



(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IN2010/000467

(22) International Filing Date:
13 July 2010 (13.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1643/MUM/2009 14 July 2009 (14.07.2009) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: AN IMPROVED PROCESS FOR PREPARATION OF OLMESARTAN

(57) Abstract: The invention relates to processes for the preparation of olmesartan medoxomil and intermediates thereof. More particularly, it relates to a process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)-biphenyl-4-yl]methyl]imidazole-5-carboxylate, and its use in the preparation of olmesartan medoxomil. The invention also relates to crystalline olmesartan medoximil and pharmaceutical compositions that include the crystalline olmesartan medoximil.



WO 2011/007368 A2

AN IMPROVED PROCESS FOR PREPARATION OF OLMESARTAN

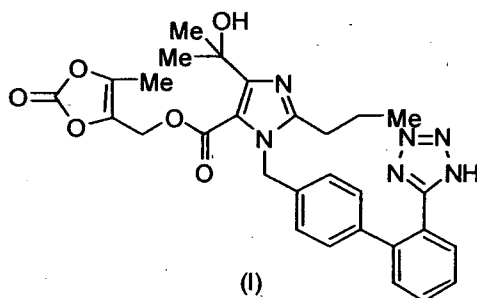
FIELD OF THE INVENTION

The invention relates to processes for the preparation of olmesartan medoxomil and intermediates thereof. More particularly, it relates to a process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]-biphenyl-4-yl]methyl]imidazole-5-carboxylate, and its use in the preparation of olmesartan medoxomil. The invention also relates to crystalline olmesartan medoximil and pharmaceutical compositions that include the crystalline olmesartan medoximil.

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

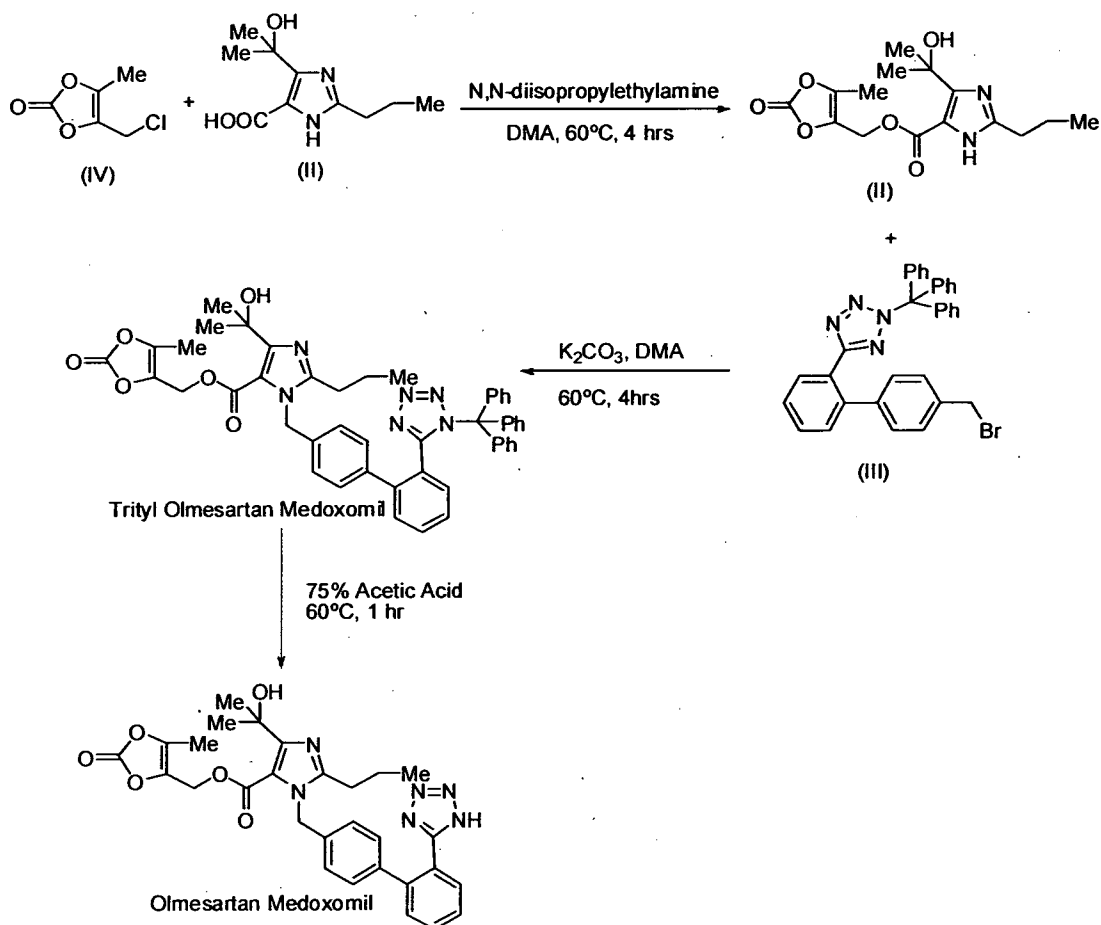
Olmesartan medoxomil is chemically, (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl)methyl)-1H-imidazole-5-carboxylate having the structural Formula (I):



