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(54) Title: PROCESS FOR PREPARATION OF LISDEXAMPHETAMINE AND SALTS THEREOF

(57) Abstract: An improved, efficient, safe and convenient process for preparation of lisdexamphetamine and its pharmaceutically acceptable salts by using novel mixed anhydride intermediate is provided. A process for preparation of diamino protected amide compound namely BOC protected lisdexamphetamine, a key intermediate in the preparation of lisdexamphetamine and its pharmaceutically acceptable salts by using novel mixed anhydride intermediate and its purification by crystallization are also provided. Further, novel mixed anhydride intermediate is provided too.

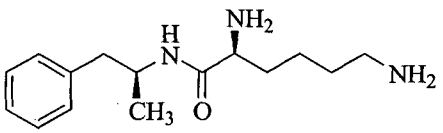
'PROCESS FOR PREPARATION OF LISDEXAMPHETAMINE AND SALTS THEREOF'

FIELD OF THE INVENTION

The present invention relates to an industrial advantageous process for preparation of pure amphetamine prodrug, in particular, lisdexamphetamine and its pharmaceutically acceptable salts. Further the present invention relates to a novel process for purification of diamino protected intermediate, chemically named as [5-tert-butoxycarbonylamino-5-(1-methyl-2-phenyl-ethylcarbamoyl)-pentyl]-carbamic acid tert-butyl ester, a key intermediate in preparation of lisdexamphetamine.

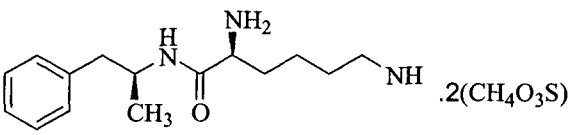
BACKGROUND OF THE INVENTION

Lisdexamphetamine of formula I, is a conjugate of D-amphetamine and L-lysine and is chemically named as (2S)-2,6-diamino-N-[(1S)-methyl-2-phenylethyl]hexan amide.



Formula- I

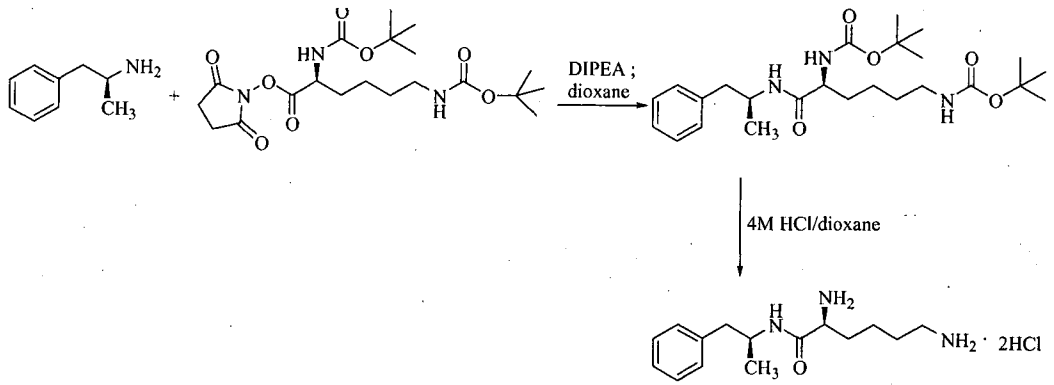
Amphetamines stimulate central nervous system (CNS). Amphetamine is prescribed for treatment of various disorders, including attention deficit hyperactivity disorder (ADHD), obesity, nacrolepsy. It is approved as lisdextamphetamine dimesylate of formula IA and



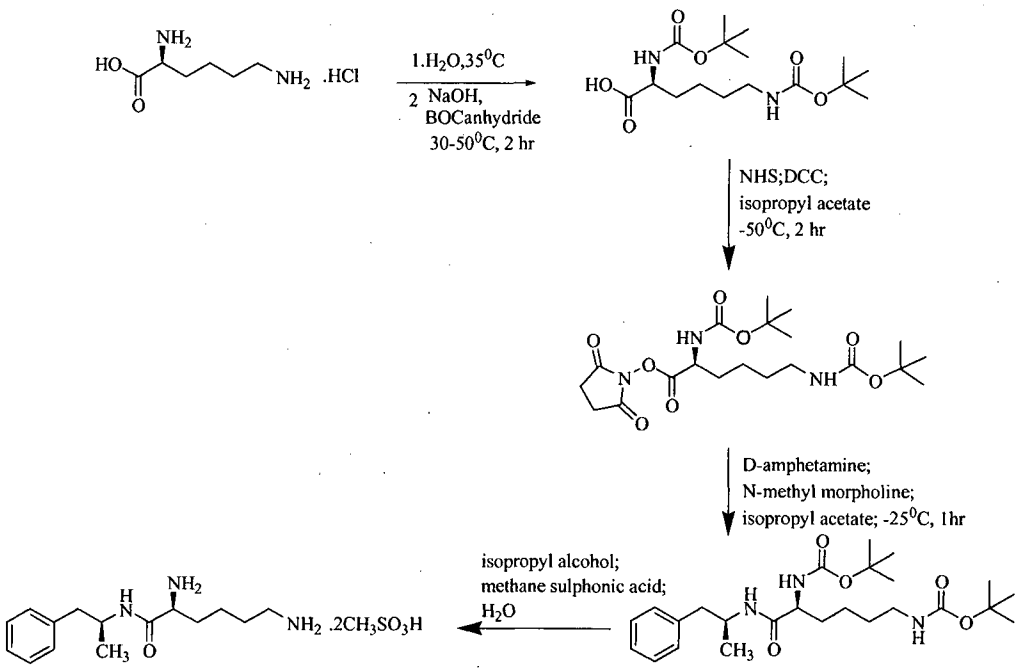
Formula- IA

marketed under trade name Vyvanse for treatment of attention-deficit hyperactivity disorder in pediatric patients.

