixture was heated to 50-55°C and stirred for 12 hours at the same temperature. After completion of the reaction, the mixture was cooled to 15-20°C and stirred for 45 mins. Filtered the unwanted product, washed with methanol. Distilled off the solvent completely from the filtrate and then co-distilled with methyl tert-butyl ether. Isopropanol (126 ml) was added to the obtained compound at 50-55°C and stirred for 30 mins. The reaction mixture was cooled to 25-30°C and methyl tert-butyl ether (504 ml) was slowly added and stirred for 1 hour at 25-30°C. Filtered the precipitated solid, washed with methyl tert-butyl ether and then dried to get title compound. Yield: 20 gms; Melting range: 145-155°C; Purity by GC: 99.43%; $[a]_D^{25}$ = -0.078° (c=l% in methanol at wave length 589 nm).

Example-29: Preparation of ethyl 2-(diphenylmethyleneamino)acetate hydrochloride (Formula-3a)

Glycine ethyl ester hydrochloride (38 g) was added to a mixture of benzophenone imine (50 g) and dichloromethane (38 g) and stirred for 5 hours at 25-30°C. After completion of the reaction, water was added to the reaction mixture and stirred for 20 mins. Both the organic and aqueous layers were separated; the solvent from the organic layer was distilled off completely to provide title compound as a residue. The residue was taken to the next step.

Example-30: Preparation of ethyl 2-amino-3-cyclobutyl propanoate (Formula-4a)

The residue obtained in example-29 was dissolved in tetrahydrofuran (150 ml) by heating

to 50°C. Cyclobutylmethyl bromide (37 g) followed by a solution of potassium tert-butoxide (28 g) in tetrahydrofuran (150 ml) were added to the reaction mixture under nitrogen atmosphere at 50-55°C and stirred for 6 hours. The reaction mixture was cooled to 5-10°C, a solution of hydrochloric acid (74 ml) in water (148 ml) was added to it at a temperature below 15°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 7 hours. After completion of the reaction, the reaction mixture containing title compound is taken to the next step.

Example-31: Preparation of ethyl 2-(tert-butoxycarbonylamino)-3-cyclobutyIpropanoate (Formula-5b)

The reaction mixture obtained in example-30 is cooled to 0-5°C. Potassium carbonate (110 g) was added to the reaction mixture in lot wise at 0-5°C. Ditert-butyl dicarbonate (45.2 g) was slowly added to the reaction mixture at 0-5°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 2 hours. After completion of the reaction, the reaction mixture was taken to the next step without isolation.

Example-32: Preparation of 2-(tert-butoxycarbonylamino)-3-cycIobutylpropanoic acid (Formula-49)

A solution of lithium hydroxide monohydrate (50 g) in water (500 ml) was added to the reaction mixture obtained in example-31 at 25-30°C. The reaction mixture was heated to 60-70°C and stirred for 5 hours. After completion of the reaction, the reaction mixture was cooled to 25-30°C. Filtered the reaction mixture to remove the by-products and washed with toluene. The filtrate containing the desired product is stirred for 15 mins and both the organic and aqueous layers were separated. Both the aqueous layers were combined and dichloromethane was added to it and cooled to 5-10°C. pH of the reaction mixture was adjusted to 3 by using aqueous ortho phosphoric acid solution at 0-5°C and stirred for 15 mins. Both the organic and aqueous layers were separated; the aqueous layer was extracted with dichloromethane. Both the organic layers were combined, washed with sodium chloride solution and distilled off the solvent from the organic layer completely and then co-distilled with cyclohexane. Cyclohexane (150 ml) was added to the obtained compound and the reaction mixture was cooled to 25-30°C and stirred for 15 mins. Further the reaction mixture was again cooled to 10-15°C and stirred for 60 mins. Filtered the precipitated solid, washed with cyclohexane and then dried to get title compound. Yield: 40 gms; Melting range: 103-1 10°C.

PXRD of the obtained compound is illustrated in figure- 1.

Example-33: Preparation of tert-butyl 3-cyclobutyl-l-(methoxy(methyi)amino)-l-oxopropan-2-ylcarbamate (Formula-50)

A mixture of carbonyl diimidazole (20 g) and tetrahydrofuran (50 ml) was cooled to 0-5°C. A solution of 2-(tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid compound of formula-49 (25 g) in tetrahydrofuran (50 ml) was added slowly to the reaction mixture at 0-5°C and stirred for 3 hours. N,O-dimethyl hydroxylamine hydrochloride (16 g) followed by diisopropyl ethylamine (16 g) was added to the reaction mixture at 0-5°C and stirred for 2 hours. After completion of the reaction, water followed by ethyl acetate were added to the reaction mixture and stirred for 15 mins. Both the organic and aqueous layers were separated; the aqueous layer was extracted with ethyl acetate. Both the organic layers were combined and cooled to 0-5°C. The organic layer was washed with hydrochloric acid solution followed by sodium bicarbonate solution. Distilled off the solvent completely from the organic layer and then co-distilled with cyclohexane. The crude compound was cooled to 25-30°C and cyclohexane (50 ml) was added to the reaction mixture and stirred for 20 mins. The reaction mixture was cooled to 10-15°C and stirred for 60 mins. Filtered the precipitated solid, washed with cyclohexane and then dried to get title compound Yield: 26 gms; Melting range: 95-98°C; Purity by HPLC: 99.9%.

Example-34: Preparation of tert-butyl l-cyclobutyl-3-oxopropan-2-ylcarbamate (Formula-51)

70% Vitride solution (38.0 ml) was slowly added to a pre-cooled mixture of tert-butyl 3-cyclobutyl-l-(methoxy(methyl)amino)-l-oxopropan-2-ylcarbamate compound of formula-50 (25 g) and dichloromethane (125 ml) at -5 to 0°C and stirred for 2 hours. A solution of sodium potassium tartarate (35 g) in water (100 ml) was added to the reaction mixture at temperature below 5°C and stirred for 15 mins. Both the organic layers were separated; the aqueous layer was extracted with dichloromethane. Both the organic layers were combined, washed with water followed by sodium chloride solution. This organic layer containing title compound is used for next step without distillation of the compound.

Example-35: Preparation of tert-butyl l-cyano-3-cyclobutyl-l-hydroxypropan-2-ylcarbamate (Formula-52)

Triethylamine (10.9 g) was added to the organic layer containing the compound of

formula-51 obtained in example-34. Acetone cyanohydrin (12.5 ml) was added to the reaction mixture at 0-5°C and stirred for 10 hours. After completion of the reaction, the reaction mixture was quenched with 10%sodium carbonate solution. Both the organic and aqueous layers were separated; the aqueous layer was extracted with dichloromethane. Both the organic layers were combined, cooled to 0-5°C and washed with 10% hydrochloric acid followed by 10% sodium chloride solution. Distilled off the solvent from the organic layer under reduced pressure to provide title compound as a residue. Yield: 20 gms.