20

Olmesartan medoxomil is an anti-hypertensive pro-drug ester that is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. It is a selective AT₁ subtype angiotensin II receptor antagonist and blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in vascular smooth muscle. Olmesartan medoxomil is indicated for the treatment of hypertension and is commercially sold under the trade name Benicar®.

Olmesartan medoxomil was first disclosed in U.S. Patent No. 5,616,599. The synthetic method employed is depicted in the following reaction **Scheme-1**, where an imidazole derivative is condensed with a dioxolyl compound, then reacted with a substituted biphenyl methyl halide to obtain trityl olmesartan medoxomil, which is then
 5 deprotected to obtain olmesartan.



Scheme 1

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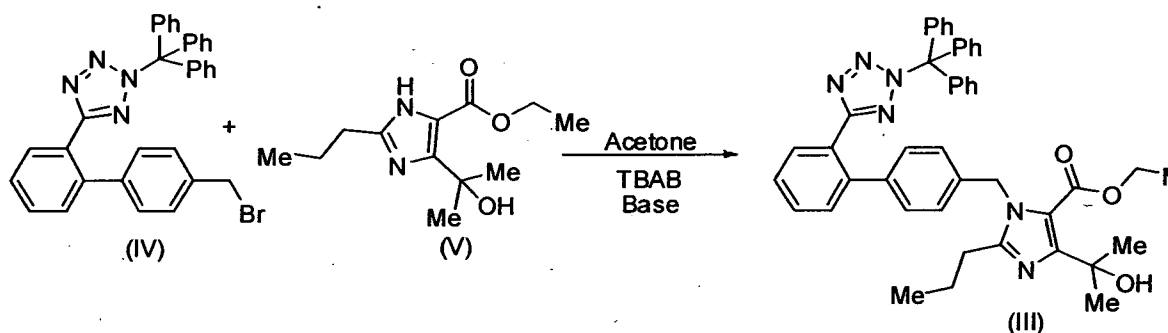
The patent also discloses a process for the preparation of olmesartan medoxomil, which involves a coupling reaction between an imidazole derivative and a substituted biphenyl methyl halide, followed by condensation with the dioxolyl compound and subsequent deprotection to get olmesartan medoxomil.

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The coupling reaction involves the use of a strong base such as sodium hydride, which is difficult to handle at an industrial scale. The coupling reaction is conducted at a temperature of 60°C. The product obtained contains impurities and requires further

