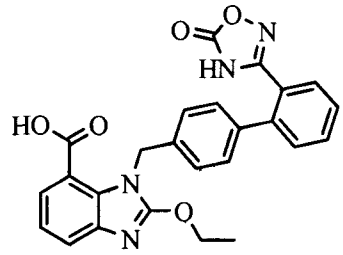
Abstract

The present invention relates to an improved process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, its derivatives and their pharmaceutically acceptable salts thereof.



Formula-2

We Claim:

1. A process for the preparation of methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10, comprising of deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 by treating it with a suitable deprotecting agent selected from methanesulfonic acid, p-toluene sulfonic acid, acetyl chloride, tri(C_1-C_6 alkyl)silyl halides in a suitable solvent selected from ketone solvents, chloro solvents, alcoholic solvents, ester solvents, polar solvents, ether solvents or mixtures thereof to provide methyl 2-((2'-cyanobiphenyl-4-yl) methylamino)-3-nitrobenzoate compound of formula-10, wherein the deprotecting agent is used in an amount of 2.0-4.0 mole ratio per one mole of compound of formula-9.

2. A process for the preparation of methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10, comprising of deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 with methanesulfonic acid in dichloromethane to provide methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10.

3. A process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, comprising of reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl) methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with a suitable cyclization agent in presence of a suitable organic or inorganic base in a suitable solvent to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2,

wherein the suitable cyclization agent is selected from N,N-carbonyldiimidazole (CDI), alkyl and aryl carbodiimides such as N,N-diisopropylcarbodiimide (DIC), N,N-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), ditolyl carbodiimide, carbonyl-di-1,2,4-triazole, alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate, benzyl chloroformate, dialkyl, diaryl and alkyl aryl carbonates of the formula R_1-O-CO-O-R_2, wherein "R_1" and "R_2" are independently selected from branched or unbranched C_1-C_4 alkyl or substituted or

unsubstituted phenyl group; and the suitable solvent is selected from chloro solvents, ether solvents, alcoholic solvents, polar solvents or mixtures thereof.

4. A process according to claim 3, wherein the cyclization agent is used in an amount of 1.0-2.5 mole ratio and the base is used in an amount of 1.0-2.5 mole ratio per one mole of compound of formula-13.

5. A process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, comprising of reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl) methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with N,N-carbonyldiimidazole (CDI) in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2.

6. A process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, comprising of;
   a) Treating the methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12 with hydroxylamine hydrochloride in presence of alkali metal carbonate in a suitable solvent selected from polar solvents, polar-aprotic solvents, alcoholic solvents or mixtures thereof to provide 2-ethoxy-1-((2'-(N'-hydroxy carbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13,
   b) reacting the compound of formula-13 with a suitable cyclization agent, in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid of formula-2.

7. A process for the preparation of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl) methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 having less than 5% of acid amide impurity, comprising of treating the methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12 with hydroxylamine

hydrochloride in presence of sodium carbonate in a solvent system comprising of mixture of dimethylsulfoxide and water in the ratio of 1:0.5-1 respectively.

8. A process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 and its potassium salt of formula-1a, comprising of;
   a) Deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 with methanesulfonic acid in a suitable solvent selected from ketone solvents, chloro solvents, alcoholic solvents, ester solvents, polar solvents, ether solvents or mixtures thereof to provide methyl 2-((2'-cyanobiphenyl-4-yl) methylamino)-3-nitrobenzoate compound of formula-10,
   b) reducing the compound of formula-10 with a suitable reducing agent selected from Raney Ni, Pd/C, Pt/C, PtO_2, Fe, Fe in acidic media like HCl, acetic acid, NH_4Cl, Sn-HCl, stannous chloride ($SnCl_2$), Zn in acidic media like HCl, acetic acid, NH_4Cl, Zinc dust, $NaBH_4$, $LiAlH_4$, diborane, hydrazine hydrate, borane-tetrahydrofuran in a suitable solvent selected from ester solvents, ether solvents, hydrocarbon solvents, alcoholic solvents, polar solvents or mixtures thereof to provide methyl 3-amino-2-((2'-cyanobiphenyl-4-yl)methylamino)benzoate of formula-11,
   c) reacting the compound of formula-11 with tetraethyl orthocarbonate in a suitable solvent to provide methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12,
   d) treating the compound of formula-12 with hydroxylamine hydrochloride in presence of alkali metal carbonate in a suitable solvent selected from polar-aprotic solvents, polar solvents, alcoholic solvents or mixtures thereof to provide 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13,
   e) reacting the compound of formula-13 with a suitable cyclization agent in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid of formula-2,
   f) condensing the compound of formula-2 with 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one in presence of a suitable organic or inorganic base optionally in presence of a suitable

phase transfer catalyst in a suitable solvent to provide (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl] methyl}-1H-benzimidazole-7-carboxylate compound of formula-1,

g) optionally converting the compound of formula-1 into its potassium salt compound of formula-1a by treating it with a suitable potassium source selected from potassium 2-ethyl hexanoate, potassium tert.butoxide in a suitable solvent selected from ketone solvents, ester solvents or mixtures thereof.