Example-36: Preparation of tert-butyl 4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamate (Formula-lla)

A solution of sodium hydroxide (0.6 g) in water (10 ml) was added to a mixture of tert-butyl l-cyano-3-cyclobutyl-l-hydroxypropan-2-ylcarbamate compound of formula-52 (25 gms) and dimethyl sulfoxide (100 ml) at 25-30°C and stirred for 10 minutes. Hydrogen peroxide (15 ml) was slowly added to the reaction mixture at 25-30°C and stirred for 3 hours. After completion of the reaction, water was added to the reaction mixture at a temperature below 10°C and stirred for 60 mins. Filtered the precipitated solid, washed with water and then dried to get title compound. Yield: 20 gms; Melting range: 175-180°C ; Purity by HPLC: 90.44%.

Example-37: Preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride (Formula-2a)

Isopropanolic hydrochloric acid (200 ml) was added to a mixture of tert-butyl 4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl carbamate compound of formula-lla (100 g) and isopropanol (300 ml) at 25-30°C. The reaction mixture was heated to 55-60°C and stirred for 3 hours. After completion of the reaction, the reaction mixture was cooled to 25-30°C and stirred for 1 hour. Filtered the precipitated solid, washed with isopropanol and then dried to get title compound. Yield: 70 gms; Melting range: 200-2 10°C; Purity by HPLC: 99.4%.

ExampIe-38: Preparation of methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (Formula-48a) using trimethylsilyl chloride and with BOC protection

Trimethyl silyl chloride (198 g) was slowly added to a solution of tert-butyl 2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate compound of formula-47 (115 g) in methanol (540 ml) at 20-25°C. The reaction mixture was heated to 50-55°C and stirred for 12 hours at the same temperature. After completion of the reaction, the mixture was cooled to 15-20°C and stirred for 45 mins. Filtered the unwanted product, washed with methanol. Distilled off the

solvent completely from the filtrate and then co-distilled with methyl tert-butyl ether. Isopropanol (126 ml) was added to the obtained residue at 50-55°C and stirred for 30 mins. The reaction mixture was cooled to 25-30°C, methyl tert-butyl ether (504 ml) was added to it over a period of 2 hours and stirred for 1 hour. Filtered the precipitated solid, washed with methyl tert-butyl ether and then dried to get title compound.

Yield: 73 gms; % yield: 73.0%; Purity by GC: 99.14%: Melting range: 149-152°C.

Example-39: Preparation of methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (Formula-48a) using methanolic hydrochloric acid

A mixture of Tert-butyl 2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate compound of formula-47 (20 g) and methanolic hydrochloric acid (80 ml) was heated to 50-55°C and stirred for 6 hours. The reaction mixture was cooled to 25-30°C and stirred for 45 mins. Filtered the bi product and distilled off the solvent from the filtrate under reduced pressure and then co-distilled with methyl tert-butyl ether. Isopropanol (28 ml) was added to the obtained residue at 50-55°C and stirred for 30 mins at the same temperature. The reaction mixture was cooled to 25-30°C, added methyl tert-butyl ether (112 ml) to it over a period of 2 hours and stirred for 60 mins. Filtered the solid, washed with methyl tert-butyl ether and then dried to get title compound.

Yield: 11.6 gms; % yield: 41.66%; Melting range: 136-139°C; Purity by GC: 48.32%.

Example-40: Preparation of methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride (Formula-48a) without BOC protection

Trimethyl silyl chloride (20 g) was added to a solution of 6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carbonitrile compound of formula-34 (5 g) in methanol (15 ml) at 25-30°C for about 30-45 minutes. The reaction mixture was heated to 50-55°C and stirred for 6 hours. After completion of the reaction, the reaction mixture was cooled to 25-30°C and stirred for 45 mins. Filtered the bi-product, washed with methanol and distilled off the solvent from the filtrate under reduced pressure and then co-distilled with methyl tert-butyl ether. Isopropanol (7 ml) was added to the obtained residue at 50-55°C and stirred for 30 mins. The reaction mixture was cooled to 25-30°C. Methyl tert-butyl ether (28 ml) was added to the reaction mixture over a period of 2 hours and stirred for 60 mins. Filtered the solid and dried to get title compound. Yield: 1.3 g; Yield: 29.87%; Melting range: 148-152°C.

Example-41: Preparation of (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethyl

butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (Formula-29)

A mixture of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 (50 g), (lR,2S,5S)-methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate hydrochloride compound of formula-53a (49.1 g), 1-hydroxybenzotriazole (5.8 g) and dichloromethane (500 ml) was cooled to 0-5°C. Diisopropylethylamine (45.3 ml) was added to the reaction mixture and stirred for 10 minutes at 0-5°C. A solution of N,N'-Dicyclohexylcarbodiimide (49.2 g) in dichloromethane (150 ml) was added to the reaction mixture. Temperature of the reaction mixture was raised to 25-30°C and stirred for 6 hours at the same temperature. After completion of the reaction, filtered the un-wanted solid and washed the bed with dichloromethane. The filtrate was washed with hydrochloric acid solution followed by sodium bicarbonate solution and sodium chloride solution. Distilled of the solvent from the organic layer to get (lR,2S,5S)-methyl 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylate compound of formula-54 as a residue. The residue was dissolved in tetrahydrofuran (250 ml). A solution of lithium hydroxide monohydrate (14.5 g) and water (250 ml) was added to the reaction mixture and stirred for 6 hours at 25-30°C. Water followed by ethyl acetate were added to the reaction mixture and stirred for 15 minutes. Both the organic and aqueous layers were separated; dichloromethane was added to the aqueous layer and pH of the reaction mixture was adjusted to below 3 by using dilute hydrochloric acid solution. Both the organic and aqueous layers were separated; the aqueous layer was extracted with dichloromethane. All the organic layers were combined and washed with sodium chloride solution. Distilled off the solvent from the organic layer and then co-distilled with cyclohexane. The obtained residue was cooled to 25-30°C, cyclohexane (375 ml) was added to the reaction mixture and stirred for 20 minutes. Filtered the solid and washed with cyclohexane. The obtained wet solid was added to a mixture of methyl tertiary butyl ether (250 ml) and cyclohexane (250 ml). The reaction mixture was heated to 65-70°C and stirred for 30 minutes at the same temperature. The reaction mixture was cooled to 10-15°C. Filtered the precipitated solid, washed with cyclohexane and then dried to get title compound as a solid. Yield: 60 gms.

Example-42: Preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyI-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butyIureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxamide (Formula-30)

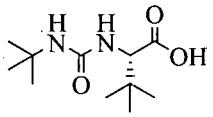
1-Hydroxybenzotriazole (1.83 g) followed by 3-amino-4-cyclobutyl-2-

hydroxybutanamide hydrochloride salt (6.24 g) and diisopropylethylamine (5.68 ml) was added to a pre-cooled mixture of (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid (10 g) and dichloromethane (100 ml) at 0-5°C. A solution of N,N'-dicyclohexylcarbodiimide (6.16 g) in dichloromethane (30 ml) was slowly added to the reaction mixture at 0-5°C. The temperature of the reaction mixture was raised to 25-30°C and stirred for 5 hours. After completion of the reaction, filtered the reaction mixture through hyflow bed and washed the bed with dichloromethane. Further the organic layer was treated with dilute hydrochloric acid followed by sodium bicarbonate solution and then with sodium chloride solution. Distilled off the solvent from the organic layer to get title compound as a solid. Yield: 13 gms.; Melting range: 125-145°C; Purity by HPLC: 99.10%.