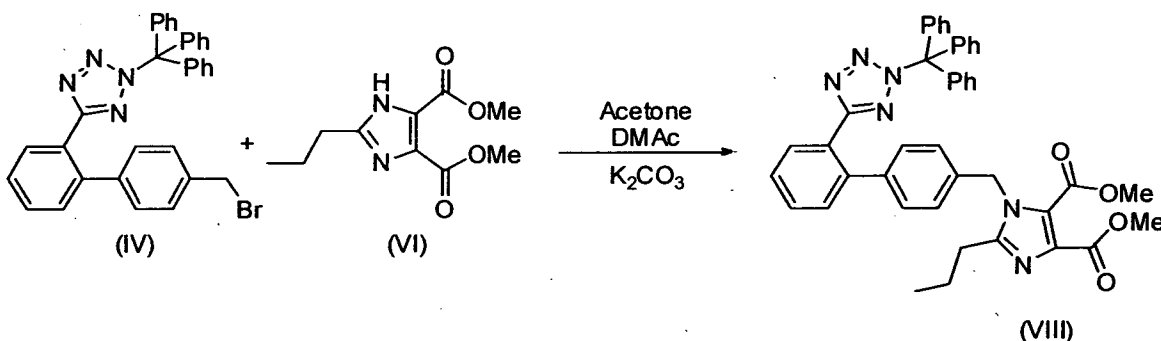
purification involving column chromatography. The overall process is hazardous, tedious, time consuming and involves many steps.

EP 1916246 A2 discloses a process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)2-propyl-1-[[2'-(triphenylmethyl)-2H-tetrazol-5yl]biphenyl-4-yl]methyl] imidazole -5-carboxylate (III) by reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate (V) with N-(triphenyl- methyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (IV) in an organic solvent in presence of a base and a phase transfer catalyst.



Scheme-2

International (PCT) Publication No. WO 2007/047838 A2 discloses a mixture of acetone and N,N-dimethylacetamide solvents for condensation of dimethyl-2-propylimidazole-4,5-dicarboxylate (VI) compound with 4-[2-trityltetrazole-5-yl]phenyl}methyl benzyl bromide of formula (IV) in presence of potassium carbonate to obtain dimethyl 2-propyl-1-[4-(2-trityltetrazol-5-yl)phenyl]phenylmethylimidazole-4,5-dicarboxylate.



Scheme-3

International (PCT) Publication No. WO 2007/017135 A2 discloses a process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)2-propyl-1-[[2'-(triphenylmethyl)-2H-tetrazol-5yl]biphenyl-4-yl]methyl] imidazole-5-carboxylate of formula (III) by reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-

carboxylate of formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (IV) in presence of K_2CO_3 in acetonitrile.

International (PCT) Publication No. WO 2007/048361 A2 discloses a process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate of formula (III) by reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of formula (IV) in the presence of potash in acetone in presence of PEG-400 as a phase transfer catalyst.

International (PCT) Publication No. WO 2007/148344 A1 discloses an in-situ process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate of formula (III) by condensing ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of formula (IV) in the presence of potassium carbonate base in acetone solvent in presence of tetrabutylammonium bromide as a phase transfer catalyst.

International (PCT) Publication No. WO 2008/043996 A2 discloses a process for the condensation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV) in the presence of a metal hydroxide/carbonate base in a polar aprotic solvent like N,N-dimethylacetamide in absence of phase transfer catalyst to provide ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III).

International (PCT) Publication No. WO 2009/019304 A1 also provides a process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III) by condensation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV) in the presence of $LiOH \cdot H_2O$ in N,N-dimethylacetamide solvent in absence of a phase transfer catalyst.

Further, in a reference article, Synthesis of a novel angiotensin II receptor antagonist olmesartan medoxomil. *Huadong Ligong Daxue Xuebao, Ziran Kexueban* (2005), 31(2), 189-192, a process for new angiotensin I receptor antagonist, olmesartan medoxomil is disclosed, which involves synthesis using tartaric acid as a starting

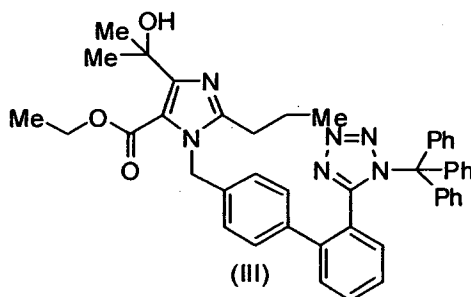
material via nitration, cyclization, esterification, Grignard reaction, N-alkylation, hydrolysis, O-alkylation and N-deprotection in 32.7% overall yield.