L-Lysine-D-amphetamine and its pharmaceutically acceptable salts were first disclosed in US patent 7,662,787 wherein it is exemplified as hydrochloride salt. Process for preparation of L-lysine-D-amphetamine includes reaction of BOC-Lys-(BOC)-hydroxysuccinimido ester with D-amphetamine in dioxane using diisopropyl ethyl amine (DIPEA) as a base to obtain BOC-protected lisdexamphetamine which is then purified using flash chromatography and further reacted with a mixture of 4M hydrochloric acid /dioxane to yield L-lysine-D-amphetamine hydrochloride. The process is as shown in following scheme:



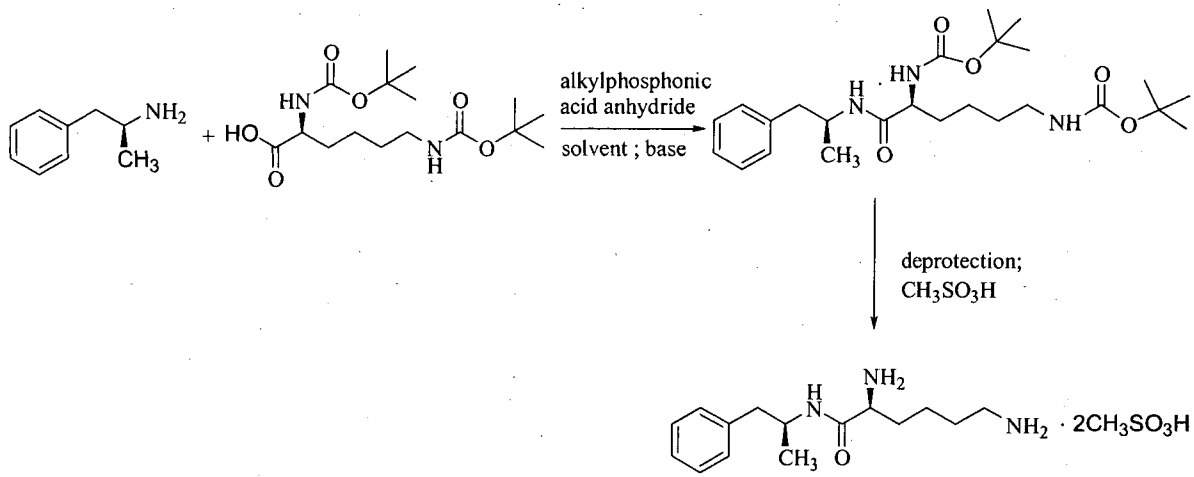
In equivalent patent US 7,659,253, process for preparation of mesylate salt is disclosed as shown below.



Process includes preparation of BOC-Lys-(BOC)-hydroxysuccinimido ester wherein use of reagents like N-hydroxy-succinimide (NHS) and N,N-dicyclohexyl- carbodimiide (DCC) is carried out, The above processes involve use of flash column chromatography to purify crude BOC- protected L-lysine-D-amphetamine intermediate. Use of column chromatography is very cumbersome, tedoius and time consuming, therefore not advisable at commercial scale. Further N,N-dicyclohexylcarbodimiide is known to be highly toxic and moisture sensitive compound, and its use leads to formation of a large amount of N,N-dicyclohexyl urea (DCU) as bye product which has to be removed from reaction mixture.. Therefore use of DCC is not advisable at industrial scale.

International patent publication WO 2010/042120 discloses a process for preparing L-lysine-D-amphetamine or its salts by reacting D-amphetamine with protected lysine or its salt by

using an alkylphosphonic acid anhydride as coupling agent in presence of a base and solvent. The process is as shown in following scheme:



The application discloses use of alkylphosphonic acid anhydrides, which are expensive. and needs additional testing to show absence of phosphic impurities in intermediate or final compound to meet regulatory requirements. So it is not appealing to use alkylphosphonic anhydrides for scale up operations.

International patent publication WO2010/148305 discloses a process for preparation of lisdexamphetamine by removal of chlorine from N,N'-bistrifluoroacetyl-chloro-lisdexamphetamine by using hydrogenation catalyst like Pd/C, under hydrogen gas to form N,N'-bistrifluoroacetyl-lisdexamphetamine which on further deprotection by using deprotecting agent to form lisdexamphetamine. Alternatively first deprotection by using deprotecting agent and then chlorine is removed by using hydrogenation catalyst like Pd/C under hydrogen gas. The process involves additional steps of inserting chloro group and thereafter removing chloro group; further Pd/C is an expensive reagent, hence not attractive option from cost point of view.

It is therefore, necessary to overcome problems associated with prior art and to provide an efficient process for preparation of lisdexamphetamine and its pharmaceutically acceptable salts using easily available, less expensive, easy to handle raw materials and avoid use of column chromatography.

OBJECTIVE OF THE INVENTION

The principle objective of present invention is to provide an industrially advantageous and efficient process for preparation of lisdexamphetamine and its pharmaceutically acceptable salts.

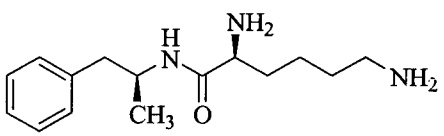
Another objective of present invention is to provide a novel process for purification of diamino protected intermediate commonly called as BOC protected lisdexamphetamine, by simple crystallization.

Yet another objective of the present invention is to provide a process for preparation of lisdexamphetamine and its pharmaceutically acceptable salts using novel mixed anhydride intermediate.

Yet another objective of the present invention is to provide a novel mixed anhydride intermediate.

SUMMARY OF THE INVENTION

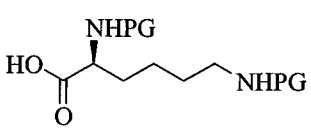
Accordingly, the present invention provides an improved and industrially advantageous process for preparation of highly pure lisdexamphetamine of formula I and its pharmaceutically acceptable salts.



Formula I

According to one embodiment, present invention provides a process for preparation of lisdexamphetamine and its pharmaceutically acceptable salts of formula I, which comprises steps of :

a) reacting L-lysine monohydrochloride with amine protecting group in the presence of a base and a solvent to give diamino protected L-lysine compound of formula II



Formula II

wherein PG is an amine protecting group

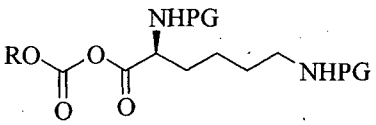
b) reacting diamino protected L-lysine compound of formula II with acid activating reagent of formula III

XCO_2R **Formula III**

wherein R can be selected from alkyl or aryl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isopentyl, phenyl, substituted phenyl, where the phenyl group is substituted by 4-methyl, 4-chloro,4- bromo, 4-iodo, 4-nitro, benzyl, substituted

benzyl, where benzyl is substituted by 4-methyl, 4-nitro, 4-chloro, 4- bromo, 4-iodo; .and X is halogen selected from chloro, bromo or iodo.,

in the presence of a base and a solvent to form a mixed anhydride intermediate of formula IV

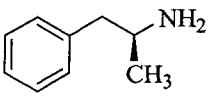


Formula IV

wherein R and PG are same as defined above

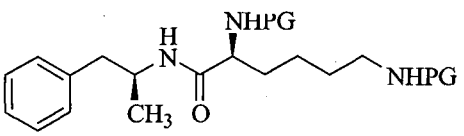
c)optionally isolating mixed anhydride intermediate of formula IV,

d)condensing mixed anhydride intermediate of formula IV with D-amphetamine of formula V and salt thereof,



Formula V

to give diamino protected amide compound of formula VI



Formula VI

wherein PG is same as defined above

e)converting diamino protected amide compound of formula VI into lisdexamphetamine and its pharmaceutically acceptable salts.

