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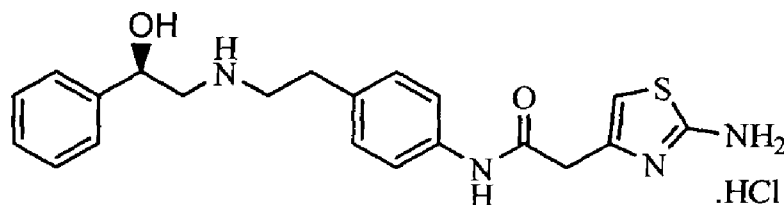
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ETHYL}AMINO}ETHYL)PHENYL]ACETAMIDE MONOHYDROCHLORIDE, ITS INTERMEDIATES AND POLYMORPH
THEREOF

Formula-1a

(57) Abstract: The present invention relates to a process for the preparation of 2-(2-aminothiazol-4-yl)- N-[4-(2- {{(2R)-2-hydroxy-
2-phenylethyl}amino} ethyl)phenyl]acetamide monohydrochloride compound of formula- 1a, its intermediates and polymorph there-
of. [Formula should be inserted here]

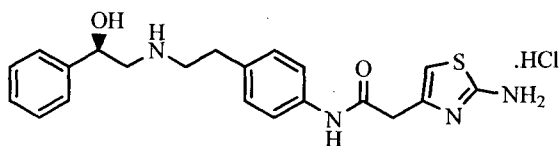
Process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenyl ethyl}amino}ethyl)phenyl]acetamide monohydrochloride, its intermediates and polymorph thereof

5 Related Applications:

This application claims the benefit of priority of our Indian patent application number 868/CHE/2013 filed on 27th Feb. 2013 which is incorporated herein by reference.

Field of the invention:

10 The present invention provides 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride salt compound of formula-1a, its hydrates, polymorphs and process for preparation thereof.



Formula-1a

15 The present invention also provides an improved process for the preparation of 2-(2-amino thiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide compound of formula-1.

20 Background of the invention:

25 2-(2-Aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl] acetamide, commonly known as Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency. It was developed by Astellas Pharma and was approved in the United States on 28th June 2012 and in Europe on 20th Dec. 2012.

2-(2-Aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl] acetamide and its pharmaceutically acceptable acid-addition salts are first disclosed in US6346532B1 (herein after referred as '532' patent). The said patent discloses a process for the

preparation of dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl] acetamide, which comprising of deprotection of tert-butyl (R)-N-[2-[4-[2-(2-amino-thiazol-4-yl)acetamido]phenyl]ethyl]-N-[(2-hydroxy-2-phenyl)ethyl] carbamate (Boc protected Mirabegron) with hydrochloric acid in a mixture of methanol and ethyl acetate followed by purification of the obtained Mirabegron by reverse phase column chromatography using water/methanol (2:1) as eluent.

The process disclosed in the said '532' patent involves the usage of reverse phase column chromatography technique for the purification of dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide, which is not suggestible on commercially scale.

Later US7342117B2 patent (herein after referred as '117' patent) discloses that the dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide is strongly hygroscopic in nature and hence unstable. Therefore its use as a medicine is problematic.

The above said '117' patent discloses the α and β -crystalline forms of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide free base and processes for preparation thereof. The disclosed processes involve rapid cooling, use of seed material and use of solvents water and ethanol only. The disclosed methods suffer from one or more drawbacks such as reproducibility, use of seed material, less yield, limited solvents, which does not result an industrially feasible process.

WO2012156998A2 discloses the amorphous form of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide and process for preparation thereof.

Hence, there is still a need in the art to develop stable and reproducible form of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide and its pharmaceutically acceptable salts.

After an intensive study, the present inventors surprisingly found that the monohydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl]

amino}ethyl)phenyl]acetamide is stable and reproducible, hence is suggestible to use as a medicine.

Till date, monohydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide is not reported in the literature.

Polymorphs are distinct solids having the same molecular formula yet having distinct advantageous physical properties compared to other polymorphic forms of the same compound. The difference in the physical properties of different polymorphic forms results from the orientation and intermolecular interactions of adjacent molecules in the bulk solid.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of polymorphic forms having distinct crystal structures and physical properties like melting point, X-ray diffraction pattern, infrared absorption and solid state NMR spectrum. One polymorphic form may give rise to thermal behavior different from that of another polymorphic form. Thermal behavior can be measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) as well as content of solvent in the polymorphic form, which have been used to distinguish polymorphic forms.

Brief description of the invention:

The first aspect of the present invention is to provide monohydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide.

The second aspect of the present invention is to provide crystalline form of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride compound of formula-1a, herein after referred as crystalline form-M.

The third aspect of the present invention is to provide a process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride salt compound of formula-1a.

The fourth aspect of the present invention is to provide a process for the preparation of N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8, comprising of reductive

amination of benzaldehyde with 2-(4-nitrophenyl)ethanamine compound of formula-3 to provide N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8.

The fifth aspect of the present invention is to provide another process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride salt compound of formula-1a.

The sixth aspect of the present invention is to provide a process for the preparation of 2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide compound of formula-1.

Brief description of the drawings:

Figure-1: Illustrates the PXRD pattern of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride (Formula-1a).

Figure-2: Illustrates the DSC thermogram of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride (Formula-1a).

Figure-3: Illustrates the thermogravimetric analysis (TGA) curve of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride (Formula-1a).

Figure-4: Illustrates the PXRD pattern of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride (Formula-1a) obtained according to example-15.

Figure-5: Illustrates the PXRD pattern of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide (Formula-1).

Detailed description of the invention:

The term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane, cycloheptane, pet ether, chlorobenzene, toluene, xylene and the like; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, di-tert-butyl ether, dimethoxy methane, 1,2-dimethoxy ethane (monoglyme), diglyme, 1,4-dioxane, tetrahydrofuran, 2-methyl tetrahydrofuran, morpholine and the like; "ester solvents"

such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate, diethyl carbonate and the like; "polar-aprotic solvents" such as dimethylacetamide (DMAc), N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), hexamethylphosphoramide (HMPA) and the like; "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile, isobutyronitrile and like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, diethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, iso-butanol, tert-butanol, 2-pentanol, ethylene glycol, diethylene glycol, propylene glycol, 2-ethyl hexanol, benzyl alcohol and the like; "polar solvents" such as water and/or mixtures thereof.

As used herein the present invention the term "suitable base" refers to "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium 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 ethoxide, sodium tert.butoxide, potassium tert.butoxide and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride and the like; "alkali metal amides" such as sodium amide, potassium amide, lithium amide, lithium diisopropyl amide (LDA) and the like; "alkali metal phosphates" such as disodium hydrogen phosphate, dipotassiumhydrogen phosphate; and "organic bases" like methyl amine, diisopropyl amine, diisopropylethyl amine, diisobutylamine, triethylamine, tert.butyl amine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo [2.2.2]octane (DABCO), imidazole or mixtures thereof.

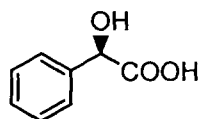
The first aspect of the present invention provides monohydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl]phenyl]acetamide.

The said monohydrochloride salt of the present invention can exists in the form of Eamhardt, hydrate and solvate thereof.

The second aspect of the present invention provides crystalline form of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride salt compound of formula-1a characterized by its powder X-ray diffraction pattern having peaks at 2.1, 4.3, 6.4, 8.5, 17.4, 19.3, 21.6, 24.3, 24.8, 27.3, 31.6, 45.4 ± 0.2 degrees of 2-theta. The said crystalline form is herein after designated as crystalline form-M. The said crystalline form-M is further characterized by its PXRD pattern as illustrated in figure-1 and its differential scanning calorimetric (DSC) thermogram having an endotherm at 201.03°C substantially in accordance with figure-2.

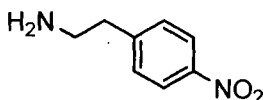
The third aspect of the present invention provides a process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride salt compound of formula-1a, comprising of;

a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2



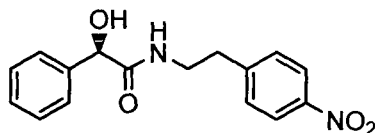
Formula-2

with 2-(4-nitrophenyl)ethanamine compound of formula-3



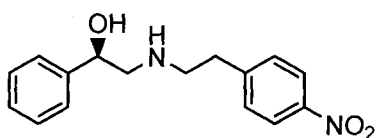
Formula-3

or its hydrochloride salt compound of formula-3a in presence of a suitable coupling agent in a suitable solvent, optionally in presence of a suitable base to provide (R)-2-hydroxy-N-(4-nitro phenethyl)-2-phenylacetamide compound of formula-4,



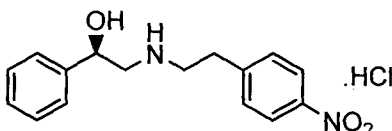
Formula-4

b) reducing the compound of formula-4 with a suitable reducing agent in a suitable solvent to provide (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5,



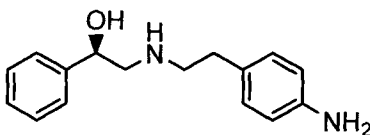
Formula-5

- c) optionally converting the compound of formula-5 into its hydrochloride salt compound of formula-5a,



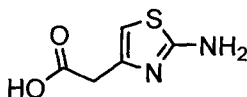
Formula-5a

- d) reducing the compound of formula-5 or its hydrochloride salt compound of formula-5a with a suitable reducing agent in a suitable solvent to provide (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6 or its hydrochloride salt compound of formula-6a,



Formula-6

- e) condensing the compound of formula-6 or its hydrochloride salt compound of formula-6a with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7



Formula-7

or its hydrochloride salt compound of formula-7a in presence of a suitable coupling agent and hydrochloric acid in a suitable solvent to provide dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl]phenyl]acetamide,

- f) treating the dihydrochloride salt obtained in step-(e) in-situ with a suitable aqueous base to provide 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl]phenyl] acetamide monohydrochloride salt compound of formula-1a.