The synthesis of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of
 5 Formula (III) described in the prior art involves use of phase transfer catalyst or specific non-aqueous solvent systems or polar aprotic solvents like dimethylacetamide, each requiring different conditions, temperature, etc. and are not suitable from commercial point of view because of low yields and purity. Hence, there is a constant need to develop more efficient and economical synthetic routes suitable for industrial
 10 scale up.

The present inventors have now found a way of synthesizing trityl olmesartan medoxomil and olmesartan medoxomil, with an improved process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III).

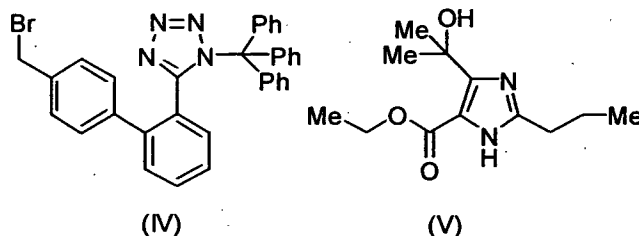
15 SUMMARY OF THE INVENTION

In one general aspect there is provided an improved process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III).



the process includes:

- 20 (a) reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV),



in one or more solvents in the presence of a base and absence of a phase transfer catalyst;

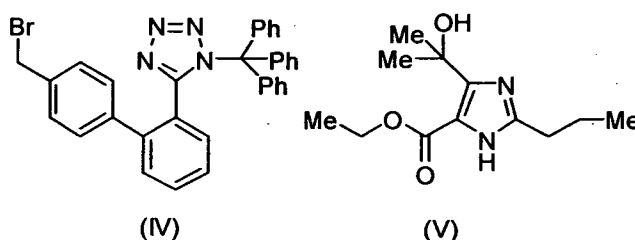
- (b) removing the solvent; and
- (c) isolating the compound of Formula (III).

5 Embodiments of the process may include one or more of the following features. For example, the reaction of ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole may be carried out at a temperature from about 40°C to about 80°C. A further or additional solvent may be added after removing the solvent. The reaction mixture may
10 be cooled before isolating the compound of Formula (III).

The process may include further drying of the product obtained.

In another general aspect there is provided a process for the preparation of olmesartan medoxomil. The process includes:

- (a) reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of
15 Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV),

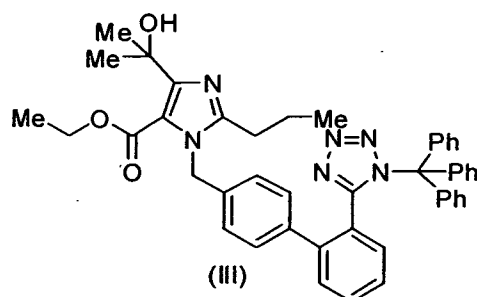


in one or more solvents in the presence of a base and absence of a phase transfer catalyst;

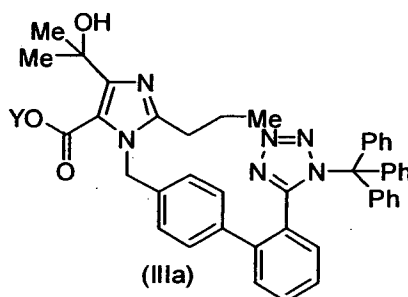
- 20 (b) removing the solvent;
- (c) isolating the compound of Formula (III); and
- (d) converting the compound of Formula (III) to olmesartan medoxomil.