According to another embodiment, the present invention provides a novel process for purification of diamino protected amide compound of formula VI, which comprises:

a) dissolving crude diamino protected amide compound of formula VI in a suitable solvent,

b) adding anti solvent to induce precipitation, and

c) isolating pure diamino protected amide compound of formula VI .

According to yet another embodiment, the present invention provides a process of preparation of diamino protected amide compound of formula VI which comprises:

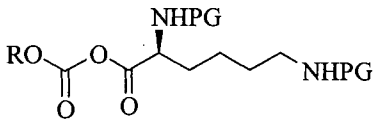
a) reacting diamino protected L-lysine compound of formula II with acid activating reagent of formula III in the presence of a suitable base and solvent to form a mixed anhydride intermediate of formula IV,

b) optionally isolating mixed anhydride intermediate of formula IV,

c) reacting mixed anhydride intermediate of formula IV with D-amphetamine of formula V to form diamino protected amide compound of formula VI.

According to yet another embodiment, the present invention provides a process for preparation of lisdexamphetamine and its pharmaceutically acceptable salts of formula I, from L-lysine in one pot without isolating intermediates.

According to still yet another embodiment, the present invention provides a novel mixed anhydride intermediate of formula IV



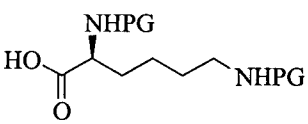
Formula IV

wherein R and PG are same as defined above.

DETAIL DESCRIPTION OF THE INVENTION

The present invention provides an improved and industrially advantageous process for preparation of highly pure lisdexamphetamine and its pharmaceutically acceptable salts of formula I.

One embodiment of the present invention provides a process for the preparation of lisdexamphetamine of formula I and its pharmaceutically acceptable salt thereof, starting from reacting L-lysine monohydrochloride with amine protecting group using base and a solvent to give diamino protected L-lysine compound of Formula II



Formula II

wherein PG is a nitrogen protecting group.

Amine protecting group may be selected from any group which is suitable to protect amine group. In general suitable amine protecting group includes, but not limited to t-butyloxycarbonyl (BOC), benzyloxycarbonyl(CBz), allyloxycarbonyl (,Alloc) fluorenyl methyloxycarbonyl (Fmoc), trimethylsilylethyloxycarbonyl (Teoc), pivaloyl, trifluoro acetyl etc. Preferably the amine protecting group is t-butyloxycarbonyl(BOC).

Base can be selected from alkali or alkaline metal hydroxides, carbonates, alkoxides and hydrides, for example sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, sodium methoxide, potassium methoxide, sodium hydride, potassium hydride, lithium hydride and the like, preferably the base used is sodium or potassium hydroxide.

Solvent can be selected from a group consisting of water or water miscible solvents like ethanol, methanol, n-propyl alcohol, isopropyl alcohol, tetrahydrofuran, N,N-dimethyl-formamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, acetone, ethyl methyl ketone, diethyl ketone and mixture thereof. Preferably solvent used for the reaction is water.

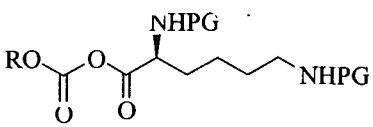
The reaction is generally performed at temperature range of 0°C to 80°C for a few minutes to few hours, especially between 5°C to 35°C during addition of ditertiary butyl dicarbonate. Further reaction temperature can be raised 40°C to 70°C and reaction mass is maintained at this tepretaure for 12 to15 hours or till completion of the reaction. The completion of reaction can be monitored by suitable chromatographic technique such as high pressure liquid chromatography (HPLC) or thin layer chromatography (TLC).

The next phase of synthetic procedure involves carboxylic acid group activation of diamino protected L-lysine compound of formula II by using acid activating reagent of formula III in the presence of a suitable base and a solvent to give

XCO_2R **Formula III**

wherein X and R are same as defined above.

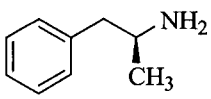
a mixed anhydride intermediate of formula IV



Formula IV

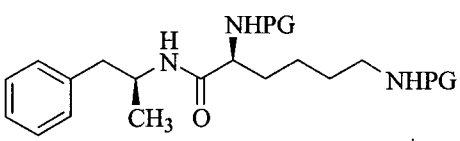
wherein R and PG are same as defined above.

and condensation of mixed anhydride intermediate of formula IV with D-amphetamine of formula V or salt thereof



Formula V

to give diamino protected amide compound of formula VI



Formula VI

wherein PG is same as defined above.

Carboxylic acid group activation and subsequent synthetic transformations can be performed in a single or multiple steps. Mixed anhydride intermediate of formula IV may be isolated or directly converted *insitu* to intermediate of formula VI.

Acid activating reagent can be selected from a group consisting of haloformate such as methyl chloroformate, ethyl chloroformate, n-propyl chloroformate, isopropyl chloroformate, isobutyl chloroformate, benzyl chloroformate, phenyl chloroformate, aryloxy chloroformate, benzyloxy chloroformate and like thereof. Preferably acid activating reagent used is isobutyl chloroformate.

Base used for carboxylic acid group activation reaction can be selected from organic base such as alkyl amine and includes but not limited to triethyl amine, di-isopropyl ethyl amine, tri-n-propyl amine, tri-n-butyl amine, pyridine, lutidine and like thereof. Preferably the base used is triethyl amine or di-isopropyl ethyl amine.

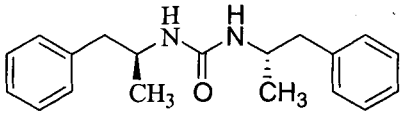
Solvent used for carboxylic acid group activation and subsequent reactions can be selected from C_{5-8} aliphatic or aromatic hydrocarbons such as n-pentane, n-hexane, n-heptane, cyclopentane, cyclohexane, cycloheptane, toluene, xylene; C_{1-4} halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane; C_{3-6} esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and like; C_{4-8} ethers such as diethyl ether, di-isopropyl ether, methyl t-butyl ether, 1,2-dimethoxy ethane, 1,2-diethoxy ethane, tetrahydrofuran, 2-methyl tetrahydrofuran and dioxane; C_{3-6} ketones such as acetone, methyl ethyl ketone, diethyl ketone, methyl isobutyl ketone, and alkylnitriles such as acetonitrile, propionitrile and amides such as N,N-dimethylformamide, N,N-dimethyl acetamide; sulfoxide such as dimethyl sulfoxide and mixture thereof. Preferably solvent used for the reaction is dichloromethane.