We claim:

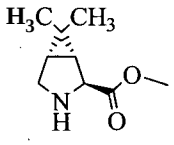
1. A process for the preparation of Boceprevir compound of formula-1, comprising of:

a) Condensing the (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27



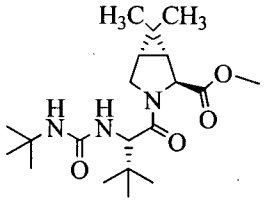
Formula-27

with (1R,2S,5S)-methyl 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-53



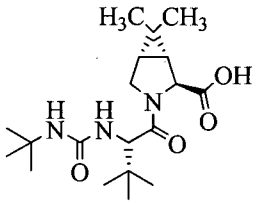
Formula-53

or its acid-addition salt in dichloromethane, in presence of dicyclohexyl carbodiimide, 1-hydroxy benzotriazole and diisopropyl ethylamine to provide (1R,2S,5S)-methyl 3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3 .1 .0]hexane-2-carboxylate compound of formula-54,



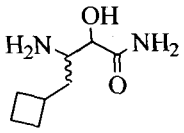
Formula-54

b) hydrolyzing the compound of formula-54 in a mixture of tetrahydrofuran and water in presence of lithium hydroxide to provide (1R,2S,5S)-3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-29,



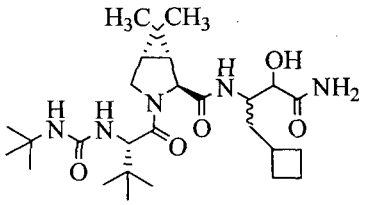
Formula-29

c) condensing the compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2



Formula-2

or its acid-addition salt in presence of dicyclohexylcarbodiimide in a suitable solvent, optionally in presence of a base and/or a catalyst to provide (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethyl butanoyl) -6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30,



Formula-30

d) oxidizing the compound of formula-30 using dess-martin periodinane in dichloromethane to provide Boceprevir compound of formula-1.

2. The process according to claim-1, wherein,

in step-c) the base is selected from inorganic bases such as alkali metal hydroxides, carbonates, bicarbonates; and organic bases; the catalyst is selected from triazole, benzotriazole and substituted benzotriazole such as hydroxy benzotriazole (HOBt), l-hydroxy-7-azabenzotriazole (HOAt), 1-hydroxy-lH-1,2,3-triazole-4-carboxylate (HOCt) and N-hydroxy succinamide (HOSu); and the suitable solvent is selected from ester solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, ketone solvents, alcoholic solvents, *chloro* solvents, nitrile *solvents, polar solvents and/or mixtures thereof.*

3. A process for the preparation of Boceprevir compound of formula-1, comprising of:

a) Condensing (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 with (lR,2S,5S)-methyl 6,6-dimethyl-3-azabicyclo[3.1 .0]hexane-2-carboxylate hydrochloride compound of formuia-53a in dichloromethane, in presence of dicyclohexyi carbodiimide, 1-hydroxy benzotriazole and diisopropyl ethylamine to provide (1R,2S,5S)-methyl 3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo

[3.1.0]hexane-2-carboxylate compound of formula-54,

b) hydrolyzing the compound of formula-54 in a mixture of tetrahydrofuran and water, in presence of lithium hydroxide to provide (lR,2S,5S)-3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-29,

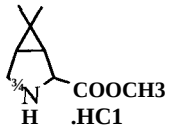
c) condensing the compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride compound of formula-2a in dichloromethane, in presence of dicyclohexyl carbodiimide, 1-hydroxy benzotriazole and diisopropyl ethylamine to provide (1R,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxamide compound of formula-30,

d) oxidizing the compound of formula-30 using dess-martin periodinane in dichloromethane to provide Boceprevir compound of formula-1.

4. A process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30, comprising of condensing the (lR,2S,5S)-3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt in presence of dicyclohexylcarbodiimide in a suitable solvent, optionally in presence of a base and/or a catalyst to provide compound of formula-30.

5. A process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30, comprising of condensation of (lR,2S,5S)-3-((R)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride salt compound of formula-2a in dichloromethane, in presence of dicyclohexyl carbodiimide, 1-hydroxy benzotriazole and diisopropyl ethylamine to provide compound of formula-30.

6. An improved process for the preparation of methyl 6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylate hydrochloride compound of formula-48a,



Formula-48a

Comprising of,

a) chlorinating the 6,6-dimethyl-3-azabicyclo[3.1.0]hexane compound of formula-42 or its acid-addition salt

Fourmula-42

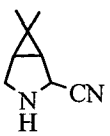
with sodium hypochlorite in toluene provides 3-chloro-6,6-dimethyl-3-azabicyclo [3.1.0]hexane compound of formula-43,

Formula-43

the obtained compound in-situ is treated with sodium methoxide in presence of tetrabutyl ammonium bromide in a mixture of toluene and dichloromethane provides 6,6-dimethyl-3-azabicyclo[3.1.0]hex-3-ene compound of formula-33,

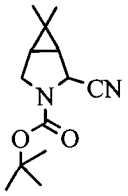
Formula-33

b) reacting the compound of formula-33 in-situ with acetone cyanohydrin and triethyl amine provides 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34,



Formula-34

c) reacting the compound of formula-34 in-situ with ditert-butyldicarbonate to provide tert-butyl 2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate compound of formula-47,



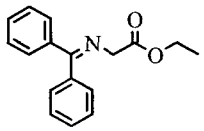
Formula-47

d) reacting the compound of formula-47 in-situ with methanol in presence of catalyst such as trimethylsilyl chloride or thionyl chloride to provide methyl 6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylate hydrochloride compound of formula-48a.

7. A process for the preparation of (lR,5S)-methyl 6,6-dimethyl-3-azabicyclo[3. 1.0]hexane-2-carboxylate hydrochloride compound of formula-48a, comprising of reacting the tert-butyl 2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate compound of formula-47 with methanol in presence of trimethylsilyl chloride provides compound of formula-48a.