In another aspect there is provided a process for the preparation of olmesartan medoxomil. The process includes:

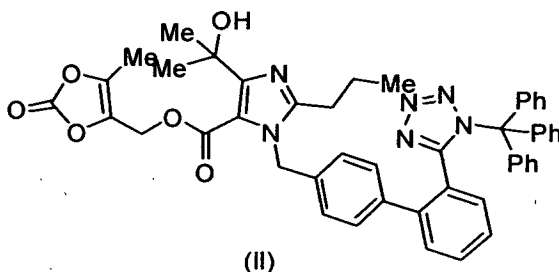
- 25 (a) hydrolyzing ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl] methyl]imidazole-5-carboxylate of Formula (III)



in one or more C₃-C₈ ketone solvents with an inorganic base to get a compound of Formula (IIIa);



- 5 wherein Y is selected from hydrogen or cation of inorganic base to form salt,
(a) esterifying the compound of Formula (IIIa) with 4-chloromethyl-5-methyl-2-oxo-
1,3-dioxolene in one or more C₃-C₈ ketone solvents in presence of a base and a
catalyst to obtain compound of Formula (II);



- 10 (b) deprotecting trityl protection group; and
(c) isolating the olmesartan medoxomil.

The process may produce crystalline olmesartan medoximil. In particular, it may produce the crystalline olmesartan medoximil having the X-ray diffraction pattern of Figure 1. The crystalline olmesartan medoximil obtained may be formed into a finished dosage form.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of crystalline olmesartan medoximil; and one or more pharmaceutically acceptable carriers, excipients or diluents.

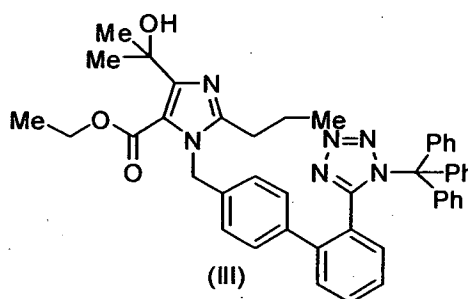
The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description.

BRIEF DESCRIPTION OF THE DRAWINGS

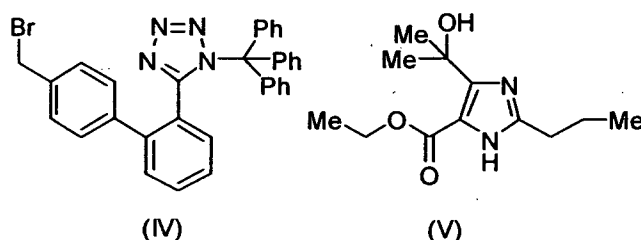
- 5 **Figure 1** is an X-ray powder diffraction pattern of crystalline olmesartan medoxomil.

DETAILED DESCRIPTION OF THE INVENTION

The inventors have developed a process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5yl]biphenyl-4-yl]methyl] imidazole-5-carboxylate of Formula (III),



10 by reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV),



- 15 in one or more solvents in the presence of one or more bases and absence of a phase transfer catalyst.

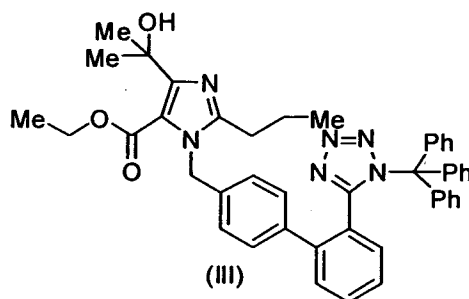
In general, the reaction of ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV) may be carried out in a mixture
20 of C₃-C₈ ketones and amides solvents.

The C₃-C₈ ketone includes one or more of acetone, methyl isobutyl ketone, methyl ethyl ketone and the like. In particular, acetone may be used. Examples of amides include solvents such as N,N-dimethylacetamide, N,N-dimethylformamide, and the like.

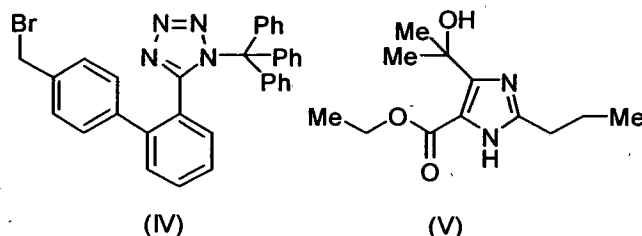
Examples of bases include sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, sodium methoxide, potassium tert-butoxide, and the like.