Carboxylic acid group activation reaction is conducted at a temperature of -30°C to 35°C for 5 to 180 minutes. Preferably reaction is carried out at a temperature of -20°C to 20°C for 60 to 120 minutes or till the completion of the reaction. The reaction completion can be monitored by thin layer chromatography (TLC) or high pressure liquid chromatography (HPLC).

The reaction of mixed anhydride intermediate of formula IV with D-amphetamine of formula V or salt thereof is conducted at a temperature of -30°C to 50°C for 30 to 180 minutes. Preferably reaction is performed at a temperature of -20°C to 30°C for 60 to 120 minutes or till the completion of the reaction.

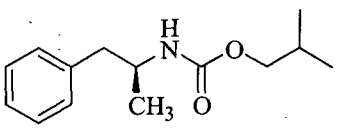
Thereafter, diamino protected amide compound of formula VI is converted to lisdexamphetamine of formula I or its pharmaceutically acceptable salts.

Optionally diamino protected amide compound of formula VI can be purified to enhance purity. In crude diamino protected amide compound of formula VI, HPLC analysis indicates the presence of impurities like 1,3-bis(1-methyl-2-phenyethyl)urea of formula VII and (1-methyl-2-phenylethyl)carbamic acid isobutyl ester of formula VIII as shown below:



Formula VII

and



Formula VIII

Crude diamino protected amide compound of formula VI may have purity 85 to 95% by HPLC

According to yet another embodiment, the present invention involves a novel process for purification of diamino protected amide compound of formula VI by simple technique to remove the impurities of formula VII and VIII which comprises dissolving crude diamino protected amide compound of formula VI having purity between 85% to 95% (by HPLC) in a suitable solvent selected from the group consisting of C_{1-5} alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol; halogenated solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane; ethers such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tertiary butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 1,2-dimethoxy ethane, 1,2-diethoxy ethane, C_{3-6} aliphatic ketones such as acetone, diethyl ketone, ethyl methyl ketone, methyl isobutyl ketone and like; alkyl nitriles such as acetonitrile, propionitrile, preferably solvent used is ethanol at a temperature of 10°C to 70°C, preferably at 20°C to 50°C to get a clear solution. Thereafter, antisolvent is added slowly to precipitate the compound. The antisolvent can be selected from water; hydrocarbon such as n-pentane, n-hexane, hexanes, n-heptane, heptanes, cyclohexane, cycloheptane, toluene, 1,2 and 1,4-xylene; alkyl nitriles such as acetonitrile, propionitrile; aliphatic ethers such as diethyl ether, isopropyl ether, methyl tertiary butyl ether and mixture thereof , preferably antisolvent used is water. Thereafter, the reaction mixture is cooled to -30°C to 60 °C, preferably at 5 to 40°C. Stirring is conducted for 20 minutes to 24 hours, preferably for 30 to180 minutes, more preferably till complete precipitation of the product. The product can be isolated by any standard method known in the art. Typically the product is isolated by filtration.

Diamino protected amide compound of formula VI obtained by the described purification may have a purity of not less than 99 % by HPLC, more preferably not less than 99.5 % and even more preferably not less than 99.9 % by HPLC. Diamino protected compound of formula VI obtained by the described purification process may contain very little amount of impurities of formula VII and VIII not more than 0.2 % and 0.5 %, preferably not more than about 0.05% each by HPLC of diamino protected amide compound of formula VI.

Diamino protected amide compound of formula VI can be deprotected by any of the methods known in the prior art to give lisdexamphetamine or its pharmaceutically acceptable salt of formula 1 by using a suitable acid. A suitable acid can be selected from the group consisting of methane sulphonic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, ortho phosphoric acid and like thereof. Acid used for deprotection depends on the amine protecting group. Solvent used for reaction can be selected from water; C_{1-5} alcohols such as methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, isobutanol, n-pentanol; C_{4-8} aliphatic hydrocarbons or aromatic hydrocarbons such as n-pentane, n-hexane, n-heptane; benzene, toluene, 1,2 and 1,4-xylene; C_{1-4} halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1.2-dichloroethane; C_{3-6} esters such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate; C_{3-5} ethers diethyl ether, diisopropyl ether, t-butyl methyl ether, 1,2-dimethoxy ethane, 1,2-diethyoxy ethane, tetrahydrofuran, 2-methyl tetrahydrofuran and dioxane; C_{3-6} ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and nitriles such as acetonitrile, propionitrile or mixture thereof.

The deprotection reaction of diamino protected amide compound of formula VI is carried at a temperature of 5°C to 140°C and for 5 to 12 hours, preferably at a temperature of 15°C to 80°C for 8 to 12 hours or till the completion of the reaction. The reaction completion can be monitored by thin layer chromatography (TLC) or high pressure liquid chromatography (HPLC). The product can be isolated by any standard method known in the art such as by filtration, centrifugation or decantation. Typically the product is isolated by filtration in laboratory on small scale & by centrifuging on commercial scale.

Alternatively lisdexamphetamine and its pharmaceutically acceptable salts of formula I can be prepared by one pot process without isolating intermediates. The process comprises of reacting L-lysine monohydrochloride with amine protecting group in presence of base and a solvent to give diamino protected L-lysine compound of Formula II. Base can be selected from alkali or alkaline metal hydroxides, carbonates, alkoxides and hydrides, for example

sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, sodium methoxide, potassium methoxide, sodium hydride, potassium hydride, lithium hydride and the like, preferably the base used is sodium or potassium hydroxide.

Solvent can be selected from the group consisting of water or water miscible solvents as described earlier. Preferably solvent used for the reaction is water.

The reaction is generally performed at temperature range of 0°C to 80°C for a few minutes to few hours, especially between 5°C to 35°C during addition of ditertbutyl dicarbonate and then in temperature range of 40°C to 70°C for 12 to15 hours or till completion of the reaction. The reaction completion can be monitored by suitable chromatographic techniques such as HPLC or TLC. After completion of reaction, reaction mixture is cooled to 20°C to 30°C. Water is added to the reaction mixture and further extracted with a suitable water immiscible solvent preferably methylene dichloride. Thereafter pH of aqueous layer is adjusted between 2 to 5, preferably 2.5 to 3.5 by using a suitable acid. Thereafter product is extracted from the aqueous layer using suitable water immiscible solvent. Solvent for extraction includes halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, esters such as methyl acetate, ethyl acetate, propyl acetate or the like. Suitable acid includes hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid, formic acid and the like.

The resulting organic layer can be washed with water and sodium chloride solution. Organic layer is dried using sodium sulfate. Organic layer having diamino protected L-lysine compound of Formula II is reacted with acid activating reagent of formula III in presence of a base in a solvent to form mixed anhydride intermediate of formula IV which is further reacted with D-amphetamine of formula V to form diamino protected compound of formula VI.

