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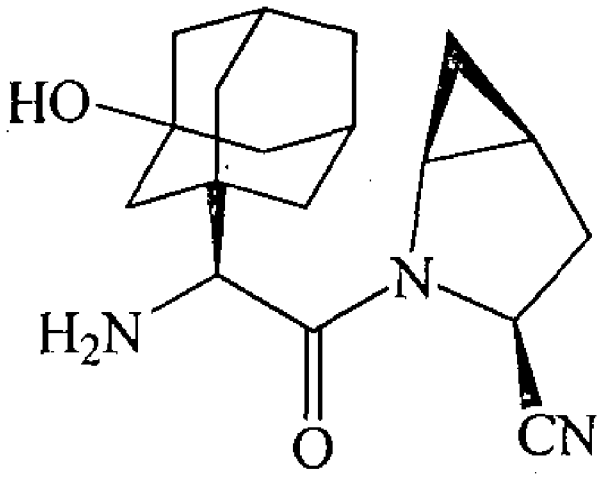
(54) Title: PROCESS FOR THE PREPARATION OF DPP-IV INHIBITOR

(57) Abstract: The present invention provides a process for the preparation of (1 S,3S,5S)-2-[(2S)-2-amino-2-(3 -hydroxyadamantan- 1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile and its pharmaceutically acceptable salts thereof, represented by the compound of formula- 1.



Formula-1

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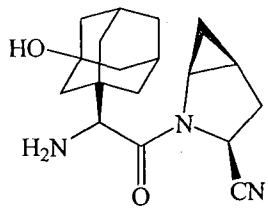
Process for the preparation of DPP-IV inhibitor

Related Application:

This application claims the benefit of priority of our Indian patent application numbers 32/CHE/2012 filed on 3rd January 2012 and 1259/CHE/2012 filed on 30th March 2012 which are incorporated herein by reference.

Field of the Invention:

The present invention relates to a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile represented by the structural formula-1,



Formula-1

its pharmaceutically acceptable salts and intermediates there of.

Background of the Invention:

(1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Cyclopropyl fused pyrrolidine based inhibitors of dipeptidyl peptidase-4 and methods for their preparation were first disclosed in US6395767 B2. The disclosed process involves the esterification of adamantane-1-carboxylic acid with trimethylsilyl diazomethane followed by the reduction of obtained methyl ester with lithium aluminium hydride to yield adamantyl methanol, which is then oxidized under Swern oxidation conditions to provide adamantyl aldehyde. The aldehyde is then treated with potassium cyanide in presence of sodium bisulfite followed by R-(-)-2-phenylglycinol to provide nitrile compound. The nitrile compound is then hydrolyzed by heating in conc. HCl and acetic acid at 80°C for 18 hrs to provide the hydrochloride salt of its corresponding acid. N-deprotection of the hydrochloride salt using Pearlman's catalyst (20% $Pd(OH)_2$)

provides hydrochloride salt of free amine compound, which is then protected with tert.butyloxy carbonyl group (Boc protection) by treating with di-tert-butyl dicarbonate in presence of potassium carbonate to provide Boc protected amine compound. The Boc protected amine is hydroxylated by treating with a solution of potassium permanganate in 2% aq.KOH to provide the corresponding hydroxy compound, which is then condensed with (1S,3S,5S)-2-azabicyclo[3.1.0] hexane-3-carboxamide trifluoroacetic acid salt in presence of 1-hydroxybenzotriazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) and triethylamine. The obtained product is treated with triethylsilyl triflate in presence of diisopropylethyl amine at -78°C to provide O-triethylsilyl protected amide compound, which is treated with imidazole and phosphorous oxychloride in anhydrous pyridine to provide corresponding cyano compound. It is then treated with trifluoroacetic acid and water at 0°C to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile trifluoroacetic acid salt.

The process disclosed in US6395767 B2 has certain disadvantages in that the process involves the usage of trimethylsilyl diazomethane for the esterification of adamantane-1-carboxylic acid, which is a neurological hazard and extremely toxic reagent.

The above disclosed process also involves the usage of lithium aluminium hydride for the reduction of adamantane-1-carboxylic acid methyl ester, which is hygroscopic and highly reactive. Hence it is not suggestible to use it on industrial scale.

Hence there is a need in the art to develop a simple, safe, industrially commercially viable process for the synthesis of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile to avoid the problems associated with prior-art.

Brief description of the Invention:

The first aspect of the present invention is to provide an improved process for the preparation of adamantyl methanol compound of formula-3, comprising of reducing the adamantane-1-carboxylic acid compound of formula-2 with a suitable reducing agent in a suitable solvent to provide adamantyl methanol compound of formula-3.

The second aspect of the present invention is to provide a process for the preparation of benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27, comprising of;

a) Reducing the adamantane-1-carboxylic acid compound of formula-2 with a suitable reducing agent in a suitable solvent to provide adamantyl methanol compound of formula-3,

b) oxidizing the compound of formula-3 with a suitable oxidizing agent optionally in presence of a suitable base in a suitable solvent to provide adamantyl aldehyde compound of formula-4,

c) treating the compound of formula-4 in-situ with a suitable alkali metal cyanide in presence of sodium bisulfite or sodium meta bisulfite in a suitable solvent followed by treating with R-(-)-2-phenylglycinol in a suitable solvent to provide phenylglycinol adamantane nitrile compound of formula-5a,

d) hydrolyzing the compound of formula-5a in presence of a suitable acid in a suitable solvent to provide its corresponding phenylglycinol adamantane carboxylic acid compound of formula-6a or its acid-addition salt,

e) deprotecting the compound of formula-6a or its acid-addition salt by treating it with a suitable deprotecting agent optionally in presence of an acid in a suitable solvent to provide amino adamantane carboxylic acid compound of formula-7 or its acid-addition salt,

f) treating the compound of formula-7 or its acid-addition salt with benzyl chloroformate in presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8,

g) hydroxylating the compound of formula-8 by treating it with a suitable hydroxylating agent in presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27.

The third aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with a suitable C_1-C_6 straight chain or branched chain alcohol in presence of a suitable catalyst to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,

b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,

c) amidation of compound of general formula-11 by treating it with a suitable amine source optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12,

d) reducing the compound of formula-12 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate compound of formula-13,

e) dehydrating the compound of formula-13 by treating it with a suitable dehydrating agent in presence or absence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,

f) converting the compound of formula-14 in to (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent.

The fourth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-tert-butyl 3-cyano-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-17, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with a suitable C_1-C_6 straight chain or branched chain alcohol in presence of a suitable catalyst to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,

b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,

c) amidation of compound of general formula-11 by treating it with a suitable amine source optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12,

d) reducing the compound of formula-12 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate compound of formula-13,

e) dehydrating the compound of formula-13 by treating it with a suitable dehydrating agent in presence or absence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-cyano-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-16,

f) converting the compound of formula-16 into (1S,3S,5S)-tert-butyl 3-cyano-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-17 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent.

The fifth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15, comprising of;

a) Amidation of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with benzyl amine in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide (S)-N-benzyl-5-oxopyrrolidine-2-carboxamide compound of formula-18,

b) treating the compound of formula-18 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-5-oxopyrrolidine-1-carboxylate compound of formula-19,

c) reducing the compound of formula-19 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-(benzylcarbamoyl)-5-hydroxypyrrolidine-1-carboxylate compound of formula-20,

d) dehydrating the compound of formula-20 by treating it with a suitable dehydrating agent in presence or absence of a base in a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-21,

e) converting the compound of formula-21 into (1S,3S,5S)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-

22 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent,

f) debenzylating the compound of formula-22 by treating it with a suitable debenzylating agent optionally in presence of a suitable acid in a suitable solvent to provide (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15.

The sixth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with a suitable C_1-C_6 straight chain or branched chain alcohol in presence of a suitable catalyst to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,

b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,

c) reducing the compound of general formula-11 with a suitable reducing agent in a suitable solvent to provide (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23,

d) dehydrating the compound of general formula-23 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate compound of general formula-24,

e) hydrolyzing the compound of general formula-24 in-situ in presence of a suitable base in a suitable solvent to provide (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-25,

f) treating the compound of formula-25 in-situ with methane sulfonyl chloride in presence of a suitable base followed by in-situ treating the obtained compound with a suitable amine source to provide (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,

g) optionally isolating the compound of formula-14, converting the compound of formula-14 into (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent,

h) deprotecting the compound of formula-15 by treating it with a suitable deprotecting agent in a suitable solvent to provide (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt.

The seventh aspect of the present invention is to provide an improved process for the preparation of (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23, comprising of reducing the (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11 with a suitable reducing agent in a suitable solvent to provide (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23.

The eighth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

a) Reducing the adamantane-1-carboxylic acid compound of formula-2 with a suitable reducing agent in a suitable solvent to provide adamantyl methanol compound of formula-3,

b) oxidizing the compound of formula-3 with a suitable oxidizing agent optionally in presence of a suitable base and a suitable catalyst in a suitable solvent to provide adamantyl aldehyde compound of formula-4,

c) treating the compound of formula-4 in-situ with a suitable alkali metal cyanide in presence of sodium bisulfite or sodium metabisulfite in a suitable solvent followed by in-situ treating with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-5,

d) hydrolyzing the compound of general formula-5 in presence of a suitable acid in a suitable solvent to provide compound of general formula-6 or its acid-addition salt,

e) deprotecting the compound of general formula-6 or its acid-addition salt with a suitable deprotecting agent optionally in presence of an acid in a suitable solvent to

provide compound of formula-7 or its acid-addition salt,

f) treating the compound of formula-7 or its acid-addition salt with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide Boc-protected amine compound of formula-28,

g) hydroxylating the compound of formula-28 by treating it with a suitable hydroxylating agent optionally in presence of a suitable base in a suitable solvent followed by in-situ treating with a suitable O-protecting agent to provide di-protected compound of general formula-29,

h) condensing the compound of general formula-29 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt in presence of a suitable coupling agent and optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-30,

i) dehydrating the compound of general formula-30 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-31,

j) deprotecting the compound of general formula-31 by treating with a suitable deprotecting agent in a suitable solvent to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1.

The ninth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

a) Condensing the compound of general formula-29 with (1S,3S,5S)-2-azabicyclo[3.1.0] hexane-3-carbonitrile hydrochloride salt compound of formula-32 in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-31,

b) deprotecting the compound of general formula-31 by treating it with a suitable deprotecting agent in a suitable solvent to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

The tenth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

a) Condensing the compound of general formula-29 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexan-3-ylmethanamine hydrochloride salt compound of formula-33 in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-34,

b) treating the compound of general formula-34 with trichloroisocyanuric acid (TCICA) in presence or absence of a suitable catalyst or a suitable base in a suitable solvent followed by deprotecting the obtained compound to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1.

The eleventh aspect of the present invention is to provide a process for the preparation of compound of general formula-30, comprising of;

a) Condensing the compound of general formula-29 with (1S,3S,5S)-N-benzyl-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-35 in presence of a suitable coupling agent and optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-36,

b) debenzylating the compound of general formula-36 with a suitable debenzylating agent optionally in presence of a suitable acid in a suitable solvent to provide compound of general formula-30.

The twelfth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

a) Condensing the compound of general formula-37 with (1S,3S,5S)-2-azabicyclo [3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-41,

b) reacting the compound of general formula-41 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-42,

c) dehydrating the compound of general formula-42 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-39,

d) reducing the compound of general formula-39 with a suitable reducing agent in a suitable solvent to provide compound of general formula-40,

e) deprotecting the compound of general formula-40 by treating it with a suitable deprotecting agent in a suitable solvent to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

The thirteenth aspect of the present invention is to provide a process for the preparation of compound of general formula-40, comprising of;

a) Condensing the compound of general formula-37 with (1S,3S,5S)-2-azabicyclo [3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-41,

b) reacting the compound of general formula-41 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-42,

c) reducing the compound of general formula-42 with a suitable reducing agent in a suitable solvent to provide compound of general formula-43,

d) dehydrating the compound of general formula-43 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-40.

The fourteenth aspect of the present invention is to provide a process for the preparation of compound of general formula-43, comprising of;

a) Reacting the compound of general formula-37 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-44,

b) reducing the compound of general formula-44 with a suitable reducing agent in a suitable solvent to provide compound of general formula-45,

c) condensing the compound of general formula-45 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition

salt in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-43.

The fifteenth aspect of the present invention is to provide a process for the preparation of compound of general formula-42, comprising of;

a) Reacting the compound of general formula-37 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-44,
b) condensing the compound of general formula-44 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-42.

The sixteenth aspect of the present invention is to provide a process for the preparation of adamantyl aldehyde compound of formula-4 comprising oxidizing the adamantyl methanol compound of formula-3 with a suitable oxidizing agent optionally in presence of a suitable base or a suitable catalyst in a suitable solvent to provide adamantyl aldehyde compound of formula-4.

The seventeenth aspect of the present invention is to provide a novel process for the preparation of compound of formula-28, comprising of;

a) Treating glycine with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide N-Boc protected glycine compound of formula-46,
b) reacting the compound of formula-46 with (R)-4-phenyloxazolidin-2-one optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-oxo-2-(2-oxo-4-phenyloxazolidin-3-yl)ethylcarbamate compound of formula-47,
c) reacting the compound of formula-47 with adamantyl bromide compound of formula-48 in presence of a suitable base in a suitable solvent to provide compound of formula-49,
d) hydrolyzing the compound of formula-49 in presence of a suitable base in a suitable solvent to provide compound of formula-28.

The eighteenth aspect of the present invention is to provide a novel process for the preparation of compound of formula-28, comprising of;

a) Reacting the adamantyl bromide compound of formula-48 with (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine compound of formula-50 in presence of a suitable base in a suitable solvent to provide compound of formula-51,
b) treating the compound of formula-51 with a suitable acid in a suitable solvent to provide methyl ester compound of formula-52,
c) treating the compound of formula-52 with di-tertiary butyl dicarbonate in presence of a suitable base in a suitable solvent to provide compound of formula-63,
d) hydrolyzing the compound of formula-63 in presence of a suitable base in a suitable solvent to provide its corresponding carboxylic acid compound of formula-28.

The nineteenth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexan-3-ylmethanamine hydrochloride compound of formula-33, comprising of;

a) Reducing the (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-53 with a suitable reducing agent in a suitable solvent to provide (S)-tert-butyl 2-(hydroxymethyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-54,
b) mesylation of compound of formula-54 with methane sulfonyl chloride in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-((methylsulfonyloxy)methyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-55,
c) azidation of compound of formula-55 by treating with a suitable azide source in a suitable solvent to provide (S)-tert-butyl 2-(azidomethyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-56,
d) reducing the compound of formula-56 with a suitable reducing gent in a suitable solvent to provide (S)-tert-butyl 2-(aminomethyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-57,
e) treating the compound of formula-57 with a suitable methylene source in presence of a suitable catalyst in a suitable solvent to provide (1S,3S,5S)-tert-butyl 3-(aminomethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-58,

f) deprotecting the compound of formula-58 with hydrochloric acid in a suitable solvent to provide (1S,3S,5S)-2-azabicyclo[3.1.0]hexan-3-ylmethanamine hydrochloride salt compound of formula-33.

The twentieth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-N-benzyl-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-35, comprising of;

a) Amidation of (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-53 with benzylamine in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-59,

b) Treating the compound of formula-59 with a suitable methylene source in presence of a suitable catalyst in a suitable solvent to provide (1S,3S,5S)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-60,

c) deprotecting the compound of formula-60 with hydrochloric acid in a suitable solvent to provide (1S,3S,5S)-N-benzyl-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-35.

Detailed description of the Invention:

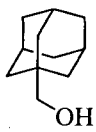
As used herein the present invention, the term "suitable solvent" refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, xylene and the like; "ether solvents" such as dimethylether, diethylether, methyl tert-butyl ether, 1,2-dimethoxy ethane, tetrahydrofuran and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide, dimethylformamide, dimethylsulphoxide, dioxane and the like; "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform and the like; "ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol and the like; "polar solvents" such as water; and/or their

mixtures thereof.

As used herein the present invention the term "suitable base" refers to "alkali metal carbonates" such as sodium carbonate, potassium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium tert.butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride, lithium hydride; alkali meta amides such as sodium amide, potassium amide, lithium amide and the like, ammonia; and organic bases like dimethylamine, diethylamine, diisopropyl amine, diisopropylethylamine, diisobutylamine, triethylamine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), 2,6-lutidine, lithium diisopropylamide; organosilicon bases such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) and/or their mixtures thereof.

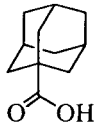
As used herein the present invention 'Cbz' represents benzyloxycarbonyl group, 'Boc' represents tert-butyloxycarbonyl group, 'Bn' represents benzyl group and 'R' represents C_1-C_6 straight chain or branched chain alkyl group, "R_1" represents $-CH_3$ or $-CH_2OH$.

The first aspect of the present invention provides an improved process for the preparation of adamantyl methanol compound of formula-3



Formula-3

comprising of reducing the adamantane-1-carboxylic acid compound of formula-2



Formula-2

with a suitable reducing agent in a suitable solvent provides adamantyl methanol

compound of formula-3.

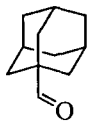
Wherein, the suitable reducing agent is preferably sodium borohydride optionally in combination with BF_3.etherate; and the suitable solvent is selected from ether solvents, ester solvents, alcoholic solvents, hydrocarbon solvents, polar solvents and/or their mixtures thereof; preferably ether solvents.

A preferred embodiment of the present invention provides an improved process for the preparation of adamantyl methanol compound of formula-3 comprising of reducing the adamantane-1-carboxylic acid compound of formula-2 with sodium borohydride-BF_3.etherate in tetrahydrofuran provides adamantyl methanol compound of formula-3.

The second aspect of the present invention provides an improved process for the preparation of benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27, comprising of;

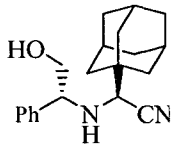
a) Reducing the adamantane-1-carboxylic acid compound of formula-2 with a suitable reducing agent in a suitable solvent to provide adamantyl methanol compound of formula-3,

b) oxidizing the compound of formula-3 with a suitable oxidizing agent optionally in presence of a suitable base in a suitable solvent to provide adamantyl aldehyde compound of formula-4,



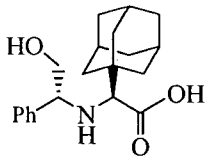
Formula-4

c) treating the compound of formula-4 in-situ with a suitable alkali metal cyanide in presence of sodium bisulfite or sodium meta bisulfite in a suitable solvent followed by treating with R-(-)-2-phenylglycinol in a suitable solvent to provide phenylglycinol adamantane nitrile compound of formula-5a,



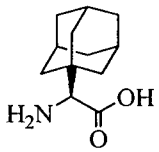
Formula-5a

d) hydrolyzing the compound of formula-5a in presence of a suitable acid in a suitable solvent to provide phenylglycinol adamantane carboxylic acid compound of formula-6a or its acid-addition salt,



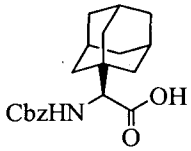
Formula-6a

e) deprotecting the compound of formula-6a or its acid-addition salt by treating it with a suitable deprotecting agent optionally in presence of an acid in a suitable solvent to provide amino adamantane carboxylic acid compound of formula-7 or its acid-addition salt,



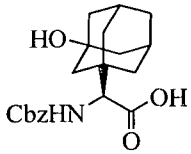
Formula-7

f) treating the compound of formula-7 or its acid-addition salt with benzyl chloroformate in presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8,



Formula-8

g) hydroxylating the compound of formula-8 with a suitable hydroxylating agent in presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27.



Formula-27

Wherein, in step-a) the suitable reducing agent is sodium borohydride optionally in

combination with BF_3.etherate; and the suitable solvent is selected from ether solvents, ester solvents, alcoholic solvents, hydrocarbon solvents, polar solvents and/or their mixtures thereof, preferably ether solvents;

in step-b) the suitable oxidizing agent is selected from oxalyl chloride/dimethyl sulfoxide, sodium hypochlorite or trichloroisocyanuric acid (TCICA) in presence of catalytic amount of TEMPO ((2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl), pyridinium chlorochromate, oxone; the suitable base is selected from organic bases, preferably triethylamine; and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ester solvents, polar-aprotic solvents and/or their mixtures thereof; preferably chloro solvents;

in step-c) the suitable solvent is selected from alcoholic solvents, chloro solvents, ester solvents, polar solvents and/or their mixtures thereof;

in step-d) the suitable acid is selected from conc. HCl, sulfuric acid; preferably conc. HCl; and the suitable solvent is selected from acetic acid and alcoholic solvents; preferably acetic acid;

in step-e) the suitable deprotecting agent is selected from Pd, Pd/C, Raney Ni, palladium acetate, platinum oxide, platinum black, Rh/C, Ru, Ir and the like in combination with hydrogen; preferably Pd/C; and the suitable acid is acetic acid; and the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar solvents and/or their mixtures thereof; preferably alcoholic solvents;

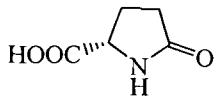
in step-f) the suitable base is selected from alkali metal carbonates and alkali metal bicarbonates; the suitable solvent is selected from ether solvents, ester solvents, polar solvents and/or their mixtures thereof;

in step-g) the suitable hydroxylating agent is selected from potassium permanganate, H_2SO_4/HNO_3; preferably potassium permanganate; the suitable base is selected from alkali metal hydroxides, alkali metal alkoxides and organic bases; the suitable solvent is selected from chloro solvents, nitrile solvents, ether solvents, polar solvents and/or their mixtures thereof.

