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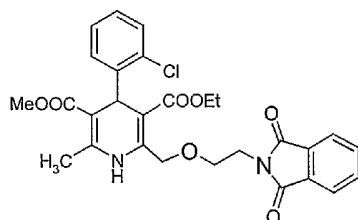
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(54) Title: PROCESS FOR THE PREPARATION OF AMLODIPINE SALTS



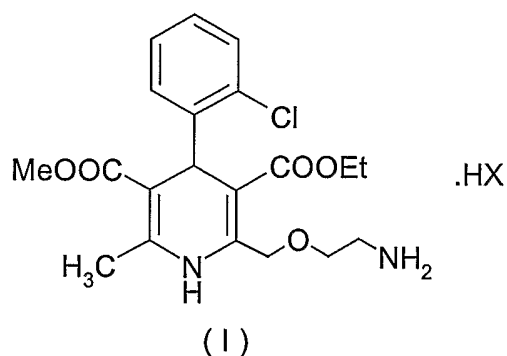
(II)

(57) Abstract: A process for the preparation of salts of amlodipine comprises subjecting a compound of formula (II) to a deprotec-
tion reaction and converting the amlodipine free base thus obtained to a salt (1) without isolating amlodipine free base. Preferably,
the maleate, besylate, malate or fumarate salt is made.

PROCESS FOR THE PREPARATION OF AMLODIPINE SALTS

The present invention relates to a process for preparing amlodipine salts and to pharmaceutical compositions containing amlodipine salts so prepared.

Amlodipine is chemically described as 2-[2-(amino ethoxy) methyl]-4-(2-chlorophenyl)-3-ethoxy carbonyl-5-methoxy carbonyl-6-methyl-1, 4-dihydropyridine (I).



The compound forms addition salts with acids of the form HX, where X typically represents maleate, mesylate, besylate, fumarate or malate anions. The compound is useful in the treatment of hypertension and angina.

A number of patents describe the synthesis of amlodipine and its salts, including the maleate, mesylate, besylate, fumarate and malate salts.

US 4,430,333 describes a process for the preparation of amlodipine salts and pharmaceutical compositions thereof for treating hypertension and ischaemia in animals.

US 5,389,654 reports a process for preparing amlodipine mono benzene sulfonate. The said process comprises reacting amlodipine with benzene sulfonic acid in methanolic or an aqueous methanolic medium at a temperature of from 20° C to reflux.

US 4,879,303 describes improved pharmaceutical salts of amlodipine, particularly the besylate salt and pharmaceutical compositions thereof in the form of tablets and capsules. This patent discloses single crystalline anhydrous besylate salt of amlodipine non-hygroscopic which is prepared by combining either benzene sulfonic acid or ammonium benzene sulfonate with a slurry of amlodipine free base in industrial methylated spirit.

EP 1,287,826 to Pfizer claims a process for preparing free base amlodipine as well as its besylate salts. The amlodipine free base as well as its salts are used to prepare medicaments for the treatment of ischaemic heart disease or hypertension.

GB 2,188,630 reports improved besylate salts of amlodipine and a pharmaceutical composition thereof for anti-ischaemia and anti-hypertension in the form of a tablet.

US 6,600,047 discloses a process for making amlodipine maleate which comprises reacting amlodipine or an acid addition salt thereof with maleic acid. Also, a purification method for the same is reported in this patent.

US 6,608,206 (CSIR) describes a process for S (-) amlodipine salts such as besylate, succinate, maleate, oxalate and tosylate in the presence of an organic solvent and at room temperature. Acid to amlodipine is used in the ratio of 1:1 and the water to solvent ratio used is 8:1.

US 6,518,288 claims amlodipine hemifumarate, crystalline salts thereof and process for the same.