Wherein, in step-a) the suitable coupling agent is selected from N,N-carbonyldiimidazole (CDI); alkyl and aryl carbodiimides such as N,N-diisopropylcarbodiimide (DIC), N,N-

dicyclohexyl carbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), ditolyl carbodiimide optionally in combination with hydroxybenzotriazole or N-hydroxysuccinimide (NHS) or N-hydroxysulfosuccinimide (Sulfo-NHS); carbonyl-di-1,2,4-triazole; alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate, benzyl chloroformate; carbonates having the formula $R_1-O-CO-O-R_2$,
5 wherein "R₁" and "R₂" are independently selected from branched or unbranched C₁-C₄ alkyl or substituted or unsubstituted phenyl group; the suitable base is selected from organic or inorganic bases; and the suitable solvent is selected from polar aprotic solvents, ketone solvents, ester solvents, chloro solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar solvents or
10 mixtures thereof;

in step-b) the suitable reducing agent is selected from diborane, borane-dimethyl sulfide, borane-THF complex, sodium triacetoxyborohydride, sodium cyanoborohydride, NaBH₄, NaBH₄/BF₃.diethyl ether, LiBH₄, LiAlH₄ and the like; and the suitable solvent is selected from alcoholic solvent, ether solvents, ester solvents, hydrocarbon solvents, polar solvents, polar
15 aprotic solvents or mixtures thereof;

in step-c) the conversion of compound of formula-5 into its HCl salt compound of formula-5a is carried out by using a suitable HCl source selected from HCl gas, HCl, aq.HCl, ethylacetate-HCl and IPA-HCl in a suitable solvent.

in step-d) the suitable reducing agent is selected from Fe, Fe in acidic media like NH₄Cl or HCl or acetic acid, Sn in acidic media like HCl, Zn dust, Zn in acidic media like HCl or NH₄Cl or acetic acid, stannous chloride (SnCl₂), NaBH₄, LiAlH₄, LiBH₄, diborane, borane-THF complex, hydrazine hydrate, hydrogenation catalysts such as Pd/C, Pt/C, PtO₂, Pd(OH)₂, Nickel, Raney nickel, Rhodium, sodium dithionate, sodium amalgam and the like; the suitable solvent is
20 selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents or mixtures thereof;

in step-e) the suitable coupling agent & suitable solvent are same as defined in step-(a);

in step-f) the suitable base can be selected from hydroxides, carbonates and bicarbonates of alkali metals.

30 A preferred embodiment of the present invention provides a process for the preparation of

2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide mono hydrochloride salt compound of formula-1a, comprising of;

- a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2 with 2-(4-nitrophenyl) ethanamine hydrochloride salt compound of formula-3a in presence of 1-ethyl-3-(-3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl)/1-hydroxybenzotriazole (HOBt) and triethylamine in N,N-dimethylformamide to provide (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide compound of formula-4,
- b) reducing the compound of formula-4 with borane-dimethyl sulfide in tetrahydrofuran to provide (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5,
- c) converting the compound of formula-5 into its hydrochloride salt compound of formula-5a by treating it with hydrochloric acid in isopropanol,
- d) reducing the compound of formula-5a with Fe-HCl in a mixture of tetrahydrofuran and water to provide (R)-2-(4-aminophenethylamino)-1-phenylethanol hydrochloride salt compound of formula-6a,
- e) condensing the compound of formula-6a with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 in presence of 1-ethyl-3-(-3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) and hydrochloric acid in water to provide dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide,
- f) treating the dihydrochloride salt obtained in step-(e) in-situ with aqueous sodium hydroxide solution to provide 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride compound of formula-1a.

US7342117B2 patent discloses the reduction of (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide compound of formula-4 to (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5 using borane-THF complex in a mixture of 1,3-dimethyl-2-imidazolidinone (DMI) and tetrahydrofuran. However, 1,3-dimethyl-2-imidazolidinone (DMI) is a toxic and high boiling solvent, hence not suggestible to use in commercial scale.

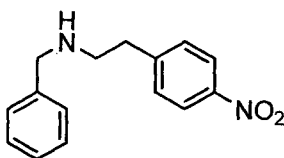
The present inventors carried out the said reduction step in tetrahydrofuran, thereby avoiding the usage of toxic and high boiling solvents like 1,3-dimethyl-2-imidazolidinone

(DMI), hence the process of the present invention is advantageous over prior-art process.

The 2-(4-nitrophenyl)ethanamine compound of formula-3 utilized in step-(a) of the third aspect of the present invention can be synthesized by any of the prior reported processes, for example it can be synthesized by the processes disclosed in *J. Org. Chem.*, 1978, 43(1), 31-33 and *Tetrahedron Letters*, Volume 10, Issue 52, 1969, 4555-4558.

The 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 utilized in step-(e) of the third aspect of the present invention can be synthesized by any of the processes known in the art such as US4391979A.

The fourth aspect of the present invention provides a process for the preparation of N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8,



Formula-8

comprising of reductive amination of benzaldehyde with 2-(4-nitrophenyl)ethanamine compound of formula-3 to provide N-benzyl-2-(4-nitrophenyl)ethanamine of formula-8.

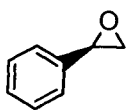
Wherein, the reductive amination step is carried out in presence of a suitable reducing agent selected from NaBH_4 , sodium cyanoborohydride, sodium triacetoxyborohydride, trihalosilanes, diisobutylaluminium hydride (DIBAL), lithium triethylborohydride, lithium tri-sec-butyl borohydride (L-selectride), trialkylsilanes optionally in combination with trifluoroacetic acid, hydrogenating agents like Pd/C, Pt/C, Ni, Raney Ni and the like in a suitable solvent selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents, polar-aprotic solvents or mixtures thereof.

A preferred embodiment of the present invention provides a process for the preparation of N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8, comprising of reductive amination of benzaldehyde with 2-(4-nitrophenyl)ethanamine compound of formula-3 in presence of sodium borohydride in methanol to provide N-benzyl-2-(4-nitrophenyl)ethanamine

compound of formula-8.

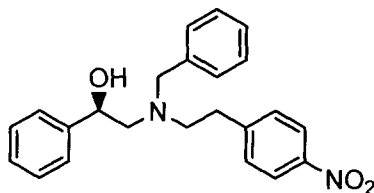
The fifth aspect of the present invention provides a process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride salt compound of formula-1a, comprising of;

- a) Reductive amination of benzaldehyde with 2-(4-nitrophenyl)ethanamine compound of formula-3 in presence of a suitable reducing agent in a suitable solvent to provide N-benzyl-2-(4-nitro phenyl)ethanamine compound of formula-8,
- b) reacting the compound of formula-8 with (R)-2-phenyloxirane compound of formula-9



Formula-9

in a suitable solvent to provide (R)-2-(benzyl(4-nitrophenethyl)amino)-1-phenylethanol compound of formula-10,



Formula-10

- c) reducing the compound of formula-10 with a suitable reducing agent in a suitable solvent to provide (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6,
- d) condensing the compound of formula-6 with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 or its hydrochloride salt compound of formula-7a in presence of a suitable coupling agent and hydrochloric acid in a suitable solvent to provide dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide,
- e) treating the dihydrochloride salt obtained in step-(d) in-situ with a suitable aqueous base to provide 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride salt compound of formula-1a.

Wherein, in step-a) suitable reducing agent and the suitable solvent are same as defined in fourth aspect of the present invention;

in step-b) the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents, ketone solvent, polar-aprotic solvents or mixtures thereof;

in step-c) the suitable reducing agent is selected from Pd/C, Pt/C, Raney Ni, PtO₂ and the like; and the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents or mixtures thereof;

in step-d) the suitable coupling agent and suitable solvent are same as defined in step-(a) of the third aspect of the present invention; and

in step-e) the suitable base is same as defined for step-(f) of the third aspect of the present invention.

The sixth aspect of the present invention provides a process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide compound of formula-1, comprising of:

- a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2 with 2-(4-nitro phenyl)ethanamine compound of formula-3 or its hydrochloride salt compound of formula-3a in presence of a suitable coupling agent in a suitable solvent, optionally in presence of a suitable base to provide (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide compound of formula-4,
- b) reducing the compound of formula-4 with a suitable reducing agent in a suitable solvent, optionally purifying the obtained compound using a suitable solvent to provide (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5,
- c) reducing the compound of formula-5 with a suitable reducing agent in a suitable solvent, optionally purifying the obtained compound using a suitable solvent to provide (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6,
- d) condensing the compound of formula-6 with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 or its hydrochloride salt compound of formula-7a in presence of a suitable coupling agent and hydrochloric acid in a suitable solvent to provide 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide compound of formula-1,

- e) optionally purifying the compound obtained in step-(d) by dissolving the compound in a suitable solvent followed by adding an anti-solvent to provide pure compound of formula-1.

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

in step-b) the suitable reducing agent and suitable solvent are same as defined in step-(b) of third aspect of the present invention respectively;

in step-c) the suitable reducing agent and suitable solvent is same as defined in step-(d) of third aspect of the present invention;

in step-d) the suitable coupling agent and suitable solvents are same as defined in step-(a) of third aspect of the present invention; and

in step-e) the suitable solvent is alcoholic solvents; the anti-solvent is selected from polar solvents.