The reaction may be carried out at a temperature in the range from about 40°C to about 80°C, for example at about 50°C to about 60°C.

The inventors also have developed a process for preparation and isolation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III),



- (a) by reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV),



in one or more solvents in the presence of a base and absence of a phase transfer catalyst;

- (b) removing the solvent; and
(c) isolating the compound of Formula (III).

The reaction of ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV) may be carried out in mixture of a C₃-C₈ ketone and an amide, for example, acetone and N,N-dimethylformamide, in presence of potassium carbonate at a temperature in the range from about 40°C to about 80°C, for example, at about 50°C to about 60°C.

After the completion of the reaction, the solvent may be removed. The solvent may be removed by a technique, which includes, for example, filtration, evaporation, distillation, distillation under vacuum, decantation and centrifugation.

In another aspect, additional solvent may be added after removing the solvent.

5 The solvent may include one or more of C₃-C₈ ketones or amides.

In another aspect, the compound of Formula (III) may be isolated. The product may be isolated by a technique, which includes one or more of filtration, filtration under vacuum, decantation and centrifugation.

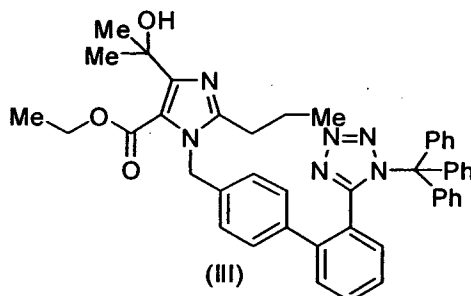
10 In one aspect, the reaction mixture containing compound (III) may be cooled before isolation to obtain better yields. It may be cooled to temperature in the range of about 0°C to about 35°C, for example, to about 20°C to about 30°C.

The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

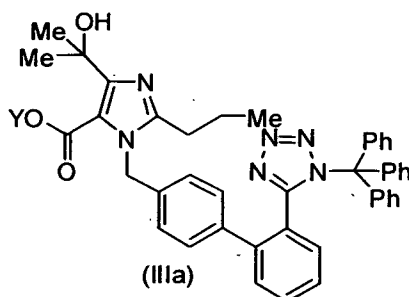
15 In yet another aspect, the compound of Formula (III) may be converted into olmesartan medoxomil.

The inventors further developed a process for the preparation of olmesartan medoxomil. The process includes:

20 (a) hydrolyzing ethyl-4-(1-hydroxy-1-methylethyl)2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl] methyl]imidazole-5-carboxylate of Formula (III),

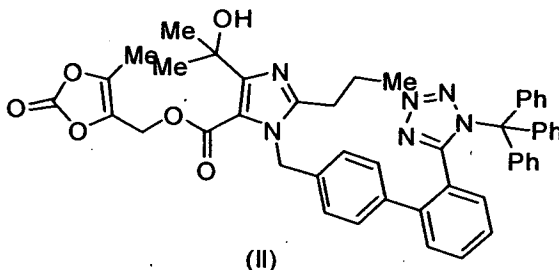


in one or more C₃-C₈ ketone solvents with an inorganic base to get a compound of Formula (IIIa);



wherein Y is selected from hydrogen or cation of inorganic base to form salt,

- (b) esterifying the compound of Formula (IIIa) with 4-chloromethyl-5-methyl-2-oxo-1,3-dioxolene in one or more C₃-C₈ ketone solvents in presence of a base and a catalyst to obtain compound of Formula (II);



- (c) deprotecting trityl protection group; and
(d) isolating the olmesartan medoxomil.

The hydrolysis of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III) may be carried out in a C₃-C₈ ketone solvent. Examples of ketone solvents include acetone, methyl isobutyl ketone, methyl ethyl ketone, and the like. Examples of bases include potassium hydroxide, sodium hydroxide, lithium hydroxide, and the like.

The hydrolyzed compound 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylic acid of Formula (IIIa) may be directly converted to trityl olmesartan medoxomil without isolation. The trityl olmesartan medoxomil can be isolated by conventional technique like removal of solvent.