Acid activating reagent can be selected from the group consisting of haloformate such as methyl chloroformate, ethyl chloroformate, n-propyl chloroformate, isopropyl chloroformate, isobutyl chloroformate, benzyl chloroformate, phenyl chloroformate, aryloxy chloroformate, benzyloxy chloroformate and like thereof. Preferably acid activating reagent used is isobutyl chloroformate.

Base used for carboxylic acid group activation reaction can be selected from triethyl amine, di-isopropyl ethyl amine, tri-n-propyl amine, tri-n-butyl amine, pyridine, lutidine and like. Preferably base is triethyl amine or di-isopropyl ethyl amine.

Carboxylic acid group activation reaction is conducted at a temperature of -30°C to 35°C for 5 to 180 minutes. Preferably reaction is carried out at a temperature of -20°C to 20°C for 60 to 120 minutes or till the completion of the reaction. The reaction completion can be monitor by TLC or HPLC or UPLC..

The reaction of mixed anhydride intermediate of formula IV with D-amphetamine of formula V is conducted at a temperature of -30°C to 50°C for 30 to 180 minutes. Preferably at a temperature of -20°C to 30°C for 60 to 120 minutes.

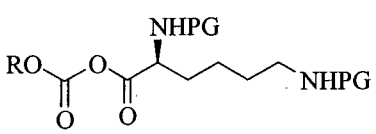
After completion of reaction, the reaction mixture is successively washed with dilute hydrochloric acid, sodium bicarbonate solution, water and sodium chloride solution followed by distillation of organic layer to afford a residue , which is treated with a suitable acid to obtain lisdexamphetamine or its pharmaceutically acceptable salt of formula 1. Particularly to the resulting residue a suitable solvent is added and then solution is treated with suitable acid. Solvent used for the reaction can be selected from water; C_{1-5} alcohols C_{4-8} aliphatic hydrocarbons or aromatic hydrocarbons C_{1-4} halogenated hydrocarbons; C_{3-6} esters; C_{3-5} ethers, 1,2-dimethoxy ethane, 1,2-diethyoxy ethane, tetrahydrofuran, 2-methyl tetrahydrofuran and dioxane; C_{3-6} ketones and nitriles or mixture thereof, as described above. Suitable acid can be selected from the group consisting of methane sulphonic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, ortho phosphoric acid and like thereof. Acid used for deprotection depends on the amine protecting group.

The deprotection reaction can be carried out at a temperature of 5°C to 140°C and it takes 5 to 12 hours for completion of reaction. The reaction completion can be monitored by TLC or HPLC. The product can be isolated by any standard method known in the art Typically product is isolated by filtration.

The product isolated can optionally be purified to enhance purity if required. Generally, resulting compound is dissolved in a suitable solvent selected from a group consisting of C_{1-6} alcohols such as methanol, ethanol, n-propanol, isopropanol n-butanol, isobutanol, n-pentanol, isopentanol, hexanol; preferably solvent used is ethanol, at a temperature of 10 to 70°C, preferably at 50 to 60°C to get a clear solution then add antisolvent selected from C_{3-6} esters such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate; C_{3-6} aliphatic ketones such as acetone, diethyl ketone, diisopropyl ketone, ethyl methyl ketone, methyl isobutyl ketone; alkyl nitrile such as acetonitrile and propionitrile; preferably antisolvent used is ethylacetate, at a temperature of 30°C to 70°C, preferably at 50°C to 60°C. The reaction mixture is cooled to -10°C to 40°C, preferably at 20°C to 30°C.

Stirring is conducted for 20 minutes to 24 hours, preferably for 30 to 120 minutes, more preferably till complete precipitation. The product can be isolated by any standard method known in the art such as by filtration, centrifugation or decantation. Typically the product is isolated by filtration. The purity of lisdexamphetamine and its pharmaceutically acceptable salt obtained by the present invention is more than 99 %, preferably more than 99.5 %, more preferably more than 99.7 %, which may be further purified by using simple process to get purity of more than 99.7 %, preferably more than 99.9 %.

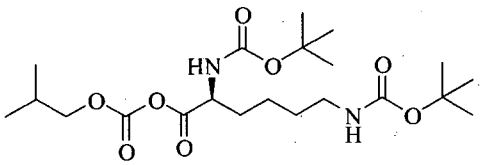
Lisdexamphetamine and its pharmaceutically acceptable salt can be purified by using simple technique which comprises dissolving crude lisdexamphetamine and its pharmaceutically acceptable salt of formula I having purity between 99% to 99.7% in a suitable solvent selected from the group consisting of C_{1-6} alcohols such as methanol, ethanol, n-propanol, isopropanol n-butanol, isobutanol, n-pentanol, isopentanol, hexanol; preferably solvent used is ethanol, at a temperature of 10 to 70°C, preferably at 50 to 60°C to get a clear solution then add antisolvent selected from C_{3-6} esters such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate; C_{3-6} aliphatic ketones such as acetone, diethyl ketone, diisopropyl ketone, ethyl methyl ketone, methyl isobutyl ketone; alkyl nitrile such as acetonitrile and propionitrile; preferably antisolvent used is ethylacetate,at a temperature of 30°C to 70°C, preferably at 50°C to 60°C. The reaction mixture is cooled to -10°C to 40°C, preferably at 20°C to 30°C. Stirring is conducted for 20 minutes to 24 hours, preferably for 30 to 120 minutes, more preferably till complete precipitation. The product can be isolated by any standard method known in the art such as by filtration, centrifugation or decantation. Typically the product is isolated by filtration. Lisdexamphetamine and pharmaceutically acceptable salt obtained by the present invention may be crystalline or amorphous form. Desired form can be obtained by modification in reaction conditions such as temperature, solvent, time and speed for stirring, temperature of precipitation and rate and time of cooling etc. speed for stirring and rate of cooling etc speed for stirring and rate of cooling etc speed for stirring and rate of cooling etc speed for stirring and rate of cooling etc According to another embodiment, the present invention provides a mixed anhydride intermediate of formula IV



Formula IV

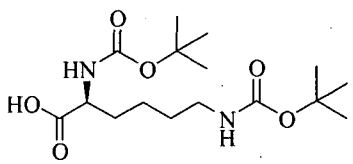
wherein R & PG are same as defined above.