A preferred embodiment of the present invention provides a process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide compound of formula-1, comprising of:

- a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2 with 2-(4-nitro phenyl)ethanamine hydrochloride salt compound of formula-3a in presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl)/1-hydroxybenzotriazole (HOBt) and triethylamine in N-methyl-2-pyrrolidone to provide (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide compound of formula-4,
- b) reducing the compound of formula-4 with sodium borohydride in presence of BF₃-diethyl ether in tetrahydrofuran, purifying the obtained compound using toluene to provide (R)-2-(4-nitro phenethylamino)-1-phenylethanol compound of formula-5,
- c) reducing the compound of formula-5 with Raney-nickel in methanol under hydrogen pressure, purifying the obtained compound using isopropanol to provide (R)-2-(4-aminophenethyl amino)-1-phenylethanol compound of formula-6,
- d) condensing the compound of formula-6 with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 in presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) and hydrochloric acid in water to provide 2-(2-aminothiazol-4-

yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide compound of formula-1,

- e) purifying the compound obtained in step-(d) by dissolving the compound in methanol followed by adding water to provide pure compound of formula-1.

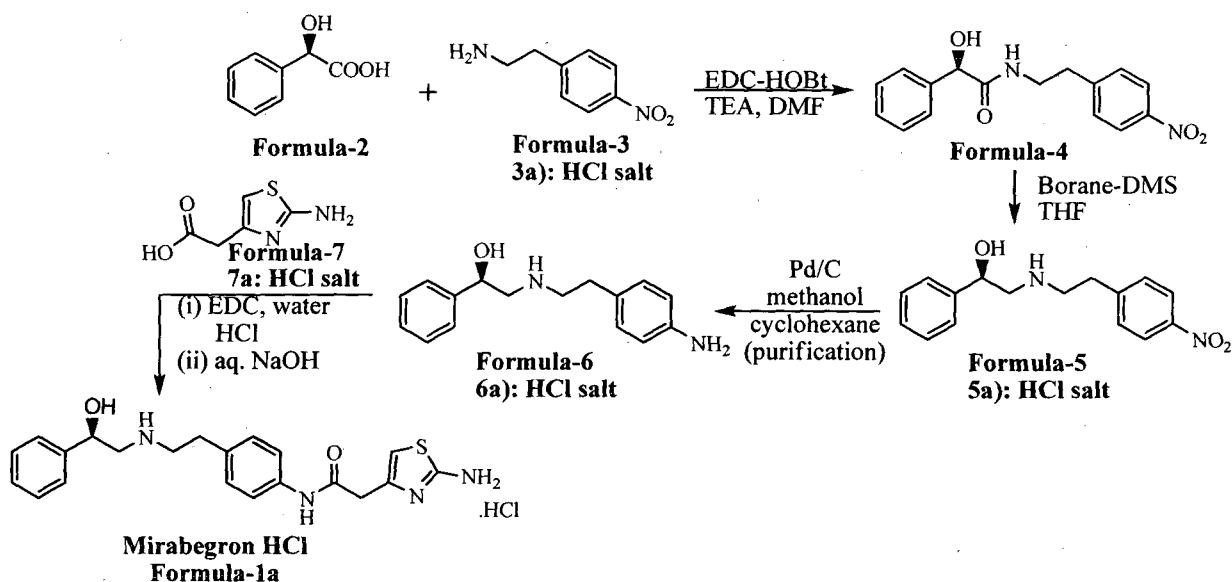
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The prior reported process involves the reduction of nitro compound of formula-5 to amine compound of formula-6 using Pd/C. When we carried out the same experiment in our laboratory, we have found the 10% of impurity along with compound of formula-6. Whereas, in the present invention the usage of Raney-Ni for the above said reduction step instead of Pd/C has decreased the impurity level up to 1% and thereby enhanced the purity of compound of formula-6.

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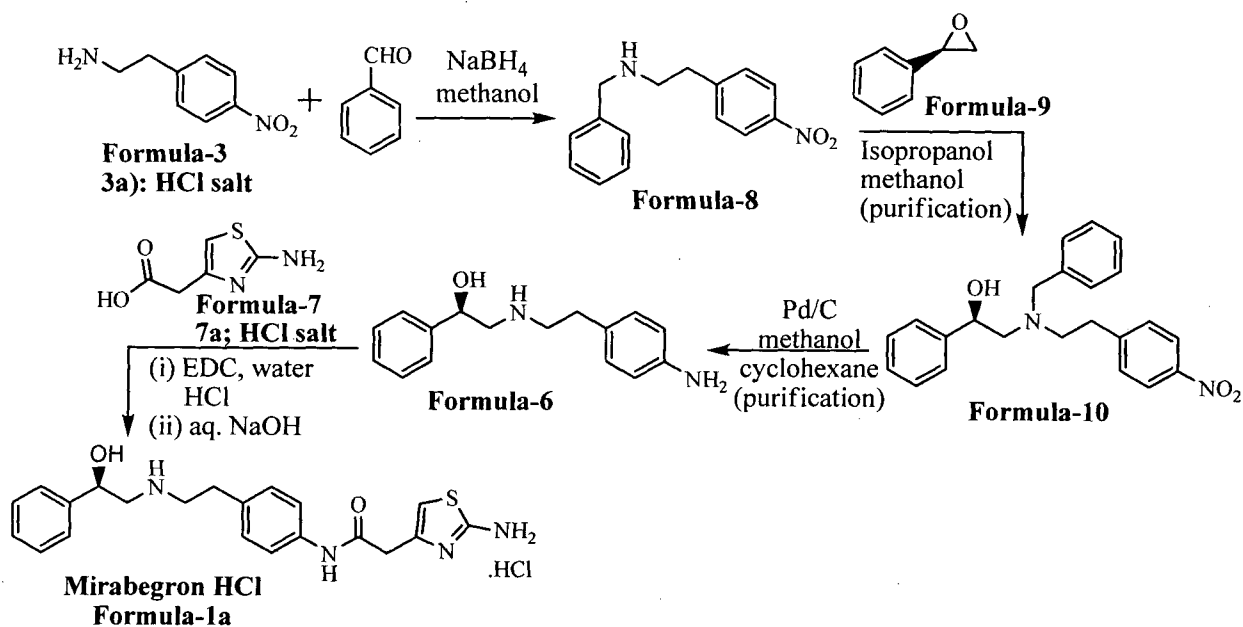
The present invention is schematically represented as follows:

15 Scheme-I:



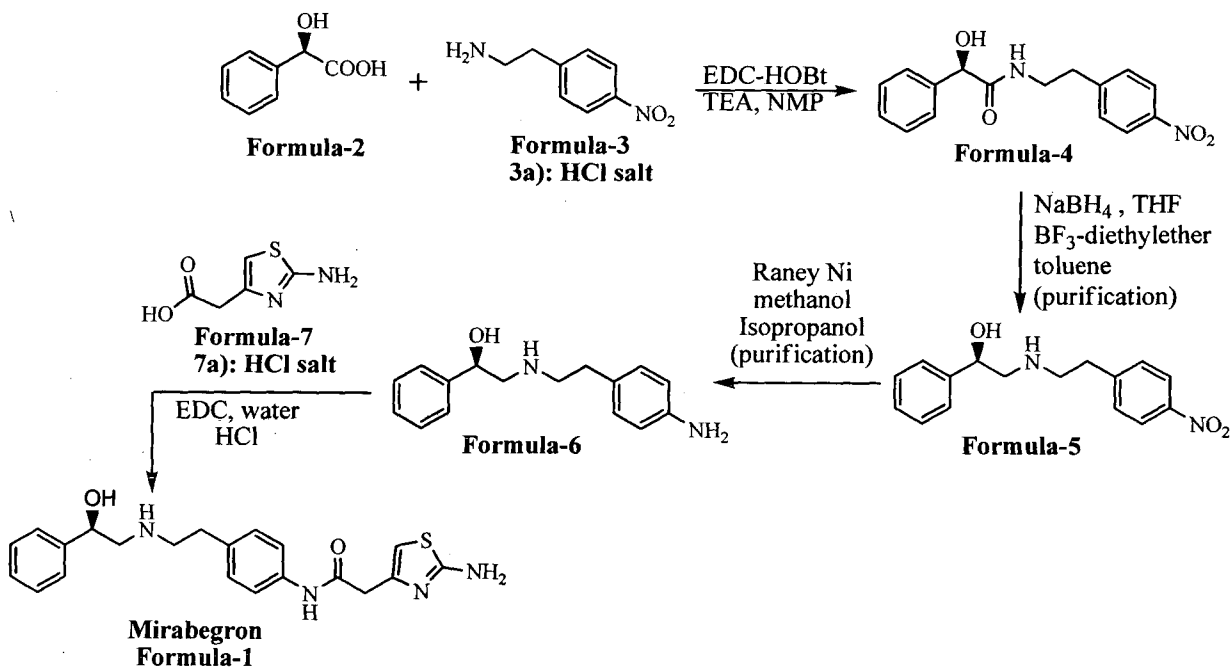
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Scheme-II:

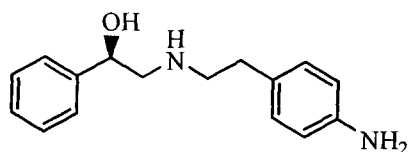


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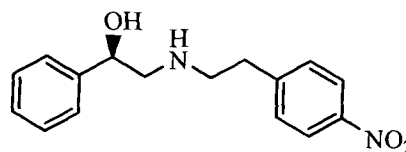
Scheme-III:



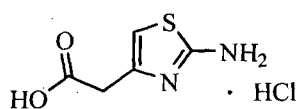
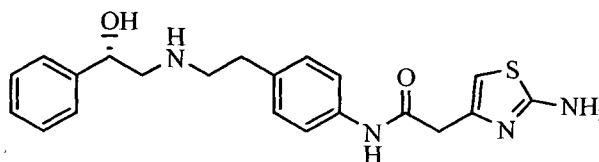
The impurities that are formed during the synthesis of 2-(2-aminothiazol-4-yl)-N-[4-(2-
 5 {[(2R)- 2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide and its hydrochloride salt are as follows:



Amine Impurity



Nitro Impurity

Thiazole acetic acid
hydrochloride

S-isomer

2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]
 10 acetamide obtained by the present invention is having purity about 99.8% by HPLC. All the impurities that are formed during the synthesis of compound of formula-1 and its mono hydrochloride salt of formula-1a are controlled to below ICH limits in which few of them are controlled to not detected level.