9. A process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 and its potassium salt compound of formula-1a, comprising of;

a) Deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 by treating it with methanesulfonic acid in dichloromethane to provide methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10,

b) reducing the compound of formula-10 with Raney Ni in ethyl acetate to provide methyl 3-amino-2-((2'-cyanobiphenyl-4-yl)methylamino)benzoate compound of formula-11,

c) reacting the compound of formula-11 with tetraethyl orthocarbonate in acetic acid to provide methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12,

d) treating the compound of formula-12 with hydroxylamine hydrochloride in presence of sodium carbonate in a mixture of dimethyl sulfoxide and water to provide 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13,

e) reacting the compound of formula-13 with N,N-carbonyl diimidazole (CDI) in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2,

f) condensing the compound of formula-2 with 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one in presence of sodium bicarbonate and tetrabutyl ammonium bromide in acetone to

provide (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1,

g) treating the compound of formula-1 with potassium 2-ethyl hexanoate in a mixture of acetone and ethyl acetate to provide its potassium salt compound of formula-1a.

10. A process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate potassium salt compound of formula-1a, comprising of;

a) Reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with N,N-carbonyl diimidazole (CDI) in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2,

b) condensing the compound of formula-2 with 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one in presence of p-toluenesulfonyl chloride, potassium carbonate, 4-dimethylamino pyridine in methyl isobutyl ketone optionally in mixture with ethyl acetate to provide compound of formula-1,

c) treating the compound of formula-1 with potassium 2-ethyl hexanoate in a mixture of acetone and ethyl acetate to provide its potassium salt compound of formula-1a.

Dated this day 02nd of March 2013.

Authorized Signatory
(Srinivasan Thirumalai Rajan)
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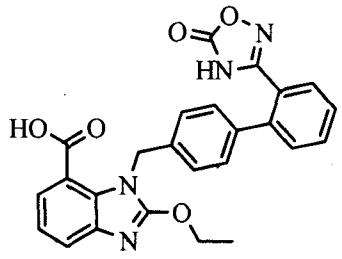
Field of the invention:

The present invention provides an improved process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, its derivatives and their pharmaceutically acceptable salts thereof.



Formula-2

Background of the invention:

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (commonly known as Azilsartan medoxomil) is developed by Takeda pharmaceuticals and is marketed under the trade name Edarbi. It was approved by USFDA on 25th Feb 2011 and EMEA on 7th Dec 2011 for the treatment of high blood pressure in adults.

US5243054A patent disclosed the benzimidazole derivatives which are used as angiotensin-II receptor antagonists and process for their preparation. Azilsartan medoxomil, its pharmaceutically acceptable salts and processes for their preparation is specifically disclosed in US7157584B2.

Brief description of the invention:

The first aspect of the present invention is to provide a process for the preparation of methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10, comprising of deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl) amino)-3-nitrobenzoate compound of formula-9 with methanesulfonic acid in a suitable solvent to provide methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10.

The second aspect of the present invention is to provide a process for the preparation of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13, comprising of treating the methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12 with hydroxylamine hydrochloride in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13.

The third aspect of the present invention is to provide a process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, comprising of reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with a suitable cyclization agent in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2.

The fourth aspect of the present invention is to provide a process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 and its potassium salt compound of formula-1a.

The fifth aspect of the present invention is to provide a process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 and its potassium salt compound of formula-1a.

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, cycloheptane, pet ether, benzene, 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, iso-butyl 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 (MIBK) 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; 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, dipotassium hydrogen phosphate and organic bases like methyl amine, diisopropyl amine, diisopropylethyl amine, diisobutylamine, triethylamine, tert.butyl amine, pyridine, 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1-methyl morpholine, imidazole or mixtures thereof.

The "suitable cyclization agent" used in the present invention can be selected from but not limited to N,N-carbonyldiimidazole (CDI), alkyl and aryl carbodiimides such as N,N-diisopropylcarbodiimide (DIC), N,N-dicyclohexyl carbodiimide (DCC), 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide hydrochloride (EDC.HCl), ditolyl carbodiimide, carbonyl-di-1,2,4-

triazole, alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate, benzyl chloroformate, dialkyl, diaryl and alkyl aryl carbonates of the formula R_1-O-CO-O-R_2, wherein "R_1" and "R_2" are independently selected from branched or unbranched C_1-C_4 alkyl or substituted or unsubstituted phenyl group.

The first aspect of the present invention provides a process for the preparation of methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10, comprising of deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 by treating it with methanesulfonic acid in a suitable solvent to provide methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10.

Wherein, the suitable solvent can be selected from ketone solvents, chloro solvents, alcoholic solvents, ester solvents, polar solvents, ether solvents or mixtures thereof.

The said deprotection is carried out using 2.0-5.0 mole ratio, preferably 3.0-4.0 mole ratio of methanesulfonic acid per one mole of compound of formula-9 and the reaction is carried out at room temperature to boiling point of the solvent, preferably at 25-30°C.

p-Toluene sulfonic acid, acetyl chloride, tri(C_1-C_6 alkyl)silyl halides can also be used for the deprotection of methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9.

A preferred embodiment of the present invention provides a process for the preparation of methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10, comprising of deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl) amino)-3-nitrobenzoate compound of formula-9 by treating it with methanesulfonic acid in dichloromethane to provide methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10.

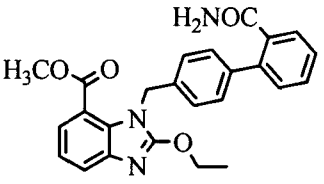
The second aspect of the present invention provides a process for the preparation of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13, comprising of treating the methyl 1-((2'-cyanobiphenyl-4-

yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12 with hydroxylamine hydrochloride in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13.

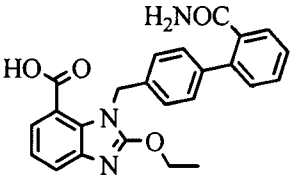
Wherein, the suitable base is selected from alkali metal carbonates and the suitable solvent is selected from polar-aprotic solvents, polar solvents, alcoholic solvents or mixtures thereof; preferably a mixture of polar and polar-aprotic solvents.