The third aspect of the present invention provides a process for the preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound

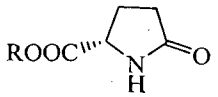
of formula-15, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9



Formula-9

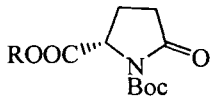
by treating it with a suitable C_1-C_6 straight chain or branched chain alcohol in presence of a suitable catalyst to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,



Formula-10

wherein, 'R' represents C_1-C_6 straight chain or branched chain alkyl;

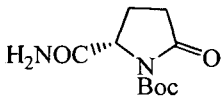
b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,



Formula-11

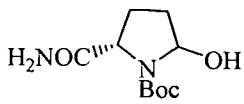
wherein, 'R' is as defined above;

c) amidation of compound of general formula-11 by treating it with a suitable amine source optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12,



Formula-12

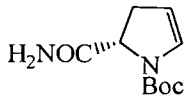
d) reducing the compound of formula-12 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate compound of formula-13,



Formula-13

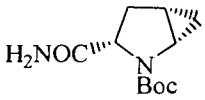
e) dehydrating the compound of formula-13 by treating it with a suitable dehydrating

agent in presence or absence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,



Formula-14

f) converting the compound of formula-14 in-situ into (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent.



Formula-15

Wherein, in step-a) the suitable catalyst is selected from thionyl chloride, hydrochloric acid, conc. sulfuric acid, trifluoro acetic acid, methane sulfonic acid and the like;

In step-b) the suitable base is selected from organic bases like 4-dimethylaminopyridine (DMAP), triethylamine, diisopropylethyl amine and inorganic bases like alkali metal hydroxides, alkali metal carbonates, alkali metal bicarbonates; the suitable solvent is selected from nitrile solvents, ketone solvents, chloro solvents, ether solvents, polar solvents and/or their mixtures thereof;

In step-c) the suitable amine source is selected from ammonia, formamide, ammonia gas, ammonium carbamate, ammonium formate, ammonium phosphate, ammonium acetate, ammonium fluoride, ammonium bromide, ammonium chloride, ammonium iodide, ammonium iodate, ammonium carbonate, ammonium citrate, ammonium chromate, ammonium dichromate, ammonium hydroxide, ammonium lactate, ammonium molybdate, ammonium nitrate, ammonium oxalate, ammonium sulfate, ammonium sulfide, ammonium tartrate, ammonium triflate, ammonium thiocyanate, ammonium dihydrogen phosphate, urea, methyl carbamate, ethyl carbamate, propyl carbamate or t-butyl carbamate and alkyl or aryl amines; the suitable base can be selected from organic and inorganic bases; the suitable solvent is selected from alcoholic solvents,

ether solvents, ester solvents, chloro solvents and/or their mixtures thereof;

In step-d) the suitable reducing agent is selected from L-selectride, sodium borohydride, potassium borohydride, vitride, diisobutyl aluminium hydride, tetralkylammonium borohydride, calcium borohydride, zinc borohydride, sodium cyanoborohydride, lithium aluminium hydride and the like; the suitable solvent is selected form ether solvents, alcoholic solvents, ester solvents, nitrile solvents and/or their mixtures thereof;

In step-e) the suitable dehydrating agent is selected from acetic anhydride, trifluoro acetic anhydride (TFAA), trifluoroacetic acid, phthalic anhydride, phosphorous pentoxide, phosphoric acid, phosphoryl chloride in presence or absence of imidazole, phosphoric acid, polyphosphoric acid, sulfuric acid, dicyclohexyl carbodiimide; and the suitable base wherever necessary is selected from organic bases like triethylamine, diisopropyl amine, diisopropyl ethylamine, 4-dimethylamino pyridine (DMAP) and the like; and the suitable solvent is selected from ether solvents, ester solvents, hydrocarbon solvents and/or their mixtures thereof;

In step-f) the suitable methylene source is selected from dihalomethanes such as diiodomethane, chloro iodomethane; the suitable catalyst is diethyl zinc; and the suitable solvent is selected from hydrocarbon solvents, ether solvents, chloro solvents and/or their mixtures thereof.

The fourth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-tert-butyl 3-cyano-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-17, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with a suitable C_1-C_6 straight chain or branched chain alcohol in presence of a suitable catalyst to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,

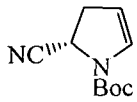
b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,

c) amidation of compound of general formula-11 by treating it with a suitable amine

source optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12,

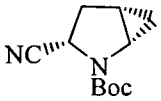
d) reducing the compound of formula-12 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate compound of formula-13,

e) dehydrating the compound of formula-13 with a suitable dehydrating agent in presence or absence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-cyano-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-16,



Formula-16

f) converting the compound of formula-16 into (1S,3S,5S)-tert-butyl 3-cyano-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-17 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent.

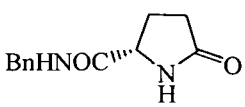


Formula-17

Wherein, the solvents, bases, catalysts, reagents used in step-a) to step-f) of the fourth aspect are same as defined in step-a) to step-f) respectively of the third aspect of the present invention.

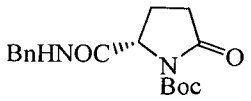
The fifth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15, comprising of;

a) Amidation of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with benzyl amine in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide (S)-N-benzyl-5-oxopyrrolidine-2-carboxamide compound of formula-18,



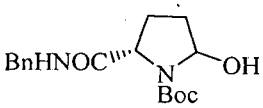
Formula-18

b) treating the compound of formula-18 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-5-oxopyrrolidine-1-carboxylate compound of formula-19,



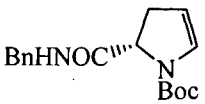
Formula-19

c) reducing the compound of formula-19 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-(benzylcarbamoyl)-5-hydroxypyrrolidine-1-carboxylate compound of formula-20,



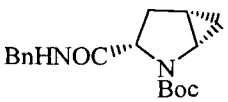
Formula-20

d) dehydrating the compound of formula-20 by treating it with a suitable dehydrating agent in presence or absence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-21,



Formula-21

e) converting the compound of formula-21 into (1S,3S,5S)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-22 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent,



Formula-22

f) debenzylating the compound of formula-22 by treating with a suitable debenzylating agent optionally in presence of a suitable acid in a suitable solvent to provide (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15.

Wherein, in step-a) the suitable coupling agent is selected from N,N'-

dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), alkyl or aryl chloroformates such as ethyl chloroformate, benzylchloroformate, diphenylphosphoroazidate (DPPA), thionyl chloride, oxalyl chloride, phosphorous oxychloride, phosphorous pentachloride, 4-methyl-2-oxopentanoyl chloride (i-BuCOCOCl), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), methane sulfonyl chloride and the like optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS), 4-dimethylaminopyridine (DMAP); the suitable base can be selected from organic or inorganic bases; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents and/or their mixtures thereof;

In step-b) the suitable base and the suitable solvent are same as defined for step-b) of the third aspect of the present invention;

In step-c) the suitable reducing agent and the suitable solvent are same as defined for step-d) of the third aspect of the present invention;

In step-d) the suitable dehydrating agent, the suitable base and the suitable solvent are same as defined for step-e) of the third aspect of the present invention;

In step-e) the suitable methylene source, the suitable catalyst and the suitable solvent are same as defined for step-f) of the third aspect of the present invention;

In step-f) the suitable debenzylating agent is selected from conc. HCl, Pd, Pd/C, Raney Ni, palladium acetate, platinum oxide, platinum black, Rh/C, Ru, Ir and the like optionally in combination with hydrogen; the suitable acid is acetic acid; and the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents, hydrocarbon solvents and/or their mixtures thereof.

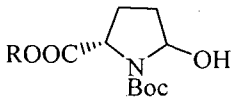
The sixth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salts, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with a suitable C_1-C_6 straight chain or branched chain alcohol in presence

of a suitable catalyst to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,

b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,

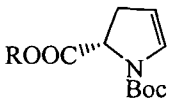
c) reducing the compound of general formula-11 with a suitable reducing agent in a suitable solvent provides (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23,



Formula-23

wherein, 'R' is as defined above;

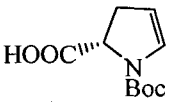
d) dehydrating the compound of general formula-23 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate compound of general formula-24,



Formula-24

wherein, 'R' is as defined above;

e) hydrolyzing the compound of general formula-24 in-situ in presence of a suitable base in a suitable solvent provides (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-25,



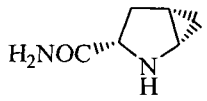
Formula-25

f) treating the compound of formula-25 in-situ with methane sulfonyl chloride in presence of a suitable base followed by in-situ treating obtained compound with a suitable amine source provides (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,

g) optionally isolating the compound of formula-14, converting it into (1S,3S,5S)-tert-

butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent,

h) deprotecting the compound of formula-15 by treating it with a suitable deprotecting agent in a suitable solvent provides (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt.



Formula-26

Wherein, in step-a) the suitable catalyst is same as defined in step-a) of the third aspect of the present invention;

In step-b) the suitable base and suitable solvent are same as defined in step-b) of third aspect of the present invention;

In step-c) the suitable reducing agent and the suitable solvent are same as defined for step-d) of the third aspect of the present invention;

In step-d) the suitable dehydrating agent, the suitable base and the suitable solvent are same as defined for step-e) of the third aspect of the present invention;

In step-e) the suitable base is selected from alkali metal hydroxides; and the suitable solvent is selected from polar solvents, alcoholic solvents, ether solvents, hydrocarbon solvents and/or their mixtures thereof;

In step-f) the suitable base is selected from organic bases like diisopropyl amine, diisopropylethylamine, triethylamine and inorganic bases like hydroxides, alkoxides, carbonates and bicarbonates of alkali metals; and the suitable amine source is same as defined in step-c) of third aspect of the present invention;

In step-g) the suitable methylene source and suitable catalyst and suitable solvent are same as defined in step-f) of third aspect of the present invention;

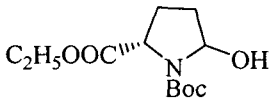
In step-h) the suitable deprotecting agent can be selected from hydrochloric acid, acetyl chloride, methane sulfonic acid, trifluoroacetic acid; and the suitable solvent is selected from ether solvents, ester solvents, hydrocarbon solvents, chloro solvents, alcoholic solvents and/or their mixtures thereof;

The preferred embodiment of the present invention provides a process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with ethanol in presence of thionyl chloride to provide (S)-ethyl 5-oxopyrrolidine-2-carboxylate compound of formula-10b,

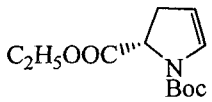
b) treating the compound of formula-10b with di-tert.butyl dicarbonate in presence of a 4-dimethylaminopyridine in dichloromethane to provide (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate compound of formula-11b,

c) reducing the compound of formula-11b with sodium borohydride in methanol provides (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b,



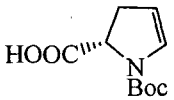
Formula-23b

d) dehydrating of compound of formula-23b by treating it with trifluoroacetic anhydride in presence of diisopropyl ethyl amine in tetrahydrofuran to provide (S)-1-tert-butyl 2-ethyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate compound of formula-24b,



Formula-24b

e) hydrolyzing the compound of formula-24b in-situ in presence of lithium hydroxide in water provides (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-25,



Formula-25

f) treating the compound of formula-25 in-situ with methane sulfonyl chloride in presence of diisopropyl ethyl amine followed by in-situ treating obtained compound with ammonia provides (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,

g) optionally isolating the compound of formula-14, converting it into (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with diiodomethane in presence of diethyl zinc in a mixture of toluene and 1,2-dimethoxy ethane,

h) deprotecting the compound of formula-15 by treating it with a suitable hydrochloric acid source such as conc. HCl, ethyl acetate-HCl, isopropyl acetate-HCl, methanolic HCl, ethanolic HCl, isopropanolic HCl or acetyl chloride in presence of alcohol in a suitable solvent provides (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its hydrochloride salt.

The seventh aspect of the present invention provides an improved process for the preparation of (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23, comprising of reducing the (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11 with a suitable reducing agent in a suitable solvent to provide (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23.

Wherein, the suitable reducing agent is selected form sodium borohydride optionally in combination with BF_3.etherate, L-selectride, diisobutyl aluminium hydride; preferably sodium borohydride; the suitable solvent is selected from hydrocarbon solvents, chloro solvents, alcoholic solvents, ether solvents, ester solvents, polar solvents and/or their mixtures thereof; preferably hydrocarbon solvents.

A preferred embodiment of the present invention provides an improved process for the preparation of (2S)-1-tert-butyl 2-ehtyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b, comprising of reducing the (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate compound of formula-11b with sodium borohydride in methanol to provide (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b.

The compound of formula-27 obtained above can be further converted into (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1 by coupling with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt

in presence of a suitable coupling agent followed by dehydration using a suitable dehydrating agent and subsequently deprotecting the Cbz group using suitable deprotecting agent provides (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1.

The suitable coupling agent, dehydrating agent are same as defined in any of the above aspects and the suitable deprotecting agent is same as the debenzylating agents as defined above.

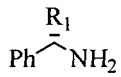
The compounds obtained as per the present invention are the useful intermediates for the preparation of DPP-IV inhibitor i.e., (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile and its pharmaceutically acceptable salts thereof.

The eighth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1, comprising of;

a) Reducing the adamantane-1-carboxylic acid compound of formula-2 with a suitable reducing agent in a suitable solvent to provide adamantyl methanol compound of formula-3,

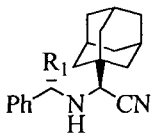
b) oxidizing the compound of formula-3 with a suitable oxidizing agent optionally in presence of a suitable base and a suitable catalyst in a suitable solvent to provide adamantyl aldehyde compound of formula-4,

c) treating the compound of formula-4 in-situ with a suitable alkali metal cyanide in presence of sodium bisulfite or sodium metabisulfite in a suitable solvent followed by treating with α-substituted chiral benzylamine of the structural formula



wherein, "R_1" represents $-CH_3$ or $-CH_2OH$

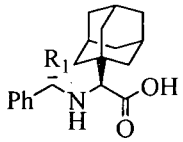
in a suitable solvent to provide compound of general formula-5,



Formula-5

wherein, "R_1" is as defined above;

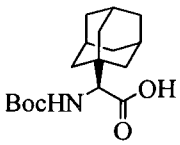
d) hydrolyzing the compound of general formula-5 in presence of a suitable acid in a suitable solvent to provide compound of general formula-6 or its acid-addition salt,



Formula-6

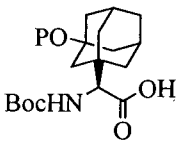
e) treating the compound of general formula-6 or its acid-addition salt with a suitable deprotecting agent optionally in presence of an acid in a suitable solvent to provide amino adamantane carboxylic acid compound of formula-7 or its acid-addition salt,

f) treating the compound of formula-7 or its acid-addition salt with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide Boc-protected amine compound of formula-28,



Formula-28

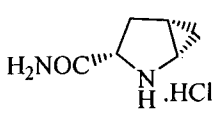
g) hydroxylating the compound of formula-28 by treating with a suitable hydroxylating agent optionally in presence of a suitable base in a suitable solvent followed by, optionally in-situ treating with a suitable O-protecting agent to provide di-protected compound of general formula-29,



Formula-29

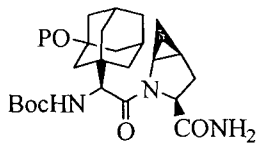
wherein, "P" represents 'H' or 'O-protecting group'

h) condensing the compound of general formula-29 with (1S,3S,5S)-2-azabicyclo[3.1.0] hexane-3-carboxamide compound of formula-26 or its hydrochloride salt compound of formula-26a



Formula-26a

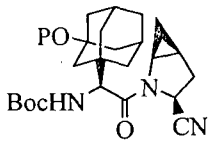
in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-30,



Formula-30

wherein, "P" is as defined above;

i) dehydrating the compound of general formula-30 by treating with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-31,



Formula-31

wherein, "P" is as defined above;

j) deprotecting the compound of general formula-31 by treating it with a suitable deprotecting agent in a suitable solvent followed by optionally treating with a suitable base to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1.

Wherein, in step-a) to step-g) the suitable reagents, the suitable bases and the suitable solvents are same as defined for step-a) to step-g) of the second aspect of the present invention;

in step-h) the suitable coupling agent, the suitable base and the suitable solvent are same as defined for step-a) of the fifth aspect of the present invention;

in step-i) the suitable dehydrating agent and the suitable solvent are same as defined for step-e) of the third aspect of the present invention;

in step-j) the suitable deprotecting agent is selected from but not limited to acids such as hydrochloric acid, aq.phosphoric acid, trifluoroacetic acid, methane sulfonic acid and the like, bases such as alkali metal hydroxides, alkali metal carbonates, cesium carbonate/imidazole, alkali metal bicarbonates and hydrogenating agents such as Pd, Pd/C, $Pd(OH)_2/C$ (Pearlman's catalyst), palladium acetate, platinum oxide, platinum

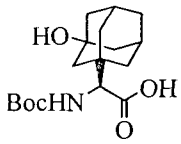
black, sodium borohydride, Raney-Ni, triethylsilane, TMSCl and the like; the suitable solvent is selected form ether solvents, hydrocarbon solvents, chloro solvents, polar-aprotic solvents, and/or their mixtures thereof.

The O-protecting group 'P' of the present invention can be selected from but not limited to tert.butoxycarbonyl (Boc), 3,4-dihydro-2H-pyran (DHP), tetrahydropyranyl (THP), acetyl, benzyl, benzoyl, trifluoroacetyl, pivaloyl, tri(C_1-C_6 alkyl)silyl (eg.,trimethylsilyl, triethylsilyl, tert.butyldimethylsilyl and the like), triphenylmethyl (trityl) groups and the like and it can be removed by treating the corresponding O-protected compound with a suitable acid or a suitable base or by hydrogenolysis depending on the nature of the protecting group employed.

The preferred embodiment of the present invention provides a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

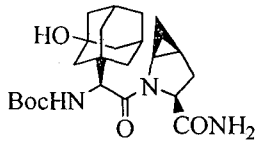
a) Reducing the adamantane-1-carboxylic acid compound of formula-2 with sodium borohydride-BF_3 etherate in tetrahydrofuran to provide adamantyl methanol compound of formula-3,
b) oxidizing the compound of formula-3 with oxalyl chloride/dimethyl sulfoxide in presence of triethylamine in dichloromethane to provide adamantyl aldehyde compound of formula-4,
c) treating the compound of formula-4 in-situ with sodium cyanide in presence of sodium metabisulfite in water followed by treating with R-(-)-2-phenyl glycinol in methanol to provide compound of formula-5a,
d) hydrolyzing the compound of formula-5a in presence of conc. hydrochloric acid in acetic acid to provide compound of formula-6a or its hydrochloride salt,
e) treating the compound of formula-6a or its hydrochloride salt with Pd/C in presence of acetic acid in methanol to provide amino adamantane carboxylic acid compound of formula-7or its hydrochloride salt,
f) treating the compound of formula-7 or its hydrochloride salt with di-tert.butyl dicarbonate in presence of sodium carbonate in water to provide Boc-protected amine compound of formula-28,
g) hydroxylating the compound of formula-28 by treating with potassium permanganate

in presence of potassium hydroxide in water provides compound of formula-29a,



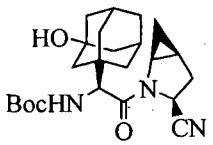
Formula-29a

h) condensing the compound of formula-29a with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a in presence of N,N'-dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBt) and diisopropylethyl amine in a mixture of ethyl acetate and acetonitrile to provide compound of formula-30a,



Formula-30a

i) dehydrating the compound of formula-30a by treating it with trifluoro acetic anhydride in presence of 2,6-lutidine in ethyl acetate to provide compound of formula-31a,

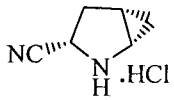


Formula-31a

j) deprotecting the compound of formula-31a by treating with acetyl chloride in methanol followed by treating with potassium carbonate to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

The ninth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1, comprising of;

a) Condensing the compound of general formula-29 with (1S,3S,5S)-2-azabicyclo[3.1.0] hexane-3-carbonitrile hydrochloride salt compound of formula-32



Formula-32

in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-31,

b) deprotecting the compound of general formula-31 by treating it with a suitable deprotecting agent in a suitable solvent to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

Wherein, in step-a) the suitable coupling agent, suitable base and the suitable solvent are same as defined for step-a) of the fifth aspect of the present invention;

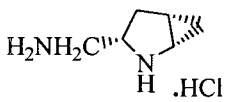
In step-b) the suitable deprotecting agent and the suitable solvent are same as defined for step-j) of the eighth aspect of the present invention.