In preferred embodiment of present invention, amide compound of formula VI is preferably amide compound of formula VI A as represented below:



Formula IVA

Typically amide compound of formula VI A is prepared by starting from L-lysine monohydrochloride. L-Lysine monohydrochloride is reacted with amine protecting group such as t-butyloxycarbonyl (BOC) using a base and a solvent to give di Boc amino protected L-lysine compound of Formula IIA

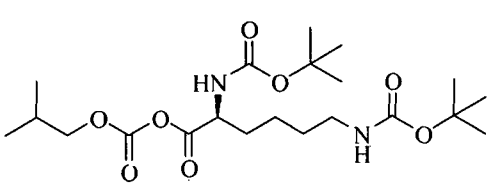


Formula II A

Base can be selected from alkali or alkaline metal hydroxides, carbonates, alkoxides and hydrides, as desribed above and preferably base used is sodium or potassium hydroxide.

Solvent can be selected from group consisting of water or water miscible solvents like ethanol, methanol, n-propyl alcohol, isopropyl alcohol, tetrahydrofuran, N,N-dimethyl-formamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, acetone, ethyl methyl ketone, diethyl ketone and mixture thereof. Preferably solvent used for the reaction is water.

The reaction is generally performed at temperature range of 0°C to 80°C for a few minutes to few hours, especially between 5°C to 35°C during addition of ditertiary butyl dicarbonate. Further reaction temperature can be raised 40°C to 70°C and reaction mass is maintained at this temperature for 12 to15 hours or till completion of the reaction. The completion of reaction can be monitored by suitable chromatographic technique such as HPLC or TLC. The next phase of synthetic procedure involves carboxylic acid group activation of diboc protected L-lysine compound of formula IIA by using isobutyl chloroformate as acid activating reagent, in the presence of a suitable base and a solvent to give a mixed anhydride intermediate of formula IV A



Formula IVA

Base used for activation reaction can be selected from organic base such as alkyl amine and includes but not limited to triethyl amine, di-isopropyl ethyl amine, tri-n-propyl amine, tri-n-butyl amine, pyridine, lutidine and like thereof. Preferably the base used is triethyl amine or di-isopropyl ethyl amine. Solvent used for activation reaction can be selected from C_{5-8} aliphatic or aromatic hydrocarbons; C_{1-4} halogenated hydrocarbons; C_{3-6} esters; C_{4-8} ethers; C_{3-6} ketones, alkylnitriles; amides; sulfoxide and mixture thereof as described above. Preferably solvent used for the reaction is dichloromethane.

Activation reaction is conducted at a temperature of -30°C to 35°C for 5 to 180 minutes. Preferably reaction is carried out at a temperature of -20°C to 20°C for 60 to 120 minutes or till the completion of the reaction. The reaction completion can be monitored by TLC or HPLC. The mixed anhydride intermediate of formula IV A is further reacted with D-amphetamine of formula V or salt thereof to prepare diBOC amino protected compound of formula VIA, which is isolated and converted to lisdexamphetamine and its pharmaceutically acceptable salts of formula I.

Major advantages realized in the present invention are cost effectiveness and efficiency of process which can be easily and conveniently scaled-up for industrial large scale production. The process is simple, economical, operationally efficient, high through output, and provides lisdexamphetamine and its pharmaceutically acceptable salts in high yield and purity without using expensive reagents. Another advantage of this process is that it involves one pot preparation of lisdexamphetamine mesylate without isolation of intermediate at various stages avoiding lengthy separation process and purification of intermediates, which in turn saves time, resources and hence increases the yield of desired compound.

Although the following examples illustrate the present invention in more detail, but should not be construed as limiting the scope of the invention.

EXAMPLES

Example1:Preparation of 2,6-bis-tertiarybutoxycarbonylamino hexanoic acid

To a solution of L-lysine monohydrochloride (25g, 0.14mol) and sodium hydroxide (15g) in water (250 ml), ditertiary butyl dicarbonate (70.0 g, 0.32 mol) was added at 15-25°C. The temperature was slowly raised to 55-60 °C and the reaction mixture was stirred for 12 hours.. After completion of reaction, (monitored by TLC), the reaction mixture was cooled to 10-15°C and pH was adjusted to 2.5-3.5 with 2N hydrochloric acid. The reaction mass was then extracted with dichloromethane (2 x 125 ml) and combined organic layer was successively washed with water (150 ml) and brine (150 ml). Dichloromethane layer was distilled under

vacuum at 30-40 °C to obtain 29.7g of title compound as a viscous oily mass having purity 96.5% by HPLC.

Example 2: Preparation of (5-tert-butoxycarbonylamino-5-(1-methyl-2-phenyl-ethylcarba moyl)-pentyl]-carbamic acid tert-butyl ester:

To a solution of 2,6-bis-tertbutoxy carbonylamino hexanoic acid (7.5g) in dichloromethane (150 ml) , triethyl amine (8.0 ml) was added at 25-30°C and the reaction mixture was stirred for 15 minutes. The solution was cooled to -15 to -10°C and isobutylchloroformate (4.35 g) was slowly added under nitrogen atmosphere and stirred for 30 minutes at -15°C to -10°C. A solution of D-amphetamine (3.85 g) in dichloromethane (10 ml) was slowly added and. the reaction mixture was stirred at 15 to -10°C for 60 minutes. The reaction completion was checked by TLC. After completion of the reaction temperature was raised to 25-30°C and reaction mixture was successively washed with 0.5 N hydrochloric acid solution (2 x 75 ml), sodium bicarbonate solution (5%w/w 75ml), water (50 ml) and brine solution (50 ml). The combined dichloromethane layer was dried over sodium sulfate (10.0 g) and distilled at 30-40°C to obtain a semisolid compound which was stirred with a mixture of n-heptane (85 ml) and ethyl acetate (5ml) at 25-30°C for 30 minutes. The solid, thus obtained, was filtered and dried to get 10.21 g of title compound having purity 89.77% by HPLC. The crude compound was dissolved in ethanol (45ml) at 50-55°C and water (50ml) was added. The reaction mixture was slowly cooled to 35-40°C, stirred for 30 minutes. The solid, thus obtained, was filtered and dried to get 7.35g of pure title compound as a white crystalline solid having purity 99.5 % by HPLC.

Example 3: Preparation of lisdexamphetamine dimesylate

(5-Tert-butoxycarbonylamino-5-(1-methyl-2-phenyl-ethylcarbamoyl)-pentyl]-carbamic acid tert-butyl ester (2.5g,) was dissolved in a mixture of isopropyl alcohol (10ml) and ethyl acetate (10ml) at 40-45°C and the reaction mass was cooled to 15-20°C. To this cold solution, methane sulphonic acid (2.5g) was added slowly and stirred for 12 hours at 15-20°C. The reaction completion was checked by HPLC. The resulting solid was filtered, washed with a mixture of chilled isopropyl alcohol (5ml) and ethyl acetate (5ml) and dried under vacuum to obtain 1.68 g of title compound as a white crystalline solid having purity 99.72 % by HPLC.