2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]
 15 acetamide and its related substances are measured by using HPLC with the following chromatographic conditions:

Apparatus: A liquid chromatograph is equipped with variable wavelength UV-detector;
 Column: symmetry shield RP18, 250 x 4.6 mm, 5 µm or equivalent; Flow rate: 1.0 ml/minute;
 20 Elution: Gradient; Wavelength: 210 nm; Column temperature: 45°C; Injection volume: 5 µL;
 Run time: 45 mins; Needle wash: Diluent; Diluent: water: acetonitrile (50:50 v/v); Mobile phase
 A: Buffer : Methanol (70: 30 v/v); Mobile phase B: Acetonitrile : Buffer (70:30 v/v); Buffer
 preparation: Transfer about 1.74 gms of anhydrous Di potassium hydrogen phosphate and 3 gms
 of anhydrous 1-octane sulfonic acid sodium salt in 1000 ml of milli-Q-water, adjust its pH of to
 25 5.0 with dil.ortho phosphoric acid and filter this solution through 0.22 µm nylon membrane filter

paper.

PXRD analysis of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl} amino}ethyl)phenyl]acetamide and its mono hydrochloride salt were carried out using BRUKER/AXS X-Ray diffractometer using Cu K α radiation of wavelength 1.5406 Å and continuous scan speed of 0.03°/min.

Differential scanning calorimetric (DSC) analysis was performed on a Q10 V9.6 Build 290 calorimeter with open aluminium pans, heating the samples from 40 to 250°C in a dry nitrogen atmosphere at a rate of 5°C/min.

Thermogravimetric analysis (TGA) was performed in TGA Q50 V20.8 Build 34 instrument. Data was collected between 30-300°C at a heating rate of 10°C/min.

2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl} amino}ethyl)phenyl] acetamide and its monohydrochloride salt produced by the present invention can be further micronized or milled to get the desired particle size, preferably less than 20 µm to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball mills, 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 best mode of carrying out the present invention is illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be construed as limitation to the scope of the invention.

Examples:

Example-1: Preparation of (R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide (or) (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide (Formula-4)

(R)-2-hydroxy-2-phenylacetic acid compound of formula-2 (75 gms), triethylamine (49.8 gms), hydroxybenztriazole (HOBt) (66.6 gms) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (94.5 gms) were added to a

mixture of 2-(4-nitrophenyl)ethylamine hydrochloride compound of formula-3a (100 gms) in N,N-dimethylformamide (370 ml) at 25-30°C and stirred for 15 hrs at the same temperature. Water (1860 ml) was added to the reaction mixture at 25-30°C and stirred for 30 mins at the same temperature. Ethyl acetate (1500 ml) was added to the reaction mixture at 25-30°C and stirred for 30 mins. Separated the both aqueous and organic layers and the organic layer was washed with 1M HCl solution, followed by 20% aqueous potassium carbonate solution and finally with water. Distill off the solvent completely from the organic layer under reduced pressure. Toluene (600 ml) was added to the obtained compound, heated the reaction mixture to 80-85°C and stirred for 15 mins at the same temperature. Cooled the reaction mixture to 20-25°C and stirred for 12 hrs at the same temperature. Filtered the precipitated solid, washed with toluene and dried to get the title compound. Yield: 129.8 gms.

Example-2: Preparation of (R)-2-[[2'-(4-nitrophenyl)-ethyl]amino]-1-phenylethanol mono hydrochloride (or) (R)-2-(4-nitrophenethylamino)-1-phenylethanol mono hydrochloride (Formula-5a)

Borane-dimethyl sulfide (500 ml) was added to a solution of (R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide compound of formula-4 (100 gms) in tetrahydrofuran (300 ml) at -10°C to -5°C and stirred for 45 mins at the same temperature. Slowly heated the reaction mixture to 70-75°C and stirred for 5 hrs at the same temperature. Cooled the reaction mixture to 0-5°C and quenched the reaction mixture by adding methanol (38.6 ml) and hydrochloric acid (78.5 ml) and stirred for 15 mins at the same temperature. Slowly heated the reaction mixture to 65-70°C and stirred for 90 mins at the same temperature. Distilled off the 50% of the solvent from the reaction mixture under reduced pressure. 30% aqueous potassium carbonate solution (800 ml), water (80 ml) and ethyl acetate (1000 ml) were added to the reaction mixture. Both the organic and aqueous layers were separated and distilled off the solvent completely from the organic layer under reduced pressure. Isopropanol (1000 ml) was added to the obtained compound and heated the reaction mixture to 35-40°C. Hydrochloric acid (32.7 gms) was added to the reaction mixture at 25-30°C and stirred for 15 hrs at the same temperature. Filtered the precipitated solid, washed with isopropanol and dried to get the title compound. Yield: 97.0 gms.

Example-3: Preparation of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride (or) (R)-2-(4-aminophenethylamino)-1-phenylethanol mono

hydrochloride**(Formula-6a)**

(R)-2-[[2'-(4-nitrophenyl)-ethyl]amino]-1-phenylethanol monohydrochloride compound of formula-5a (50 gms), methanol (500 ml) and 5% Pd/C (5 gm) were charged into an autoclave vessel. 4-5 kg/cm² hydrogen gas pressure was applied to the reaction mixture at 45-50°C and stirred for 6 hrs at the same temperature and pressure. Cooled the reaction mixture to 25-30°C and filtered through hyflo bed. Distilled off the solvent completely from the filtrate under reduced pressure and co-distilled with cyclohexane. 150 ml of cyclohexane was added to the obtained compound, heated the reaction mixture to reflux temperature and stirred for 45 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 45 mins at the same temperature. Filtered the precipitated solid, washed with cyclohexane and dried to get the title compound. Yield: 35.0 gms.

Example-4: Preparation of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol (Formula-6)

Iron powder (86.8 gms) was added to a mixture of (R)-2-[[2'-(4-nitrophenyl)-ethyl]amino]-1-phenylethanol monohydrochloride compound of formula-5a (100 gms), tetrahydrofuran (500 ml) and water (500 ml) at 25-30°C and stirred for 15 min at the same temperature. Slowly added hydrochloric acid (124 ml) to the reaction mixture at 25-30°C and stirred for 12 hrs at the same temperature. After completion of the reaction, water was added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 10-20°C and the pH of the reaction mixture was adjusted to 9.0 using aqueous sodium hydroxide solution. Ethyl acetate was added to the reaction mixture and stirred for 30 mins. Both the organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate. Distilled off the solvent from the organic layer and co-distilled with cyclohexane. 300 ml of cyclohexane was added to the obtained compound, heated the reaction mixture to reflux temperature and stirred for 30 mins at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 90 mins at the same temperature. Filtered the precipitated solid, washed with cyclohexane and dried to get the title compound. Yield: 70.0 gms.

Example-5: Preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl} amino}ethyl)phenyl]acetamide monohydrochloride (Formula-1a)

2-aminothiazol-4-yl-acetic acid (or) 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 (2.76 gms) was added to a mixture of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride compound of formula-6a (5.0 gms), hydrochloric acid (4.62 ml) and water (30 ml) at 25-30°C and stirred for 15 mins at the same temperature. A solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (3.6 ml of EDC.HCl dissolved in 45 ml of water) was added slowly to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature. The reaction mixture was treated with 1N aqueous sodium hydroxide solution at 25-30°C and stirred for 6 hrs at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound. The PXRD of the obtained compound is shown in figure-1.

Yield: 5.0 gms; Specific optical rotation: -20.582° (C= 1% in methanol); Chloride content: 8.56% w/w; Water content: 1.8% w/w.

Example-6: Preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride (Formula-1a)

2-aminothiazol-4-yl-acetic acid compound of formula-7 (5.5 gms) was added to a mixture of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol compound of formula-6 (10 gms), hydrochloric acid (3.5 gms) and water (75 ml) at 25-30°C. A solution of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) (7.5 gms of EDC.HCl dissolved in 120 ml of water) was added slowly to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature. Aqueous sodium hydroxide solution (3.13 gms of sodium hydroxide dissolved in 30 ml of water) was added to the reaction mixture and stirred for 90 mins at 25-30°C. Filtered the precipitated solid, washed with water and dried to get title compound.

Yield: 4.2 gms; Purity by HPLC: 98.33%.

Example-7: Preparation of N-benzyl-2-(4-nitrophenyl)ethanamine (Formula-8)

Sodium hydroxide (19.0 gms) was added to a mixture of 2-(4-nitrophenyl)ethylamine hydrochloride compound of formula-3a (100 gms), water (300 ml) and ethyl acetate (500 ml) at 25-30°C and stirred for 30 mins at the same temperature. Separated the both aqueous and organic layers. Distilled off the solvent completely from the organic layer under reduced pressure and the obtained compound was co-distilled with methanol. Methanol (700 ml) and benzaldehyde (61.2 gms) were added to the obtained compound at 25-30°C. Cooled the reaction mixture to 0-5°C,

sodium borohydride (18.7 gms) was slowly added and stirred for 90 mins at the same temperature. Water (700 ml) and ethyl acetate (500 ml) were added to the reaction mixture and stirred for 15 mins. Both the organic and aqueous layers were separated. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 120.0 gms.