US5243054A patent disclosed the conversion of cyanobiphenyl compound of formula-12 to the corresponding amidoxime by treating it with hydroxylamine hydrochloride in presence of sodium methoxide as a base. *J. Med. Chem. 1996, 39, 5228-5235* also discloses this step using triethylamine as a base.

When we repeated the same processes in our laboratory, we observed the formation of ester amide impurity at a level of about 30-40% along with the desired methyl 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylate(amidoxime methyl ester) product. When the amidoxime acid compound of formula-13 is prepared by hydrolyzing the obtained amidoxime methyl ester compound, we are ended up with compound of formula-13 having 30-40% of acid amide impurity.



Ester amide impurity



Acid amide impurity

Formation of impurities in such levels greatly impacts the yield, purity and cost of the desired product as well as final Azilsartan medoxomil potassium compound of formula-1a. In order to remove these impurities, additional purification steps need to be performed which further reduces the yield and increases the cost of the desired product.

The present inventors utilized different bases and solvents for the said step, and surprisingly found that the usage of alkali metal carbonate as a base in a solvent system comprising of mixture of polar and polar-aprotic solvents considerably suppresses the formation of said impurities and providing the desired product in high yield with high purity.

The reaction is carried out by employing each of hydroxylamine hydrochloride and alkali metal carbonate in 6.0-9.0 mole ratio, preferably in 7.0-8.0 mole ratio per one mole of cyanobiphenyl compound of formula-12, and the solvent system comprises of dimethylsulfoxide and water in the ratio of 1:0.5-1 respectively.

A preferred embodiment of the present invention provides a process for the preparation of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13, comprising of reacting the methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12 with hydroxylamine hydrochloride in presence of sodium carbonate in a mixture of dimethyl sulfoxide and water to provide 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13.

The third aspect of the present invention provides a process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, comprising of reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with a suitable cyclization agent in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2.

Wherein, the suitable cyclization 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, carbonyl-di-1,2,4-triazole, alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate, benzyl chloroformate, dialkyl, diaryl and alkyl aryl carbonates of the formula R_1-O-CO-O-R_2, wherein "R_1" and "R_2" are independently selected from branched or unbranched C_1-C_4 alkyl or substituted or unsubstituted phenyl group; and

The suitable base is selected from organic and inorganic bases; the suitable solvent is selected from chloro solvents, ether solvents, ester solvents, alcoholic solvents, polar solvents or mixtures thereof.

The said cyclization step is carried out by employing 1.0-3.0 mole ratio, preferably 1.5-2.5 mole ratio of the cyclization agent and 1.0-3.0 mole ratio, preferably 1.5-2.0 mole ratio of the

base per one mole of compound of formula-13, and the reaction is carried out at a temperature of room temperature to boiling point of the solvent, preferably at 25-30°C.

A preferred embodiment of the present invention provides a process for the preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2, comprising of reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with N,N-carbonyldiimidazole (CDI) in presence of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) in dichloromethane to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2.

The fourth aspect of the present invention provides a process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 and its potassium salt compound of formula-1a, comprising of;

a) Deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 by treating it with a suitable deprotecting agent in a suitable solvent to provide methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10,
b) reducing the compound of formula-10 with a suitable reducing agent in a suitable solvent to provide methyl 3-amino-2-((2'-cyanobiphenyl-4-yl)methylamino)benzoate of formula-11,
c) reacting the compound of formula-11 with tetraethyl orthocarbonate in a suitable solvent to provide methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12,
d) treating the compound of formula-12 with hydroxylamine hydrochloride in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl) biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13,
e) reacting the compound of formula-13 with a suitable cyclization agent in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid of formula-2,
f) condensing the compound of formula-2 with 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one in

presence of a suitable base optionally in presence of a suitable phase transfer catalyst in a suitable solvent to provide (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1,

g) optionally converting the compound of formula-1 into its potassium salt compound of formula-1a by treating it with a suitable potassium source in a suitable solvent.

Wherein, in step-a) the suitable deprotecting agent is selected from hydrochloric acid, trifluoroacetic acid, methanesulfonic acid, p-toluene sulfonic acid, acetyl chloride in combination with alcohol, tri(C_1-C_6 alkyl)silyl halides and the like; the suitable solvent is selected from ketone solvents, chloro solvents, alcoholic solvents, ester solvents, polar solvents, ether solvents or mixtures thereof;

In step-b) the suitable reducing agent is selected from Ni, Raney Ni, Pd/C, Pt/C, PtO_2, Fe, Fe in acidic media like HCl, acetic acid, NH_4Cl, Sn-HCl, stannous chloride ($SnCl_2$), Zn in acidic media like HCl, acetic acid, NH_4Cl, Zinc dust, sodium borohydride, lithium borohydride, lithium aluminium hydride, sodium aluminium hydride, diborane, hydrazine hydrate, sodium dithionate, sodium sulfide, ammonium sulfide, Na-Hg/H_2, borane-tetrahydrofuran and the like; the suitable solvent is selected from ester solvents, ether solvents, hydrocarbon solvents, alcoholic solvents, polar solvents or mixtures thereof;

In step-c) the suitable solvent is acetic acid;

In step-d) the suitable base is selected from carbonates and bicarbonates of alkali metals, preferably alkali metal carbonates; and the suitable solvent is selected from polar-aprotic solvents, polar solvents, alcoholic solvents or mixtures thereof; preferably a mixture of polar and polar-aprotic solvents;