WO02,053,135 discloses a pharmaceutical tablet composition comprising an effective amount of amlodipine free base in crystalline form I and II with pharmaceutically acceptable excipients. Also claimed is a process for the preparation of amlodipine free base and its method of crystallization for Form I and II. The said process comprises deprotecting an N-protected amlodipine and precipitating amlodipine free base and isolation of the same.

WO 03,004,025 describes a process for highly pure amlodipine benzene sulfonate salt and use of this salt to prepare a medicament in the form of a tablet for the treatment of heart disease or hypertension.

Patent application number US 20020,068,831 discloses a process for the preparation of intermediates of amlodipine such as ethyl-3-amino-4-(2-(phthalimido)ethoxy)crotonate.

Another application number US 20020,143,046 describes a process for making amlodipine derivatives and a precursor thereof. Pharmaceutically acceptable acid addition salts produced in this patent application are amlodipine maleate, mesylate or besylate.

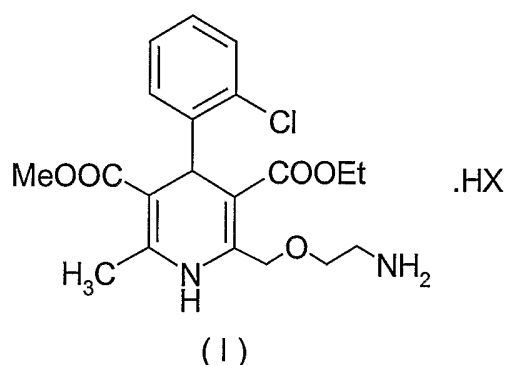
US 20030,022,922 describes a process for the preparation of crystalline amlodipine free base of Form I and II with particle size of at least 100 micron which is used to prepare the formulation in an oral dosage form such as a tablet with less stickiness and punch residue.

Patent application number US 20030,139,455 discloses a process for the preparation of crystalline amlodipine besylate hydrate (ie. monohydrate and dihydrate) and amlodipine besylate anhydrides.

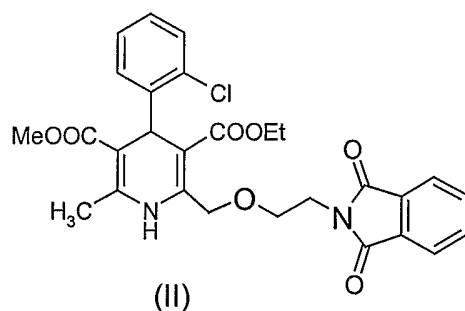
EP 244944, WO 02/053535 and WO 99/52873 describe processes to make amlodipine salts, namely the besylate by prior isolation of amlodipine free base.

All the above patents describe the isolation of amlodipine base after deprotection step using various deprotecting agents. We have now found that contrary to previous teaching, isolation of the base can in fact be dispensed with without affecting the process: indeed, improvement can be obtained.

According to the present invention, there is provided a process for the preparation of an amlodipine salt of formula (I)



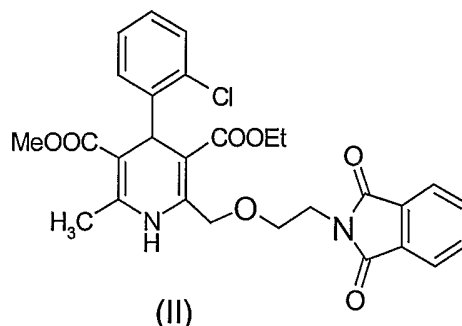
where X is the anion of a pharmaceutically acceptable acid, which process comprises subjecting a compound of formula (II)



to a deprotection reaction and converting the amlodipine free base thus obtained to a salt (I) without isolating amlodipine free base.

Our process is an improved process over above reported process for amlodipine salts where amlodipine free base is prepared and thereafter converted into the salts. The present invention uses a protected amlodipine compound as a starting material and converts this into the desired salt in one step in high purity and yield without isolating the free base. By not isolating the free base, we mean that the base is not separated from the reaction mixture before conversion to the salt.