Example-8: Preparation of (R)-2-(benzyl(4-nitrophenethyl)amino)-1-phenylethanol (Formula-10)

(R)-2-phenyloxirane compound of formula-9 (113 gms) and isopropanol (1100 ml) were added to N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8 (110 gms) at 25-30°C.

Heated the reaction mixture to reflux temperature and stirred for 24 hrs at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure and the obtained compound was co-distilled with methanol. 70 ml of methanol was added to the obtained compound. Heated the reaction mixture to reflux temperature and stirred for 30 mins at the same temperature. Cooled the reaction mixture to 25-30°C, further cooled to 0-5°C and stirred for 90 mins at the same temperature. Filtered the precipitated solid; washed with methanol and dried to get the title compound.

Yield: 84.0 gms.

Example-9: Preparation of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol (Formula-6)

5% Pd/C (6 gms) was added to a solution of (R)-2-(benzyl(4-nitrophenethyl)amino)-1-phenylethanol compound of formula-10 (21 gms) dissolved in methanol (210 ml) at 25-30°C. 4-5 kg/Cm² of hydrogen gas pressure was applied to the reaction mixture at 25-30°C and stirred for 8 hrs at the same temperature. Filtered the reaction mixture through hyflo bed, distilled off the solvent completely from the filtrate and the obtained compound was co-distilled with cyclohexane. 63 ml of cyclohexane was added to the obtained compound, heated the reaction mixture to reflux temperature and stirred for 30 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 1 hr at the same temperature. Filtered the precipitated solid, washed with cyclohexane and dried to get the title compound. Yield: 10 gms.

Example-10: Preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-[[2-(2-hydroxy-2-phenylethyl) amino}ethyl)phenyl]acetamide monohydrochloride (Formula-1a)

2-aminothiazol-4-yl-acetic acid compound of formula-7 (2.76 gms) was added to a mixture of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol compound of formula-6 (5.0 gms), hydrochloric acid (4.62 ml) and water (30 ml) at 25-30°C and stirred the reaction mixture for 15 mins at the same temperature. A solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (3.6 ml of EDC.HCl dissolved in 45 ml of water) was added slowly to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature. The reaction mixture was treated with 1N sodium hydroxide solution at 25-30°C and stirred for 6 hrs at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound. The PXRD of the obtained compound is shown in figure-1. Yield: 5.0 gms; Chloride content: 8.4% w/w; Water content: 1.86% w/w.

When the compound is dried at 100°C the water content is reduced to 0.1% w/w. The PXRD of the obtained compound is similar to figure-1. When the dried compound having 0.1% w/w water content is kept in open air atmosphere at 25-30°C, the water content becomes 1.8-1.9% w/w.

The TGA of the obtained compound is shown in figure-3, which indicates that the obtained 2-(2-aminothiazol-4-yl)-N-[4-(2-(((2R)-2-hydroxy-2-phenylethyl)amino)ethyl)phenyl]acetamide monohydrochloride salt is anhydrous in nature.

¹H NMR (DMSO-d₆, 300 MHz) δ 2.93-3.17 (6H, m), 3.46 (2H, s), 4.96-4.99 (1H, m), 6.19-6.21 (1H, d), 6.29 (1H, s), 6.91 (2H, bs), 7.15-7.18 (2H, d), 7.29-7.40 (5H, m), 7.55-7.58 (2H, d); MS-ESI(+ve) m/z = 397.2 ; FTIR: ν 3555.99, 3303.99, 1662.67 cm⁻¹.

Example-11: Preparation of (R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide (Formula-4)

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (113.5 gms), hydroxybenztriazole (HOBt) (66.6 gms), (R)-2-hydroxy-2-phenylacetic acid compound of formula-2 (75 gms) and triethylamine (49.8 gms) were added to a mixture of 2-(4-nitrophenyl)ethylamine hydrochloride compound of formula-3a (100 gms) in N-methyl-2-pyrrolidone (400 ml) at 25-30°C and stirred for 4 hrs at the same temperature. Water (1000 ml) was added to the reaction mixture at 25-30°C and stirred for 45 mins at the same temperature. Ethyl acetate (500 ml) was added to the reaction mixture at 25-30°C and stirred for 30 mins. Separated the both aqueous and organic layers and the organic layer was washed with aqueous

hydrochloric acid solution (10 ml of HCl in 90 ml of water) followed by 5% aqueous sodium bicarbonate solution. Distilled off the solvent completely from the organic layer under reduced pressure. Toluene (500 ml) was added to the obtained compound, heated the reaction mixture to 60-65°C and stirred for 45 mins at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 90 mins at the same temperature. Filtered the precipitated solid, washed with toluene and dried to get the title compound.

Yield: 118 gms; Melting Range: 105-115°C; Purity by HPLC: 97.71%.

Example-12: Preparation of (R)-2-[[2'-(4-nitrophenyl)-ethyl]amino]-1-phenylethanol (Formula-5)

(R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide (90 gms) was added to a mixture of sodium borohydride (16.53 gms) and tetrahydrofuran (450 ml) at 25-30°C under nitrogen atmosphere and stirred for 15 mins at the same temperature. Cooled the reaction mixture to 0-5°C and BF₃-diethyl ether (123.4 gms) was slowly added to it at the same temperature. Raised the temperature of the reaction mixture to 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 6 hrs at the same temperature. Cooled the reaction mixture to a temperature below 40°C and further to 0-5°C. Quenched the reaction mixture with water followed by aqueous hydrochloric acid at 0-5°C. Heated the reaction mixture to 60-65°C and stirred for 5 hrs. Cooled the reaction mixture to 0-5°C and aqueous sodium carbonate solution (105.24 gms of sodium carbonate in 270 ml of water) was slowly added to it. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 mins. Ethyl acetate was added to the reaction mixture and stirred for 30 mins. Separated the both organic and aqueous layers, distilled off the solvent completely from the organic layer under reduced pressure and then co-distilled with toluene. Toluene (360 ml) was added to the obtained compound, heated to 70-75°C and stirred for 30 mins at the same temperature. Cooled the reaction mixture to 25-30°C and further to 0-5°C. Stirred the reaction mixture for 90 mins at 0-5°C. Filtered the precipitated solid, washed with toluene and then dried to get title compound.

Yield: 68 gms; Melting Range: 92-96°C; Purity by HPLC: 98.6%.

Example-13: Preparation of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol (Formula-6)

(R)-2-[[2'-(4-nitrophenyl)-ethyl]amino]-1-phenylethanol compound of formula-5 (220

gms), methanol (2200 ml) and Raney nickel (88 gms) were charged into an autoclave vessel. 4-5 kg/cm² hydrogen gas pressure was applied to the reaction mixture at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 16 hrs at the same temperature and pressure. Cooled the reaction mixture to 25-30°C and removed the hydrogen gas pressure under nitrogen atmosphere. Filtered the reaction mixture through hyflo bed, washed the bed with methanol and distilled off the solvent completely from the filtrate completely under reduced pressure. Cooled the obtained compound to a temperature below 40°C. Isopropanol (330 ml) was added to the obtained compound, heated the reaction mixture to 70-75°C and stirred for 45 mins. Cooled the reaction mixture to 25-30°C, further to 0-5°C and stirred for 90 mins at the same temperature. Filtered the precipitated solid, washed with isopropanol and dried to get title compound. Yield: 175 gm; Melting Range: 91-97°C; Purity by HPLC: 99.3%.

Example-14: Preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-[(2R)-2-hydroxy-2-phenylethyl] amino)ethyl]phenyl]acetamide (Formula-1)

A mixture of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol compound of formula-6 (150 gms), hydrochloric acid (79.15 ml), water (750 ml) was stirred for 15 min at 25-30°C. 2-aminothiazol-4-yl-acetic acid compound of formula-7 (102.5 gms) was added to the reaction mixture at 25-30°C and stirred for 15 mins at the same temperature. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (222.3 gms) was slowly added to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature. Cooled the reaction mixture to 0-5°C. pH of the reaction mixture was adjusted to 9.0 using aqueous sodium hydroxide solution (66.9 gms of sodium hydroxide dissolved in 1350 ml of water) at 0-5°C and stirred for 90 mins at 0-5°C. Filtered the precipitated solid and washed with water. Water (1200 ml) was added to the obtained solid at 25-30°C and stirred for 90 mins at the same temperature. Filtered the solid and washed with water. Methanol (1050 ml) was added to the wet solid, heated to 40-45°C and stirred for 15 min at the same temperature. Carbon (5 gms) was added to the reaction mixture and stirred for 45 min. Filtered the reaction mixture through hyflo bed washed with methanol. The solution of 2-(2-aminothiazol-4-yl)-N-[4-(2-[(2R)-2-hydroxy-2-phenyl ethyl]amino)ethyl]phenyl]acetamide compound of formula-1 (1.5 gms) in water (1950 ml) was added to the obtained filtrate at 25-30°C and stirred for 3 hrs at the same temperature. Filtered the precipitated solid, washed with water and dried to get title compound. Yield: 144 gms; Melting Range: 200-

210°C; Purity by HPLC: 99.85%; Water content: 3.4 % w/w.

The PXRD of the obtained compound is illustrated in figure-5.

Example-15: Preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl) amino)ethyl]phenyl]acetamide monohydrochloride (Formula-1a)

5 A mixture of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl) amino)ethyl] phenyl]acetamide compound of formula-1 (80 gms) and methanol (560 ml) was heated to 40-45°C and stirred for 15 mins at the same temperature. Cooled the reaction mixture to 25-30°C, IPA-HCl (24 ml) was added to it at 25-30°C and stirred for 3 hrs at the same temperature. Filtered the precipitated solid, washed with isopropanol and then dried to get title
10 compound. Yield: 70 gms; Purity by HPLC: 99.83 %.