The (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrochloride salt compound of formula-32 utilized in the above condensation step-a) of the ninth aspect can be synthesized by dehydrating the (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 obtained by the process as described above with a suitable dehydrating agent in presence of a suitable base in a suitable solvent, followed by converting the (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carbonitrile free base into its hydrochloride salt.

Wherein, the suitable dehydrating agent, the suitable base and the suitable solvent are same as described for step-i) of the eighth aspect of the present invention.

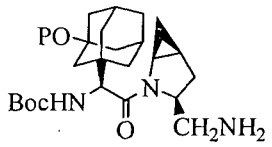
The tenth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1, comprising of;

a) Condensing the compound of general formula-29 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexan-3-ylmethanamine hydrochloride salt compound of formula-33



Formula-33

in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-34,



Formula-34

wherein, "P" represents 'H' or 'O-protecting group'

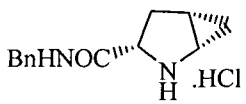
b) treating the compound of general formula-34 with trichloroisocyanuric acid (TCICA) in presence or absence of a suitable catalyst or a suitable base in a suitable solvent followed by deprotecting the obtained compound to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1.

Wherein, the suitable coupling agent, the suitable base and the suitable solvent used in step-a) are same as described for step-a) of the fifth aspect of the present invention;

In step-b) the suitable catalyst is selected from (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), 4-hydroxy-TEMPO, 4-acetamido-TEMPO; the suitable base is selected from organic bases and ammonia; and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, polar-aprotic solvents and/or their mixtures thereof;

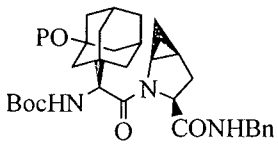
The eleventh aspect of the present invention provides a process for the preparation of compound of general formula-30, comprising of;

a) Condensing the compound of general formula-29 with (1S,3S,5S)-N-benzyl-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-35



Formula-35

in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-36,



Formula-36

wherein 'P' is hydrogen or O-protecting group as defined above;

b) debenzylating the compound of general formula-36 with a suitable debenzylating agent in a suitable solvent to provide compound of general formula-30.

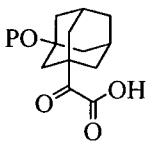
Wherein, the suitable coupling agent, the suitable base and the suitable solvent used in step-a) are same as described for step-a) of the fifth aspect of the present invention;

In step-b) the suitable debenzylating agent and the suitable solvent are same as defined for step-f) of the fifth aspect of the present invention;

The compound of general formula-30 obtained in the eleventh aspect of the present invention can be further converted to (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1 according to the process disclosed in the eighth aspect of the present invention.

The twelfth aspect of the present invention is to provide a process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

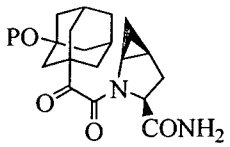
a) Condensing the compound of general formula-37



Formula-37

wherein, "P" represents 'H' or 'O-protecting group'

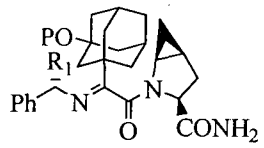
with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-41,



Formula-41

wherein, "P" is as defined above;

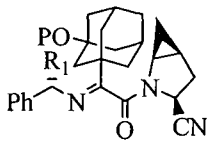
b) reacting the compound of general formula-41 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-42,



Formula-42

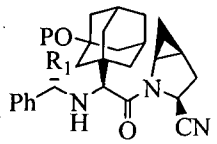
wherein, "P" and "R_1" are as defined above;

c) dehydrating the compound of formula-42 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-39,



Formula-39

d) reducing the compound of formula-39 with a suitable reducing agent in a suitable solvent to provide compound of general formula-40,



Formula-40

e) deprotecting the compound of formula-40 by treating it with a suitable deprotecting agent in a suitable solvent to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

Wherein, in step-a) the suitable coupling agent, the suitable base and the suitable solvent are same as defined for step-h) of the eighth aspect of the present invention;

In step-b) the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ether solvents, ester solvents and/or their mixtures thereof;

In step-c) the suitable dehydrating agent, the suitable base and the suitable solvent are same as defined for step-i) of the eighth aspect of the present invention;

In step-d) the suitable reducing agent is selected from sodium borohydride,

sodium cyanoborohydride, lithium aluminium hydride, lithium borohydride, Pd/C, Pt/C, PtO_2, Raney Ni, sodium bis(2-methoxyethoxy)aluminum hydride (vitride), diisobutylaluminium hydride (DIBAL or DIBAL-H or DIBAH) and the like; and the suitable solvent is selected from hydrocarbon solvents, chloro solvents, ether solvents, ester solvents, alcoholic solvents and/or their mixtures thereof;

In step-e) the suitable deprotecting agent and the suitable solvent are same as defined for step-j) of the eighth aspect of the present invention.

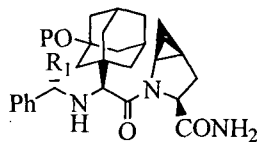
The compound of general formula-37 utilized in the condensation step-a) of the twelfth aspect can be synthesized by treating the corresponding hydroxy compound with a suitable protecting agent.

The thirteenth aspect of the present invention is to provide a process for the preparation of compound of general formula-40, comprising of;

a) Condensing the compound of formula-37 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-41,

b) reacting the compound of general formula-41 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-42,

c) reducing the compound of general formula-42 with a suitable reducing agent in a suitable solvent to provide compound of general formula-43,



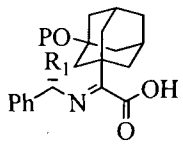
Formula-43

wherein, "P" and "R_1" are same as defined above;

d) dehydrating the compound of general formula-43 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide compound of general formula-40.

The fourteenth aspect of the present invention provides a process for the preparation of compound of general formula-43, comprising of;

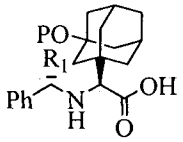
a) Reacting the compound of general formula-37 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-44,



Formula-44

wherein, "R_1" & "P" are same as defined above;

b) reducing the compound of general formula-44 with a suitable reducing agent in a suitable solvent to provide compound of general formula-45,



Formula-45

c) condensing the compound of general formula-45 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-43.

Wherein, the suitable coupling agent, the suitable base and the suitable solvent used in step-a) and step-c) respectively of the thirteenth and fourteenth aspects are same as defined for step-a) of the fifth aspect of the present invention;

The suitable solvent used in step-b) & step-a) respectively of the thirteenth and fourteenth aspects is selected from chloro solvents, hydrocarbon solvents, ether solvents, ester solvents and/or their mixtures thereof;

The suitable reducing agent and the suitable solvent used in step-c) & step-b) respectively of the thirteenth and fourteenth aspects are same as defined for step-d) of the twelfth aspect of the present invention;

The suitable dehydrating agent, the suitable base and the suitable solvent used in step-d) of the thirteenth aspect are same as defined for step-e) of the third aspect of the present invention.

The fifteenth aspect of the present invention provides a process for the preparation of compound of general formula-42, comprising of;

a) Reacting the compound of general formula-37 with α-substituted chiral benzylamine in a suitable solvent to provide compound of general formula-44,

b) condensing the compound of general formula-44 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of general formula-42.

Wherein, in step-a) the suitable solvent is selected form alcoholic solvents, chloro solvents, ether solvents, ester solvents, hydrocarbon solvents and/or their mixtures thereof;

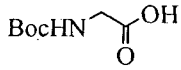
In step-b) the suitable coupling agent, the suitable base and the suitable solvent are same as defined for step-a) of the fifth aspect of the present invention.

The sixteenth aspect of the present invention is to provide a process for the preparation of adamantyl aldehyde compound of formula-4 comprising oxidizing the adamantyl methanol compound of formula-3 with a suitable oxidizing agent optionally in presence of a suitable base or a suitable catalyst in a suitable solvent to provide adamantyl aldehyde compound of formula-4.

Wherein, the suitable oxidizing agent is selected from trichloroisocyanuric acid (TCICA), bis(acetoxy)iodo benzene (BAIB), sodium hypochlorite, N-chlorosuccinimide (NCS), oxone, pyridinium chlorochromate, chromium trioxide and the like; the suitable catalyst wherever necessary is selected from (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), 4-hydroxy-TEMPO, 4-acetamido TEMPO and the like; the suitable base wherever necessary is selected from organic bases; and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, polar-aprotic solvents and/or their mixtures thereof;

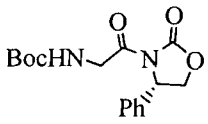
The seventeenth aspect of the present invention provides a novel process for the preparation of compound of formula-28, comprising of;

a) Treating glycine with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide N-Boc protected glycine compound of formula-46,



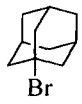
Formula-46

b) reacting the compound of formula-46 with (R)-4-phenyloxazolidin-2-one in a suitable solvent to provide (S)-tert-butyl 2-oxo-2-(2-oxo-4-phenyloxazolidin-3-yl)ethylcarbamate compound of formula-47,



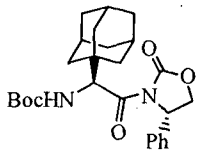
Formula-47

c) reacting the compound of formula-47 with adamantyl bromide compound of formula-48



Formula-48

in presence of a suitable base in a suitable solvent to provide compound of formula-49,



Formula-49

d) hydrolyzing the compound of formula-49 in presence of a suitable base in a suitable solvent to provide compound of formula-28.

Wherein, in step-a) the suitable base and the suitable solvent are same as defined for step-b) of the third aspect of the present invention;

In step-b) the suitable solvent is selected form hydrocarbon solvents, chloro solvents, ether solvents, ester solvents, polar-aprotic solvents and/or their mixtures thereof;

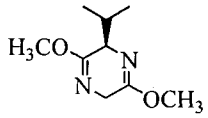
In step-c) the suitable base is selected from organic bases and organosilicon bases; and the suitable solvent is selected from hydrocarbon solvents, chloro solvents, ether solvents, ester solvents, polar-aprotic solvents and/or their mixtures thereof;

In step-d) the suitable base is selected from alkali metal hydroxides, alkali metal alkoxides, alkali metal carbonates and the suitable solvent is selected from hydrocarbon

solvents, chloro solvents, ether solvents, ester solvents, polar-aprotic solvents and/or their mixtures thereof;

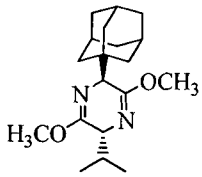
The eighteenth aspect of the present invention provides a novel process for the preparation of compound of formula-28, comprising of;

a) Reacting the adamantyl bromide compound of formula-48 with (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine compound of formula-50



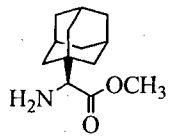
Formula-50

in presence of a suitable base in a suitable solvent to provide compound of formula-51,



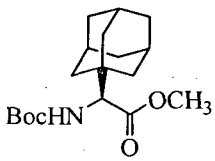
Formula-51

b) treating the compound of formula-51 with a suitable acid in a suitable solvent to provide methyl ester compound of formula-52,



Formula-52

c) treating the compound of formula-52 with di-tert-butyl dicarbonate in presence of a suitable base in a suitable solvent provides Boc protected compound of formula-63,



Formula-63

d) hydrolyzing compound of formula-63 in presence of a suitable base in a suitable solvent to provide compound of formula-28.

Wherein, in step-a) the suitable base is selected from organic bases and organosilicon bases; and the suitable solvent is selected from hydrocarbon solvents, chloro solvents, ether solvents, ester solvents and/or their mixtures thereof;

In step-b) the suitable acid is hydrochloric acid; and the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, polar-aprotic solvents and/or their mixtures thereof;

In step-c) the suitable base is selected from organic and inorganic bases and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ether solvents, ester solvents and/or their mixtures thereof;

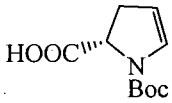
in step-d) the suitable base is selected from hydroxides, alkoxides, bicarbonates of alkali metals and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ether solvents, ester solvents, alcohol solvents and/or their mixtures thereof;

The (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine compound of formula-50 utilized in step-a) of the eighteenth aspect of the present invention is commercially available or it can be synthesized by the methods known in the art for example Org. Process Res. Dev., 2005, 9(2), 185–187, Tetrahedron: Asymmetry 1998, 9, 321-327.

The compounds of formulae-28 & 7 obtained in the seventeenth and eighteenth aspects respectively can be converted to (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile compound of formula-1 as per the process disclosed in the eighth aspect of the present invention.

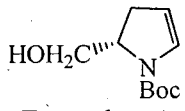
The nineteenth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexan-3-ylmethanamine hydrochloride compound of formula-33, comprising of;

a) Reducing the (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-53



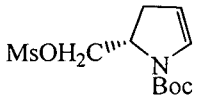
Formula-53

with a suitable reducing agent in a suitable solvent to provide (S)-tert-butyl 2-(hydroxymethyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-54,



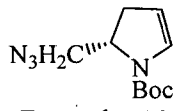
Formula-54

b) mesylation of compound of formula-54 with methane sulfonyl chloride in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-((methylsulfonyloxy)methyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-55,



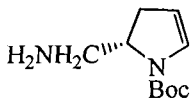
Formula-55

c) azidation of compound of formula-55 by treating it with a suitable azide source in a suitable solvent to provide (S)-tert-butyl 2-(azidomethyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-56,



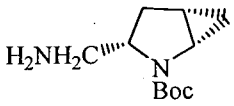
Formula-56

d) reducing the azide compound of formula-56 with a suitable reducing gent in a suitable solvent to provide (S)-tert-butyl 2-(aminomethyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-57,



Formula-57

e) treating the compound of formula-57 with a suitable methylene source in presence of a suitable catalyst in a suitable solvent to provide (1S,3S,5S)-tert-butyl 3-(aminomethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-58,



Formula-58

f) deprotecting the compound of formula-58 with hydrochloric acid in a suitable solvent to provide (1S,3S,5S)-2-azabicyclo[3.1.0]hexan-3-ylmethanamine hydrochloride salt compound of formula-33.

Wherein, in step-a) the suitable reducing agent is selected from sodium borohydride-BF_3.etherate, sodium cyanoborohydride, lithium aluminium hydride, lithium borohydride, borane-dimethyl sulfide, sodium bis(2-methoxyethoxy)aluminum hydride (vitride), diisobutyl aluminium hydride (DIBAL); and the suitable solvent is selected from alcoholic solvents, ether solvents, chloro solvents, hydrocarbon solvents, ester solvents and/or their mixtures thereof;

In step-b) the suitable base is selected from organic bases and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents and/or their mixtures thereof;

In step-c) the suitable azide source is selected from sodium azide, bis(p-nitrophenyl) phosphorazidate, azidotrimethylsilane, hydrogen azide (HN_3) and the like; and the suitable solvent is selected from ether solvents, chloro solvents, hydrocarbon solvents and/or their mixtures thereof;

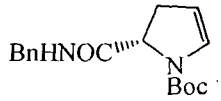
In step-d) the suitable reducing agent is selected from sodium borohydride, lithium aluminium hydride, H2/Lindlar catalyst, Zn/NH_4Cl, dichloroindium hydride, $Fe/AlCl_3$, $Fe/BiCl_3$, triphenyl phosphine (Staudinger reaction), hydroiodic acid; and the suitable solvent is selected from alcoholic solvents, ether solvents, chloro solvents, hydrocarbon solvents, ester solvents and/or their mixtures thereof;

In step-e) the suitable methylene source is selected from dihalomethanes such as diiodomethane, chloroiodomethane and the suitable catalyst is diethyl zinc; the suitable solvent is selected from hydrocarbon solvents, ether solvents, chloro solvents and/or their mixtures thereof;

In step-f) the suitable solvent is selected from hydrocarbon solvents, chloro solvents, ether solvents and/or their mixtures thereof.

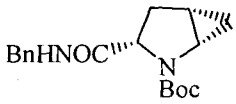
The twentieth aspect of the present invention provides a process for the preparation of (1S,3S,5S)-N-benzyl-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-35, comprising of;

a) Amidation of (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-53 with benzylamine in presence of a suitable coupling agent optionally in presence of a suitable base a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-59,



Formula-59

b) treating the compound of formula-59 with a suitable methylene source in presence of a suitable catalyst in a suitable solvent to provide (1S,3S,5S)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-60,



Formula-60

c) deprotecting the compound of formula-60 with hydrochloric acid in a suitable solvent to provide (1S,3S,5S)-N-benzyl-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride compound of formula-35.

Wherein, in step-a) the suitable coupling agent, the suitable base and the suitable solvent are same as defined for step-a) of the fifth aspect of the present invention;

In step-b) the suitable methylene source, the suitable catalyst and the suitable solvent are same as described for step-f) of the third aspect of the present invention;

In step-c) the suitable solvent is selected from hydrocarbon solvents, chloro solvents, ether solvents and/or their mixtures thereof.

The compound (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile obtained in the present invention is in the form of monohydrate.

The (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile compound of formula-1 and its hydrochloride salt compound of formula-1a obtained by the present invention upon treatment with ethylene glycol or 1,3-propane diol optionally in presence of water they were ended with corresponding ethylene glycol solvate or 1,3-propane diol solvate forms.

The (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile and its hydrochloride salt of the present invention were analyzed by HPLC under the following conditions:

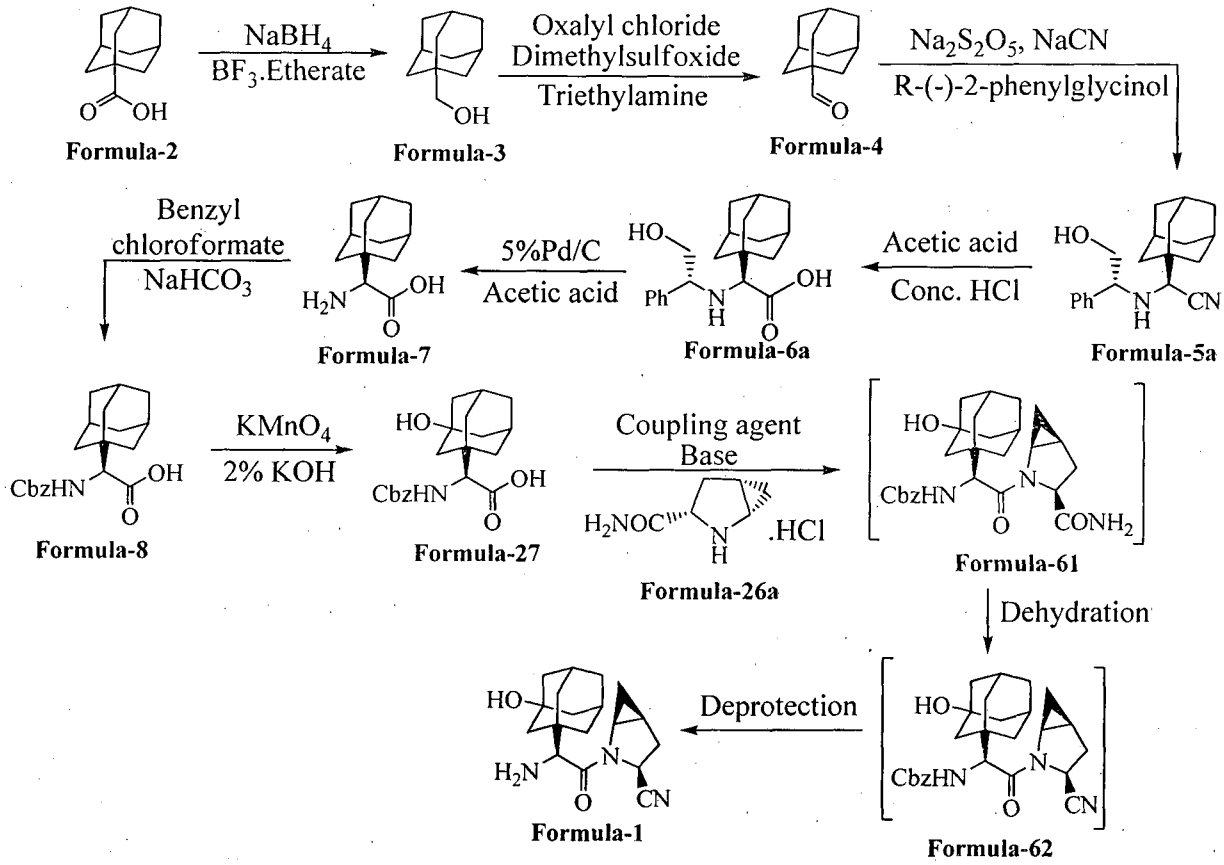
Apparatus: A liquid chromatographic system equipped with variable wavelength UV-detector and integrator; Column: Symmetry C18, 150×4.6 mm, 3.5 µm or equivalent; Flow rate: 1.2 mL/min; Wavelength: 215 nm; Column temperature: 45°C; Auto sampler temperature: 5°C; Injection volume: 5 µL; Run time: 43 min; Diluent: 0.1% H_3PO_4 and acetonitrile in the ration of (9:1 v/v); Elution: gradient; Buffer: Weigh accurately 1.36 gm of potassium dihydrogen orthophosphate and 6.0 gm of 1-octane sulfonic acid sodium salt anhydrous into 1000 ml of milli-Q-water and adjusted the pH to 2.5 with diluted ortho phosphoric acid (85%). Filtered the solution through 0.22 µm Nylon membrane filter paper and sonicated to degas it.