The present invention provides for an improved one pot process for preparation of amlodipine salts from the phthaloyl protected amlodipine (II) by a process involving deprotection of the phthalimido group and converting the free base thus obtained to the desired salt (I)



without isolating the amlodipine free base. It was found that, surprisingly, this process gives yields that are at least 20% higher than the processes disclosed in the prior art patents.

In the newly developed process, phthaloyl amlodipine (II) is used as the starting material to prepare amlodipine (I) and its salts. Phthaloyl amlodipine (II) is preferably treated with aqueous solutions of primary amines in water immiscible solvents such as methylene chloride, ethylene dichloride, chloroform ethyl acetate and toluene or alcoholic solutions of primary amines followed by treatment of the organic phase with suitable organic acids to give amlodipine in the form of a pharmaceutically acceptable salt.

The product so obtained is preferably purified using C-1 to C-4 aliphatic alcohols, or esters or mixtures thereof to give an amlodipine salt having a uniform particle size, free flowing powder characteristics and low levels of impurities.

In a preferred embodiment of the invention, the process comprises producing 2-[2-(aminoethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine mesylate by the deprotection reaction of phthaloyl amlodipine (II) with aqueous monomethylamine in solvents selected from methylene chloride, ethylene dichloride, toluene, and chloroform, followed by treatment with methane sulfonic acid. Amlodipine mesylate thus produced may be crystallized from a suitable solvent or mixtures of suitable solvents.

In another preferred embodiment of the invention, the process comprises producing 2-[2-(amino ethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine mesylate by the deprotection reaction of phthaloyl amlodipine (II) with methanolic monomethylamine followed by treatment with methane sulfonic acid. Amlodipine mesylate thus produced may be crystallized from a suitable solvent or mixtures of suitable solvents.

In another preferred embodiment of the invention, the process comprises producing 2-[2-(amino ethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro pyridine besylate by the deprotection reaction of phthaloyl amlodipine (II) with aqueous monomethylamine in solvents selected from methylene chloride, ethylene dichloride, toluene, and chloroform, followed by treatment with benzene sulfonic acid. Amlodipine besylate thus produced may be crystallized from a suitable solvent or mixtures of suitable solvents.

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In another preferred embodiment of the invention, the process comprises producing 2-[2-(amino ethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro pyridine malate by the deprotection reaction of phthaloyl amlodipine (II) with aqueous monomethylamine in solvents selected from methylene chloride, ethylene dichloride, toluene, and chloroform, followed by treatment with malic acid. Amlodipine malate thus produced may be purified from a suitable solvent or mixtures of suitable solvents.

In another preferred embodiment of the invention, the process comprises producing 2-[2-(amino ethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro pyridine malate by the deprotection reaction of phthaloyl amlodipine (II) with methanolic

monomethylamine followed by treatment with malic acid. Amlodipine malate thus produced may be purified from a suitable solvent or mixtures of suitable solvents.

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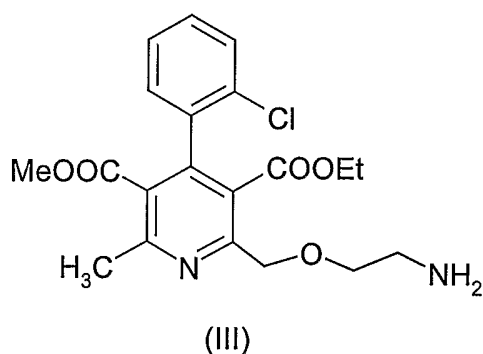
In another preferred embodiment of the invention, the process comprises producing 2-[2-(aminoethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro pyridine maleate by the deprotection reaction of phthaloyl amlodipine (II) with methanolic mono methylamine followed by treatment with maleic acid. Amlodipine maleate thus produced may be purified from a suitable solvent or mixtures of suitable solvents.