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

In step-f) the suitable base is selected from inorganic bases and organic bases; the suitable phase transfer catalyst is selected from tetra alkyl ammonium halide, tetra aryl ammonium halide, $(alkyl)_m(aryl)_{4-m}$ ammonium halide, tetra alkyl ammonium hydroxide, tetra aryl ammonium hydroxide, $(alkyl)_m(aryl)_{4-m}$ ammonium hydroxide, wherein, the alkyl groups can be

same or different in tetra alkyl ammonium halide/hydroxide, $(alkyl)_m(aryl)_{4-m}$ ammonium halide/hydroxide; the aryl groups can be same or different in tetra aryl ammonium halide/hydroxide, $(alkyl)_m(aryl)_{4-m}$ ammonium halide/ hydroxide, wherein 'm' is between 1and 3; and alkyl represents C_1-C_8 straight chain or branched chain alkyl, aryl represents substituted or unsubstituted C_6-C_{10} aryl; halide represents chloride, bromide or iodide; hexadecyl tributyl phosphonium bromide, preferably tetrabutyl ammonium bromide; and the suitable solvent is selected from ketone solvents, polar-aprotic solvents, chloro solvents, ester solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar solvents or mixtures thereof;

In step-g) the suitable potassium source is selected from potassium 2-ethyl hexanoate, potassium tert.butoxide, potassium hydroxide and the like; and the suitable solvent is selected from ketone solvents, ester solvents or mixtures thereof.

A preferred embodiment of the present invention provides a process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1and its potassium salt compound of formula-1a, comprising of;

a) Deprotecting the methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 by treating it with methanesulfonic acid in dichloromethane to provide methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10,
b) reducing the compound of formula-10 with Raney Ni in ethyl acetate to provide methyl 3-amino-2-((2'-cyanobiphenyl-4-yl)methylamino)benzoate compound of formula-11,
c) reacting the compound of formula-11 with tetraethyl orthocarbonate in acetic acid to provide methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12,
d) treating the compound of formula-12 with hydroxylamine hydrochloride in presence of sodium carbonate in a mixture of dimethyl sulfoxide and water to provide 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13,
e) reacting the compound of formula-13 with N,N-carbonyldiimidazole (CDI) in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to provide 2-ethoxy-1-{[2'-

(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2,

f) condensing the compound of formula-2 with 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one in presence of sodium bicarbonate and tetrabutyl ammonium bromide in acetone to provide (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1,

g) treating the compound of formula-1 with potassium 2-ethyl hexanoate in a mixture of acetone and ethyl acetate to provide its potassium salt compound of formula-1a.

The methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 utilized in step-a) of the fourth aspect can be synthesized by the following process;

a) Esterification of 3-nitro phthalic acid compound of formula-3 with methanol in presence of sulfuric acid or thionyl chloride to provide 2-(methoxycarbonyl)-6-nitro benzoic acid compound of formula-4,

b) converting the compound of formula-4 into methyl 2-(chlorocarbonyl)-3-nitrobenzoate compound of formula-5 by treating it with thionyl chloride in a mixture of dichloromethane and catalytic amount of N,N-dimethyl formamide,

c) treating the compound of formula-5 in-situ with sodium azide in N,N-dimethyl formamide to provide methyl 2-(azidocarbonyl)-3-nitrobenzoate compound of formula-6,

d) treating the compound of formula-6 in-situ with tert.butanol to provide methyl 2-(tert-butoxycarbonylamino)-3-nitrobenzoate compound of formula-7,

e) condensing the compound of formula-7 with 4'-(bromomethyl)biphenyl-2-carbonitrile compound of formula-8 in presence of potassium carbonate and tetra butyl ammonium bromide in acetone to provide methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl) methyl)amino)-3-nitrobenzoate compound of formula-9.

The 3-nitro phthalic acid compound of formula-3 used in step-a) of the above process can be synthesized by any of the processes known in the art such as *Journal of the American Chemical Society,* 1925, 47(7), 1980-1981; *Journal of the chemical society*, 1914, 105, 2476; *Organic Syntheses*, Coll.Vol. 1, p.408 (1941); Vol. 7, p.70 (1927) etc.

The fifth aspect of the present invention provides a process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 and its potassium salt compound of formula-1a, comprising of;

a) Reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with a suitable cyclization agent in presence of a suitable base in a suitable solvent to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2,

b) condensing the compound of formula-2 with 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one in presence of a suitable catalyst or a suitable condensing agent and a suitable base optionally in presence of a suitable phase transfer catalyst in a suitable solvent to provide (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1,

c) optionally treating the compound of formula-1 with a suitable potassium source in a suitable solvent to provide its potassium salt compound of formula-1a.

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

In step-b) the suitable catalyst is selected from p-toluene sulfonyl chloride, benzene sulfonyl chloride, methanesulfonyl chloride, ethane sulfonyl chloride, thionyl chloride, oxalyl chloride, acylating agents represented by the formula R-CO-X, wherein "R" represents C_1-C_6 straight chain or branched chain alkyl group, such as methyl, ethyl, propyl, tert-butyl and the like, a C_1-C_6 alkoxy group such as methoxy, ethoxy, propoxy, isobutyloxy and the like; substituted or unsubstituted phenyl group; "X" represents halogens such as Cl, Br & I;

The suitable condensing 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, carbonyl-di-1,2,4-triazole, alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate, benzyl chloroformate, dialkyl, diaryl and alkyl aryl carbonates of the formula R_1-O-CO-O-R_2, wherein "R_1" and "R_2" are independently selected

from branched or unbranched C_1-C_4 alkyl or substituted or unsubstituted phenyl group;

The suitable phase transfer catalyst, the suitable base and the suitable solvent are same as defined in step-f) of the fourth aspect of the present invention;

In step-c) the suitable potassium source and the suitable solvent are same as defined in step-g) of the fourth aspect of the present invention.