The particle size distribution of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile and its hydrochloride salt of the present invention is measured using Malvern Mastersizer 2000 instrument.

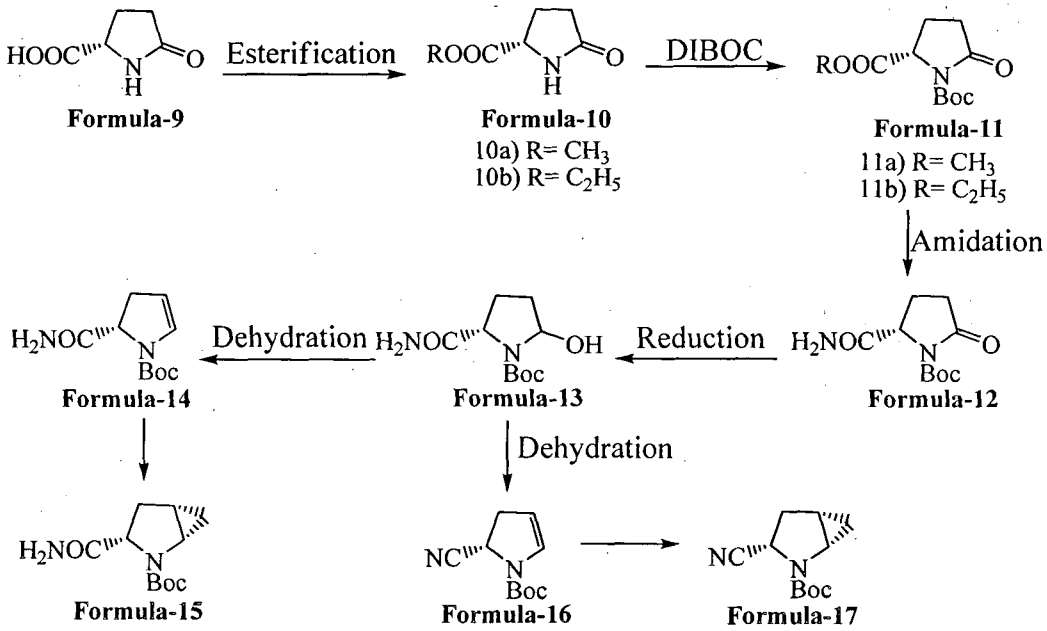
The (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile compound or its hydrochloride salt produced by the present invention can be further micronized or milled to get the desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball, roller and hammer mills, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

The present invention is schematically represented as follows.

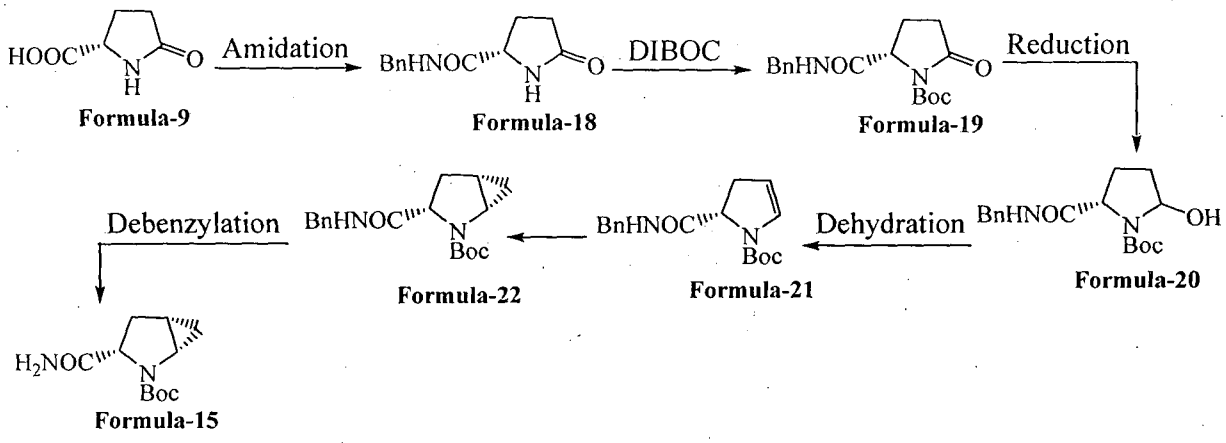
Scheme-1:



Scheme-2:



Scheme-3:



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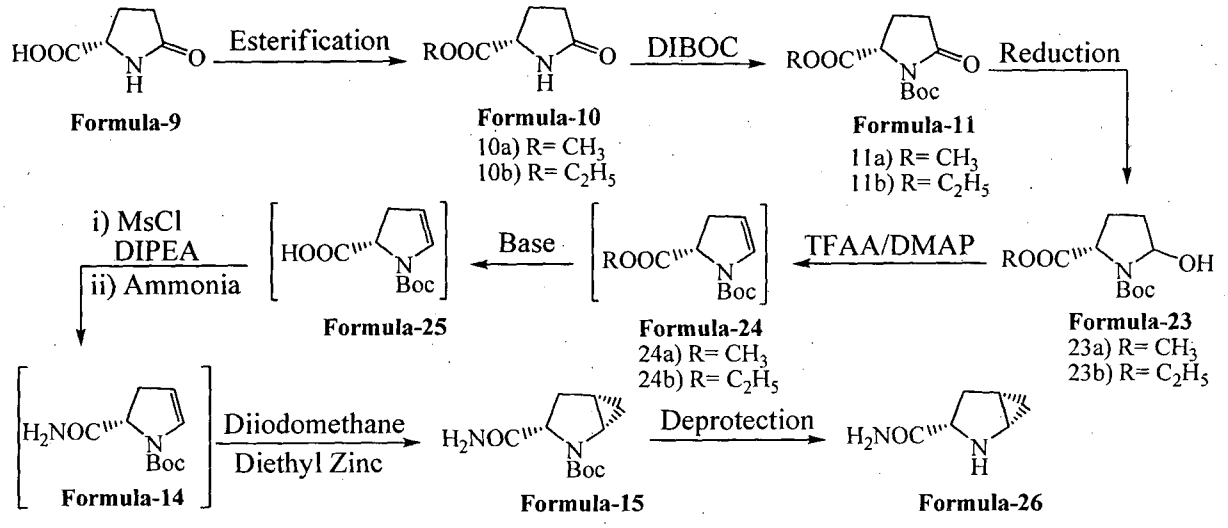
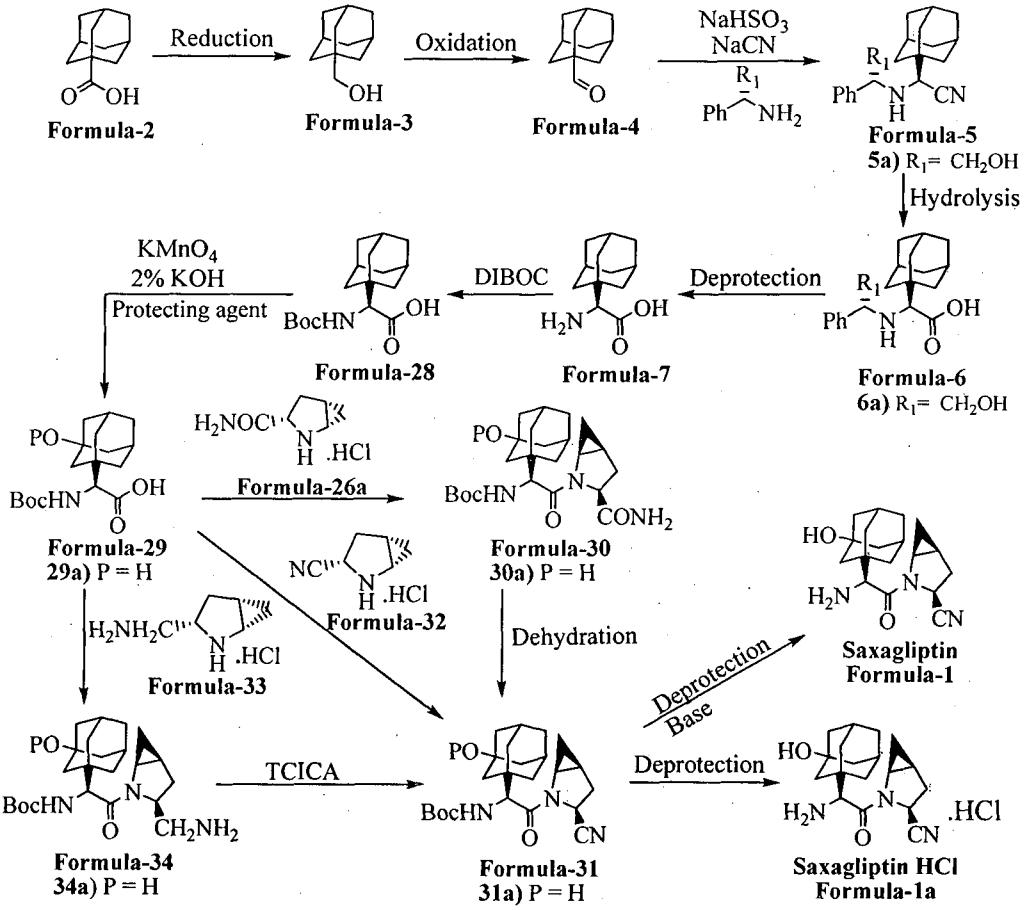
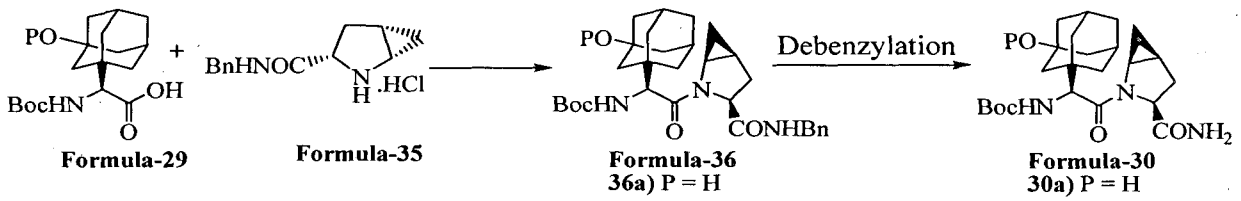


Scheme-5:



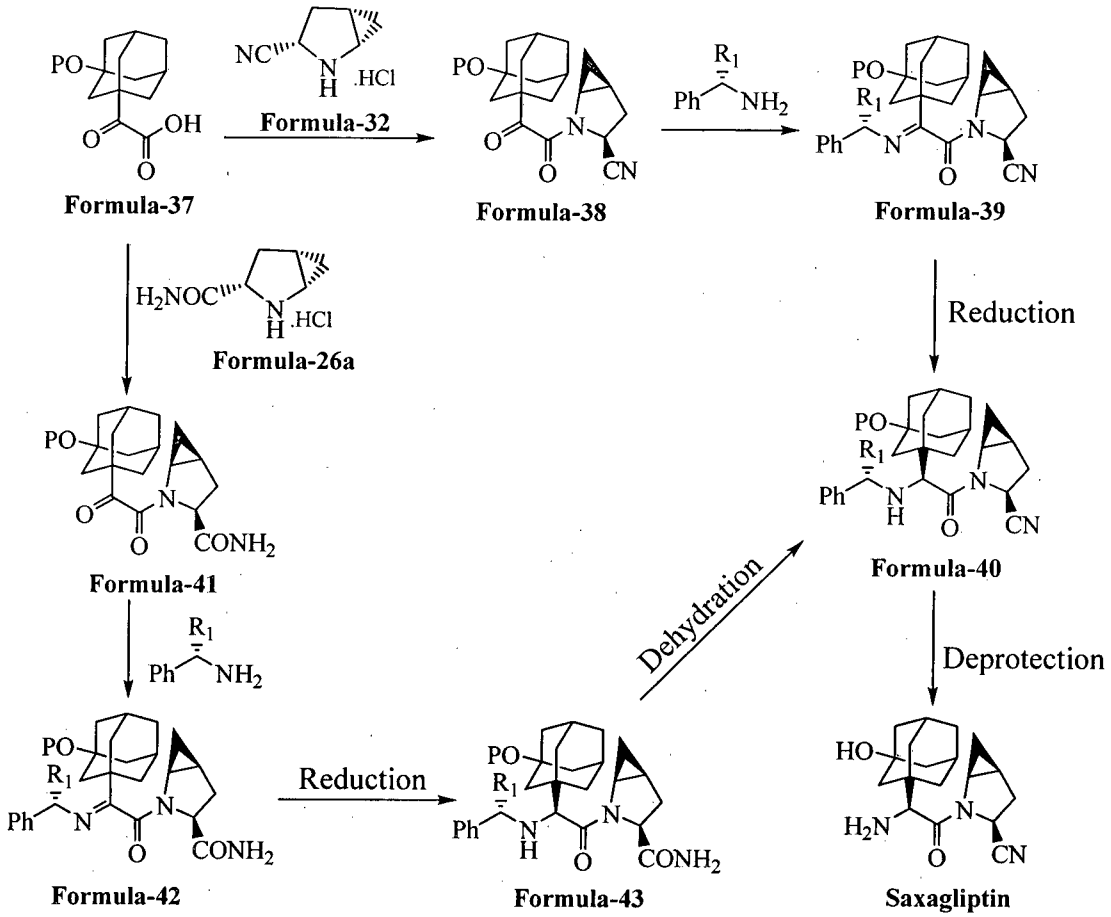
Wherein, "R_1" is CH_3, CH_2OH; P is H or O-protecting group as defined in detailed description

Scheme-6:

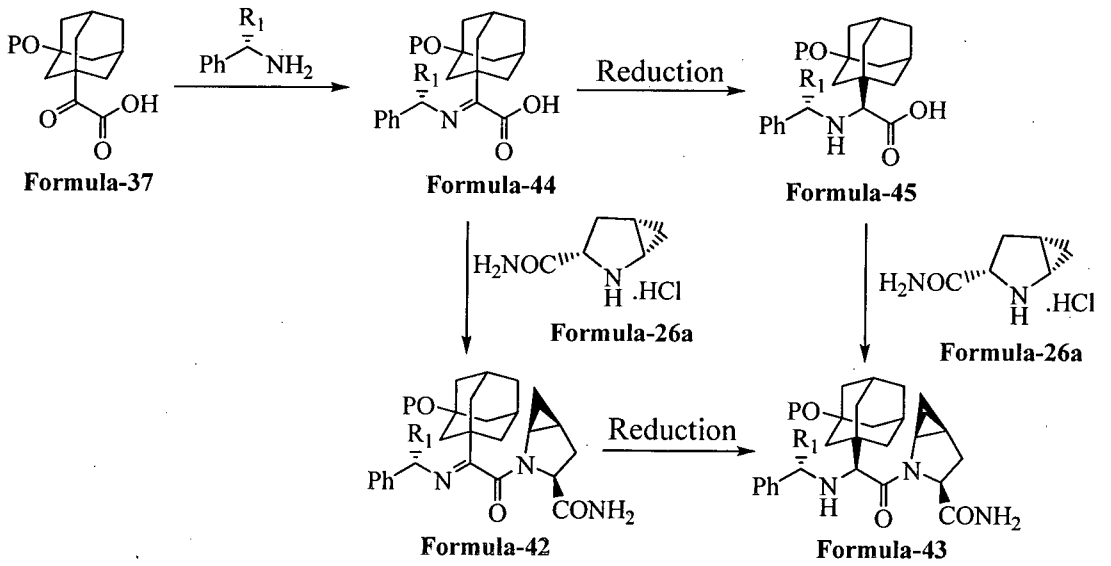


Wherein P is H or O-protecting group as defined in detailed description

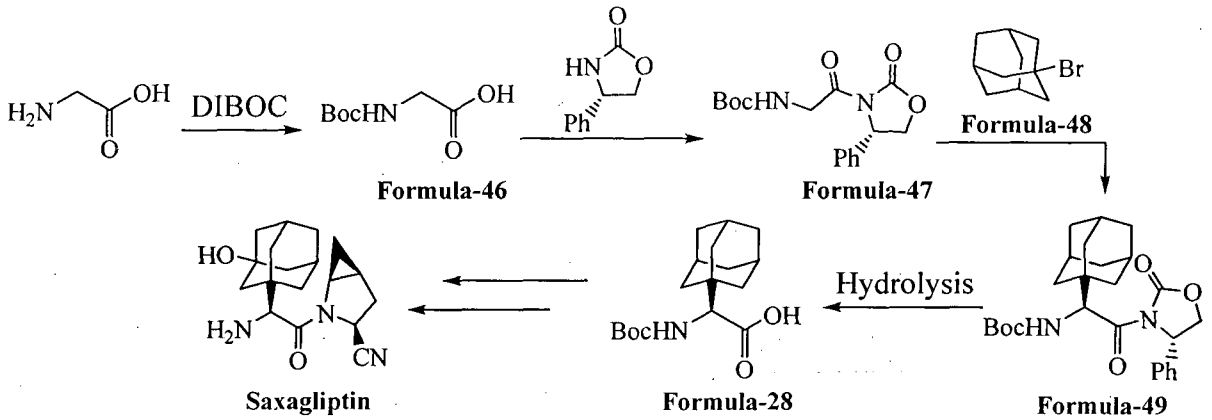
Scheme-7:



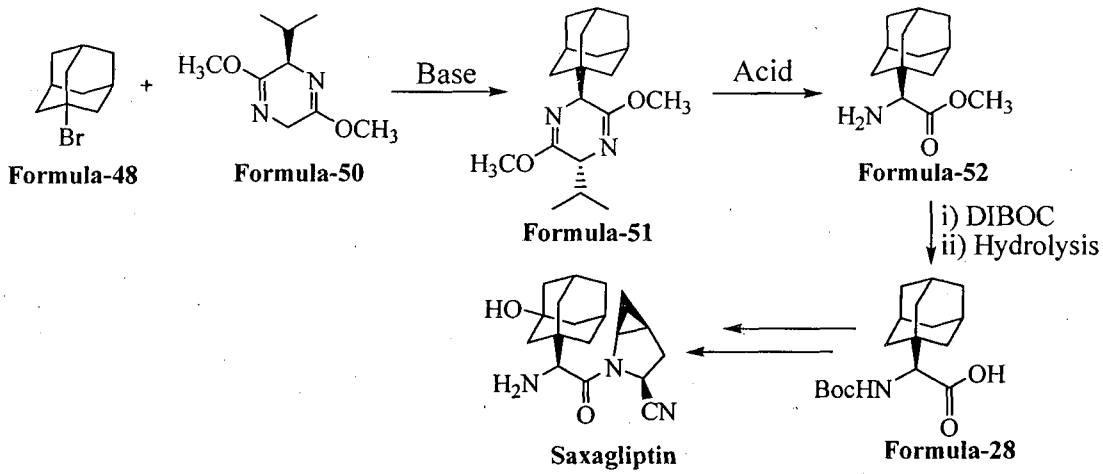
Scheme-8:



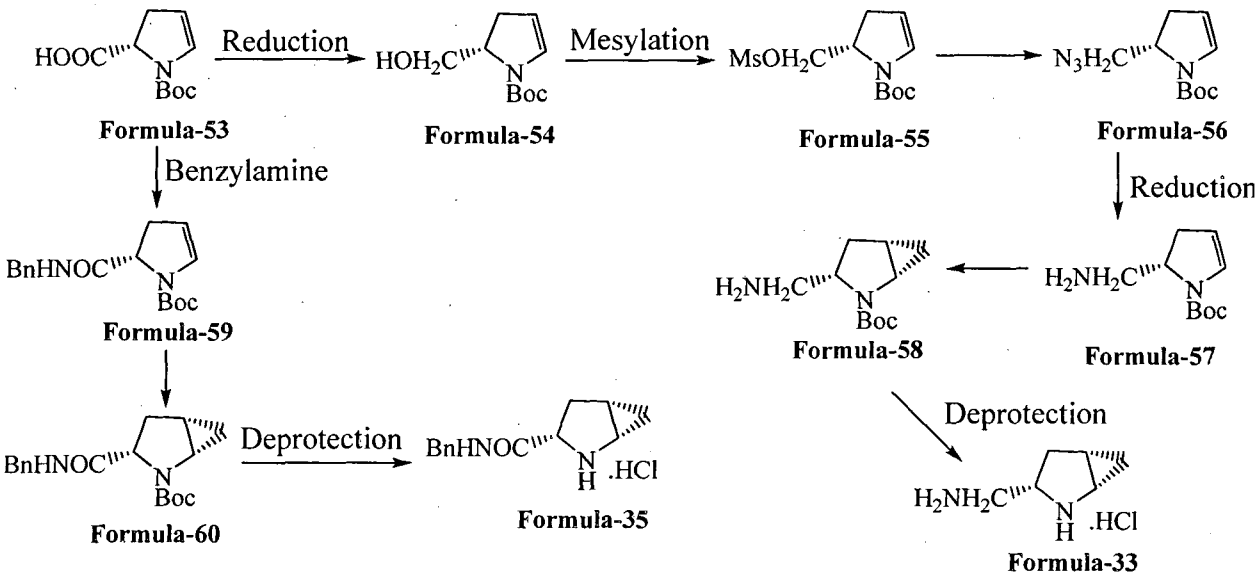
Scheme-9:



Scheme-10:



Scheme-11:



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 adamantyl methanol (Formula-3)

Tetrahydrofuran (2000 ml) and sodium borohydride (63 gm) were charged in to a clean and dry RBF at 25-30°C under nitrogen atmosphere. The reaction mixture was cooled to 0-5°C and a solution of adamantane-1-carboxylic acid (250 gm) in tetrahydrofuran (1000 ml) was slowly added. Stirred the reaction mixture for 1 hr at 0-5°C and BF_3.etherate (280 ml) was slowly added to it at the same temperature. Heated the reaction mixture to 25-35°C and stirred for 7 hrs at the same temperature. After the completion of the reaction, the reaction mixture was cooled to 0-5°C and water (2000 ml) was slowly added at the same temperature. Conc.HCl (150 ml) followed by dichloromethane (2000 ml) were slowly added to the reaction mixture. Heated the reaction mixture to 25-35°C and stirred for 45 min at the same temperature. Both the organic and aqueous layers were separated, dichloromethane (1000 ml) was added to the aqueous layer and stirred for 30 min. Separated the organic and aqueous layers and a solution of sodium bicarbonate (100 gm) in water (1000 ml) was added to the total organic layer. Stirred the reaction mixture for 30 min at 25-35°C and separated the organic and aqueous layers. Dried the organic layer over sodium sulfate and distilled off completely at 50-55°C. The obtained solid was filtered, washed with dichloromethane and then dried to get the title compound as a solid. Yield: 210 gms.