In another preferred embodiment of the invention, the process comprises producing 2-[2-(aminoethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro pyridine fumarate by the deprotection reaction of phthaloyl amlodipine (II) with aqueous monomethylamine in solvents selected from methylene chloride, ethylene dichloride, toluene, and chloroform, followed by treatment with fumaric acid. Amlodipine fumarate thus produced may be purified from a suitable solvent or mixtures of suitable solvents.

In another preferred embodiment of the invention, the process comprises producing 2-[2-(aminoethoxy)-methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro pyridine fumarate by the deprotection reaction of phthaloyl amlodipine (II) with methanolic monomethylamine followed by treatment with fumaric acid. Amlodipine fumarate thus produced may be purified from a suitable solvent or mixtures of suitable solvents.

The preferred solvent for the deprotection is methylene chloride. The reaction is preferably carried out at ambient temperature (for example, 20°C to 30°C). After the deprotection reaction the aqueous phase containing, for example, mono methylamine is separated and the organic phase is washed with water to remove excess mono methylamine. The neutral organic layer is taken directly for salt formation or is partially replaced by another solvent before salt formation.

The salt obtained is preferably crystallized from C-1 to C-4 alcohols or esters or mixtures thereof. Amodipine salts prepared by the process of the present invention are characterized by high purity of more than 99.7%. The product is further characterized by a very low level of the pyridine impurity (III), preferably the impurity is less than 0.1% (percentages are by weight of product).



The invention is further illustrated by the following examples.

Example 1 :

100 grams of phthaloyl amlodipine is stirred in a mixture of 40% aqueous monomethylamine (700 ml) and methylene chloride (500ml) at ambient temperature for 12 hours. After reaction completion, the MDC layer is separated and the organic layer is washed with water. The MDC layer is dried over sodium sulfate and distilled to about half the original volume. Isopropyl alcohol (700 ml) is added and the distillation continued till a total volume of 600 ml is left behind. The contents are then cooled to 25 - 30°C.

Benzene sulfonic acid (30 gm) is dissolved in 100 ml of isopropyl alcohol and is added to the above solution in 30 – 45 mins. at 25 - 30°C. Then the contents are stirred for 1 hour at 0 – 5 °C for 30 mins and filtered to give amlodipine besylate.

Example 2 :

100 grams of phthaloyl amlodipine is stirred in 20% methanolic monomethylamine (1000 ml.) for 12 hours at room temperature. After reaction completion, the reaction mass is distilled to half of its original volume and 800 ml of MDC is added and further distilled till a total of 500 ml remains in the reaction flask. The MDC layer is washed with water and dried over sodium sulfate. The MDC layer is distilled to half the original volume. 800 ml isopropyl alcohol is added and further distilled till 600ml of solution is retained. The contents are then cooled to 25 - 30°C

30 gm of Benzene sulfonic acid dissolved in 100 ml of isopropyl alcohol is added to the above solution in 30 – 45 mins. at 25 - 30°C. Then the contents are stirred for 1 hour at 0 – 5 °C for 30 mins. and filtered to give amlodipine besylate.

This amlodipine besylate is dissolved in 300 ml of methanol at 40 - 45°C. 400 ml of isopropyl alcohol is added at 35 - 40°C. The contents are then stirred at 25 - 30°C for 1 hour, cooled and filtered.

Example 3

100 grams of phthaloyl amlodipine is stirred in a mixture of 40% aqueous monomethylamine (700 ml) and methylene chloride (500ml) at ambient temperature for 12 hours. After reaction completion, the MDC layer is separated and the organic layer is washed with water. The MDC layer is dried over sodium sulfate and distilled to about half the original volume. Ethyl acetate (1000 ml) is added and the distillation continued till a total volume of 600 ml is left behind. The contents are then cooled to 25 - 30°C.