Example 4: Preparation of lisdexamphetamine dimesylate:

(5-Tert-butoxycarbonylamino-5-(1-methyl-2-phenyl-ethylcarbamoyl)-pentyl]-carbamic acid tert-butyl ester (2.5 g,) was dissolved in ethanol (20 ml) at 25-30°C. To the reaction mixture,

methane sulphonic acid (2.5 g) was slowly added and the reaction mixture was heated to 55-60°C and stirred for 3 hours at 55-60°C. The reaction mixture was cooled to 25-30°C, stirred for 2 hours, filtered, washed with ethanol (10ml) and dried under vacuum to obtain 1.55g of lisdexamphetamine dimesylate having purity 99.61 % by HPLC.

Example 5: Purification of lisdexamphetamine dimesylate

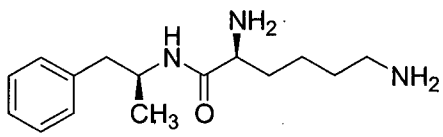
Lisdexamphetamine dimesylate (1.40g,) was dissolved in ethanol (10 ml) at 50-55 °C and ethyl acetate (10 ml) was slowly added at 50-55 °C. The reaction mixture was cooled to 20-25°C and stirred for 30 minutes. The resulting solid was filtered, washed with a mixture of ethanol and ethyl acetate (3 ml, 1:1) and dried under vacuum at 55-60°C to obtain 1.28g of pure lisdexamphetamine dimesylate as a white crystalline solid having purity 99.90 % by HPLC.

Example 6: Preparation of lisdexamphetamine dimesylate

To a stirred solution of L-lysine monohydrochloride (50g) and sodium hydroxide (30 g) in water (500ml) at 15-25°C, ditertbutyl dicarbonate(140g) was added. The temperature was slowly raised to 55-60°C and reaction mixture was stirred for 12 hours. After completion of reaction, the reaction mixture was cooled to 10-15°C and pH was adjusted to 2.5-3.5 with 2N hydrochloric acid. The reaction mixture was then extracted with dichloromethane (2 x 250 ml) and combined dichloromethane layer was successively washed with water (300 ml) and brine (300 ml). To the organic layer triethyl amine (58g) in dichloromethane (500 ml) was added. The solution was cooled to -15 to -20°C and isobutylchloroformate (42.5 g) was slowly added at -15 to -20°C and stirred for 1 hour. A solution of D-amphetamine (41.85 g) in dichloromethane (100 ml) was slowly added to reaction mixture at -15 to -20 °C and stirred. After completion of the reaction, the reaction mixture was successively washed with 0.5 N hydrochloric solution (2 x 450 ml), sodium bicarbonate solution (5%w/w, 450 ml), water (450 ml) and brine solution (450 ml). The organic layer was dried over sodium sulfate and distilled under vacuum at 30-40°C to afford a residue. To this residue, ethanol (480 ml) was added followed by slow addition of methane sulphonic acid (55 g) under nitrogen atmosphere. The reaction temperature was raised 55-60°C and after completion of reaction, the reaction mixture was cooled to 20-25°C and stirred for 2 hours. The resulting solid was filtered, washed with ethanol (50 ml) and suck dried for 30 minutes, further washed with ethanol and dried to obtain lisdexamphetamine dimesylate.

WE CLAIM:

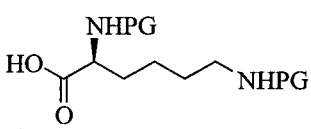
1. A process for preparation of lisdexamphetamine of formula I and its pharmaceutically acceptable salts,



Formula- I

which comprises steps of :

a) reacting L-lysine monohydrochloride with amine protecting group in the presence of a base in a solvent to give diamino protected L-lysine compound of formula II



Formula II

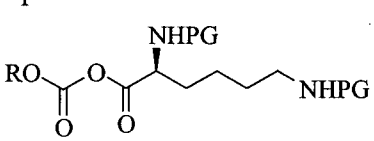
wherein PG is an amine protecting group

b) reacting diamino protected L-lysine compound of formula II with acid activating reagent of formula III

XCO_2R **Formula III**

wherein R is selected from alkyl or aryl or substituted aryl groups and X is halogen selected from chloro, bromo, Iodo.

in presence of a base in a solvent to form a mixed anhydride intermediate of formula IV,



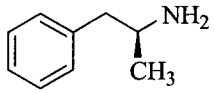
Formula IV

wherein R and PG are same as defined above

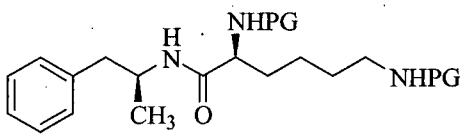
c)optionally isolating mixed anhydride intermediate of formula IV,

d)condensing mixed anhydride intermediate of formula IV with D-amphetamine of formula V,

Formula V



to give diamino protected amide compound of formula VI



Formula VI

wherein PG is same as defined above

e)converting diamino protected amide compound of formula VI into lisdexamphetamine and its pharmaceutically acceptable salts.

2. The process according to claim 1, wherein in step a) base is selected from alkali or alkaline metal hydroxides, carbonates, alkoxides and hydrides thereof, and solvents is selected from water or water miscible solvent like methanol, ethanol, n-propyl alcohol, isopropyl alcohol, tetrahydrofuran, *N,N*-dimethylformamide, *N,N*-dimethyl acetamide, dimethyl sulfoxide, acetonitrile, propionitrile, acetone, ethyl methyl ketone, diethyl ketone and mixture thereof. .

3. The process according to claim 1, wherein in step b) base is selected from triethyl amine, di-isopropyl ethyl amine, tri-n-propyl amine, tri-n-butyl amine, pyridine, lutidine and like thereof and solvent is selected from C_{5-8} aliphatic or aromatic hydrocarbons such as n-pentane, n-hexane, n-heptane, cyclopentane, cyclohexane, cycloheptane, toluene, 1,2 and 1,4 xylene; C_{1-4} halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1.2-dichloroethane; C_{3-6} esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate; C_{4-8} ethers such as diethyl ether, di-isopropyl ether, t-butyl methyl ether, 1,2-dimethoxy ethane, 1,2-diethoxy ethane, tetrahydrofuran, 2-methyl tetrahydrofuran and dioxane; C_{3-6} ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diethyl ketone; alkylnitriles such as acetonitrile, propionitrile; amides such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide; sulfoxide such as dimethyl sulfoxide and mixture thereof.

4. A process for purification of diamino protected amide compound of formula VI, which comprises the steps of:

a) dissolving crude diamino protected compound of formula VI in a suitable solvent,

b) adding anti solvent to precipitate the compound, and

c) isolating pure diamino protected amide compound of formula VI .