Example-2: Purification of adamantyl methanol

Pet ether (250 ml) and adamantyl methanol obtained in above example-1 were charged in to a clean and dry RBF at 25-35°C and the resulting reaction mixture was stirred for 2 hrs at the same temperature. The obtained solid was filtered, washed with pet ether and then dried at 50-55°C to get the title compound as a pure solid.

Yield: 193 gm.

Example-3: Preparation of adamantyl aldehyde (Formula-4)

Dichloromethane (1500 ml) and oxalyl chloride (280 ml) were charged in to a clean and dry RBF under nitrogen atmosphere at 25-30°C. Cooled the reaction mixture to

-78°C, dimethyl sulfoxide (270 ml) was slowly added and stirred for 2½ hrs at the same temperature. A solution of adamantyl methanol (150 gm) in dichloromethane (1500 ml) was slowly added to the reaction mixture at -78°C and stirred for 2½ hrs at the same temperature. Slowly added triethylamine (1000 ml) to the reaction mixture at -78°C and stirred for 1½ hrs at the same temperature. After the completion of the reaction, the temperature of the reaction mixture was raised to 25-35°C and stirred for 30 min at the same temperature. Water (1500 ml) was added to the reaction mixture at 25-35°C and stirred for 45 min at the same temperature. Both the organic and aqueous layers were separated, dichloromethane (750 ml) was added to the aqueous layer at 25-35°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and a solution of sodium chloride (75 gm) in water (1500 ml) was added to the organic layer. Stirred the reaction mixture at 25-35°C for 45 min and the organic and aqueous layers were separated. Distilled off the organic layer under reduced pressure at below 50-55°C to get the title compound as a residue.

Example-4: Preparation of phenylglycinol adamantane nitrile compound of formula-5a

Water (3000 ml) and sodium bisulfite (150 gm) were added to the residue obtained in above example-3 in a clean and dry RBF at 25-35°C and stirred for 2 hrs at the same temperature. Sodium cyanide (49 gm) was added to the reaction mixture at 25-35°C and stirred for 30 min at the same temperature. A solution of R-(-)-2-phenylglycinol (140 gm) in methanol (900 ml) was added to the reaction mixture at 25-35°C. Heated the reaction mixture to 80-85°C and stirred for 15 hrs at the same temperature. After the completion of the reaction, the reaction mixture was cooled to 25-35°C. Ethyl acetate (3000 ml) was added to the reaction mixture at 25-35°C and stirred for 45 min at the same temperature. Both the organic and aqueous layers were separated, ethyl acetate (1500 ml) was added to the aqueous layer at 25-35°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and a solution of sodium chloride (150 gm) in water (1500 ml) was added to the organic layer at 25-35°C and stirred for 30 min at the same temperature. Separated the organic and aqueous layers, dried the organic layer over sodium sulfate and distilled at below 55°C under reduced pressure. The obtained residue was cooled to 25-35°C and methanol (225

ml) was added. Water (2000 ml) and conc.HCl (600 ml) was charged in to another RBF and slowly added the above obtained methanolic solution at 25-35°C and stirred for 4 hrs at the same temperature. Filtered the solid, washed with water and then suck dried to get the title compound.Yield: 207 gm.

Example-5: Purification of phenylglycinol adamantane nitrile compound of formula-5a

Phenylglycinol adamantane nitrile compound of formula-5a (207 gm) and cyclohexane (750 ml) were charged in to a clean and dry RBF at 25-35°C and stirred for 3 hrs at the same temperature. The obtained compound was filtered, washed with cyclohexane and then dried to get the title compound as a pure solid.
Yield: 192 gm.

Example-6: Preparation of phenylglycinol adamantane carboxylic acid compound of formula-6a

Phenylglycinol adamantane nitrile compound of formula-5a (150 gm), acetic acid (450 ml) and conc. HCl (750 ml) were charged in to a clean and dry RBF at 25-35°C. The reaction mixture was heated to 80-85°C and stirred for 12 hrs at the same temperature. After the completion of the reaction, the reaction mixture was completely distilled off at 80-85°C. Cooled the reaction mixture to 0-5°C and water (750 ml) was added and stirred for 2 hrs at the same temperature. The obtained solid was filtered, washed with water and then dried to get the title compound as hydrochloride salt. Yield: 130 gm.

Example-7: Preparation of amino adamantane carboxylic acid compound of formula-7

Hydrochloride salt of carboxylic acid compound of formula-6a (50 gm), methanol (500 ml), acetic acid (500 ml) and 5% Pd/C (50 gm) were charged in to a clean and dry autoclave vessel and 5 kg pressure of hydrogen gas was applied to the reaction mixture. The resulting mixture was heated to 40-45°C and stirred for 12 hrs under 5 kg hydrogen pressure at the same temperature. After the completion of the reaction, the reaction mixture was cooled to 25-35°C and filtered through hyflow bed. Washed the Pd/C with

methanol and decomposed using dilute hydrochloric acid. The filtrate was distilled off under reduced pressure at 50-55°C. Added methyl tert.butyl ether (250 ml) to the obtained gummy solid at 25-35°C and stirred for 1½ hrs at the same temperature. The obtained solid was filtered, washed with methyl tert.butyl ether and then dried to get the title compound as hydrochloride salt. Yield: 28.0 gm.

Example-8: Preparation of benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8

Sodium bicarbonate (20 gm) and tetrahydrofuran (50 ml) were added to a solution of amino adamantane carboxylic acid compound of formula-7 (10 gm) in water (100 ml) at 25-30°C. Benzyl chloroformate (12.5 gm) was slowly added to the resulting reaction mixture at 25-30°C and stirred for 12 hrs at the same temperature. Ethyl acetate (100 ml) was added to the reaction mixture at 0-5°C and the pH of the resulting mixture was adjusted to 3 by adding 2N HCl solution at 0-5°C. Both the organic and aqueous layers were separated and the product was extracted from the aqueous layer using ethyl acetate. The total organic layer was washed with saturated sodium chloride solution and the organic layer was concentrated under reduced pressure to get the pure title compound. Yield: 15.8 gm.

Example-9: Preparation of benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27

Potassium hydroxide (4.0 gm) was added to a solution of benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8 (10 gm) in water (100 ml) at 25-30°C. The reaction mixture was cooled to 0-5°C and solid potassium permanganate (9.5 gm) was added at the same temperature. Heated the reaction mixture to 25-30°C and stirred at the same temperature up to the completion of the reaction. Cooled the reaction mixture to 0-5°C and methyl tert.butyl ether (50 ml) was slowly added. The pH of the reaction mixture was adjusted to 3 by adding 2N HCl solution. Both the organic and aqueous layers were separated and the aqueous layer was extracted with methyl tert.butyl ether. The total organic layer was washed with sodium chloride solution and the organic layer was concentrated under reduced pressure to get the title compound.

The obtained compound is further purified by column chromatography on silica gel to get the title compound. Yield: 6.5 gm.

Example-10: Preparation of benzyloxycarbonyl protected amino adamantane carboxylic acid (Formula-8)

Amino adamantane carboxylic acid compound of formula-7 (10 gm) and water (150 ml) were charged into a clean and dry RBF at 25-30°C and stirred for 20 min at the same temperature. Cooled the reaction mixture to 15-20°C and sodium bicarbonate (10 gm) was slowly added for 3 hrs. Slowly added benzyl chloroformate (19.5 gm, 50% solution in toluene) to the reaction mixture at 15-20°C and stirred for 24 hrs at 20-25°C. After completion of the reaction, filtered the reaction mixture and both the organic and aqueous layers were separated from the filtrate. Washed the aqueous layer with cyclohexane, cooled to 0-5°C. Dichloromethane was added to the aqueous layer at 0-5°C. Adjusted the pH of the reaction mixture to below 1.5 using 5% aq.HCl at 0-5°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated, extracted the aqueous layer with dichloromethane and distilled off the solvent completely from the organic layer to get the title compound.

Example-11: Preparation of (S)-ethyl 5-oxopyrrolidine-2-carboxylate (Formula-10b)

Thionyl chloride (67.9 ml) was slowly added to a pre-cooled solution of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 (100 gm) in ethanol (200 ml) at 0-5°C and stirred for 3 hrs at the same temperature. Distilled the reaction mixture at below 40°C under reduced pressure and then cooled to 25-30°C. Dichloromethane (1000 ml) followed by water (200 ml) were added to the reaction mixture and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 10% sodium bicarbonate solution followed by 10% sodium chloride solution and dried over sodium sulfate. The resulting organic layer containing (S)-ethyl 5-oxopyrrolidine-2-carboxylate was utilized in the next step without isolating the title compound.

Example-12: Preparation of (S)-methyl 5-oxopyrrolidine-2-carboxylate (Formula-10a)

The title compound is prepared by the process described in example-11, using methanol instead of ethanol for the esterification step.

Example-13: Preparation of (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (Formula-11b)

4-dimethylaminopyridine (4.8 gm) followed by di-tert-butyl dicarbonate (236.5 gm) were slowly added to the organic layer containing (S)-ethyl 5-oxopyrrolidine-2-carboxylate obtained in example-11 at 25-30°C and stirred for 3 hrs at the same temperature. After completion of the reaction, the reaction mixture was quenched with water. Both the organic and aqueous layers were separated. Organic layer was washed with 2% HCl solution followed by with 10% sodium chloride solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely from the organic layer. Pet ether (100 ml) was added to the obtained solid and heated the reaction mixture to 35-40°C and stirred for 20 min at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure, pet ether (300 ml) was added to the obtained compound and stirred for 10 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 60 min at the same temperature. Filtered the precipitated solid, washed with pet ether and then dried to get the title compound.

Yield: 160.0 gm; M.P: 40-45°C.

Example-14: Preparation of (S)-1-tert-butyl 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate (Formula-11a)

The title compound is prepared by the process described in example-13, using (S)-methyl 5-oxopyrrolidine-2-carboxylate (Formula-10a) instead of (S)-ethyl 5-oxopyrrolidine-2-carboxylate (Formula-10b) as a starting material.

Example-15: Preparation of (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate (Formula-12)

(S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate compound of formula-11b (10 gm) and formamide (5 gm) were charged into a clean and dry RBF at 25-30°C and stirred for 15 min at the same temperature. Cooled the reaction mixture to 0-5°C, sodium methoxide solution (20 ml) was added and stirred for 2½ hrs at the same temperature. After completion of the reaction, water was slowly added to the reaction

mixture at 0-5°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and the aqueous layer was extracted with n-butanol. The combined organic layer dried over sodium sulfate. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 3.5 gm.

Example-16: Preparation of (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate (Formula-13)

Sodium borohydride (1.25 gm) was slowly added to a solution of (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12 (5 gm) in methanol (25 ml) at -10 to -15°C and stirred for 60 min at the same temperature. After completion of the reaction, 1% sodium bicarbonate solution followed by dichloromethane was slowly added to the reaction mixture at -10 to -15°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with 10% sodium chloride solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 3.5 gm.

Example-17: Preparation of (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate (Formula-14)

Diisopropylethyl amine (9.8 gm) was slowly added to (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate compound of formula-13 (3.5 gm) in tetrahydrofuran (45 ml) at -65°C to -75°C and stirred for 20 min at the same temperature. Trifluoroacetic anhydride (4.7 gm) was slowly added to the reaction mixture at -65°C to -75°C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 20-25°C and stirred for 3 hrs at the same temperature. Add water to the reaction mixture and followed by ethyl acetate. Stirred the reaction mixture for 10 minutes. Separated the both aqueous and organic layers and washed the organic layer with aqueous HCl solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 2.4 gm.

Example-18: Preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-

azabicyclo[3.1.0]hexane-2-carboxylate (Formula-15)

Diiodomethane (15.1 ml) and 20% diethyl zinc solution (58 ml) were slowly added to a mixture of (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14 (10 gm) in toluene (200 ml) and 1,2-dimethoxy ethane (13.8 ml) at -10-0°C under N_2 atmosphere and stirred for 15 min at the same temperature. Heated the reaction mixture to 40-45°C and stirred for 3 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 0-5°C and 10% sodium bicarbonate solution was added. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Filtered the reaction mixture and washed with toluene. Both the organic and aqueous layers were separated from the filtrate and extracted the aqueous layer with ethyl acetate. Distilled off the solvent completely from the combined organic layer under reduced pressure and co-distilled with pet ether. To the obtained residue, pet ether (50 ml) was added at 25-30°. Cooled the reaction mixture to 0-5°C and stirred for 30 min at the same temperature. Filtered the precipitated solid, washed with pet ether and dried to get the title compound. Yield: 6.5 gm.

Example-19: Preparation of (S)-tert-butyl 2-cyano-2,3-dihydro-1H-pyrrole-1-carboxylate (Formula-16)

Diisopropylethyl amine (11 gm) was slowly added to a solution of (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate compound of formula-13 (5 gm) in tetrahydrofuran (65 ml) at -65°C to -75°C and stirred for 20 min at the same temperature. Trifluoroacetic anhydride (10 gm) was slowly added to the reaction mixture at -65°C to -75°C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 20-25°C and stirred for 3 hrs at the same temperature. Add water to the reaction mixture and followed by ethyl acetate. Stirred the reaction mixture for 10 minutes. Separated the both aqueous and organic layers and washed the organic layer with aqueous HCl solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 3.3 gm.

Example-20: Preparation of (1S,3S,5S)-tert-butyl 3-cyano-2-azabicyclo[3.1.0]hexane-2-carboxylate (Formula-17)

Diiodomethane (8.3 ml) and 20% diethyl zinc solution (31.5 ml) were slowly added to a solution of (S)-tert-butyl 2-cyano-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-16 (5 gm) in toluene (100 ml) and 1,2-dimethoxy ethane (7.5 ml) at -10°C to 0°C under N_2 atmosphere and stirred the reaction mixture for 15 min at the same temperature. Raised the temperature of the reaction mixture to 40-45°C and stirred for 3 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 0-5°C and 10% sodium bicarbonate solution was added. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Filtered the reaction mixture and washed with toluene. Both the organic and aqueous layers were separated from the filtrate and the aqueous layer was extracted with ethyl acetate. Distilled off the solvent completely from the combined organic layer under reduced pressure and co-distilled with pet ether. To the obtained residue, pet ether (25 ml) was added and cooled the reaction mixture to 0-5°C and stirred for 30 min at the same temperature. Filtered the precipitated solid, washed with pet ether and dried to get the title compound. Yield: 3.6 gm.

Example-21: Preparation of (S)-N-benzyl-5-oxopyrrolidine-2-carboxamide (Formula-18)

(S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 (10 gm) and ethyl acetate (50 ml) were charged into a clean and dry RBF at 25-30°C and stirred for 20 min at the same temperature. Slowly heated the reaction mixture to 40-45°C, benzylamine (8.6 gm) was added and stirred for 90 min at the same temperature. Slowly heated the reaction mixture to 50-55°C, thionyl chloride (12 gm) was added and stirred for 5 hrs at the same temperature. After completion of the reaction, water was added to the reaction mixture at 25-30°C and stirred for 10 min at the same temperature. Further cooled the reaction mixture to 10-15°C and dichloromethane was added. Basified the reaction mixture using 10% sodium bicarbonate solution at 10-15°C. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. The combined organic layer was washed with water and distilled off the solvent completely from the organic layer under reduced pressure to get the title compound as a solid. Yield: 6.0 gm.

Example-22: Preparation of (S)-tert-butyl 2-(benzylcarbamoyl)-5-oxopyrrolidine-1-carboxylate (Formula-19)

4-Dimethylaminopyridine (0.15gm) followed by di-tert-butyl dicarbonate (7.0 gm) were slowly added to a solution of (S)-N-benzyl-5-oxopyrrolidine-2-carboxamide compound of formula-18 (5 gm) in dichloromethane (50 ml) at 25-30°C and stirred for 3 hrs at the same temperature. After completion of the reaction quenched the reaction mixture with water. Both the organic and aqueous layers were separated, and the organic layer was washed with 2% HCl solution at 5-10°C and followed by washed with 10% sodium chloride solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 5.1 gm.

Example-23: Preparation of (2S)-tert-butyl 2-(benzylcarbamoyl)-5-hydroxypyrrolidine-1-carboxylate (Formula-20)

Sodium borohydride (0.9 gm) was slowly added to a solution of (S)-tert-butyl 2-(benzylcarbamoyl)-5-oxopyrrolidine-1-carboxylate compound of formula-19 (5 gm) in methanol (25 ml) at -10 to -15°C and stirred for 60 min at the same temperature. After completion of the reaction, 1% sodium bicarbonate solution followed by dichloromethane were slowly added to the reaction mixture at -10 to -15°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with 10% sodium chloride solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 3.4 gm.

Example-24: Preparation of (S)-tert-butyl 2-(benzylcarbamoyl)-2,3-dihydro-1H-pyrrole-1-carboxylate (Formula-21)

Diisopropylethyl amine (10 gm) was slowly added to a solution of (2S)-tert-butyl 2-(benzylcarbamoyl)-5-hydroxypyrrolidine-1-carboxylate compound of formula-20 (5 gm) in tetrahydrofuran (60 ml) at -65°C to -75°C and stirred for 20 min at the same temperature. Trifluoroacetic anhydride (4.9 gm) was slowly added to the reaction mixture

at -65°C to -75°C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 20-25°C and stirred for 3 hrs at the same temperature. Add water to the reaction mixture and followed by ethyl acetate. Stirred the reaction mixture for 10 minutes. Separated the both aqueous and organic layers and washed the organic layer with aqueous HCl solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 3.2 gm.