Methane sulfonic acid (18 gm) is dissolved in 100 ml of ethyl acetate and is added to the above solution in 30 – 45 mins. at 20 - 25°C maintaining an inert atmosphere. Then the contents are stirred for 1 hour at 0 – 5 °C for 30 mins and filtered to give amlodipine mesylate.

Example 4 :

100 grams of phthaloyl amlodipine is stirred in 20% methanolic monomethylamine (1000 ml.) for 12 hours at room temperature. After reaction completion, the reaction mass is distilled to half of its original volume and 800 ml of MDC is added and further distilled till a total of 500 ml remains in the reaction flask. The MDC layer is washed with water and dried over sodium sulfate. The MDC layer is distilled to half the original volume. 1000 ml ethyl acetate is added and further distilled till 600ml of solution is retained. The contents are then cooled to 25 - 30°C.

18 gm of methane sulfonic acid dissolved in 100 ml of ethyl acetate is added to the above solution in 30 – 45 mins. at 20 - 25°C under an inert atmosphere. Then the contents are stirred for 1 hour at 0 – 5 °C for 30 mins. and filtered to give amlodipine mesylate.

This amlodipine mesylate is dissolved in 900 ml of ethyl acetate, 100 ml methanol and 10ml purified water at 40 - 45°C. The contents are then stirred at 25 - 30°C for 1 hour, cooled and filtered.

Example 5

100 grams of phthaloyl amlodipine is stirred in a mixture of 40% aqueous monomethylamine (700 ml) and methylene chloride (500ml) at ambient temperature for 12 hours. After reaction completion, the MDC layer is separated and the organic layer is washed with water. The MDC layer is dried over sodium sulfate and distilled to about half the original volume. Ethyl acetate (1000 ml) is added and the distillation continued till a total volume of 600 ml is left behind. The contents are then cooled to 25 - 30°C.

Malic acid (17.8g) dissolved in 50ml of methanol and is added to above solution in 30-45mins at 25-30C. Then the contents were stirred at 25-30C for 1hour and filtered to give amlodipine malate.

Example 6 :

100 grams of phthaloyl amlodipine is stirred in 20% methanolic monomethylamine (1000 ml.) for 12 hours at room temperature. After reaction completion, the reaction mass is distilled to half of its original volume and 800 ml of MDC is added and further distilled till a total of 500 ml remains in the reaction flask. The MDC layer is washed with water and dried over sodium sulfate. The MDC layer is distilled to half the original volume. 1000 ml ethyl acetate is added and further distilled till 600ml of solution is retained. The contents are then cooled to 25 - 30°C. Malic acid (17.8g) dissolved in 50ml of methanol is added to above solution in 30-45mins at 25-30C. Then the contents were stirred at 25-30C for 1hour and filtered to give amlodipine malate. This amlodipine malate is stirred in 900 ml of ethyl acetate and 100 ml methanol at 40 - 45°C. The contents are then stirred at 25 - 30°C for 1 hour and filtered.

Example 7

100 grams of phthaloyl amlodipine is stirred in 20% methanolic monomethylamine (1000 ml.) for 12 hours at room temperature. After reaction completion, the reaction mass is distilled to half of its original volume and 800 ml of MDC is added and further distilled till a total of 500 ml remains in the reaction flask. The MDC layer is washed with water and dried over sodium sulfate. The MDC layer is distilled to half the original volume. 400ml Isopropyl is added and further distilled till 250ml of solution is retained. The contents are then cooled to 25 - 30°C and to this 100ml methanol is added. The contents then cooled to 25-30C. Maleic acid (21g) dissolved in 50ml of methanol and is added to above solution in 30-45 mins at 25-30C. Then the contents were stirred at 25-30C for 1hour and filtered to give amlodipine maleate.