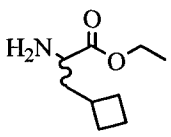
8. An improved process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride salt compound of formula-2a, which comprises of:

a) Reacting the ethyl 2-(diphenylmethyleneamino)acetate compound of formula-3A or its acid-addition salt



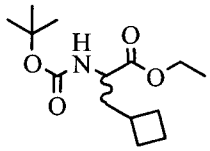
Formula-3A

with cyclobutylmethylbromide in presence of potassium tert-butoxide in tetrahydrofuran, followed by treating with an aqueous hydrochloric acid to provide ethyl 2-amino-3-cyclobutylpropanoate compound of formula-4a,



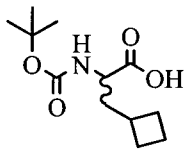
Formula-4a

b) treating the compound of formula-4a in-situ with ditert-butyl dicarbonate in presence of potassium carbonate to provide ethyl 2-(tert-butoxycarbonylamino)-3-cyclobutyl propanoate compound of formula-5b,



Formula-5b

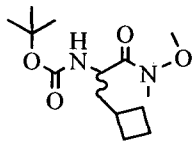
c) hydrolyzing the compound of formula-5b in-situ in presence of aqueous lithium hydroxide provides 2-(tert-butoxycarbonylamino)-3-cyclobutyl propanoic acid compound of formula-49,



Formula-49

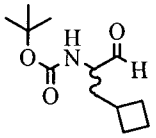
d) isolating the compound of formula-49 as a solid using hydrocarbon solvent such as cyclohexane,

e) condensation of 2-(tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid compound of formula-49 with N,O-dimethylhydroxylamine hydrochloride in tetrahydrofuran, in presence of carbonyl diimidazole (CDI) and diisopropyl ethylamine to provide tert-butyl 3-cyclobutyl-l-(methoxy(methyl)amino)-l-oxopropan-2-ylcarbamate compound of formula-50,



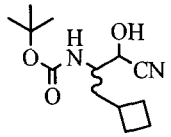
Formula-50

f) reducing the compound of formula-50 with vitride in a mixture of toluene and dichloromethane provides tert-butyl l-cyclobutyl-3-oxopropan-2-ylcarbamate compound of formula-51,



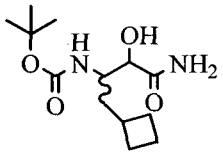
Formula-5 1

g) reacting the compound of formula-51 in-situ in presence of acetone cyanohydrin and triethylamine provides tert-butyl l-cyano-3-cyclobutyl-l-hydroxypropan-2-ylcarbamate compound of formula-52,



Formula-52

h) converting the compound formula-52 to tert-butyl 4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamate compound of formula- 11a



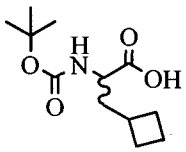
Formula-lla

by treating it with hydrogen peroxide in presence of aqueous sodium hydroxide in dimethylsulfoxide,

i) deprotecting the compound of formula-lla using isopropanolic hydrochloride in isopropanol provides compound of formula-2a.

9. 2-(Tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid as a crystalline solid.

10. The crystalline solid compound of 2-(tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid (designated as crystalline form-M) according to claim-9,



Formula-49

is characterized by its powder X-ray powder diffractogram having peaks at 8.05, 13.7, 13.9, 19.5, 20.4 and 21.3± 0.2 theta and substantially as shown in figure- 1.

11. A process for the preparation of crystalline form-M of 2-(tert-butoxycarbonylamino)-3-cyclobutylpropanoic acid compound of formula-49, comprising of:

a) Adding a solution of lithium hydroxide in water to a solution of ethyl 2-

(tert-butoxycarbonylamino)-3-cyclobutyl propanoate compound of formula-5b in tetrahydrofuran,

b) heating the reaction mixture to 60-70°C and stirring the reaction mixture at the same temperature,

c) filtering the reaction mixture and washing with toluene,

d) separating the organic and aqueous layers from the filtrate,

e) adding dichloromethane to the aqueous layer,

f) acidifying the reaction mixture with orthophosphoric acid solution,

g) separating the organic and aqueous layers,

h) distilling off the solvent from the organic layer,

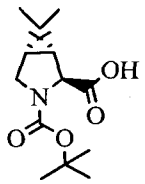
i) adding cyclohexane to the compound obtained in step-(i),

j) cooling the reaction mixture to 10-15°C and stirring the reaction mixture,

k) filtering the precipitated solid, washing with cyclohexane and then dried to get crystalline form-M of compound of formula-49.

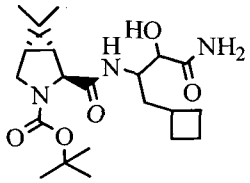
12. A process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-aza bicycle[3.1.0] hexane-2-carboxamide compound of formula-30, comprising of:

a) Condensing the (lR,2S,5S)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-44



Formula-44

with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst provides. (lR,2S,5S)-tert-butyl 2-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0] hexane-3-carboxylate compound of formula-45,



Formula-45

b) deprotecting of the compound of formula-45 with a suitable deprotecting agent in a suitable solvent provides (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-46, Optionally converting it into its acid-addition salt,

c) condensing the compound of formula-46 or its acid-addition salt with (S)-2-(3-tert-butylureido)-3,3-dimethyl butanoic acid compound of formula-27 in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide compound of formula-30.

13. The process according to claim 12, wherein,

In step-(a) & step-(c) the suitable condensing agent is selected from alkyl (or) aryl chloroformates, alkyl or aryl sulfonyl halides, and alkyl or aryl sulfonyl anhydrides; carbonyldiimidazole (CDI), carbonyl ditriazole; carbodiimides, (benzotriazol-1-yloxy)tris(dimethyl amino)phosphonium hexafluorophosphate (BOP), *0-(7*-azabenzotriazol-l-y ^-*N* ,*NN'*,/V-tetramethyl uronium hexafluoro phosphate (HATU), (benzotriazol-l-yloxy)tripyrrolidino phosphonium hexafluoro phosphate (PyBOP), oxalyl chloride, thoinyl chloride, di phenylphosphoroazidate (DPPA) and $P_2 0_5$; the catalyst is selected from 1-hydroxy benzotriazole (HOBt), l-hydroxy-7-azatriazole (HOAt), l-hydroxy-lH-l,2,3-triazole-4-carboxylate (HOCt), N-hydroxy succinamide (HOSu) and (2-(lH-benzotriazol-l-yl)-l,l,3,3-tetra methyl uronium tetrafluoro borate (TBTU); and the base is selected from inorganic bases and organic bases;

In step-(b) the suitable deprotecting agent is selected from acids like hydrochloric acid, isopropanolic hydrochloric acid, ethyl acetate-hydrochloric acid, ether-hydrochloric acid, hydrobromic acid, sulfuric acid, periodic acid, formic acid, trichloroisocyanuric acid, phosphoric acid, acetic acid, p-toluene sulfonic acid and trifluoroacetic acid; hydrogenating agents such as palladium, palladium on carbon and rhodium on carbon under hydrogen pressure; bases like piperidine, ammonia and methylamine; ammonium

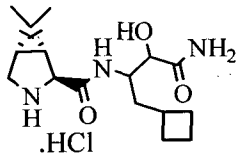
cerium (IV) nitrate; sodium in liquid ammonia; sodium naphthalenide and tetrabutyl ammonium fluoride; and

the suitable solvent in step-a) to step-c) is selected from ester solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, ketone solvents, alcoholic solvents, chloro solvents, nitrile solvents, polar solvents and/or mixtures thereof.