Chloride content: 8.12% w/w; Water content: 0.27% w/w.

The PXRD of the obtained compound is illustrated in figure-4.

Example-16: Preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl) amino)ethyl]phenyl]acetamide (Formula-1)

15 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl]phenyl] acetamide can be prepared according to example-14 by using 2-aminothiazol-4-yl-acetic acid hydrochloride compound of formula-7a in place of 2-aminothiazol-4-yl-acetic acid compound of formula-7.

Example-17: Preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl) amino)ethyl]phenyl]acetamide (Formula-1)

20 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl]phenyl] acetamide monohydrochloride (50 gms) in water (50 ml) at 25-30°C was stirred for 5 minutes at 25-30°C. Basify the reaction mixture using aqueous sodium hydroxide (24 gms of Sodium hydroxide in 25 ml of water) solution at 25-30°C. Stirred the reaction mixture for 10 minutes at
25 25°C to 30°C. Filtered the precipitated solid, washed with water and dried to get the title compound.

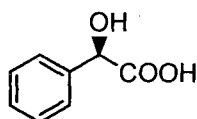
Yield: 43 gms

We Claim:

1. 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride.
2. The compound according to claim 1, wherein the monohydrochloride salt is in the form of anhydrate or hydrate or solvate thereof.
3. Crystalline form-M of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride, characterized by;
 - a) its powder X-ray diffraction pattern having peaks at about 2.1, 4.3, 6.4, 8.5, 17.4, 19.3, 21.6, 24.3, 24.8, 27.3, 31.6, 45.4 ± 0.2 degrees of 2-theta, and
 - b) its powder X-ray diffraction pattern substantially in accordance with figure-1.
4. Crystalline form-M according to claim 3, which is further characterized by its DSC thermogram having an endotherm at 201.03°C substantially in accordance with figure-2.
5. Crystalline form-M according to claim 3, is anhydrate form.
6. A process for the preparation of (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6 or its hydrochloride salt compound of formula-6a, comprising of reducing the (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5 or its hydrochloride salt compound of formula-5a with a suitable reducing agent in a suitable solvent to provide (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6 or its hydrochloride salt compound of formula-6a.
7. The process according to claim 6, wherein, the suitable reducing agent is selected from Fe, Fe in acidic media like NH_4Cl or HCl or acetic acid, Sn in acidic media like HCl , Zn dust, Zn in acidic media like HCl or NH_4Cl or acetic acid, stannous chloride (SnCl_2), NaBH_4 , LiAlH_4 , LiBH_4 , diborane, borane-THF complex, hydrazine hydrate and hydrogenation catalysts such as Nickel, Raney nickel, Rhodium, sodium amalgam, Pt/C , PtO_2 and $\text{Pd}(\text{OH})_2$.
8. The process according to claim 6, wherein, the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents or mixtures

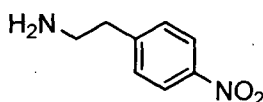
thereof.

9. A process for the preparation of (R)-2-(4-aminophenethylamino)-1-phenylethanol hydrochloride salt compound of formula-6a, comprising of reducing the (R)-2-(4-nitrophenethylamino)-1-phenylethanol hydrochloride salt compound of formula-5a with Fe in presence of acetic media such as HCl in a mixture of tetrahydrofuran and water to provide compound of formula-6a.
10. A process for the preparation of (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6, comprising of reducing the (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5 with Raney nickel in methanol to provide compound of formula-6.
11. A process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenyl ethyl)amino)ethyl]phenyl]acetamide monohydrochloride compound of formula-1a, comprising of;
 - a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2



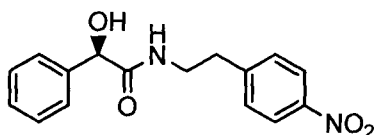
Formula-2

with 2-(4-nitrophenyl)ethanamine compound of formula-3



Formula-3

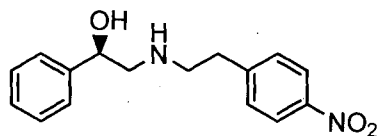
or its hydrochloride salt compound of formula-3a in presence of a suitable coupling agent in a suitable solvent, optionally in presence of a suitable base to provide (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide compound of formula-4,



Formula-4

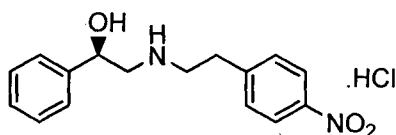
- b) reducing the compound of formula-4 with a suitable reducing agent in a suitable

solvent to provide (R)-2-(4-nitrophenethylamino)-1-phenylethanol of formula-5,



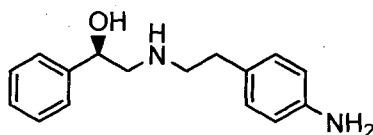
Formula-5

- c) optionally converting the compound of formula-5 into its hydrochloride salt compound of formula-5a,



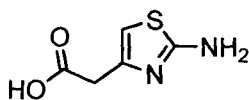
Formula-5a

- d) reducing the compound of formula-5 or its hydrochloride salt compound of formula-5a with a suitable reducing agent in a suitable solvent to provide (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6 or its hydrochloride salt compound of formula-6a,



Formula-6

- e) condensing the compound of formula-6 or its hydrochloride salt compound of formula-6a with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7



Formula-7

or its hydrochloride salt compound of formula-7a in presence of a suitable coupling agent and hydrochloric acid in a suitable solvent to provide dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl]phenyl]acetamide,

- f) treating the dihydrochloride salt obtained in step-(e) in-situ with a suitable aqueous base to provide 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl)amino)ethyl]phenyl]acetamide monohydrochloride salt compound of formula-1a.

12. The process according to claim 11, wherein,

in step-a) the suitable coupling agent is selected from N,N-carbonyldiimidazole (CDI); alkyl and aryl carbodiimides optionally in combination with hydroxybenzotriazole or N-hydroxysuccinimide (NHS) or N-hydroxysulfosuccinimide (Sulfo-NHS); carbonyl-di-1,2,4-triazole; alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate and benzyl chloroformate; and carbonates having the formula $R_1-O-CO-O-R_2$, wherein "R₁" and "R₂" are independently selected from branched or unbranched C₁-C₄ alkyl or substituted or unsubstituted phenyl group; the suitable base is selected from organic or inorganic bases; and the suitable solvent is selected from polar aprotic solvents, ketone solvents, ester solvents, chloro solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar solvents or mixtures thereof;

in step-b) the suitable reducing agent is selected from diborane, borane-dimethyl sulfide, borane-THF complex, sodium triacetoxyborohydride, sodium cyanoborohydride, NaBH₄, NaBH₄/BF₃-diethyl ether, LiBH₄ and LiAlH₄; and the suitable solvent is selected from alcoholic solvent, ether solvents, ester solvents, hydrocarbon solvents, polar solvents, polar aprotic solvents or mixtures thereof;

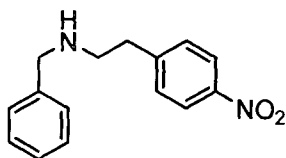
in step-d) the suitable reducing agent is selected from Fe, Fe in acidic media like NH₄Cl or HCl or acetic acid, Sn in acidic media like HCl, Zn dust, Zn in acidic media like HCl or NH₄Cl or acetic acid, stannous chloride (SnCl₂), NaBH₄, LiAlH₄, LiBH₄, diborane, borane-THF complex, hydrazine hydrate and hydrogenation catalysts such as Pd/C, Pt/C, PtO₂, Pd(OH)₂, Nickel, Raney nickel, Rhodium and sodium amalgam; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents or mixtures thereof;

in step-e) the suitable coupling agent & suitable solvent are same as defined in step-a); and

in step-f) the suitable base is selected from hydroxides, carbonates and bicarbonates of alkali metals.

13. A process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-[(2R)-2-hydroxy-2-phenyl ethyl]amino)ethyl]phenyl]acetamide monohydrochloride compound of formula-1a, comprising of;

- a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2 with 2-(4-nitrophenyl)ethanamine hydrochloride salt compound of formula-3a in presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl)/1-hydroxy benzotriazole (HOBt) and triethylamine in N,N-dimethylformamide to provide (R)-2-hydroxy-N-(4-nitro phenethyl)-2-phenylacetamide compound of formula-4,
- b) reducing the compound of formula-4 with borane-dimethyl sulfide in tetrahydrofuran to provide (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5,
- c) converting the compound of formula-5 into its hydrochloride salt compound of formula-5a by treating it with hydrochloric acid in isopropanol,
- c) reducing the compound of formula-5a with Fe-HCl in a mixture of tetrahydrofuran and water to provide (R)-2-(4-aminophenethyl amino)-1-phenylethanol hydrochloride salt compound of formula-6a,
- d) condensing the compound of formula-6a with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 in presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) and hydrochloric acid in water to provide dihydrochloride salt of 2-(2-aminothiazol-4-yl)-N-[4-(2-[(2R)-2-hydroxy-2-phenylethyl]amino)ethyl]phenyl] acetamide,
- e) treating the dihydrochloride salt obtained in step-(e) in-situ with aqueous sodium hydroxide solution to provide 2-(2-aminothiazol-4-yl)-N-[4-(2-[(2R)-2-hydroxy-2-phenylethyl] amino)ethyl]phenyl]acetamide monohydrochloride compound of formula-1a.
14. A process for preparation of N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8,



Formula-8

comprising of reductive amination of benzaldehyde with 2-(4-nitrophenyl)ethanamine compound of formula-3 in presence of a suitable reducing agent in a suitable solvent to

provide N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8.