Example 8

100 grams of phthaloyl amlodipine is stirred in a mixture of 40% aqueous monomethylamine (700 ml) and Methylene chloride (500ml) at ambient temperature for 12 hours. After reaction completion, the MDC layer is separated and the organic layer is washed with water. The MDC layer is dried over sodium sulfate and distilled to about half the original volume. 400ml Isopropyl is added and further distilled till 250ml of solution is retained. The contents are then cooled to 25 - 30°C and to this 100ml methanol is added. The contents then cooled to 25-30°C. Maleic acid (21g) dissolved in 50ml of methanol is added to above solution in 30-45 mins at 25-30°C. Then the contents were stirred at 25-30°C for 1 hour and filtered to give amlodipine maleate. This amlodipine maleate is stirred in 700 ml of Isopropyl alcohol and 300 ml methanol at 40 - 45°C. The contents are then stirred at 25 - 30°C for 1 hour and filtered.

Example 9

100 grams of phthaloyl amlodipine is stirred in a mixture of 40% aqueous monomethylamine (700 ml) and methylene chloride (500ml) at ambient temperature for 12 hours. After reaction completion, the MDC layer is separated and the organic layer is washed with water. The MDC layer is dried over sodium sulfate and distilled to about half the original volume. 400ml Isopropyl alcohol is added and further distilled till 250ml of solution is retained. The contents are then cooled to 25 - 30°C and to this 100ml methanol is added. The contents then cooled to 25-30°C. Fumaric acid (21g) dissolved in 50ml of methanol is added to above solution in 30-45 mins at 25-30°C. Then the contents were stirred at 25-30°C for 1 hour and filtered to give amlodipine fumarate.

Example 10

100 grams of phthaloyl amlodipine is stirred in 20% methanolic monomethylamine (1000 ml.) for 12 hours at room temperature. After reaction completion, the reaction mass is distilled to half of its original volume and 800 ml of MDC is added and further distilled till a total of 500 ml remains in the reaction flask. The MDC layer is washed with water and dried over

sodium sulfate. The MDC layer is distilled to half the original volume. 400ml Isopropyl alcohol is added and further distilled till 250ml of solution is retained. The contents are then cooled to 25 - 30°C and to this 100ml methanol is added. The contents then cooled to 25-30°C. Fumaric acid (21g) dissolved in 50ml of methanol and is added to above solution in 30-45mins at 25-30°C. Then the contents were stirred at 25-30°C for 1 hour and filtered to give amlodipine fumarate. This amlodipine fumarate is stirred in 700 ml of Isopropyl alcohol and 300 ml methanol at 40 - 45°C. The contents are then stirred at 25 - 30°C for 1 hour and filtered.

Example 11

Tablet containing amlodipine besylate made according to the process of the invention.

Sr. no	Ingredients	Mg/tab
1.	Amlodipine besylate	13.87
2.	Microcrystalline cellulose	110.00
3.	Dibasic calcium phosphate	48.93
4.	Sodium starch glycollate	4.00
5.	Colloidal silicon dioxide	1.00
6.	Magnesium stearate	2.20

Manufacturing Procedure:

Cosift 1 with 3 to form premix A. Cosift 4 with 5 to form premix B. Load premix A followed by 2 and premix B in a suitable blender. Lubricate the above blend with 6 and compress to form tablets.

Example 12

Tablet containing amlodipine mesylate made according to the process of the invention.

Sr. no	Ingredients	Mg/tab
1.	Amlodipine mesylate	12.79
2.	Microcrystalline cellulose	110.00
3.	Dibasic calcium phosphate	50.01

4.	Sodium starch glycollate	4.00
5.	Colloidal silicon dioxide	1.00
6.	Magnesium stearate	2.20

Manufacturing process.