A preferred embodiment of the present invention provides a process for the preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 and its potassium salt compound of formula-1a, comprising of;

a) Reacting the 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 with N,N-carbonyldiimidazole in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane to provide 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2,

b) condensing the compound of formula-2 with 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one in presence of p-toluenesulfonyl chloride, 4-dimethylamino pyridine and potassium carbonate in acetone to provide (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1,

c) optionally treating the compound of formula-1 with potassium 2-ethyl hexanoate in a mixture of acetone and ethyl acetate to provide its potassium salt compound of formula-1a.

2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 was analyzed by HPLC under the following conditions; Apparatus: A liquid chromatographic system equipped with variable wavelength UV-detector and integrator; Column: Kromasil 100-5C18 250×4.6mm, 5µm or equivalent; Flow rate: 1.0 mL/min; Wavelength: 210 nm; Column temperature: 40°C; Injection volume: 5 µL; Run time: 38 min; Elution: gradient; Buffer: Transfer accurately 1 mL of orthophosphoric acid (85%) in 1000 mL of Milli-Q-water and filter through 0.22µm Nylon membrane filter paper; Mobile phase-A: Buffer (100%); Mobile phase-B: Acetonitrile: Water (90:10, v/v); Diluent: Acetonitrile: water (80:20, v/v).

The 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2 was analyzed by HPLC under the following conditions;

Apparatus: A liquid chromatographic system equipped with variable wavelength UV-detector and integrator; Column: Kromasil 100-5C18 250×4.6mm, 5µm or equivalent; Flow rate: 1.0 mL/min; Wavelength: 210 nm; Column temperature: 35°C; Injection volume: 5 µL; Run time: 42 min; Elution: gradient; Buffer: Weigh accurately about 2.0 gm of 1-octane sulfonic acid sodium salt anhydrous and add 2 mL of ortho phosphoric acid (85%) in 1000 mL of Milli-Q-water. Adjust the pH to 3.0 with dil.NaOH and filter through 0.45 µm Nylon membrane filter paper; Mobile phase-A: Buffer (100%); Mobile phase-B: Acetonitrile:Buffer (70:30, v/v); Diluent: Methanol.

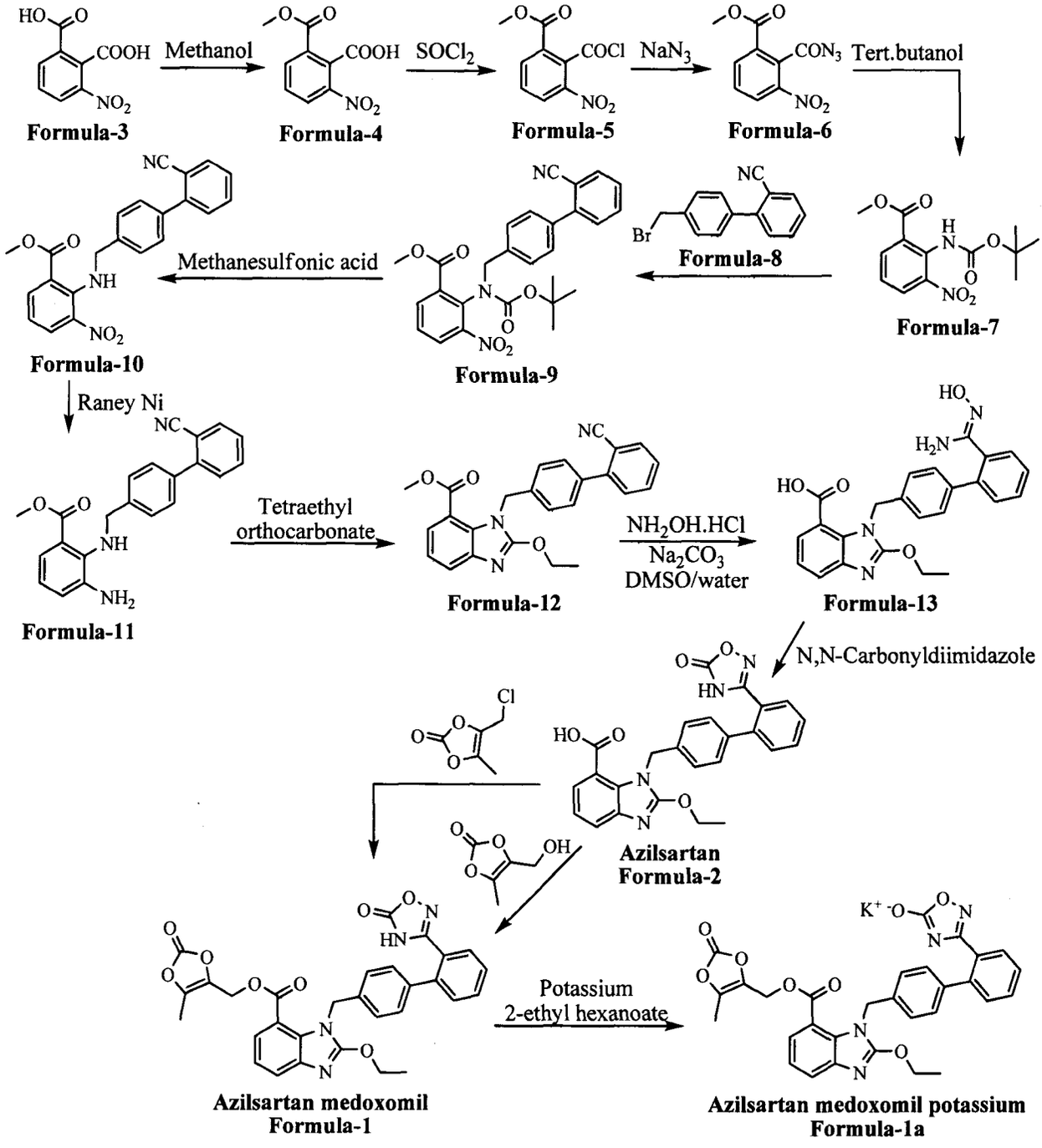
(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate and its potassium salt were analyzed by HPLC under the following conditions;