14. A process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-aza bicyclo[3.1.0] hexane-2-carboxamide compound of formula-30, comprising of:

a) Condensation of (lR,2S,5S)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo [3.1.0] hexane-2-carboxylic acid compound of formula-44 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 in a mixture of dichloromethane and dimethyl formamide, in presence of l-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (EDC-HC1), 1-hydroxybenzo triazole (HOBT) and diisopropylethylamine provides compound of formula-45,

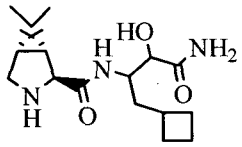
b) deprotecting the compound of formula-45 with isopropanolic-hydrochloride in isopropanol provides compound of formula-46a,



Formula-46a

c) condensation of compound of formula-46a with (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 in acetonitrile in presence of 0-(7-azabeiizotriazol-l-yl ***)-N,N,N,N***-tetramethyl uronium hexafluoro phosphate (HATU) and diisopropylethylamine (DIPEA) to provide compound of formula-30.

15. A process for the preparation of (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30, comprising of condensation of ((lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-46 or its acid-addition salt



Formula-46

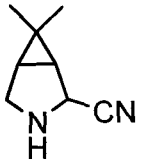
with (S)-2-(3-tert-butylureido)-3,3-dimethyl butanoic acid compound of formula-27 in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide compound of formula-30.

16. A process for the preparation of Boceprevir, comprises of;

a) reacting the 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33

Formula-33

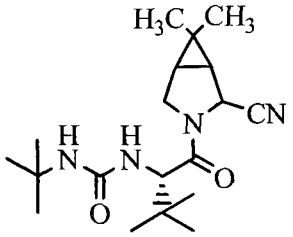
in presence of a suitable cyanating agent base in a suitable solvent, optionally in presence of an acid or a base to provide 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34,



Formula-34

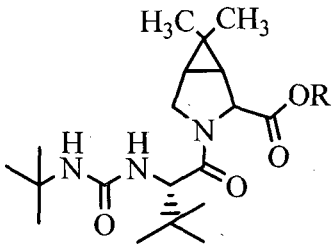
optionally isolating the compound of formula-34 as an acid-addition salt,

b) condensing the compound of formula-34 or its acid-addition salt with (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27 in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35,



Formula-35

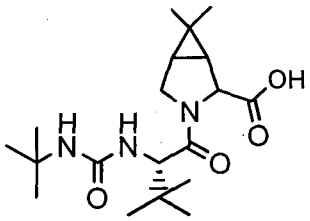
c) reacting the compound of formula-35 with an alcohol of formula R-OH in presence of a catalyst to provide compound of general formula-36,



Formula-36

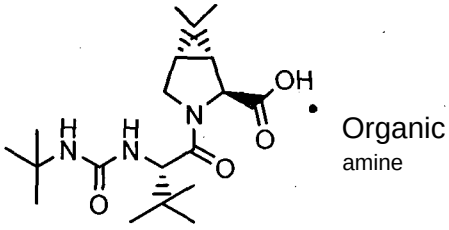
wherein, R represents C_1-C_4 alkyl group,

d) hydrolyzing the compound of general formula-36 with an aqueous base or aqueous acid in a suitable solvent to provide compound of formula-37,



Formula-37

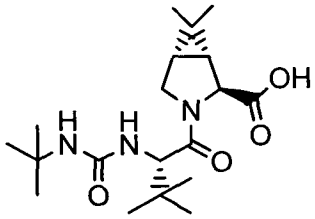
e) treating the diastereomeric mixture of compound of formula-37 with an organic amine to provide compound of general formula-38, optionally isolating the compound of general formula-38,



Formula-38

wherein, organic amine may be chiral or achiral and selected from 1,2,3,4-tetrahydronaphthalene-1 -amine, (S)-l,2,3,4-tetrahydronaphthalene-l-amine and (R)-1,2,3,4-tetrahydro naphthalene- 1-amine,

f) treating the compound of general formula-38 with an acid to provide (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3 .1.0]hexane-2-carboxylic acid compound of formula-29,



Formula-29

g) condensing the compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxamide compound of formula-30,

h) oxidizing the compound of formula-30 with a suitable oxidizing agent in a suitable solvent, optionally in presence of a catalyst provides Boceprevir.

17. The process according to claim 16, wherein,

in step-a) the acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; the base is selected from inorganic bases and organic bases; and the suitable cyanating agent is selected from hydrogen cyanide, acetone cyanohydrin, trimethyl silyl cyanide, metal cyanides of formula MCN (where M=Li, Na, and K);

in step-b) & step-g) the base is selected from inorganic bases such as alkali metal hydroxides, carbonates, bicarbonates; and organic bases; the catalyst is selected from triazole, benzotriazole and substituted benzotriazole such as hydroxy benzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), 1-hydroxy- lH-1, 2,3-triazole-4-carboxylate (HOCt) and N-hydroxy succinamide (HOSu); and the suitable condensing agent is selected from

alkyl or aryl chloroformates, alkyl or aryl sulfonyl halides, alkyl or aryl sulfonyl anhydride, carbonyldiimidazole (CDI); carbonyl ditriazole; carbodiimides, (benzotriazol-l-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), *O*-(7-azabenzotriazol-l-yl *)-N,N,N*,ivMetramethyl uronium hexafluoro phosphate (HATU), (benzotriazol-l-yloxy) tripyrrolidino phosphonium hexafluoro phosphate (PyBOP), oxalyl chloride, thoinyl chloride, di phenyl phosphoroazidate (DPPA) and P2O5.

in step-c) the catalyst is selected from dry HC1 gas, HC1 solution, thionyl chloride, trialkyl silyl halides and triaryl silyl halides;

in step-d) the base is selected from alkali metal hydroxides, carbonates and bicarbonates; and the acid is inorganic acid selected from hydrochloric acid, hydrobromic acid, nitric acid and sulfuric acid;

in step-e) the organic amine may be chiral or achiral. The organic amine is selected from 1,2,3,4-tetrahydronaphthalene-l-amine, 2-phenyl glycinol, (S)-l,2,3,4-tetrahydro naphthalene- 1-amine, (R)-l,2,3,4-tetrahdyro naphthalene- 1-amine, (R)-2-phenyl glycinol and (S)-2-phenyl glycinol;

in step-f) the acid is inorganic acid selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid;

in step-h) the catalyst is selected from is selected from TEMPO, 4-methoxy TEMPO and 4-amino TEMPO; and the oxidizing agent is selected from dess-martin periodinane (DMP), trichloroisocyanuric acid, pyridinium chlorochromate, potassium dichrormate, manganese dioxide, chromium trioxide, manganese dioxide, pyridinium dichromate, aluminium triisopropoxide in acetone, oxalyl chloride/dimethylsulfoxide/base; quaternary ammonium salt-TEMPO-oxone, N-chloro succinamide/dimethylsulfide/base and EDC-dichloroacetic acid;

in step-a) to step-h) the suitable solvent is selected from ester solvents, ether solvents, hydrocarbon solvent, polar aprotic solvent, ketone solvents, alcoholic solvents, chloro solvents, nitrile solvents, polar solvent and/or mixtures thereof.