Same as example 11

Example 13

Tablet containing amlodipine maleate made according to the process of the invention

Sr. no	Ingredients	Mg/tab
1.	Amlodipine maleate	12.84
2.	Microcrystalline cellulose	110.00
3.	Dibasic calcium phosphate	49.96
4.	Sodium starch glycollate	4.00
5.	Colloidal silicon dioxide	1.00
6.	Magnesium stearate	2.20

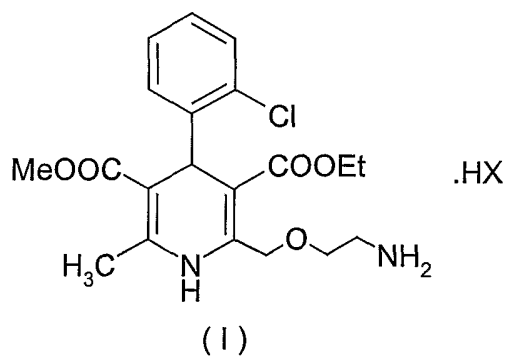
Manufacturing process

Same as example 11

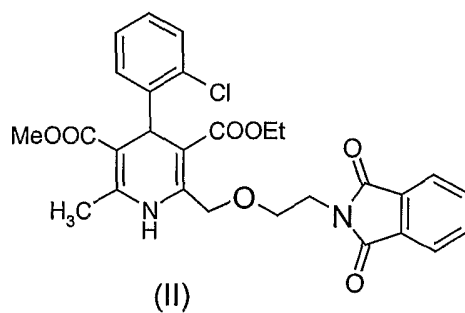
While the present invention is described above in connection with preferred or illustrative embodiments, these embodiments are not intended to be exhaustive or limiting of the invention. Rather, the invention is intended to cover all alternatives, modifications and equivalents included within its spirit and scope, as defined by the appended claims.

CLAIMS

1. A process for the preparation of an amlodipine salt of formula (I)

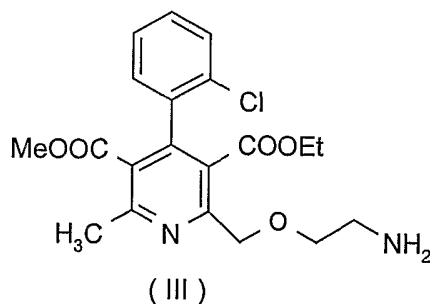


where X is the anion of a pharmaceutically acceptable acid, which process comprises subjecting a compound of formula (II)



to a deprotection reaction and converting the amlodipine free base thus obtained to a salt (I) without isolating amlodipine free base.

2. A process according to claim 1 wherein X is maleate, mesylate, besylate, malate or fumarate.
3. A process according to claim 1 or 2 wherein the deprotection reaction is carried out in the presence of an aqueous solution of a primary amine in a water immiscible solvent, or is carried out using an alcoholic solution of a primary amine.
4. A process according to claim 3 wherein the primary amine is monomethyl amine.
5. A process according to claim 3 or 4 wherein the water immiscible solvent is methylene chloride, ethyl acetate, toluene or chloroform.
6. A process according to claim 3, 4 or 5 wherein the deprotection reaction is carried out in the presence of an alcoholic solution of monomethyl amine.
7. A process according to claim 3, 4 or 6 wherein the alcohol used is methanol, ethanol or isopropanol.
8. A process according to any preceding claim wherein the salt (I) is crystallized from C1 to C4 alcohol or esters or mixtures thereof.
9. A process according to any preceding claim wherein the compound of formula (I) has total impurities less than 0.3% and pyridine impurity (III) less than 0.1% (by weight of the compound (I)).



10. A process for the preparation of a compound of formula (I) as claimed in claim 1 substantially as described herein are with reference to Examples 1 to 10.
11. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 and prepared in accordance with the process of any preceding claim, and a pharmaceutically acceptable carrier.
12. A process according to any one of claims 1 to 10 which is a one pot process.

INTERNATIONAL SEARCH REPORT

National Application No

Г/GB2004/003756

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D211/90 A61K31/4422 A61P9/12 A61P9/10		
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 7 C07D		
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 practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 572 909 A (CROSS PETER E ET AL) 25 February 1986 (1986-02-25) example 22, method A, col.16 -----	1-12
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