Apparatus: A liquid chromatographic system equipped with variable wavelength UV-detector and integrator; Column: Cosmicsil column, 150×4.6 mm, 5.0 µm or equivalent; Flow rate: 1.5 mL/min; Wavelength: 220 nm; Column temperature: 40°C; Injection volume: 10 µL; Run time: 33 min; Diluent: acetonitrile:buffer (80:20, v/v); Elution: gradient; Buffer: Weigh accurately 1.36 gm of potassium dihydrogen orthophosphate into 1000 ml of milli-Q-water. Adjust the pH to 2.8 with diluted ortho phosphoric acid and filtered the solution through 0.22 µm Nylon membrane filter paper; Mobile phase-A: Buffer; Mobile phase-B: acetonitrile:water (90:10 v/v); Auto sampler temperature: 5°C.

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate and its potassium 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 mills, roller and hammer mills and jet mills. Milling or micronization may be performed before drying or after drying of the product.

The present invention is schematically represented as follows.

Scheme-I:



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 2-(methoxycarbonyl)-6-nitro benzoic acid (Formula-4)

Conc. sulfuric acid (93 gm) was slowly added to a pre-cooled mixture of 3-nitro phthalic acid (100 gm) in methanol (200 ml) at 10-15°C. Heated the reaction mixture to 45-50°C and stirred for 20 hrs at the same temperature. After completion of the reaction, distilled off methanol completely from the reaction mixture under reduced pressure and co-distilled with toluene. Water and toluene were added to the reaction mixture at 25-30°C and stirred for 60 min at the same temperature. Filtered the precipitated solid, washed with water followed by toluene to get the title compound.

Yield: 95.0 gm; M.R: 155-160°C.

Example-2: Preparation of methyl 2-(chlorocarbonyl)-3-nitrobenzoate (Formula-5)

Thionyl chloride (97.8 gm) was slowly added to a pre-cooled mixture of 2-(methoxycarbonyl)-6-nitro benzoic acid (100 gm), dichloromethane (500 ml) and N,N-dimethyl formamide (2.5 ml) at 10-15°C under nitrogen atmosphere. Heated the reaction mixture to 40-45°C and stirred for 7 hrs under nitrogen atmosphere at the same temperature. After completion of the reaction, the reaction mixture was added to ice-cooled water and stirred for 15 min at 10-15°C. Both the organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with 5% sodium carbonate solution. Distilled off the solvent completely from the organic layer and co-distilled with dichloromethane to get the title compound.

Example-3: Preparation of methyl 2-(tert-butoxycarbonylamino)-3-nitrobenzoate (Formula-7)

N,N-Dimethyl formamide (100 ml) and tert.butanol (300 ml) were added to methyl 2-(chlorocarbonyl)-3-nitrobenzoate compound of formula-5 obtained in example-2 at 0-5°C and stirred for 20 min at the same temperature. Sodium azide (39.85 gm) was slowly added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 60 min at the same temperature. After completion of the reaction, heated the reaction mixture to 55-60°C and stirred for 4 hrs at the same temperature. After completion of the reaction, water was added to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature.

Filtered the precipitated solid and washed with water. Cyclohexane (300 ml) was added to the obtained solid and the reaction mixture was heated to reflux temperature and stirred for 45 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 60 min at the same temperature. Filtered the solid and washed with cyclohexane to get the pure title compound.
Yield: 100.0 gm; M.R: 106-108°C; Purity by HPLC: 91.58%.

Example-4: Preparation of methyl 2-(tert-butoxycarbonyl ((2'-cyanobiphenyl-4-yl)methyl) amino)-3-nitrobenzoate (Formula-9)

A mixture of methyl 2-(tert-butoxycarbonylamino)-3-nitrobenzoate compound of formula-7 (100 gm), acetone (600 ml), potassium carbonate (56 gm), tetra butyl ammonium bromide (10.9 gm) and 4'-(bromomethyl)biphenyl-2-carbonitrile compound of formula-8 (92 gm) was heated to reflux and stirred for 12 hrs at the same temperature. After completion of the reaction, filtered the reaction mixture at 25-30°C and distilled off the solvent completely from the filtrate under reduced pressure and co-distilled with methanol. Methanol (300 ml) was added to the obtained compound at 25-30°C, 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 60 min at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound.
Yield: 148.0 gm; M.R: 140-150°C.

Example-5: Preparation of methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate (Formula-10)

Methanesulfonic acid (78.9 gm) was slowly added to a mixture of methyl 2-(tert-butoxycarbonyl((2'-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate compound of formula-9 (100 gm) in dichloromethane (600 ml) at 25-30°C and stirred for 3 hrs at the same temperature. After completion of the reaction, the reaction mixture was added to cool water at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with 5% sodium bicarbonate solution followed by water. Distilled off solvent completely from the organic layer under reduced pressure and co-distilled with methanol. Methanol (400 ml) was added to the obtained compound at 25-30°C, heated the reaction mixture to 45-50°C and stirred for 30 min at the same temperature. Cooled the reaction

mixture to 25-30°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: 75.0 gm; M.R: 135-145°C.