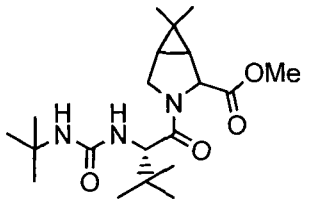
18. A process for the preparation of Boceprevir, comprises of:

a) reacting the 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33 with acetone cyanohydrin and triethylamine in toluene provides 6,6-dimethyl-3-

azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34,

b) condensing the compound of formula-34 in-situ with (S)-2-(3-tert-butylureido)-3,3-dimethyl butanoic acid compound of formula-27 in presence of l-(3-dimethylaminopropyl)-3-ethyl carbodimide hydrochloride (EDC-HC1) and 2,6-lutidine in toluene to provide l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo [3.1.0] hexan-3-yl)-3, 3-dimethyl- l-oxobutan-2-yl) urea compound of formula-35,

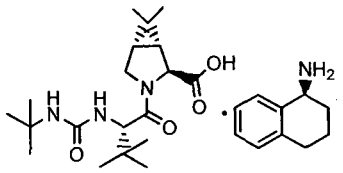
c) reacting the compound of formula-35 with methanol in presence of thionyl chloride provides methyl 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-36a,



Formula-36a

d) hydrolyzing the compound of formula-36a with lithium hydroxide in a mixture of tetrahydrofuran and water to provide compound of formula-37,

e) treating the diastereomeric mixture of compound of formula-37 with (S)- 1,2,3,4-tetrahydronaphthalene-1 -amine in ethyl acetate provides (S)- 1,2,3,4-tetrahydronaphthane-1-amine salt of (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-38a,



Formula-38a

f) treating the compound of formula-38a in-situ with hydrochloric acid to provide (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-29,

g) condensing the compound of formula-29 with 3-amino-4-cyclobutyl-2-hydroxy butanamide hydrochloride salt compound of formula-2a in presence of dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBT) and diisopropyl

ethylamine in dichloromethane provides (lR,2S,5S)-N-(4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-yl)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide compound of formula-30,

h) oxidation of compound of formula-30 with Dess-martin periodinane (DMP) in dichloromethane provides Boceprevir compound of formula-1.

19. A process for diastereomeric resolution of 3-((S)-2-(3-tert-butylureido)-3,3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylic acid compound of formula-37 with chiral amine selected from (S)-l,2,3,4-tertahydronaphthalene-l amine and (R)-l,2,3,4-tertahydronaphthalene-lamine, followed by treating with an acid to provide (lR,2S,5S)-3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-29.

20. A process for the preparation of l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo [3.1.0]hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35, comprising of:

a) reacting the 6,6-dimethyl-3-azabicyclo[3.1.0]hex-2-ene compound of formula-33 in presence of a suitable cyanating agent in a suitable solvent, optionally in presence of an acid or a base to provide 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonitrile compound of formula-34, optionally isolating the compound of formula-34 as an acid-addition salt,

b) condensing the compound of formula-34 or its acid-addition salt with (S)-2-(3-tert-butyl ureido)-3,3-dimethylbutanoic acid compound of formula-27 in presence of a suitable condensing agent in a suitable solvent, optionally in presence of a base and/or a catalyst to provide compound of formula-35.

21. A process for the preparation of 3-((S)-2-(3-tert-butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-37, comprises of:

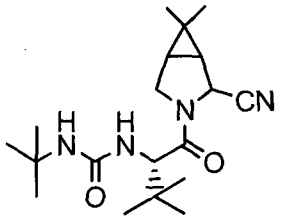
a) Reacting the l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35 with alcohol of formula R-OH in presence of a catalyst to provide corresponding alkyl 3-((S)-2-(3-tert-

butylureido)-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0] hexane-2-carboxylate compound of general formula-36,

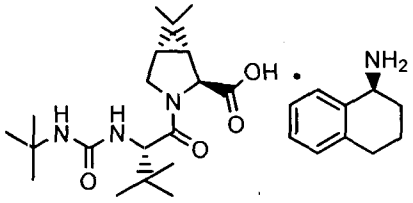
b) hydrolyzing the compound of general formula-36 in a suitable solvent, in presence of an acid or a base provides compound of formula-37.

22. A process for the preparation of 3-((S)-2-(3-tert-butylureido)-3, 3-dimethyl butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid compound of formula-37, comprising of hydrolyzing the l-tert-butyl-3-((2S)-l-(2-cyano-6,6-dimethyl-3-azabicyclo[3.1.0] hexan-3-yl)-3,3-dimethyl-l-oxobutan-2-yl)urea compound of formula-35 in presence of acid or base to provide compound of formula-37.

23. The compounds having the following structural formulae:



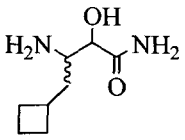
Formula-35



Formula-38a

and stereoisomers thereof,

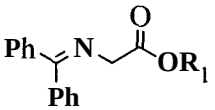
24. A novel process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt,



Formula-2

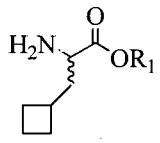
comprising of:

a) Reacting ketimide compound of general formula-3



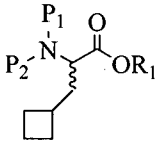
Formula-3; wherein, Ri is alkyl.

with (halomethyl)cyclobutane in a suitable solvent and in presence of a base, followed by treating with an acid to provide amino acid ester compound of general formula-4,



Formula-4; wherein, R*i* is alkyl.

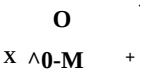
b) protecting the amine group of general formula-4 with an amine protecting agent in a suitable solvent, optionally in presence of a base to provide N-protected amino acid ester compound of general formula-5,



Formula-5;

wherein, Ri is alkyl; P_1 and P_2 both are same or different and independently selected from hydrogen and amine protecting group.

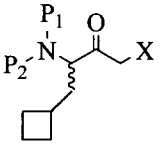
c) reacting the compound of general formula-5 with a-halo acetic acid salt compound of general formula-6



Formula-6;

wherein, X is halogen; M is alkali metal such as sodium, potassium and lithium.

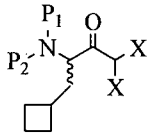
in a suitable solvent, in presence of alkyl magnesium halide and a base, followed by decarboxylation to provide a-halo ketone compound of general formula-7,



Formula-7;

wherein, R_1, P_1, P_2 and X are same as defined above.

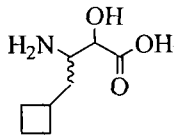
d) halogenating the compound of general formula-7 with a suitable halogenating agent in a suitable solvent, optionally in presence of a catalyst to provide α,α-dihalo ketone compound of general formula-8,



Formula-8;

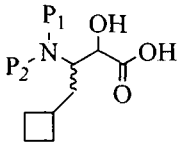
wherein, Pi, P_2 and X are same as defined above.

e) treating the compound of general formula-8 with alkali metal hydroxide in a suitable solvent to provide β-amino-a-hydroxy acid compound of formula-9,



Formula-9

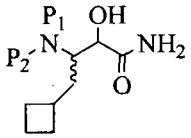
f) protecting the amine group of formula-9 with an amine protecting agent in a suitable solvent, optionally in presence of a base to provide N-protected β-amino-a-hydroxy acid compound of general formula-10,



Formula-10;

wherein, P_1 and P_2 both are same or different and independently selected from hydrogen and amine protecting group;

g) reacting the compound of general formula-10 with ammonium chloride in a suitable solvent, in presence of carbonyl diimdazole and a base to provide N-protected β-amino-a-hydroxy amide compound of general formula-11,



Formula-11

wherein, P_1 and P_2 are same as defined above;

h) deprotecting the compound of general formula-11 with a suitable deprotecting agent in a suitable solvent to provide 3-amino-4-cyclobutyl-2-hydroxybutanamide compound of formula-2 or its acid-addition salt.