Example-25: Preparation of (1S,3S,5S)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (Formula-22)

Diiodomethane (5.3 ml) and 20% diethyl zinc solution (20 ml) were slowly added to a mixture of (S)-tert-butyl 2-(benzylcarbamoyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-21 (5 gm) in toluene (100 ml) and 1,2-dimethoxy ethane (5 ml) at -10°C to 0°C under N_2 atmosphere and stirred for 15 min at the same temperature. Heated the reaction mixture to 40-45°C and stirred for 3 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 0-5°C and 10% sodium bicarbonate solution was added. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Filtered the reaction mixture and washed with toluene. Both the organic and aqueous layers were separated from the filtrate, extracted the aqueous layer with ethyl acetate. Combined the organic layers and distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 3.6 gm.

Example-26: Preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (Formula-15)

(1S,3S,5S)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-22 (5 gm), methanol (35 ml), acetic acid (35 ml) were charged into a clean and dry RBF at 25-30° and stirred for 15 min at the same temperature. Carbon (2 gm) was added to the reaction mixture at 25-30°C and stirred for 90 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with a mixture of methanol and acetic acid. A solution of 5% Pd/C (2 gm) in methanol (5 ml) was added to the filtrate under nitrogen atmosphere in an autoclave vessel at 25-30°C. 4-5 kg/Cm^2 of hydrogen gas pressure was applied to the reaction

mixture at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 12 hrs at the same temperature. After completion of the reaction, the reaction mixture was filtered through hyflow bed at 25-35°C and washed with methanol. Distilled off the solvent from the filtrate under reduced pressure and co-distilled with methyl tert. butyl ether to get the title compound. Yield: 3.2 gm.

Example-27: Preparation of (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate (Formula-23b)

Sodium borohydride (22 gm) was slowly added to a solution of (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate compound of formula-11b (100 gm) in methanol (500 ml) at -10 to -15°C and stirred for 60 min at the same temperature. After completion of the reaction, 1% sodium bicarbonate solution followed by dichloromethane were slowly added to the reaction mixture at -10 to -15°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with 10% sodium chloride solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 93.0 gm.

Example-28: Preparation of (S)-1-tert-butyl 2-ethyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate (Formula-24b)

Diisopropylethyl amine (250 gm) was slowly added to a solution of (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b obtained in example-27 in tetrahydrofuran (1000 ml) at -65°C to -75°C and stirred for 20 min at the same temperature. Trifluoroacetic anhydride (122 gm) was slowly added to the reaction mixture at -65°C to -75°C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 20-25°C and stirred for 3 hrs at the same temperature. Add water to the reaction mixture and followed by ethyl acetate. Stirred the reaction mixture for 10 minutes. Separated the both aqueous and organic layers and washed the organic layer with aqueous HCl solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound.

Example-29: Preparation of (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (Formula-25)

Aq.lithium hydroxide solution (79.2 gm of LiOH in 400 ml of water) was slowly added to a mixture of (S)-1-tert-butyl 2-ethyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate compound of formula-24b obtained in example-28 and tetrahydrofuran (1000 ml) at 0-5°C and stirred for 30 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Water followed by methyl tert.butyl ether were added to the reaction mixture at 25-30°C and stirred for 20 min at the same temperature. Both the organic layer and the aqueous layers were separated and the aqueous layer was washed with methyl tert.butyl ether. Toluene was added to the aqueous layer at 25-30°C and cooled the reaction mixture to 0-5°C. Adjusted the pH of the aqueous layer to 3.5 using orthophosphoric acid at 0-5°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and the resulting organic layer containing (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid was utilized in the next step without isolating the title compound.

Example-30: Preparation of (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate (Formula-14)

Diisopropylethyl amine (150 gm) was slowly added to the organic layer obtained in example-29 at -15°C to -20°C under nitrogen atmosphere. Methanesulfonyl chloride (66.7 gm) was added to the reaction mixture at -15°C to -20°C and stirred for 3 hrs at the same temperature. Slowly passed ammonia gas into the reaction mixture for 2-3 hrs at -15°C to -20°C. Expel the reaction mixture using N_2 gas to the reaction mixture for 2-3 hrs at 0-5°C. Sodium bicarbonate solution was slowly added to the reaction mixture at 0-5°C and stirred for 45 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with toluene. Both the organic layers were combined and distilled off the solvent completely from the organic layer under reduced pressure and co-distilled with cyclohexane. Toluene (50 ml) was added to the obtained compound and stirred for 60 min. at 25-30°C. Cyclohexane (300 ml) was slowly added to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature. Filtered the precipitated solid, washed with cyclohexane and dried to get the title compound.

Yield: 50.0 gm; M.R: 100-104°C; SOR: (-)128.93°(C= 1% in methanol at 25°C, 589 nm).

Example-31: Preparation of (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate (Formula-14)

Diisopropylethyl amine (250 gm) was slowly added to a solution of (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b obtained in example-27 in tetrahydrofuran (1000 ml) at -65°C to -75°C and stirred for 20 min at the same temperature. Trifluoroacetic anhydride (122 gm) was slowly added to the reaction mixture at -65°C to -75°C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 20-25°C and stirred for 3 hrs at the same temperature. Cooled the reaction mixture to 0-5°C, aq.lithium hydroxide solution (79.2 gm of LiOH in 400 ml of water) was slowly added and stirred for 30 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Water (500 ml) followed by methyl tert.butyl ether (800 ml) were added to the reaction mixture at 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and the aqueous layer was washed with methyl tert.butyl ether. Toluene (1000 ml) was added to the aqueous layer at 25-30°C and cooled the reaction mixture to 0-5°C. Adjusted the pH of the aqueous layer to 3.5 using orthophosphoric acid at 0-5°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with toluene. The combined organic layers were washed with 10% sodium chloride solution and dried over sodium sulfate. Diisopropylethyl amine (150 gm) followed by methanesulfonyl chloride (66.7 gm) was slowly added to the organic layer at -15°C to -20°C under nitrogen atmosphere and stirred for 3 hrs at the same temperature. Slowly passed ammonia gas into the reaction mixture for 2-3 hrs at -15°C to -20°C. Expel the reaction mixture using N_2 gas to the reaction mixture for 2-3 hrs at 0-5°C. Sodium bicarbonate solution was slowly added to the reaction mixture at 0-5°C and stirred for 45 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with toluene. Both the organic layers were combined and distilled off the solvent completely from the organic layer under reduced pressure and co-distilled with cyclohexane. Toluene (50 ml) was added to the obtained compound and stirred for 60 min. at 25-30°C. Cyclohexane (300 ml) was slowly added to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature. Filtered

the precipitated solid, washed with cyclohexane and dried to get the title compound. Yield: 50.0 gm; M.R: 100-104°C; SOR: (-) 128.93°(C= 1% in methanol at 25°C and 589 nm).

Example-32: Preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt (Formula-26a)

Hydrochloric acid (25 ml, 2.5M solution in ethyl acetate) was added to a solution of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 (5 gm) in tetrahydrofuran (20 ml) at 25-30°C and stirred for 18 hrs at the same temperature. After completion of the reaction, methyl tert.butyl ether was added to the reaction mixture at 25-30°C and stirred for 30 min at the same temperature. Filtered the solid, washed with methyl tert.butyl ether and dried to get the title compound. Yield: 3.6 gm.

Example-33: Preparation of phenylglycinol adamantane nitrile compound of formula-5a

Water (3000 ml) and sodium meta bisulfite (150 gm) were added to the residue obtained in above example-3 in a clean and dry RBF at 25-35°C and stirred for 2 hrs at the same temperature. Sodium cyanide (49 gm) was added to the reaction mixture at 25-35°C and stirred for 30 min at the same temperature. A solution of R-(-)-2-phenylglycinol (140 gm) in methanol (900 ml) was added to the reaction mixture at 25-35°C. Heated the reaction mixture to 80-85°C and stirred for 15 hrs at the same temperature. After the completion of the reaction, the reaction mixture was cooled to 25-35°C. Ethyl acetate (3000 ml) was added to the reaction mixture at 25-35°C and stirred for 45 min at the same temperature. Both the organic and aqueous layers were separated, ethyl acetate (1500 ml) was added to the aqueous layer at 25-35°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and a solution of sodium chloride (150 gm) in water (1500 ml) was added to the organic layer at 25-35°C and stirred for 30 min at the same temperature. Separated the organic and aqueous layers, dried the organic layer over sodium sulfate and distilled at below 55°C under reduced pressure. The obtained residue was cooled to 25-35°C and methanol (225 ml) was added. Water (2000 ml) and conc.HCl (600 ml) was charged in to another RBF

and slowly added the above obtained methanolic solution at 25-35°C and stirred for 4 hrs at the same temperature. Filtered the solid, washed with water and then suck dried to get the title compound. Yield: 206 gm.

Example-34: Preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1

Ethyl acetate-HCl (75 ml) was slowly added to a solution of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 (5 gm) in tetrahydrofuran (20 ml) at 25-30°C and stirred for 6 hrs at the same temperature. Filtered the solid under nitrogen atmosphere, washed with ethyl acetate and suck dried for 40 min. The obtained solid was kept aside. Hydroxybenzotriazole (3 gm) was added to a solution of adamantyl intermediate compound of formula-27 (7.5 gm) in acetonitrile (22 ml) and ethyl acetate (10 ml) in another RBF at 0-5°C and stirred for 10 min at the same temperature. N,N'-Dicyclohexylcarbodiimide (5.5 gm) was added to the reaction mixture at 0-5°C and stirred for 60 min at the same temperature. To the obtained reaction mixture, the above obtained solid followed by diisopropylethyl amine (12 gm) were slowly added at 0-5°C and stirred for 5 hrs at the same temperature. Filtered the reaction mixture and washed with chilled ethyl acetate. Water (50 ml) and dichloromethane (50 ml) were added to the filtrate at 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with 20% hydrochloric acid solution followed by 10% sodium bicarbonate solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely under reduced pressure. To the obtained compound ethyl acetate (80 ml) and 2,6-lutidine (7.2 gm) were added and cooled the reaction mixture to 0-5°C. Trifluoroacetic anhydride (9.0 gm) was slowly added to the reaction mixture at 0-5°C and stirred for 60 min at the same temperature. Another 2.0 gm of 2,6-lutidine and 1.8 gm of trifluoroacetic anhydride were slowly added to the reaction mixture at 0-5°C and stirred for 60 min at the same temperature. Quenched the reaction mixture with water at below 10°C and slowly raised the temperature of the reaction mixture to 25-30°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and water was added to the organic layer. Cooled the reaction mixture to 5-10°C and the pH of the reaction mixture was slowly adjusted to 2.5 using hydrochloric acid. Both the organic and

aqueous layers were separated. Potassium carbonate solution followed by methanol were added to the organic layer at 10-15°C and stirred for 10 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with 10% sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure. Added methanol (35 ml) to the obtained compound and charged in an autoclave vessel. Acetic acid (35 ml) was added to the reaction mixture. A solution of 5% Pd/C (2 gm) in methanol (5 ml) was added to the reaction mixture under nitrogen atmosphere at 25-30°C. 4-5 kg/Cm^2 of hydrogen gas pressure was applied to the reaction mixture at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 12 hrs at the same temperature. After completion of the reaction, the reaction mixture was filtered through hyflow bed at 25-35°C and washed with methanol. Distilled off the solvent from the filtrate under reduced pressure to get the title compound. Yield: 3.0 gm.

Example-35: Purification of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1

Methanol (150 ml) was added to (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (100 gm) at 25-30°C and stirred for 20 min at the same temperature. Carbon (10 gm) was added to the reaction mixture at 25-30°C and stirred for 60 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with methanol. Water (170 ml) was added to the filtrate at 0-5°C and stirred for 3 hrs at the same temperature. Filtered the solid, washed with chilled water and dried under vacuum to get pure title compound. Yield: 60.0 gm; Purity by HPLC: 99.97%; Deshydroxy impurity: Not detected; Cyclic amidine impurity: 0.01%.

Particle size distribution: D(0.1) is 3.99 µm; D(0.5) is 16.45 µm; D(0.9) is 42.02 µm, D(4,3) is 20.54 µm.

Example-36: Preparation of compound of formula-52

n-Butyl lithium (5.2 ml) was slowly added to a solution of (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine compound of formula-50 (1.3 gm) in tetrahydrofuran (10

ml) at -75°C to -80°C and stirred for 1 hr at the same temperature. A solution of adamantyl bromide (1.0 gm) in tetrahydrofuran (5 ml) was slowly added to the reaction mixture at -75°C to -80°C. Raised the temperature of the reaction mixture to 0-5°C and stirred for 6 hrs at the same temperature. 2N hydrochloric acid (10 ml) was added to the reaction mixture at 0-5°C and stirred for 2 hrs at the same temperature. The reaction mixture was slowly added to chilled saturated sodium bicarbonate solution. Dichloromethane was added to the obtained reaction mixture and both the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane and the combined organic layer was washed with water. Distilled off the solvent completely from the organic layer to get the title compound. Yield: 0.7 gm.

Example-37: Preparation of compound of formula-7

Lithium hydroxide hydrate (0.17 gm) was added to a solution of compound of formula-52 (0.5 gm) in methanol (3 ml) and water (2 ml) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 7 hrs at the same temperature. Water (10 ml) and methyl tert.butyl ether (5 ml) were added to the reaction mixture at 25-30°C. Both the organic and aqueous layers were separated, dichloromethane (15 ml) was added to the aqueous layer at 0-5°C. Adjusted the pH of the reaction mixture to 3.0 using phosphoric acid. Both the organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with 10% sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 0.35 gm.

Example-38: Preparation of compound of formula-63

Slowly added di-tert.butyl dicarbonate (0.52 gm) to a solution of compound of formula-52 (0.5 gm), 4-dimethylaminopyridine (0.15 gm) in dichloromethane (10 ml) at 25-30°C and stirred for 4 hrs at the same temperature. Cooled the reaction mixture to 0-5°C and washed with 1N hydrochloric acid. Both the organic and aqueous layers were separated and the organic layer was washed with 10% sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 0.7 gm.

Example-39: Preparation of compound of formula-28

Lithium hydroxide hydrate (0.1 gm) was added to a solution of compound of formula-63 (0.5 gm) in methanol (3 ml) and water (2 ml) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 7 hrs at the same temperature. Water (10 ml) and methyl tert.butyl ether (5 ml) were added to the reaction mixture at 25-30°C. Both the organic and aqueous layers were separated, dichloromethane (15 ml) was added to the aqueous layer at 0-5°C. Adjusted the pH of the reaction mixture to 3.0 using phosphoric acid. Both the organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with 10% sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get title compound.
Yield: 0.3 gm.

Example-40: Preparation of compound of formula-28

Hydrochloride salt compound of formula-7 (100 gm) was added to a mixture of water (1000 ml) and sodium carbonate (108 gm) at 25-30°C. Di-tert.butyl dicarbonate (134 gm) was slowly added to the reaction mixture at 25-30°C and stirred for 22 hrs at the same temperature. After completion of the reaction, ethyl acetate was added to the reaction mixture at 25-30°C and cooled the reaction mixture to 0-5°C. Adjusted the pH of the reaction mixture to 3.5 using aqueous hydrochloric acid solution at 0-5°C and stirred for 30 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with ethyl acetate. Both the organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate. Distilled off the solvent completely from the combined organic layer under reduced pressure and co-distilled with pet ether. 300 ml of pet ether was added to the obtained solid at 25-30°C and stirred for 2 hrs at the same temperature. Filtered the solid, washed with pet ether and dried to get the title compound.
Yield: 90.0 gm; SOR: (+) 20.1°(C=1% in methanol).

Example-41: Preparation of compound of formula-29a

A mixture of water (2500 ml) and potassium hydroxide (26.7 gm) was stirred for 20 min at 25-30°C. Compound of formula-28 (100 gm) was added to the reaction mixture at 25-30°C. Potassium permanganate (102 gm) was added to the reaction mixture

at 0-5°C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 20 hrs at the same temperature. After completion of the reaction, 25% sodium thiosulfate solution was slowly added to the reaction mixture at 0-5°C and stirred for 60 min at the same temperature. Filtered the reaction mixture and washed with water. Adjusted the pH of the filtrate to 3.0 using aqueous hydrochloric acid at 0-5°C and stirred for 30 min at the same temperature. Methyl isobutyl ketone was added to the reaction mixture at 0-5°C and stirred for 45 min at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with water followed by methyl isobutyl ketone. Distilled off the solvent completely from the organic layer under reduced pressure and co-distilled with ethyl acetate. 150 ml of ethyl acetate was added to the obtained solid, heated the reaction mixture to 60-65°C and stirred for 60 min at the same temperature. Reduced the temperature of the reaction mixture to 25-30°C and stirred for 4 hrs at the same temperature. Filtered the solid, washed with ethyl acetate and dried to get the title compound. Yield: 56.0 gm.

Example-42: Purification of compound of formula-29a

Compound of formula-29 (50 gm) was added to ethyl acetate (80 ml) at 25-30°C and stirred for 20 min at the same temperature. Heated the reaction mixture to 70-75°C and stirred for 60 min at the same temperature. Slowly cooled the reaction mixture to 0-5°C and stirred for 4 hrs at the same temperature. Filtered the precipitated solid, washed with chilled ethyl acetate and dried to get the pure title compound. Yield: 40.0 gm.

Example-43: Preparation of compound of formula-30a

Ethyl acetate-HCl (1500 ml) was slowly added to a solution of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 (100 gm) in tetrahydrofuran (400 ml) at 25-30°C and stirred for 6 hrs at the same temperature. Filtered the solid under nitrogen atmosphere, washed with ethyl acetate and suck dried for 40 min. The obtained solid was kept aside and hydroxybenzotriazole (60 gm) was added to a solution of adamantyl compound of formula-29a (135 gm) in acetonitrile (425 ml) and ethyl acetate (200 ml) in another RBF at 0-5°C and stirred for 10 min at the same temperature. N,N'-Dicyclohexylcarbodiimide (109.5 gm) was added

to the reaction mixture at 0-5°C and stirred for 60 min at the same temperature. To the obtained reaction mixture, the above obtained solid followed by diisopropylethyl amine (237 gm) were slowly added at 0-5°C and stirred for 5 hrs at the same temperature. Filtered the reaction mixture and washed with chilled ethyl acetate. Water (1000 ml) and dichloromethane (1000 ml) were added to the filtrate at 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with 20% hydrochloric acid solution followed by 10% sodium bicarbonate solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely under reduced pressure. Toluene (300 ml) was added to the obtained residue at 35-40°C and stirred for 30 min at the same temperature. Reduced the temperature of the reaction mixture to 25-30°C and filtered. The filtrate was slowly added to n-heptane (900 ml) at 25-30°C and stirred for 3 hrs at the same temperature. Filtered the precipitated solid, washed with n-heptane and dried to get the title compound.
Yield: 170.0 gm;

Example-44: Preparation of compound of formula-31a

Trifluoroacetic acetic anhydride (121.5 gm) was slowly added to a mixture of amide compound of formula-30a (100 gm), ethyl acetate (1000 ml) and 2,6-lutidine (99 gm) at 0-5°C and stirred for 60 min at the same temperature. Another 25 gm of 2,6-lutidine and 24 gm of trifluoroacetic anhydride were slowly added to the reaction mixture at 0-5°C and stirred for 60 min at the same temperature. Quenched the reaction mixture with water at below 10°C and slowly raised the temperature of the reaction mixture 25-30°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and water was added to the organic layer. Cooled the reaction mixture to 5-10°C and the pH of the reaction mixture was slowly adjusted to 2.5 using hydrochloric acid. Both the organic and aqueous layers were separated. Potassium carbonate solution followed by methanol (300 ml) were added to the reaction mixture at 10-15°C and stirred for 10 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with 10% sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure. Methanol (150 ml) was added to the obtained solid at 25-30°C and stirred for 10 min at

the same temperature. Isopropyl alcohol (150 ml) was added to the reaction mixture at 25-30°C and stirred for 30 min at the same temperature. Carbon (10 gm) was added to the reaction mixture at 25-30°C and stirred for 60 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with methanol followed by isopropyl alcohol. Water (1000 ml) was slowly added to the filtrate at 25-30°C and stirred for 3 hrs at the same temperature. Filtered the solid, washed with water and dried to get the title compound. Yield: 60.0 gm; Purity by HPLC: 97.8%.

Example-45: Preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile (Formula-1)

Acetyl chloride (57 gm) was slowly added to a solution of compound of formula-31a (100 gm) in methanol (400 ml) at 0-5°C and stirred for 10 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 4 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 10-15°C. Water (1000 ml) was slowly added to the reaction mixture at 10-15°C and stirred for 15 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C, dichloromethane (300 ml) was added and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and dichloromethane (500 ml) was added to the aqueous layer. Slowly adjusted the pH of the reaction mixture to 10.0 using potassium carbonate solution at 10-15°C and stirred for 30 min at the same temperature. Sodium chloride was added to the reaction mixture at 10-15°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Distilled off the solvent completely from the organic layer under reduced pressure at below 40°C. Ethyl acetate (400 ml) was added to the obtained solid at 25-30°C, heated the reaction mixture to 35-40°C and stirred for 20 min at the same temperature. Cooled the reaction mixture to 25-30°C, water (100 ml) was added and stirred for 20 min at the same temperature. Cooled the reaction mixture to 0-5° and stirred for 3 hrs at the same temperature. Filtered the solid, washed with a mixture of chilled ethyl acetate and water and dried to get the title compound. Yield: 60.0 gm.