5. The process according to claim 4, wherein in step a) suitable solvent is selected from - C_{1-5} alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, pentanol; halogenated solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane; ethers such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tertiary butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 1,2-dimethoxy ethane, 1,2-diethoxy ethane, C_{3-6} aliphatic ketones such as acetone, diethyl ketone, methyl isobutyl ketone , ethyl methyl ketone and like thereof and in step b) anti solvent is selected from water; aliphatic or aromatic hydrocarbons such as n-pentane, n-hexane, hexanes, n-heptane, heptanes, cyclohexane, cycloheptane, toluene, 1,2 and 1,4 xylene; alkyl nitriles such as acetonitrile, propionitrile; aliphatic ethers such as diethyl ether, diisopropyl ether, methyl tertiary butyl ether and mixture thereof.

6. A process of preparation of diamino protected amide compound of formula VI which comprises the step of :

a)reacting diamino protected L-lysine derivative of formula II with a compound of formula III in the presence of a suitable base in a solvent to form mixed anhydride intermediate of formula IV,

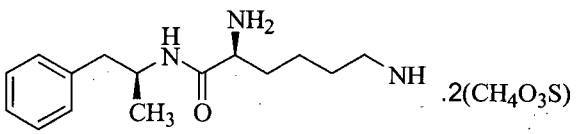
b) optionally isolating mixed anhydride intermediate of formula IV,

c) reacting mixed anhydride intermediate of formula IV with D-amphetamine of formula V to form diamino protected compound of formula VI.

7. The process according to claim 6, wherein base is selected from triethyl amine, di-isopropyl ethyl amine, tri-n-propyl amine, tri-n-butyl amine, pyridine, lutidine and like thereof and solvent is selected from C_{5-8} aliphatic or aromatic hydrocarbons such as n-pentane, n-hexane, n-heptane, cyclopentane, cyclohexane, cycloheptane, toluene, 1,2 or 1,4 xylene; C_{1-4} halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane; C_{3-6} esters such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate; C_{4-8} ethers such as diethyl ether, diisopropyl ether, t-butyl methyl ether, 1,2-dimethoxy ethane, 1,2-diethoxy ethane, tetrahydrofuran, 2-methyl tetrahydrofuran and dioxane; C_{3-6} ketones such as acetone, methyl ethyl ketone, diethyl

ketone, methyl isobutyl ketone, and amides such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, sulfoxide such as dimethyl sulfoxide; alkyl nitriles such as acetonitrile, propionitrile and mixture thereof.

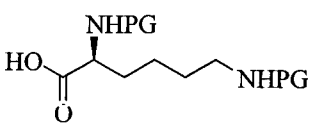
8. A one pot process for preparation of lisdexamphetamine dimesylate of formula IA,



Formula- IA

which comprises steps of :

a) reacting L-lysine monohydrochloride with amine protecting group in the presence of a base in a solvent to give diamino protected L-lysine compound of formula II



Formula II

wherein PG is an amine protecting group

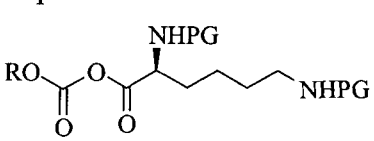
b) reacting diamino protected L-lysine compound of formula II with acid activating reagent of formula III

XCO_2R **Formula III**

wherein R is selected from alkyl or aryl or substituted aryl groups

and X is halogen selected from chloro, bromo, Iodo.

in presence of a base in a solvent to form a mixed anhydride intermediate of formula IV,

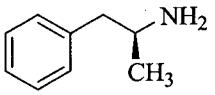


Formula IV

wherein R and PG are same as defined above

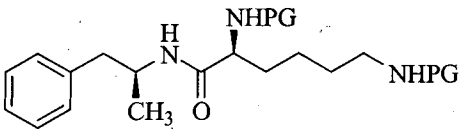
c)optionally isolating mixed anhydride intermediate of formula IV,

d)condensing mixed anhydride intermediate of formula IV with D-amphetamine of formula V,



Formula V

to give diamino protected amide compound of formula VI,



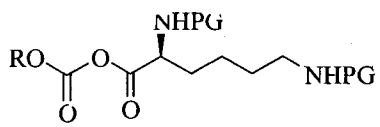
Formula VI

wherein PG is same as defined above

e) treating diamino protected amide compound of formula VI with methane sulphonic acid to obtain lisdexamphetamine dimesylate of formula IA.

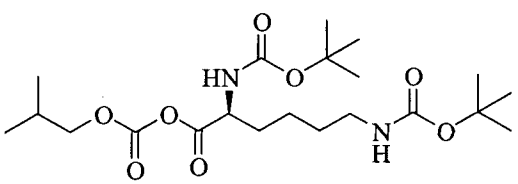
9. The process according to claim 8, further comprises step of purifying lisdexamphetamine dimesylate of formula IA by simple recrystallization.

10. Mixed anhydride intermediates of formulae IV and IVA



Formula IV

wherein R is selected from alkyl or aryl or substituted aryl groups and PG is amine protecting group



Formula IVA

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2012/000506

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07C 237/-, C07C 231/-, C07C 271/-, C07 C269/-

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CNKI, CNPAT, REGISTRY, CAPLUS, CA: lisdexamphetamine, BOC, diamino, purification, crystallization, formate, lysine, amphetamine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/148305 Al (CAMBREX CHARLES CITY, INC. et al.) 23 Dec. 2010 (23.12.2010) abstract, page 8 scheme 1, pages 45-48 examples 1-4	4-5
A		1-3,6-10
A	WO 2010/042120 Al (ARCHIMICA, INC. et al.) 15 Apr. 2010 (15.04.2010) abstract, page 5 equation 2	1-10
A	US 2008/0086016 Al (MICKLE, Travis et al.) 10 Apr. 2008 (10.04.2008) abstract, page 12 examples 1-2, Figures 1-5	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 Nov. 2012 (07.11.2012)	**06 Dec. 2012 (06.12.2012)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer LI, Heng Telephone No. (86-10)82246740

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2012/000506

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2010/148305 Al	23.12.2010	US2012190880A1	26.07.2012
WO 2010/042120 Al	15.04.2010	US 2011196173 A1	11.08.2011
US 2008/086016 A1	10.04.2008	WO 2005000334 A1	06.01.2005
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		EP 1644019 B1	15.02.2012

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2012/000506

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		JP 4898445 B2	14.03.2012

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2012/000506

A. CLASSIFICATION OF SUBJECT MATTER

C07C 237/06 (2006.01) i

C07C 231/02 (2006.01) i

C07C 271/22 (2006.01) i

C07C 269/04 (2006.01) i