25. A process according to claim 24, wherein

in step-a) the base is inorganic base; acid is inorganic acid selected from hydrochloric acid, hydrobromic acid and sulfuric acid;

in step-b) & step-f) the base is selected from inorganic base and organic base; the amino protecting agent is selected from di-tert.butyl dicarbonate (DIBOC), benzyl chloroformate, fluorenylmethyloxy carbonyl chloride (FMOC chloride), acetyl chloride, acetic anhydride, benzoyl halides, benzyl halides, alkyl or aryl sulfonyl halides, alkyl or alkenyl trifluoroacetates, trifluoroacetic acid and trifluoroacetyl chloride;

in step-c) the alkyl magnesium halide is tert-butyl magnesium chloride and tert-butyl magnesium bromide; the base is organic base; the a-halo acetic acid salt is preferably alkali metal salt, such as lithium, sodium and potassium salt of a-halo acetic acid;

in step-d) the suitable halogenating agent is selected from phosphorous trichloride, phosphorous penta chloride, phosphorous tribromide, phosphorous penta bromide, N-bromo succinamide, N-chloro succinamide, chlorine, bromine, sulfuryl chloride, copper (II) chloride, copper (II) bromide, ferric chloride and ferric bromide; the catalyst is p-toluene sulfonyl chloride;

in step-e) alkali metal hydroxide is selected from sodium hydroxide, potassium hydroxide and lithium hydroxide;

in step-g) the suitable base is inorganic base or organic base;

in step-h) the base is organic base or inorganic base; the suitable deprotecting agent is selected from acids like hydrochloric acid, isopropanolic hydrochloric acid, ethyl acetate-hydrochloric acid, ether-hydrochloric acid, hydrobromic acid, sulfuric acid, periodic acid, formic acid, trichloroisocyanuric acid, phosphoric acid, acetic acid, p-toluene sulfonic acid and trifluoroacetic acid; hydrogenating agents such as palladium, palladium on carbon and rhodium on carbon under hydrogen pressure; bases like piperidine, ammonia and methylamine; ammonium cerium (IV) nitrate; sodium in liquid ammonia; sodium naphthalenide and tetrabutyl ammonium fluoride.

in step-a) to step-h) the suitable solvent is selected from hydrocarbon solvents,- chloro solvents, ester solvents, polar aprotic solvents, ether solvents, alcoholic solvents, ketone solvents, polar solvents and their mixtures.

26. A novel process for the preparation of 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride compound of formula-2a, comprising of:

a) Reacting ethyl 2-(diphenylmethyleneamino)acetate compound of formula-3A with (bromomethyl)cyclobutane in tetrahydrofuran and in presence of potassium ter-butoxide, followed by treating it with hydrochloric acid to provide ethyl 2-amino-3-cyclobutylpropanoate compound of formula-4a,

b) protecting the amino group of formula-4a with benzyl chloroformate in a mixture of acetonitrile and water, in presence of sodium bicarbonate to provide ethyl 2-(benzyloxycarbonylamino)-3-cyclobutylpropanoate compound of formula-5a,

c) reacting the compound of formula-5a with sodium mono chloroacetate compound of formula-6a in a mixture of toluene and tetrahydrofuran, in presence of tert-butyl magnesium chloride and triethylamine, followed by decarboxylation to provide benzyl 4-chloro- 1-cyclobutyl-3-oxobutan-2-ylcarbamate compound of formula-7a,

d) chlorinating the compound of formula-7a with sulfuryl chloride in ethyl acetate and in presence of p-toluene sulfonyl chloride to provide benzyl 4,4-dichloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate compound of formula-8a,

e) treating the compound of formula-8a with aqueous sodium hydroxide solution in toluene to provide 3-amino-4-cyclobutyl-2-hydroxybutanoic acid compound of formula-9,

f) protecting the amino group of formula-9 in-situ with di-tert-butyl carbonate in a mixture of 1,4-dioxane and water to provide 3-(tert-butoxycarbonylamino)-4-cyclobutyl-2-hydroxybutanoic acid compound of formula- 10a,

g) reacting the compound of formula- 10a with ammonium chloride in dimethylformamide, in presence of carbonyl diimidazole and diisopropyl ethylamine to provide tert-butyl 4-amino-l-cyclobutyl-3-hydroxy-4-oxobutan-2-ylcarbamate compound of formula- 1la,

h) deprotecting the compound of formula-l la with isopropanolic hydrochloric acid in isopropanol to provide 3-amino-4-cyclobutyl-2-hydroxybutanamide hydrochloride compound of formula-2a.

27. A process for the preparation of preparation of alkyl 2-(benzyloxycarbonylamino)-3-cyclobutylpropanoate compound of general formula-5A, comprising of protecting the amine group of amino acid ester compound of general formula-4 with benzyloxy carbonyl chloride in a suitable solvent, optionally in presence of a base to provide compound of general formula-5A.

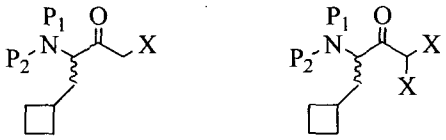
28. A process for the preparation of N-protected β-amino-a-hydroxy acid compound of general formula-10, comprising of:

a) Treating α,α-dihalo ketone compound of general formula-8 with alkali metal hydroxide in a suitable solvent to provide β-amino-a-hydroxy acid compound of formula-9,

b) reacting the compound of formula-9 in-situ with a suitable amine protecting agent in a suitable solvent, optionally in presence of a base to provide compound of general formula-10.

29. A process for the preparation of N-protected β-amino-a-hydroxy amide compound of general formula-11, comprising of reacting N-protected β-amino-a-hydroxy acid compound of general formula-10 with ammonium chloride in a suitable solvent, in presence of carbonyldiimidazole and a base to provide compound of general formula-11.

30. The compounds having the following structural formulae:



wherein, P_1 and P_2 both same or different and independently selected from hydrogen and amine protecting group; X represents halogen.

31. The compounds according to claim 30, are

a) benzyl 4-chloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate; and

b) benzyl 4,4-dichloro-l-cyclobutyl-3-oxobutan-2-ylcarbamate

32. A process for the preparation of α,α-dihalo ketone compound of general formula-8, comprising of halogenating the a-halo ketone compound of general formuia-7 with a suitable halogenating agent in a suitable solvent, optionally in presence of a catalyst to provide compound of general formula-8.

33. A process for the preparation of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27, comprising of reacting the (S)-2-amino-3,3-dimethylbutanoic acid compound of formula-25 (or) its ester with 2-methylpropan-2-amine compound of

formula-26 or its salt in a suitable solvent and in presence of a suitable condensing agent to provide compound of formula-27.