Example-46: Preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrochloride (Formula-1a)

Acetyl chloride (60 gm) was slowly added to a solution of compound of formula-31a (100 gm) in methanol (400 ml) at 0-5°C and stirred for 10 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 0-5°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid to get the title compound. Yield: 70 grams; Purity by HPLC: 99.98%;

Particle size distribution: D(0.1) is 1.30 μm; D(0.5) is 8.98 μm; D(0.9) is 48.67 μm, D(4,3) is 18.05 μm.

Example-47: Preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrochloride salt (Formula-1a)

(1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile (10 gm) and methanol (30 ml) were charged into a clean and dry RBF at 25-30°C and stirred for 15 min at the same temperature. Carbon (1.0 gm) was added to the reaction mixture at 25-30° and stirred for 30 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with methanol. Cooled the filtrate to 0-5°C, isopropyl alcohol-HCl (6.5 ml) and isopropyl alcohol (43.5 ml) were added at 0-5°C and stirred for 60 min at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound. Yield: 4.9 gm;

Example-48: Preparation of compound of formula-36a

Ethyl acetate-HCl (75 ml) was slowly added to a solution of (1R,3R,5R)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-22 (5 gm) in tetrahydrofuran (20 ml) at 25-30°C and stirred for 6 hrs at the same temperature. Filtered the solid under nitrogen atmosphere, washed with ethyl acetate and suck dried for 40 min. The obtained solid was kept aside and hydroxybenzotriazole (2 gm) was added to a solution of adamantyl intermediate compound of formula-29 (5 gm) in acetonitrile (22 ml) and ethyl acetate (10 ml) in another RBF at 0-5°C and stirred for 10 min at the same temperature. N,N'-Dicyclohexylcarbodiimide (3.7 gm) was added to

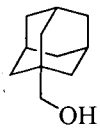
the reaction mixture at 0-5°C and stirred for 60 min at the same temperature. To the obtained reaction mixture, the above obtained solid followed by diisopropylethyl amine (8 gm) were slowly added at 0-5°C and stirred for 5 hrs at the same temperature. Filtered the reaction mixture and washed with chilled ethyl acetate. Water (50 ml) and dichloromethane (50 ml) were added to the filtrate at 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with 20% hydrochloric acid solution followed by 10% sodium bicarbonate solution. Dried the organic layer over sodium sulfate and distilled off the solvent completely under reduced pressure. Toluene (15 ml) was added to the obtained residue at 35-40°C and stirred for 30 min at the same temperature. Reduced the temperature of the reaction mixture to 25-30°C and filtered. The filtrate was slowly added to n-heptane (45 ml) at 25-30°C and stirred for 3 hrs at the same temperature. Filtered the precipitated solid, washed with n-heptane and dried to get the title compound.
Yield: 6.0 gm.

Example-49: Preparation of compound of formula-30a

Compound of formula-36a (5 gm), methanol (35 ml), acetic acid (35 ml) were charged into a clean and dry RBF at 25-30° and stirred for 15 min at the same temperature. Carbon (2 gm) was added to the reaction mixture at 25-30°C and stirred for 90 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with a mixture of methanol and acetic acid. A solution of 5% Pd/C (2 gm) in methanol (5 ml) was added to the filtrate under nitrogen atmosphere in an autoclave vessel at 25-30°C. 4-5 kg/Cm^2 of hydrogen gas pressure was applied to the reaction mixture at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 12 hrs at the same temperature. After completion of the reaction, the reaction mixture was filtered through hyflow bed at 25-35°C and washed with methanol. Distilled off the solvent from the filtrate under reduced pressure at 50-55°C and co-distilled with methyl tert.butyl ether. 25 ml of methyl tert.butyl ether was added to the obtained solid at 25-35°C and stirred for 3 hrs at the same temperature. The obtained solid was filtered, washed with methyl tert.butyl ether and then dried to get the title compound. Yield: 2.8 gm.

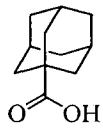
We Claim:

1) A process for the preparation of adamantyl methanol compound of formula-3



Formula-3

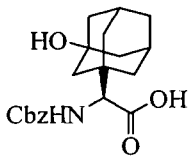
comprising of reducing the adamantane-1-carboxylic acid compound of formula-2



Formula-2

with sodium borohydride optionally in combination with BF_3.etherate in a suitable solvent selected from ether solvents, ester solvents, alcoholic solvents, hydrocarbon solvents, polar solvents or their mixtures thereof to provide adamantyl methanol compound of formula-3.

2) A process for the preparation of benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27, comprising of;



Formula-27

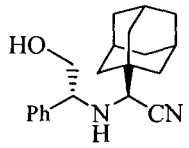
a) Reducing the adamantane-1-carboxylic acid compound of formula-2 with a suitable reducing agent in a suitable solvent to provide adamantyl methanol compound of formula-3,

b) oxidizing the compound of formula-3 with a suitable oxidizing agent optionally in presence of a suitable base in a suitable solvent to provide adamantyl aldehyde of formula-4,

Formula-4

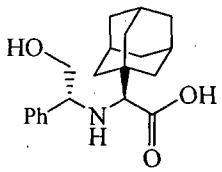
c) treating the compound of formula-4 in-situ with a suitable alkali metal cyanide in

presence of sodium meta bisulfite in a suitable solvent followed by treating with R-(-)-2-phenylglycinol in a suitable solvent to provide phenylglycinol adamantane nitrile compound of formula-5a,



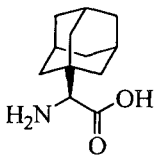
Formula-5a

d) hydrolyzing the compound of formula-5a in presence of a suitable acid in a suitable solvent to provide its corresponding phenylglycinol adamantane carboxylic acid compound of formula-6a or its acid-addition salt,



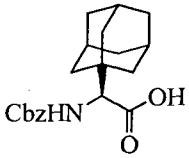
Formula-6a

e) deprotecting the compound of formula-6a or its acid-addition salt by treating it with a suitable deprotecting agent optionally in presence of an acid in a suitable solvent to provide amino adamantane carboxylic acid compound of formula-7 or its acid-addition salt,



Formula-7

f) treating the compound of formula-7 or its acid-addition salt with benzyl chloroformate in presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8,



Formula-8

g) hydroxylating the compound of formula-8 with a suitable hydroxylating agent in

presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27.

3) A process according to claim 2, wherein,

in step-a) the suitable reducing agent is sodium borohydride optionally in combination with BF_3.etherate; and the suitable solvent is selected from ether solvents, ester solvents, alcoholic solvents, hydrocarbon solvents, polar solvents or their mixtures thereof;

in step-b) the suitable oxidizing agent is selected from oxalyl chloride/dimethyl sulfoxide, sodium hypochlorite, trichloroisocyanuric acid (TCICA) in presence of catalytic amount of TEMPO ((2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl), pyridinium chlorochromate; and the suitable base is selected from organic bases, preferably triethylamine; and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ester solvents, polar-aprotic solvents and/or their mixtures thereof; preferably chloro solvents;

in step-c) the suitable alkali metal cyanide is selected from sodium cyanide or potassium cyanide and the suitable solvent is selected from alcoholic solvents, chloro solvents, ester solvents, polar solvents and/or their mixtures thereof;

in step-d) the suitable acid is selected from conc.HCl, sulfuric acid; preferably conc. HCl; and the suitable solvent is selected from acetic acid and alcoholic solvents; preferably acetic acid;

in step-e) the suitable deprotecting agent is selected from Pd, Pd/C, Raney Ni, palladium acetate, platinum oxide, platinum black, Rh/C, Ru, Ir and the like in combination with hydrogen; preferably Pd/C; the suitable acid is acetic acid; and the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar solvents or their mixtures thereof; preferably alcoholic solvents;

in step-f) the suitable base is selected from alkali metal carbonates and alkali metal bicarbonates; and the suitable solvent is selected from ether solvents, ester solvents, polar solvents or their mixtures thereof;

in step-g) the suitable hydroxylating agent is preferably potassium permanganate; and the suitable base is selected from alkali metal hydroxides, alkali metal alkoxides and pyridine; and the suitable solvent is selected from chloro solvents, nitrile solvents, ether solvents, polar solvents or their mixtures thereof.

4) A process for the preparation of benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27, comprising of;

a) Reducing the adamantane-1-carboxylic acid compound of formula-2 with sodium borohydride-BF_3.etherate in tetrahydrofuran to provide adamantyl methanol compound of formula-3,

b) oxidizing the compound of formula-3 by treating it with oxalyl chloride and dimethylsulfoxide in presence of triethylamine in dichloromethane to provide adamantyl aldehyde of formula-4,

c) treating the compound of formula-4 in-situ with sodium cyanide in presence of sodium meta bisulfite in water followed by treating with R-(-)-2-phenylglycinol in methanol to provide phenylglycinol adamantane nitrile compound of formula-5a,

d) hydrolyzing the compound of formula-5a in presence of conc.HCl in acetic acid to provide phenylglycinol adamantane carboxylic acid compound of formula-6a as hydrochloride salt,

e) deprotecting the compound of formula-6a by treating it with Pd/C in presence of acetic acid in methanol to provide amino adamantane carboxylic acid compound of formula-7 as hydrochloride salt,

f) treating the compound of formula-7 with benzyl chloroformate in presence of sodium bicarbonate in a mixture of water and tetrahydrofuran to provide benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8,

g) hydroxylating the compound of formula-8 by treating it with potassium permanganate in presence of potassium hydroxide in water to provide benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27.

5) A process for the preparation of benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27, comprising of;

a) Reacting the amino adamantane carboxylic acid compound of formula-7 or its acid-addition salt with benzyl chloroformate in presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8,

b) hydroxylating the compound of formula-8 with a suitable hydroxylating agent in presence of a suitable base in a suitable solvent to provide benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27.

6) A process according to claim 5, wherein,

in step-a) the suitable base is selected from alkali metal carbonates and alkali metal bicarbonates; and the suitable solvent is selected from ether solvents, ester solvents, polar solvents or their mixtures thereof;

in step-b) the suitable hydroxylating agent is preferably potassium permanganate; and the suitable base is selected from alkali metal hydroxides, alkali metal alkoxides and organic bases; and the suitable solvent is selected from chloro solvents, nitrile solvents, ether solvents, polar solvents or their mixtures thereof.

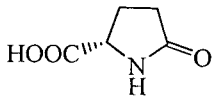
7) A process for the preparation of benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27, comprising of;

a) Reacting the hydrochloride salt of amino adamantane carboxylic acid compound of formula-7 with benzyl chloroformate in presence of sodium bicarbonate in a mixture of water and tetrahydrofuran to provide benzyloxycarbonyl protected amino adamantane carboxylic acid compound of formula-8,

b) hydroxylating the compound of formula-8 by treating it with potassium permanganate in presence of potassium hydroxide in water to provide benzyloxycarbonyl protected amino hydroxy adamantane carboxylic acid compound of formula-27.

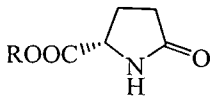
8) A process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9



Formula-9

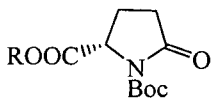
by treating it with a suitable C_1-C_6 straight chain or branched chain alcohol in presence of a suitable catalyst to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,



Formula-10

wherein, the 'R' represents C_1-C_6 straight chain or branched chain alkyl;

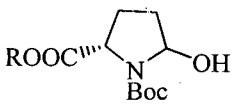
b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,



Formula-11

wherein, "R" is same as defined above;

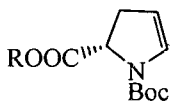
c) reducing the compound of general formula-11 with a suitable reducing agent in a suitable solvent to provide (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23,



Formula-23

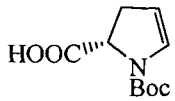
wherein, "R" is same as defined above;

d) dehydrating the compound of general formula-23 by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate compound of general formula-24,



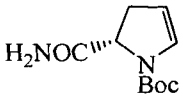
Formula-24

e) hydrolyzing the compound of general formula-24 in-situ in presence of a suitable base in a suitable solvent to provide (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-25,



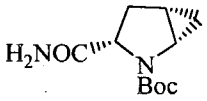
Formula-25

f) treating the compound of formula-25 in-situ with methane sulfonyl chloride in presence of a suitable base followed by in-situ treating the obtained compound with a suitable amine source to provide (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,



Formula-14

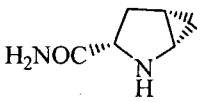
g) in-situ converting the compound of formula-14 into (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15



Formula-15

by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent,

h) deprotecting the compound of formula-15 by treating it with a suitable deprotecting agent in a suitable solvent to provide (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or its acid-addition salt.



Formula-26

9) A process according to claim 8, wherein

in step-a) the suitable catalyst is selected from thionyl chloride, hydrochloric acid, conc. sulfuric acid, trifluoro acetic acid, methane sulfonic acid;

in step-b) the suitable base is selected from organic bases like 4-dimethylaminopyridine (DMAP), triethylamine, diisopropylethylamine and inorganic bases like alkali metal hydroxides, alkali metal carbonates, alkali metal bicarbonates; and the suitable solvent is selected from nitrile solvents, chloro solvents, ether solvents, polar solvents or their mixtures thereof;

in step-c) the suitable reducing agent is selected from L-selectride, sodium borohydride, potassium borohydride, vitride, tetralkylammonium borohydride, sodium cyanoborohydride, lithium aluminium hydride and the like; and the suitable solvent is selected form alcohol solvents, ketone solvents, ether solvents, ester solvents, nitrile solvents or their mixtures thereof;

in step-d) the suitable dehydrating agent is selected from acetic anhydride, trifluoro acetic anhydride (TFAA), trifluoroacetic acid, phosphorous pentoxide, phosphoryl chloride, phosphoric acid, sulfuric acid, dicyclohexyl carbodiimide; the suitable base is selected from alkali metal hydroxides; the suitable solvent is selected from ether solvents, hydrocarbon solvents, chloro solvents or their mixtures thereof;

in step-e) the suitable base is selected from inorganic bases like hydroxides, alkoxides, carbonates and bicarbonates of alkali metals; and the suitable solvent is selected from polar solvents, ether solvents;

in step-f) the suitable amine source is selected from ammonia, formamide, ammonia gas, ammonium formate, ammonium phosphate, ammonium acetate, ammonium chloride, ammonium carbonate, ammonium hydroxide; the suitable base is selected from hydroxides and alkoxides of alkali metals; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents or their mixtures thereof;

in step-g) the suitable methylene source is diiodomethane, chloro iodomethane and the suitable catalyst is diethyl zinc; and the suitable solvent is selected from hydrocarbon solvents, ether solvents, chloro solvents and/or their mixtures thereof.

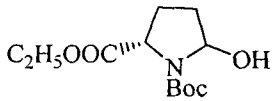
in step-h) the suitable deprotecting agent is selected from hydrochloric acid, acetyl chloride, methane sulfonic acid, trifluoroacetic acid; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, hydrocarbon solvents, chloro solvents or their mixtures thereof.

10) A process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with ethanol in presence of thionyl chloride to provide (S)-ethyl 5-oxopyrrolidine-2-carboxylate compound of formula-10b,

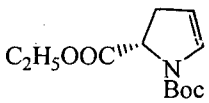
b) treating the compound of formula-10b with di-tert.butyl dicarbonate in presence of a 4-dimethylaminopyridine in dichloromethane to provide (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate compound of formula-11b,

c) reducing the compound of formula-11b with sodium borohydride in methanol to provide (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b,



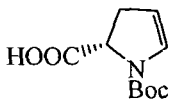
Formula-23b

d) dehydration of compound of formula-23b by treating it with trifluoro acetic anhydride in presence of diisopropyl ethyl amine in tetrahydrofuran to provide (S)-1-tert-butyl 2-ethyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate compound of formula-24b,



Formula-24b

e) hydrolyzing the compound of formula-24b in-situ in presence of lithium hydroxide in water to provide (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-25,

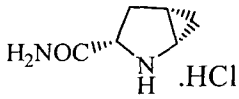


Formula-25

f) treating the compound of formula-25 in-situ with methane sulfonyl chloride in presence of diisopropyl ethyl amine followed by in-situ treating the obtained compound with ammonia provides (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,

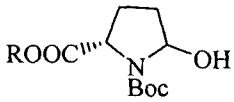
g) in-situ converting the compound of formula-14 into (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with diiodomethane in presence of diethyl zinc in a mixture of toluene and 1,2-dimethoxy ethane,

h) deprotecting the compound of formula-15 by treating it with ethyl acetate HCl in tetrahydrofuran to provide (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a.



Formula-26a

11) A process for the preparation of (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23,



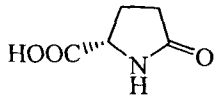
Formula-23

wherein, 'R' represents C_1-C_6 straight chain or branched chain alkyl;

comprising of reducing the (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11 with sodium borohydride in a suitable solvent selected from alcoholic solvents, ether solvents, ester solvents, hydrocarbon solvents, polar solvents or their mixtures thereof to provide (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23.

12) A process for the preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0] hexane-2-carboxylate compound of formula-15, comprising of;

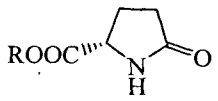
a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9



Formula-9

by treating it with a suitable C_1-C_6 straight or branched chain alcohol in presence of a suitable catalyst selected from thionyl chloride, hydrochloric acid, conc.

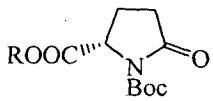
sulfuric acid, trifluoro acetic acid and methane sulfonic acid to provide corresponding (S)-alkyl 5-oxopyrrolidine-2-carboxylate compound of general formula-10,



Formula-10

wherein, 'R' represents C_1-C_6 straight chain or branched chain alkyl;

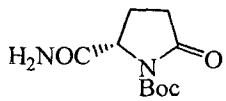
b) treating the compound of general formula-10 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11,



Formula-11

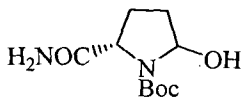
wherein, 'R' is as defined above;

c) amidation of compound of general formula-11 by treating it with a suitable amine source optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12,



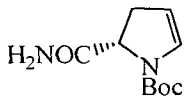
Formula-12

d) reducing the compound of formula-12 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-carbamoyl-5-hydroxypyrrolidine-1-carboxylate compound of formula-13,



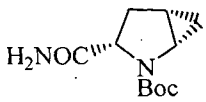
Formula-13

e) dehydrating the compound of formula-13 by treating it with a suitable dehydrating agent in presence or absence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,



Formula-14

f) in-situ converting the compound of formula-14 into (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent.



Formula-15

13) The process according to claim 12, wherein,

in step-b) the suitable base is selected from organic bases like 4-dimethylaminopyridine (DMAP), triethylamine, diisopropylethyl amine and inorganic bases like alkali metal hydroxides, alkali metal carbonates, alkali metal bicarbonates; and the suitable solvent is selected from nitrile solvents, chloro solvents, ether solvents, polar solvents or their mixtures thereof;

in step-c) the suitable amine source is selected from ammonia, formamide, ammonia gas, ammonium formate, ammonium phosphate, ammonium acetate, ammonium chloride, ammonium carbonate, ammonium hydroxide; the suitable base is selected from hydroxides and alkoxides of alkali metals; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents or their mixtures thereof;

in step-d) the suitable reducing agent is selected from lithium tri-sec-butyl(hydrido)borate(1-) (L-selectride), sodium borohydride, vitride, diisobutyl aluminium hydride, tetralkylammonium borohydride, sodium cyanoborohydride, lithium aluminium hydride and the like; and the suitable solvent is selected form ether solvents, alcoholic solvents, ester solvents, acetonitrile or their mixtures thereof;

in step-e) the suitable dehydrating agent is selected from acetic anhydride, trifluoro acetic anhydride, trifluoro acetic acid, phosphorous pentoxide, phosphoryl chloride, phosphoric acid, sulfuric acid, dicyclohexyl carbodiimide; and the suitable

base is selected from organic bases like triethylamine, diisopropyl amine, diisopropyl ethylamine, 4-dimethylamino pyridine and the like; the suitable solvent is selected from ether solvents, ester solvents or their mixtures thereof.

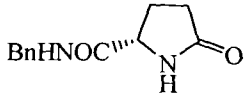
in step-f) the suitable methylene source is diiodomethane, chloro iodomethane and the suitable catalyst is diethyl zinc; and the suitable solvent is selected from hydrocarbon solvents, ether solvents, chloro solvents and/or their mixtures thereof.