15. The process according to claim 14, wherein, the suitable reducing agent is selected from sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, trihalosilanes, diisobutylaluminium hydride (DIBAL), lithium triethylborohydride, lithium tri-sec-butyl borohydride (L-selectride), trialkylsilanes optionally in combination with trifluoroacetic acid; and hydrogenating agents such as Pd/C, Pt/C, Ni and Raney Ni.
16. The process according to claim 14, wherein, the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents, polar-aprotic solvents or mixtures thereof.
17. A process for the preparation of N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8, comprising of reductive amination of benzaldehyde with 2-(4-nitrophenyl)ethanamine compound of formula-3 in presence of sodium borohydride in methanol to provide N-benzyl-2-(4-nitrophenyl)ethanamine compound of formula-8.
18. A process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenyl ethyl)amino)ethyl]phenyl]acetamide compound of formula-1, comprising of:
- a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2 with 2-(4-nitro phenyl)ethanamine compound of formula-3 or its hydrochloride salt compound of formula-3a in presence of a suitable coupling agent in a suitable solvent, optionally in presence of a suitable base to provide (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide compound of formula-4,
 - b) reducing the compound of formula-4 with a suitable reducing agent in a suitable solvent, optionally purifying the obtained compound using a suitable solvent to provide (R)-2-(4-nitrophenethylamino)-1-phenylethanol compound of formula-5,
 - c) reducing the compound of formula-5 with a suitable reducing agent in a suitable solvent, optionally purifying the obtained compound using a suitable solvent to provide (R)-2-(4-aminophenethylamino)-1-phenylethanol compound of formula-6,
 - d) condensing the compound of formula-6 with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 or its hydrochloride salt compound of formula-7a in presence of a suitable coupling agent and hydrochloric acid in a suitable solvent to provide 2-

(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino} ethyl)phenyl] acetamide compound of formula-1,

- e) optionally purifying the compound obtained in step-(d) by dissolving the compound in a suitable solvent, followed by adding an anti-solvent to provide pure compound of formula-1.

19. The process according to claim 18, wherein:

in step-a) the suitable coupling agent is selected from N,N-carbonyldiimidazole (CDI); alkyl and aryl carbodiimides optionally in combination with hydroxybenzotriazole or N-hydroxysuccinimide (NHS) or N-hydroxysulfosuccinimide (Sulfo-NHS); carbonyl-di-1,2,4-triazole; alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate and benzyl chloroformate; and carbonates having the formula $R_1-O-CO-O-R_2$, wherein "R₁" and "R₂" are independently selected from branched or unbranched C₁-C₄ alkyl or substituted or unsubstituted phenyl group; the suitable base is selected from organic or inorganic bases; and the suitable solvent is selected from polar aprotic solvents, ketone solvents, ester solvents, chloro solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar solvents or mixtures thereof;

in step-b) the suitable reducing agent is selected from diborane, borane-dimethyl sulfide, borane-THF complex, sodium triacetoxyborohydride, sodium cyanoborohydride, NaBH₄, NaBH₄/BF₃-diethyl ether, LiBH₄ and LiAlH₄; and the suitable solvent is selected from alcoholic solvent, ether solvents, ester solvents, hydrocarbon solvents, polar solvents, polar aprotic solvents or mixtures thereof;

in step-c) the suitable reducing agent is selected from Fe, Fe in acidic media like NH₄Cl or HCl or acetic acid, Sn in acidic media like HCl, Zn dust, Zn in acidic media like HCl or NH₄Cl or acetic acid, stannous chloride (SnCl₂), NaBH₄, LiAlH₄, LiBH₄, diborane, borane-THF complex, hydrazine hydrate and hydrogenation catalysts such as Pd/C, Pt/C, PtO₂, Pd(OH)₂, Nickel, Raney nickel, Rhodium and sodium amalgam; the suitable solvent is selected from alcoholic solvents, ether solvents, ester solvents, polar solvents, hydrocarbon solvents or mixtures thereof;

in step-d) the suitable coupling agent and suitable solvent are same as defined in step-(a); and

in step-e) the suitable solvent is alcoholic solvent; and the anti-solvent is polar solvent.

20. A process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide compound of formula-1, comprising of:

- a) Condensing the (R)-2-hydroxy-2-phenylacetic acid compound of formula-2 with 2-(4-nitro phenyl)ethanamine hydrochloride salt compound of formula-3a in presence of 1-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride (EDC.HCl)/1-hydroxybenzotriazole (HOBt) and triethylamine in N-methyl-2-pyrrolidone to provide (R)-2-hydroxy-N-(4-nitrophenethyl)-2-phenylacetamide compound of formula-4,
- b) reducing the compound of formula-4 with sodium borohydride in presence of BF₃-diethyl ether in tetrahydrofuran, purifying the obtained compound using toluene to provide (R)-2-(4-nitro phenethylamino)-1-phenylethanol compound of formula-5,
- c) reducing the compound of formula-5 with Raney-nickel in methanol under hydrogen pressure, purifying the obtained compound using isopropanol to provide (R)-2-(4-aminophenethyl amino)-1-phenylethanol compound of formula-6,
- d) condensing the compound of formula-6 with 2-(2-aminothiazol-4-yl)acetic acid compound of formula-7 in presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) and hydrochloric acid in water to provide 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide compound of formula-1,
- e) purifying the compound obtained in step-(d) by dissolving the compound in methanol followed by adding water to provide pure compound of formula-1.

21. A pharmaceutical composition comprising 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride according to claim-1 and at least one pharmaceutically acceptable excipient.

22. Use of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride for the preparation of pharmaceutical composition.

23. Use of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide monohydrochloride compound of formula-1a for the preparation of

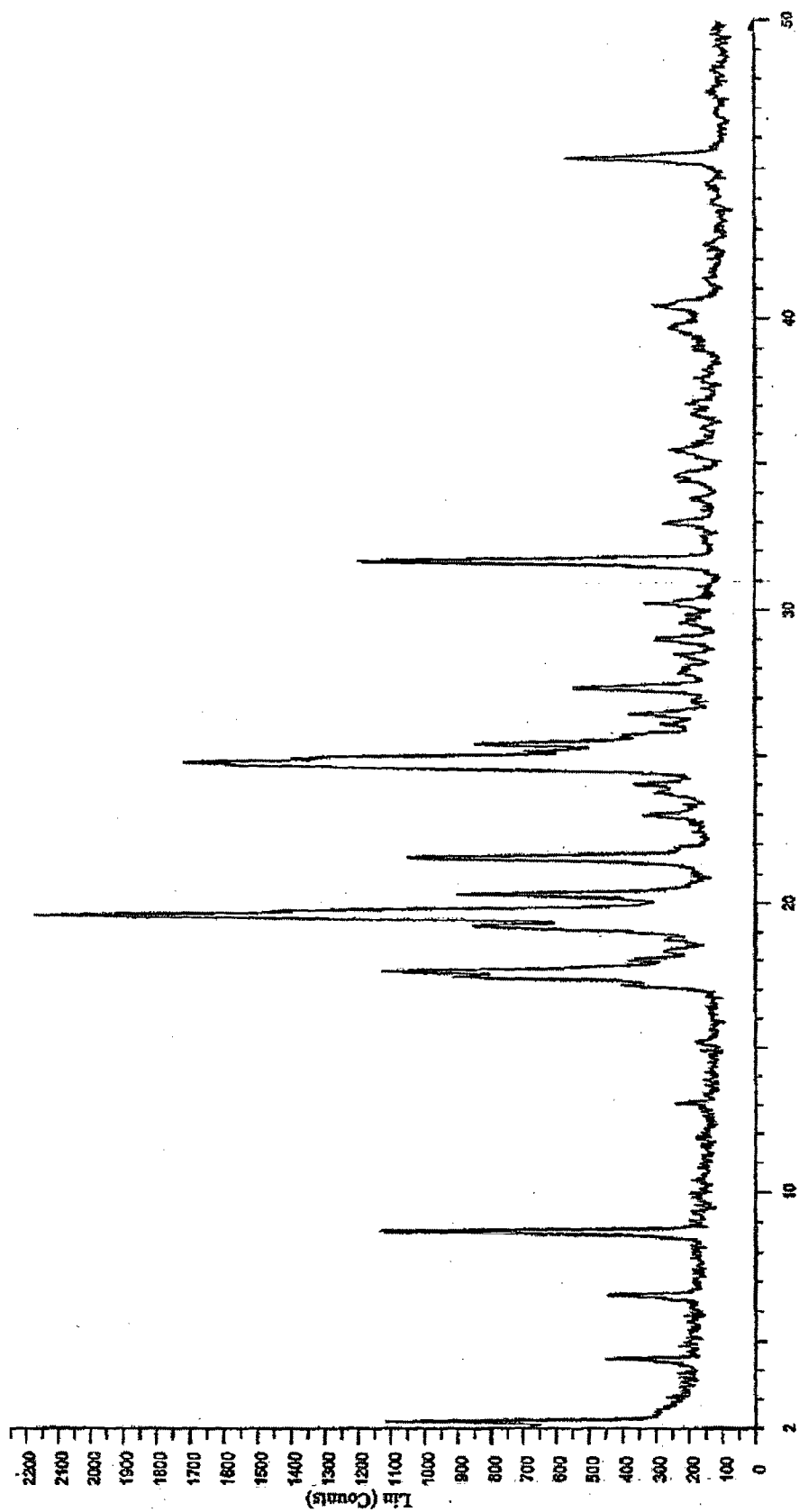
compound of formula-1.

24. A process for the preparation of 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl} amino}ethyl) phenyl]acetamide compound of formula-1 comprising of,
5 treating the compound of formula-1a with a suitable base in a suitable solvent provides compound of formula-1.