34. A process for the preparation of (S)-2-(3-tert-butylureido)-3,3-dimethylbutanoic acid compound of formula-27, comprising of reacting the (S)-trimethylsilyl 2-amino-3,3-dimethylbutanoate compound of formula-25a with 2-methylpropan-2-amine hydrochloride compound of formula-26a in a mixture of dichloromethane and tetrahydrofuran and in presence of a suitable condensing agent, optionally in presence of a base or a catalyst to provide compound of formula-27.

35. Use of compounds of claim-23, claim-30 and claim-31 as intermediates in the preparation of Boceprevir compound of formula- 1.

36. Use of crystalline compound of claim-9 and claim-10 in the preparation of highly pure compound of formula-2 as well as in the preparation of Boceprevir compound of formula- 1.

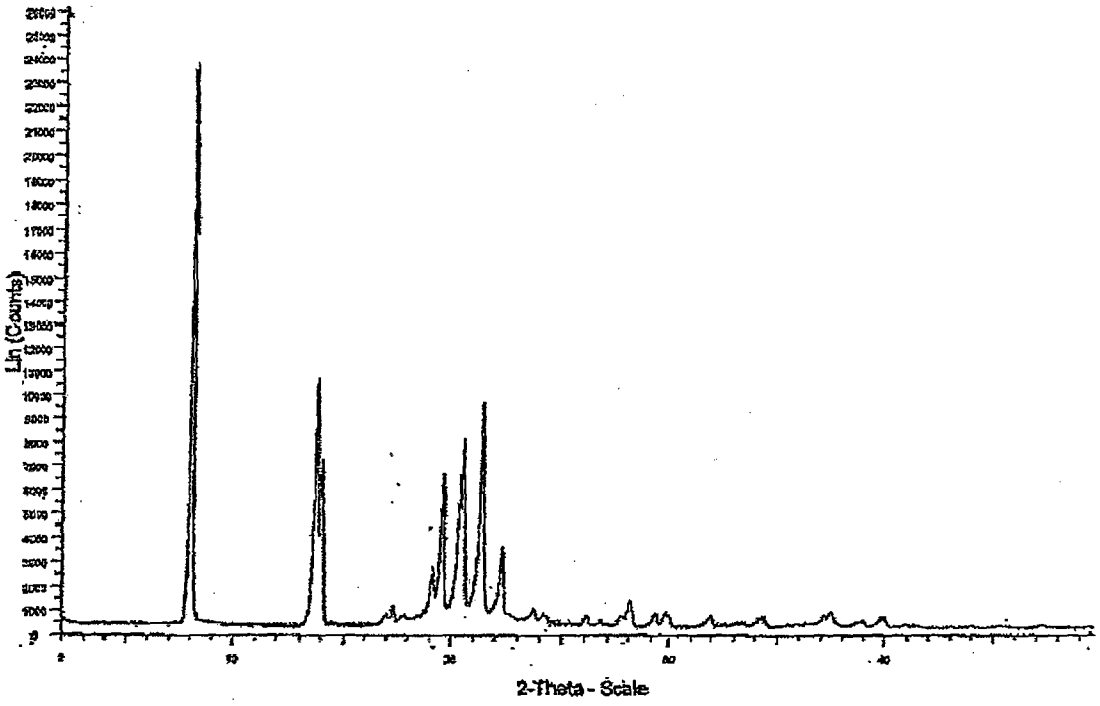


Figure-1

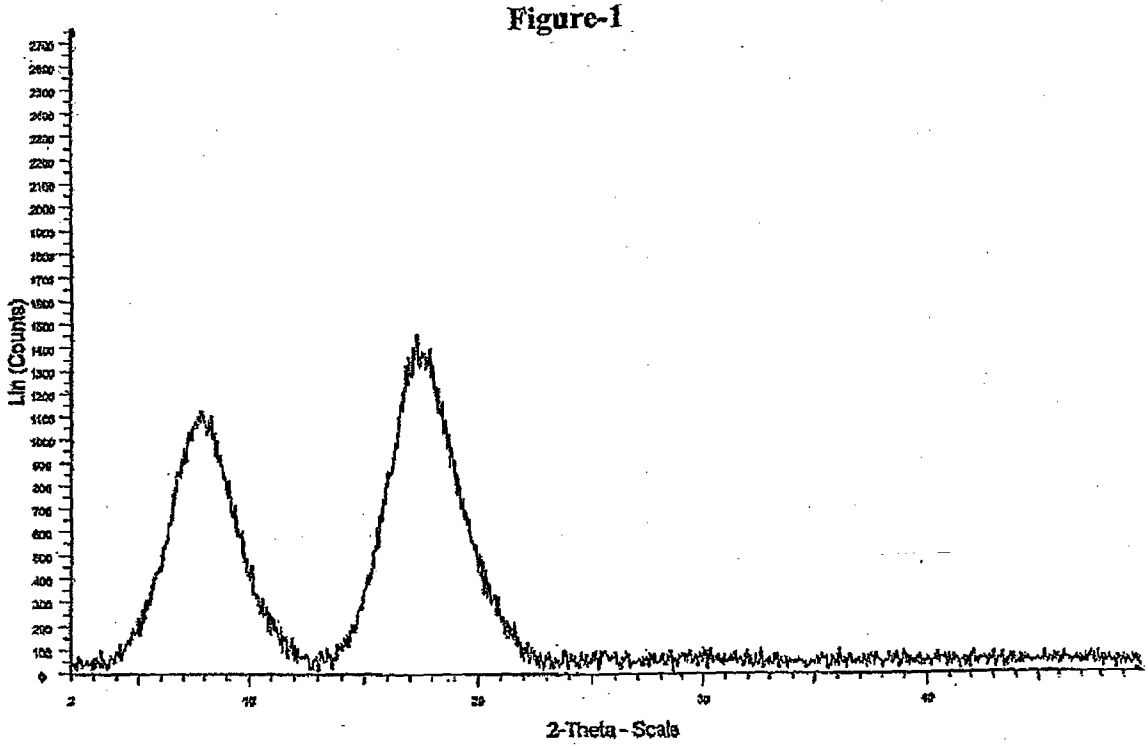


Figure-2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2013/000631

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet

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)

IPC: C07D 209/-; C07C 233/-; C07K 5/-

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)

WPI, EPODOC, CNKI, CNPAT,CAPLUS, REGISTRY: amino, cyclobutylmethyl, oxopropyl, azabicyclo, carboxamide, HCV, hepatitis, Boceprevir, protease

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 20070149459 A1 (SCHERING CORPORATION) 28 June 2007 (28.06.2007) the whole document	1-36

☐ 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

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2014 (26.02.2014)	**03 Apr. 2014 (03.04.2014)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer **SHIJie** Telephone No. (86-10)**82246672**

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International application No.
PCT/IN2013/000631

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2013/000631

Continuation of A. CLASSIFICATION OF SUBJECT MATTER

C07D 209/52 (2006.01) i

C07C 233/08 (2006.01) i

C07K 5/08 (2006.01) i