14) A process for the preparation of (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12, comprising of amidation of (S)-1-tert-butyl 2-alkyl 5-oxopyrrolidine-1,2-dicarboxylate compound of general formula-11 by treating it with a suitable amine source optionally in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-carbamoyl-5-oxopyrrolidine-1-carboxylate compound of formula-12.

15) The process according to claim 14, wherein the suitable amine source is selected from ammonia, formamide, ammonia gas, ammonium formate, ammonium phosphate, ammonium acetate, ammonium chloride, ammonium carbonate, ammonium hydroxide and the like; the suitable base is selected from hydroxides and alkoxides of alkali metals; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents or their mixtures thereof.

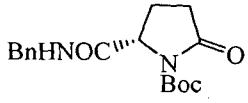
16) A process for the preparation of (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0] hexane-2-carboxylate compound of formula-15, comprising of;

a) Amidation of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it with benzyl amine in presence of a suitable coupling agent optionally in presence of a suitable base in a suitable solvent to provide (S)-N-benzyl-5-oxopyrrolidine-2-carboxamide compound of formula-18,



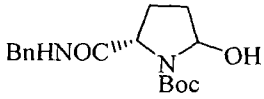
Formula-18

b) treating the compound of formula-18 with di-tert.butyl dicarbonate in presence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-5-oxopyrrolidine-1-carboxylate compound of formula-19,



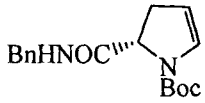
Formula-19

c) reducing the compound of formula-19 with a suitable reducing agent in a suitable solvent to provide (2S)-tert-butyl 2-(benzylcarbamoyl)-5-hydroxypyrrolidine-1-carboxylate compound of formula-20,



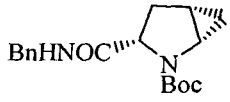
Formula-20

d) dehydrating the compound of formula-20 by treating it with a suitable dehydrating agent in presence or absence of a suitable base in a suitable solvent to provide (S)-tert-butyl 2-(benzylcarbamoyl)-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-21,



Formula-21

e) converting the compound of formula-21 into (1S,3S,5S)-tert-butyl 3-(benzylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-22 by treating it with a suitable methylene source in presence of a suitable catalyst in a suitable solvent,



Formula-22

f) debenzylating the compound of formula-22 by treating it with a suitable debenzylating agent optionally in presence of a suitable acid in a suitable solvent to provide (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15.

17) A process according to claim 16, wherein,

in step-a) the suitable coupling reagent is selected from N,N'-dicyclohexyl carbodiimide (DCC) in presence of hydroxybenzotriazole (HOBT), N,N'-dicyclohexyl carbodiimide (DCC) in presence of 4-dimethylaminopyridine (DMAP), thionyl chloride, phosphorous pentachloride and the like; the suitable base is selected from organic or inorganic bases; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents or their mixtures thereof;

in step-b) the suitable base is selected from organic bases like 4-dimethylaminopyridine, triethylamine, diisopropyl ethylamine and inorganic bases like alkali metal hydroxides, alkali metal carbonates, alkali metal bicarbonates; the suitable solvent is selected from nitrile solvents, chloro solvents, ether solvents, polar solvents or their mixtures thereof;

in step-c) the suitable reducing agent is selected from L-selectride, sodium borohydride, vitride, diisobutyl aluminium hydride, tetralkylammonium borohydride, sodium cyanoborohydride, lithium aluminium hydride and the like; and the suitable solvent is selected form ether solvents, alcoholic solvents, ester solvents, nitrile solvents or their mixtures thereof;

in step-d) the suitable dehydrating agent is selected from acetic anhydride, trifluoro acetic anhydride, trifluoro acetic acid, phosphorous pentoxide, phosphoryl chloride, phosphoric acid, sulfuric acid, dicyclohexyl carbodiimide; the suitable base is selected from organic bases like triethylamine, diisopropyl amine, diisopropyl ethylamine, 4-dimethylamino pyridine (DMAP) and the like; and the suitable solvent is selected from ether solvents, ester solvents or their mixtures thereof;

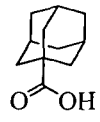
in step-e) the suitable methylene source is diiodomethane, chloro iodomethane and the suitable catalyst is diethyl zinc; the suitable solvent is selected from hydrocarbon solvents, ether solvents, chloro solvents or their mixtures thereof;

in step-f) the suitable debenzylating agent is selected from Pd, Pd/C, Raney Ni, palladium acetate, platinum oxide, platinum black, Rh/C, Ru, Ir and the like in combination with hydrogen; the suitable acid is acetic acid; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents, hydrocarbon solvents or their mixtures thereof.

18) A process for the preparation of (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b, comprising of reducing the (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate compound of formula-11 with sodium borohydride in methanol to provide (2S)-1-tert-butyl 2-ethyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of general formula-23b.

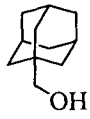
19) A process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

a) Reducing the adamantane-1-carboxylic acid compound of formula-2



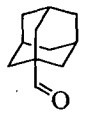
Formula-2

with sodium borohydride-BF_3 etherate in tetrahydrofuran to provide adamantyl methanol compound of formula-3,



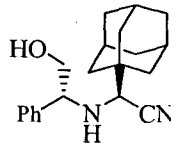
Formula-3

b) oxidizing the compound of formula-3 with oxalyl chloride/dimethyl sulfoxide in presence of triethylamine in dichloromethane to provide adamantyl aldehyde compound of formula-4,



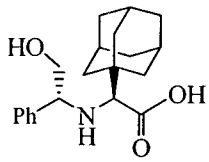
Formula-4

c) treating the compound of formula-4 in-situ with sodium cyanide in presence of sodium bisulfite in water followed by treating with R-(-)-2-phenyl glycinol in methanol to provide compound of formula-5a,



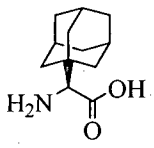
Formula-5a

d) hydrolyzing the compound of formula-5a in presence of conc. Hydrochloric acid in acetic acid to provide compound of formula-6a or its hydrochloride salt,



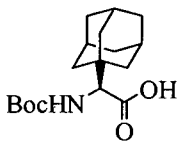
Formula-6a

e) treating the compound of formula-6a or its hydrochloride salt with Pd/C in presence of acetic acid in methanol to provide compound of formula-7or its hydrochloride salt,



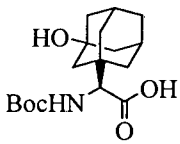
Formula-7

f) treating the compound of formula-7 or its hydrochloride salt with di-tert.butyl dicarbonate in presence of sodium carbonate in water to provide Boc-protected amine compound of formula-28,



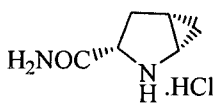
Formula-28

g) hydroxylating the compound of formula-28 by treating with potassium permanganate in presence of potassium hydroxide in water provides compound of formula-29a,



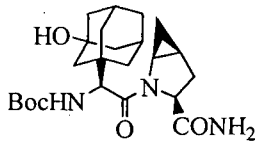
Formula-29a

h) condensing the compound of formula-29a with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a



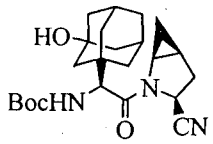
Formula-26a

in presence of N,N'-dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBt) and diisopropylethyl amine in a mixture of ethyl acetate and acetonitrile to provide compound of formula-30a,



Formula-30a

i) dehydrating the compound of formula-30a by treating with trifluoroacetic anhydride in presence of 2,6-lutidine in ethyl acetate to provide compound of formula-31a,

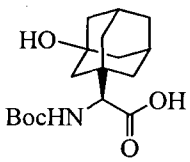


Formula-31a

j) deprotecting the compound of formula-31a by treating with acetyl chloride in methanol followed by treating with potassium carbonate to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile compound of formula-1.

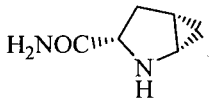
20) A process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrochloride compound of formula-1a, comprising of;

a) Condensing the boc protected hydroxy adamantyl glycine compound of formula-29a



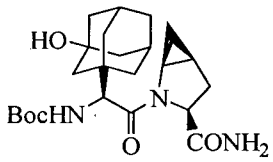
Formula-29a

with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26,



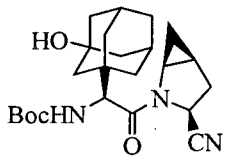
Formula-26

or its hydrochloride salt in presence of N,N'-dicyclohexylcarbodiimide (DCC) optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), 4-dimethylaminopyridine (DMAP) and the like in presence of a suitable base in a suitable solvent to provide compound of formula-30a,



Formula-30a

b) dehydrating the compound of formula-30a by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide nitrile compound of formula-31a,

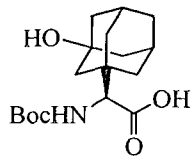


Formula-31a

c) deprotecting the compound of formula-31a by treating it with acetyl chloride in a suitable alcohol solvent to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrochloride compound of formula-1a.

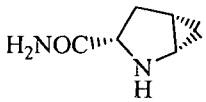
21) A process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

a) Condensing the boc protected hydroxy adamantyl glycine compound of formula-29a



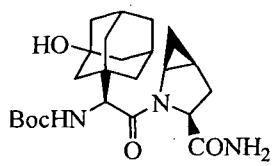
Formula-29a

with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26,



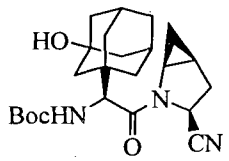
Formula-26

or its hydrochloride salt in presence of N,N'-dicyclohexylcarbodiimide (DCC) optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), 4-dimethylaminopyridine (DMAP) and the like in presence of a suitable base in a suitable solvent to provide compound of formula-30a,



Formula-30a

b) dehydrating the compound of formula-30a by treating it with a suitable dehydrating agent optionally in presence of a suitable base in a suitable solvent to provide nitrile compound of formula-31a,



Formula-31a

c) deprotecting the compound of formula-31a by treating it with acetyl chloride in a suitable alcohol solvent followed by treating with alkali metal carbonate base to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

22) A process according to claim 20 & 21, wherein,

in step-a) the suitable base is selected from organic bases; and the suitable solvent is selected from ester solvents, nitrile solvents, polar-aprotic solvents, alcoholic solvents, ether solvents, chloro solvents or their mixtures thereof;

in step-b) the suitable dehydrating agent is selected from acetic anhydride, trifluoro acetic anhydride (TFAA), phosphorous pentoxide, phosphoryl chloride, phosphoric acid, sulfuric acid, dicyclohexyl carbodiimide; and the suitable base wherever necessary is selected from organic bases; and the suitable solvent is selected from ether solvents, ester solvents or their mixtures thereof;

in step-c) the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, chloro solvents, hydrocarbon solvents, polar solvents or their mixtures thereof.

23) A process for the preparation of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1, comprising of;

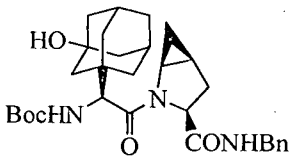
a) Condensing the boc protected hydroxy adamantyl glycine compound of formula-29a with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt in presence of N,N'-dicyclohexylcarbodiimide (DCC) in combination with 1-hydroxybenzotriazole (HOBt) and diisopropylethyl amine in a mixture of ethyl acetate and acetonitrile to provide compound of formula-30a,

b) dehydrating the compound of formula-30a by treating it with trifluoroacetic anhydride in presence of 2,6-lutidine in ethyl acetate to provide nitrile compound of formula-31a,

c) deprotecting the compound of formula-31a by treating it with acetyl chloride in methanol to provide (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

24) A process for the preparation of compound of formula-36a comprising of condensing the boc protected hydroxy adamantyl glycine compound of formula-29a with (1S,3S,5S)-N-benzyl-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of

formula-26 or its hydrochloride salt in presence of a suitable coupling agent and a suitable base in a suitable solvent to provide compound of formula-36a,

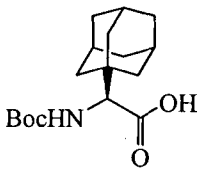


Formula-36a

25) A process according to claim 24, wherein,

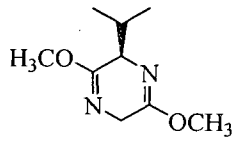
in step-a) the suitable coupling agent is selected from N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), alkyl or aryl chloroformates such as ethyl chloroformate, benzylchloroformate, diphenylphosphoroazidate (DPPA), thionyl chloride, phosphorous pentachloride and the like wherein the carbodiimides is used optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS), 4-dimethylaminopyridine (DMAP); the suitable base is selected from organic bases; and the suitable solvent is selected from ester solvents, nitrile solvents, polar-aprotic solvents, alcoholic solvents, ether solvents, chloro solvents or their mixtures thereof;

26) A process for the preparation of compound of formula-28, comprising of;



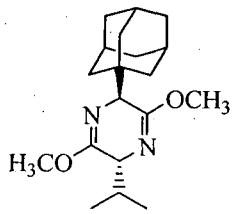
Formula-28

a) Reacting the (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine compound of formula-50



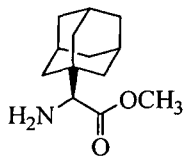
Formula-50

with adamantyl bromide compound of formula-48 in presence of a suitable base in a suitable solvent to provide adamantyl pyrazine compound of formula-51,



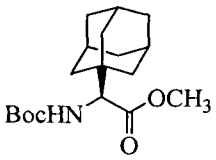
Formula-51

b) treating the compound of formula-51 with a suitable acid in a suitable solvent to provide methyl ester compound of formula-52,



Formula-52

c) treating the compound of formula-52 with di-tert-butyl dicarbonate in presence of a suitable base in a suitable solvent provides Boc protected compound of formula-63,



Formula-63

d) hydrolyzing compound of formula-63 in presence of a suitable base in a suitable solvent to provide compound of formula-28.

27) The process according to claim 26, wherein,

in step-a) the suitable base is selected from organic bases and organosilicon bases; and the suitable solvent is selected from hydrocarbon solvents, chloro solvents, ether solvents, ester solvents and/or their mixtures thereof;

in step-b) the suitable acid is hydrochloric acid; and the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, polar-aprotic solvents and/or their mixtures thereof;

in step-c) the suitable base is selected from organic and inorganic bases and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ether solvents, ester solvents and/or their mixtures thereof;

in step-d) the suitable base is selected from hydroxides, alkoxides, bicarbonates of alkali metals and the suitable solvent is selected from chloro solvents, hydrocarbon solvents, ether solvents, ester solvents, alcohol solvents and/or their mixtures thereof;

28) A process for the preparation of compound of formula-28, comprising of;

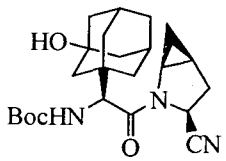
a) Reacting the (R)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine compound of formula-50 with adamantyl bromide compound of formula-48 in presence of n-butyl lithium in tetrahydrofuran to provide adamantyl pyrazine compound of formula-51,

b) treating the compound of formula-51 with hydrochloric acid to provide methyl ester compound of formula-52,

c) treating the compound of formula-52 with di-tert-butyl dicarbonate in presence of 4-dimethylaminopyridine in dichloromethane to provide compound of formula-63,

d) hydrolyzing the compound of formula-63 in presence of aq.lithium hydroxide in methanol to provide compound of formula-28.

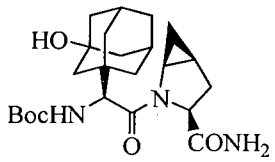
29) A process for preparing (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1 comprising of, deprotecting the nitrile compound of formula-31a,



Formula-31a

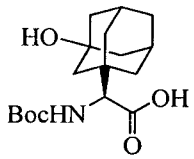
by treating it with acetyl chloride in a suitable alcohol solvent followed by treating with a suitable base selected from alkali metal carbonates or alkali metal bicarbonates provides (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1.

30) A process for preparing the compound of formula-30a,



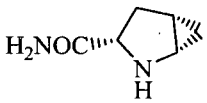
Formula-30a

comprising of, condensing the boc protected hydroxy adamantyl glycine compound of formula-29a



Formula-29a

with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26,



Formula-26

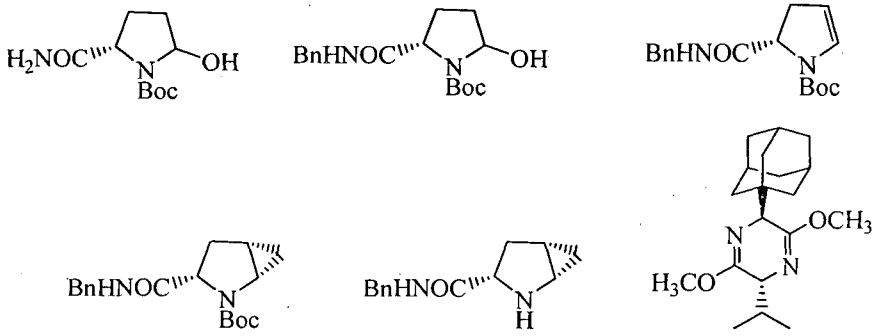
or its hydrochloride salt in presence of N,N'-dicyclohexylcarbodiimide (DCC) in presence of 1-hydroxybenzotriazole (HOBt) in presence of a base in a suitable solvent.

31) The process according to claim 30, the suitable solvent is selected from ether solvents, ester solvents, nitrile solvents, chloro solvents, hydrocarbon solvents and/or their mixtures thereof.

32) The process according to claim 30, the suitable solvent is mixture of ethyl acetate and acetonitrile.

33) A process for the purification of (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile compound of formula-1 comprising of recrystallizing the compound of formula-1 from mixture of water and methanol.

34) Compounds having the structural formulae

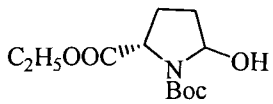


35) A process for the preparation of (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide compound of formula-26 or it's acid addition salt, comprising of;

a) Esterification of (S)-5-oxopyrrolidine-2-carboxylic acid compound of formula-9 by treating it ethanol in presence of thionyl chloride to provide (S)-ethyl 5-oxopyrrolidine-2-carboxylate compound of formula-10b,

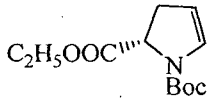
b) treating the compound of formula-10b with di-tert.butyl dicarbonate in presence of 4-dimethylamino pyridine in dichloromethane to provide (S)-1-tert-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate compound of formula-11b,

c) reducing the compound of formula-11b with sodium borohydride in methanol to provide (2S)-1-tert-butyl 2-alkyl 5-hydroxypyrrolidine-1,2-dicarboxylate compound of formula-23b,



Formula-23b

d) dehydrating the compound of formula-23b by treating it with trifluoro acetic anhydride (TFAA) in presence of diisopropyl ethyl amine in tetrahydrofuran to provide (S)-1-tert-butyl 2-ethyl 2,3-dihydro-1H-pyrrole-1,2-dicarboxylate compound of formula-24b,



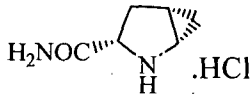
Formula-24b

e) hydrolyzing the compound of formula-24b in-situ in presence of aqueous lithium hydroxide in tetrahydrofuran to provide (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid compound of formula-25,

f) treating the compound of formula-25 in-situ with methane sulfonyl chloride in presence of diisopropylethylamine followed by in-situ treating the obtained compound with ammonia to provide (S)-tert-butyl 2-carbamoyl-2,3-dihydro-1H-pyrrole-1-carboxylate compound of formula-14,

g) converting the compound of formula-14 in-situ into (1S,3S,5S)-tert-butyl 3-carbamoyl-2-azabicyclo[3.1.0]hexane-2-carboxylate compound of formula-15 by treating it with diiodomethane in presence of diethyl zinc in a mixture of toluene and 1,2-dimethoxy ethane,

h) deprotecting the compound of formula-15 by treating it ethyl acetate-HCl in tetrahydrofuran to provide (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride salt compound of formula-26a.



Formula-26a

36) (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile having particle size distribution of D(0.9) in the range of 20 μm to 120 μm.

37) (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile having particle size distribution of D(4,3) in the range of 5 μm to 40 μm.

38) (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile hydrochloride having particle size distribution of D(0.9) in the range of 20 μm to 120 μm.

39) (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile hydrochloride having particle size distribution of D(4,3) in the range of 5 μm to 40 μm.

40) (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo [3.1.0]hexane-3-carbonitrile having purity greater than 99.90%, preferably 99.95%, more preferably 99.97% by HPLC.

41) (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile hydrochloride salt having purity greater than 99.90%, preferably 99.95%, more preferably 99.97% by HPLC.

Dated this day 01st of January 2013.

Authorized Signatory
(Srinivasan Thirumalai Rajan)
MSN Laboratories Limited.

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