25. The process according to claim-24, wherein the suitable base is selected from hydroxides, carbonates and bicarbonates of alkali metals.

26. 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl] acetamide is having purity greater than 99% by HPLC, preferably greater than 99.5% by HPLC, more preferably greater than 99.8% by HPLC.

27. 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl] acetamide monohydrochloride is having purity greater than 99% by HPLC, preferably greater than 99.5% by HPLC, more preferably greater than 99.8% by HPLC.



2-Theta - Scale

Figure-1

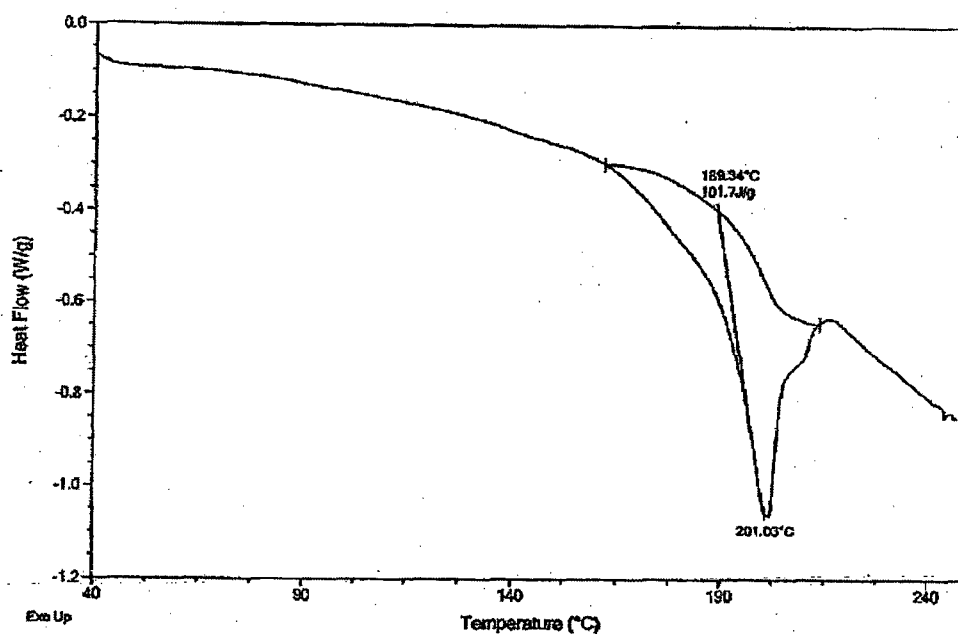


Figure-2

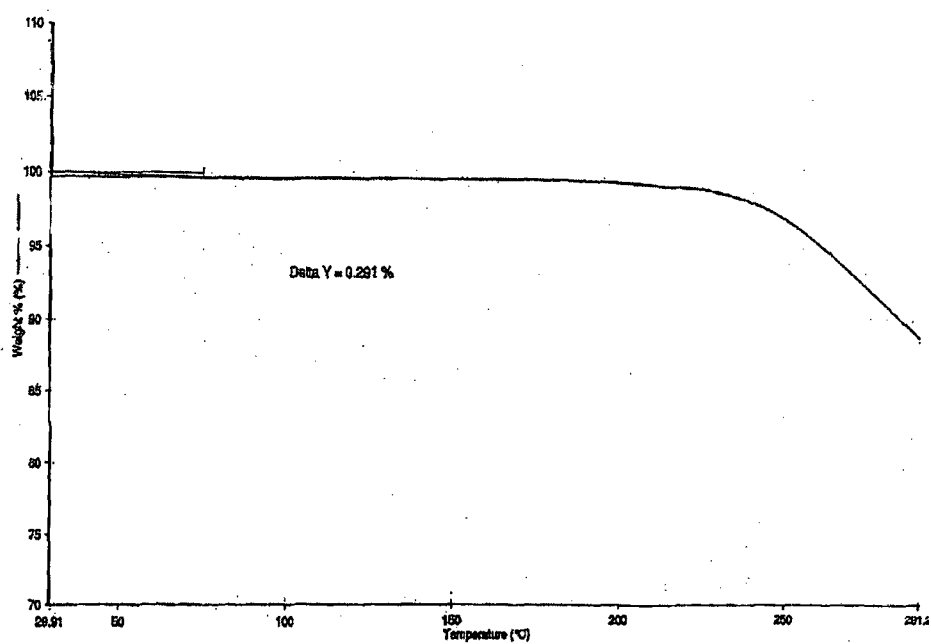
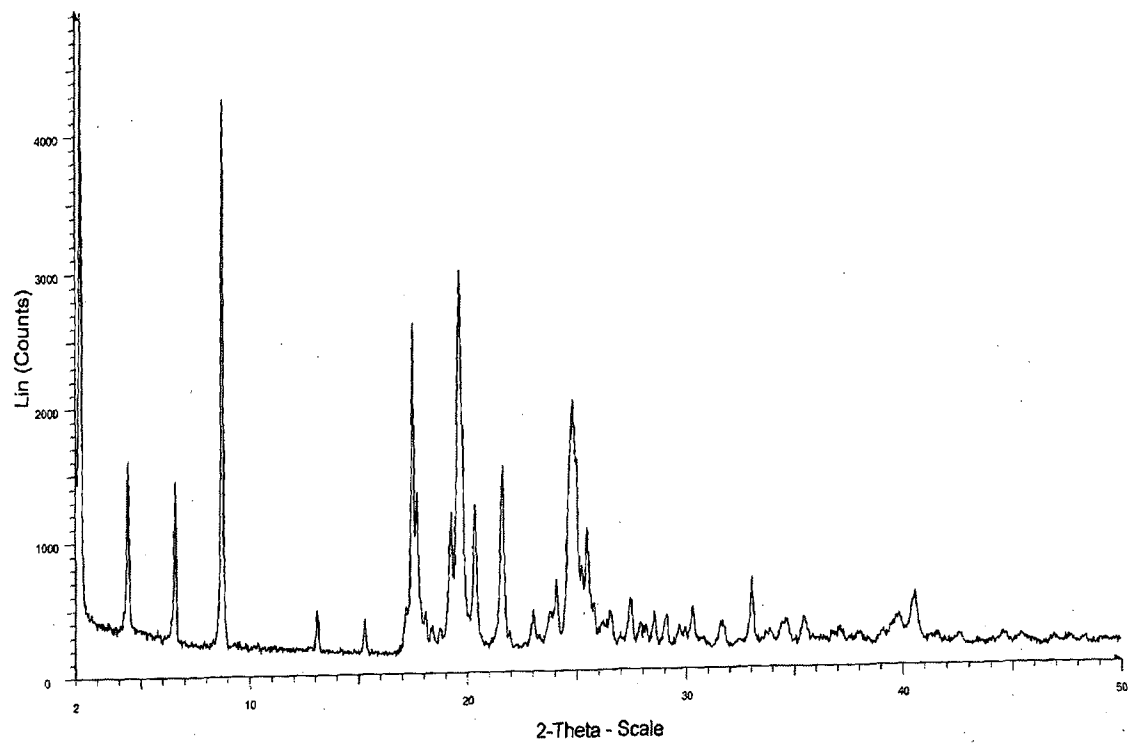
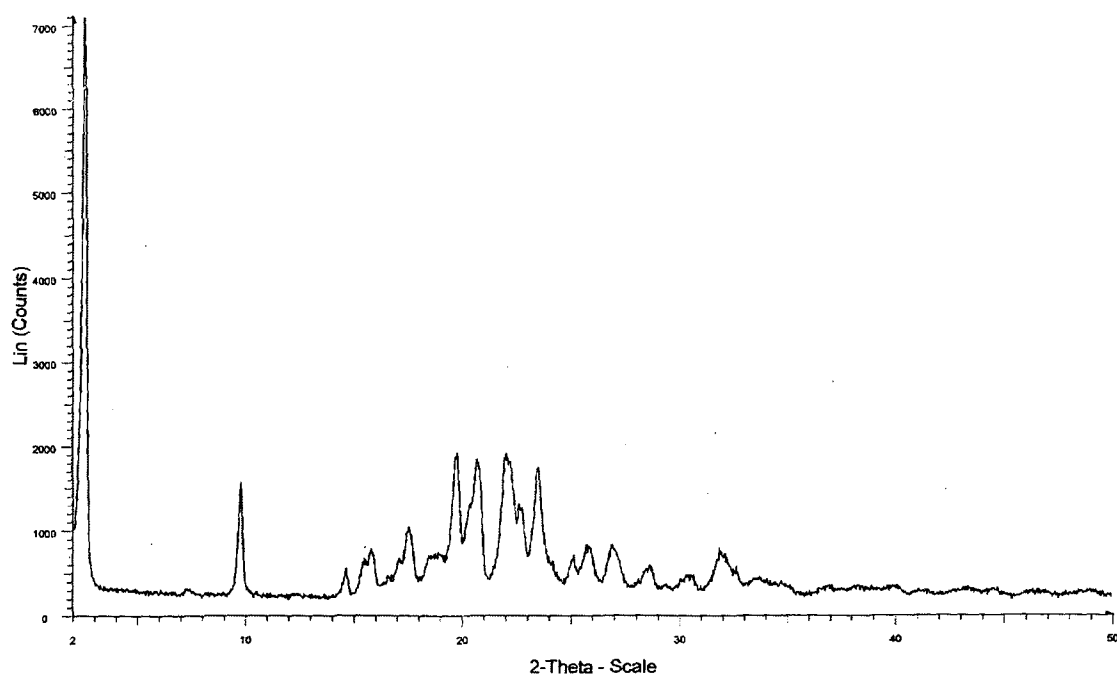


Figure-3

**Figure-4****Figure-5**