Example-6: Preparation of methyl 3-amino-2-((2'-cyanobiphenyl-4-yl)methylamino) benzoate (Formula-11)

Methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate compound of formula-10 (100 gm), ethyl acetate (1000 ml) and Raney Ni (50 gm) were charged into an autoclave vessel at 25-30°C and stirred for 10 min at the same temperature. 3-4 Kg/cm^2 hydrogen gas pressure was applied to the reaction mixture at 25-30°C and stirred for 5 hrs at the same temperature. After completion of the reaction, filtered the reaction mixture through hyflow bed and washed with ethyl acetate. Distilled off the solvent completely from the filtrate under reduced pressure and co-distilled with methanol. 300 ml of methanol was added to the obtained compound at 25-30°C, heated the reaction mixture to reflux temperature and stirred for 30 min at the same temperature. Cooled the reaction mixture to 10-15°C and stirred for 45 min at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound.

Yield: 82.0 gm.

Example-7: Preparation of methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate (Formula-12)

Methyl 3-amino-2-((2'-cyanobiphenyl-4-yl)methylamino)benzoate compound of formula-11 (82 gm) was added to acetic acid (225 ml) at 25-30°C and the reaction mixture was stirred for 10 min at the same temperature. Slowly added tetraethyl orthocarbonate (73 gm) to the reaction mixture at 25-30°C 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 60 min at the same temperature. Filtered the solid and washed with water to get the title compound.

Yield: 83.0 gm.

Example-8: Purification of methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate (Formula-12)

A mixture of methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12 (83 gm) and toluene (300 ml) was heated to 60-65°C and stirred for 45 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 60 min at the same temperature. Filtered the precipitated solid and washed with toluene to get pure compound of formula-12.

Yield: 74.0 gm; M.R: 155-165°C; Purity by HPLC: 99.66%.

Example-9: Preparation of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl) methyl)-1H-benzimidazole-7-carboxylic acid (Formula-13)

Hydroxylamine hydrochloride (127 gm) was added to a mixture of dimethyl sulfoxide (1000 ml), water (1000 ml) and sodium carbonate (193.5 gm) at 25-30°C and stirred for 15 min at the same temperature. Methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzimidazole-7-carboxylate compound of formula-12 (100 gm) was added to the reaction mixture at 25-30°C. Slowly heated the reaction mixture to 115-120°C and stirred for 7 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 10-15°C. Filtered the reaction mixture and washed with ethyl acetate. Water was added to the filtrate and washed with ethyl acetate. Ethyl acetate was added to the reaction mixture at 25-30°C and cooled to 10-15°C. Adjusted the pH of the reaction mixture to 7.5 using hydrochloric acid at 10-15°C and stirred for 3 hrs at the same temperature. Filtered the precipitated solid and washed with water to get title compound.

Yield: 95.0 gm; M.R: 200-205°C; Purity by HPLC: 92.97%; Amide impurity: 1.65%.

Example-10: Purification of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl) methyl)-1H-benzimidazole-7-carboxylic acid (Formula-13)

A mixture of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 (100 gm) and methanol (500 ml) was heated to 45-50°C and stirred for 45 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the precipitated solid and washed with chilled methanol to get pure compound of formula-13.

Yield: 90.0 gm; Purity by HPLC: 98.01%; Amide impurity: 0.57%.

Example-11: Preparation of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid (Formula-2)

1,8-diazabicyclo[5.4.0]undec-7-ene (53 gm) and N,N-carbonyl diimidazole (75.5 gm) were added to a mixture of 2-ethoxy-1-((2'-(N'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid compound of formula-13 (100 gm) and dichloromethane (500 ml) at 25-30°C and stirred for 6 hrs at the same temperature. After completion of the reaction, distilled off the solvent completely from the reaction mixture. Water (1000 ml) followed by sodium hydroxide (27.8 gm) were added to the reaction mixture. Heated the reaction mixture to 50-55°C and stirred for 3 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 25-30°C and washed with dichloromethane. Dichloromethane was added to the reaction mixture and cooled to 10-15°C. Acidified the reaction mixture with hydrochloric acid at 10-15°C and stirred for 2 hrs at the same temperature. Filtered the precipitated solid and washed with water to get the title compound.

Yield: 95.0 gm; M.R: 195-205°C; Purity by HPLC: 98.04%.

Example-12: Purification of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid (Formula-2)

A mixture of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2 (100 gm) and methanol (500 ml) was heated to reflux temperature and stirred for 45 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the precipitated solid and washed with methanol to get pure compound of formula-2.

Yield: 95.0 gm; M.R: 200-205°C; Purity by HPLC: 99.15%.

Example-13: Preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (Formula-1)

A mixture of 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl] methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2 (100 gm), acetone (2000 ml), sodium bicarbonate (18.4 gm) and tetra butyl ammonium bromide (4 gm) was heated to 40-45°C and stirred for 45 min at the same temperature. 4-(chloromethyl)-5-methyl-1,3-dioxol-

2-one (32.5 gm) was added to the reaction mixture at 40-45°C and stirred for 24 hrs at the same temperature. Sodium bicarbonate (9.2 gm) and 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one (16.3 gm) were added to the reaction mixture at 40-45°C and stirred for 24 hrs at the same temperature. After completion of the reaction, filtered the reaction mixture and the solvent was completely distilled off from the filtrate under reduced pressure. Ethyl acetate was added to the obtained compound, cooled the reaction mixture to 5-10°C and water followed by sodium carbonate were added. Sodium chloride was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and the organic layer was washed with 5% aqueous sodium chloride solution, 0.5% hydrochloric acid, water, 0.5% sodium bicarbonate solution followed by again with 5% sodium chloride solution. Distilled off the solvent completely form the organic layer under reduced pressure and co-distilled with acetonitrile. Acetonitrile (150 ml) was added to the obtained compound at 25-30°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the solid and washed with acetonitrile to get title compound.

Yield: 40.0 gm.

Example-14: Preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate using acetone as solvent (Formula-1)

p-Toluene sulfonyl chloride (46 gm), 4-dimethylamino pyridine (6.2 gm), potassium carbonate (45.5 gm) followed by 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2 (100 gm) were added to a pre-cooled mixture of 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (40 gm) and acetone (1000 ml) at 0-5°C. Raised the temperature of the reaction mixture to 10-15°C and stirred for 6 hrs at the same temperature. After completion of the reaction, water was added to the reaction mixture. Extracted the reaction mixture with ethyl acetate and the organic layer was washed with water, 2% hydrochloric acid, 2% sodium bicarbonate solution followed by again with water. Distilled off the solvent completely from the organic layer and co-distilled with cyclohexane. 300 ml of cyclohexane was added to the obtained compound, heated the reaction mixture to 50-55°C and stirred for 45 min at the same temperature. Cooled the reaction mixture

to 25-30°C and stirred for 45 min at the same temperature. Filtered the solid and washed with cyclohexane to get the title compound.

Yield: 95.0 gm.

Example-15: Purification of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (Formula-1)

A mixture of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1 (95 gm) and acetonitrile (500 ml) was heated to reflux temperature and stirred for 30 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the solid, washed with acetonitrile and dried to get pure compound of formula-1.

Yield: 85.0 gm.

Example-16: Preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate using methyl isobutyl ketone as solvent (Formula-1)

p-Toluene sulfonyl chloride (46 gm), 4-dimethylamino pyridine (6.0 gm), potassium carbonate (39.5 gm) followed by 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2 (100 gm) were added to a pre-cooled mixture of 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (34.2 gm) and methyl isobutyl ketone (1000 ml) at 0-5°C and stirred for 15 min at the same temperature. Heated the reaction mixture 40-45°C and stirred for 18 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 0-5°C, filtered the reaction mixture and washed with methyl isobutyl ketone. Acetone (750 ml) and water (500 ml) were added to the obtained wet compound at 25-30°C and stirred for 15 min at the same temperature. Extracted the reaction mixture with ethyl acetate and the organic layer was washed with 10% sodium chloride solution, aqueous hydrochloric acid solution, water, sodium bicarbonate solution followed by again 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. Ethyl acetate

(300 ml) was added to the obtained compound, heated the reaction mixture to 45-50°C and stirred for 45 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the precipitated solid and washed with ethyl acetate to get title compound.

Yield: 75.0 gm; Purity by HPLC: 98.96%.

Example-17: Preparation of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate using mixture of methyl isobutyl ketone/ethyl acetate as solvent (Formula-1)

p-Toluenesulfonyl chloride (46 gm), 4-dimethylamino pyridine (6.0 gm), potassium carbonate (39.5 gm) followed by 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylic acid compound of formula-2 (100 gm) were added to a pre-cooled mixture of 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (34.2 gm), methyl isobutyl ketone (1000 ml) and ethyl acetate (100 ml) at 0-5°C and stirred for 15 min at the same temperature. Heated the reaction mixture to 40-45°C and stirred for 18 hrs at the same temperature. After completion of the reaction, cooled the reaction mixture to 0-5°C, filtered the compound and washed with methyl isobutyl ketone. Acetone (750 ml) and water (500 ml) were added to the obtained wet compound at 25-30°C and stirred for 15 min at the same temperature. Extracted the reaction mixture with ethyl acetate and the organic layer was washed with 10% sodium chloride solution, 1% hydrochloric acid solution, water, 1% sodium bicarbonate solution followed by again with 10% sodium chloride solution. Dried the organic layer over sodium sulfate followed by distilled off the solvent completely from the organic layer under reduced pressure. Ethyl acetate (300 ml) was added to the obtained compound, heated the reaction mixture to 40-45°C and stirred for 45 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the precipitated solid, washed with ethyl acetate and dried to get the title compound.

Yield: 70.0 gm; Purity by HPLC: 99.22%.

Example-18: Preparation of potassium salt of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (Formula-1a)

A mixture of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (100 gm) and acetone (1500 ml) was heated to 45-50°C and stirred for 30 min at the same temperature. Carbon (5 gm) was added to the reaction mixture at 45-50°C and stirred for 15 min at the same temperature. Filtered the reaction mixture through hyflow bed and cooled the filtrate to 0-5°C. A solution of potassium 2-ethyl hexanoate (32 gm) in ethyl acetate (500 ml) was added to the filtrate at 0-5°C and stirred for 90 min at the same temperature. Filtered the precipitated solid and washed with ethyl acetate to get the title compound.

Yield: 80.0 gm; Purity by HPLC: 97.9%.

Example-19: Purification of potassium salt of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (Formula-1a)

A mixture of potassium salt of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate compound of formula-1a (80 gm) and ethyl acetate (400 ml) was heated to 45-50°C and stirred for 20 min at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 min at the same temperature. Filtered the solid and washed with ethyl acetate to get pure compound of ormula-1a.

Yield: 70.0 gm; M.R: 209-213°C; Purity by HPLC: 99.85%.