The trityl olmesartan medoxomil can be isolated by extracting the reaction mass with organic solvent like methylene dichloride, ethyl acetate, butyl acetate, isopropyl acetate, toluene, xylene, preferably ethyl acetate and cooling the extracted organic solvent mass to precipitate trityl olmesartan medoxomil. The precipitated product can

be isolated by filtration and optionally washing with an alcohol like methanol, ethanol, isopropanol, butanol etc., preferably methanol.

In one aspect, olmesartan medoxomil may be prepared in-situ by esterification of compound of Formula (IIIa) in a C₃-C₈ ketone solvent with 4-chloromethyl-5-methyl-2-oxo-1,3-dioxolene in presence of a base and a catalyst.

The suitable base for the esterification of compound of Formula (IIIa) may include one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, sodium methoxide, potassium tert-butoxide, and the like. The suitable catalyst may include potassium iodide. The esterification may be followed by detritylation of trityl olmesartan medoxomil, for example with aqueous acetic acid.

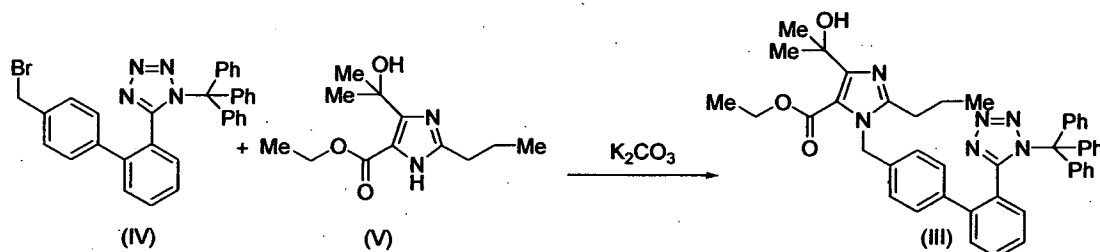
The process may produce olmesartan medoxomil in crystalline form. The crystalline form of olmesartan medoxomil may be characterized by X-ray diffraction pattern having characteristic peaks at 2-theta values 7.3, 9.2, 12.7 and 16.6±0.2°.

The crystalline olmesartan medoxomil can also be characterized by X-ray diffraction pattern having characteristic peaks at 2-theta values 10.7, 11.7, 14.6, 14.9, 19.7, 20.6, 21.9, 23.4, 24.8, 25.3 and 27.6±0.2°.

The crystalline olmesartan medoximil may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

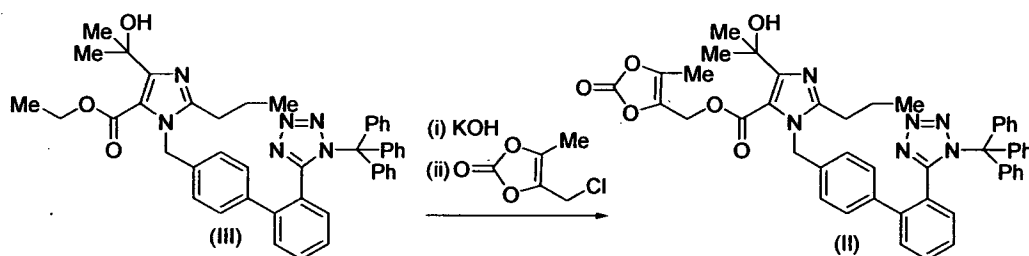
The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example-1: Preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl)methyl]imidazole-5-carboxylate of formula (III)



100 g of ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V), 172.4 g of potassium carbonate and 700 ml of acetone were taken in a round bottom flask at 25°C to 35°C. 258.4 g of N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV) and 100 ml of N,N-dimethylformamide were added to the reaction mixture. The reaction mixture was heated to 55°C to 60°C for 20 hours. After completion of the reaction as monitored by TLC, acetone was distilled under vacuum at 45°C to 50°C. The residue was further treated with 200 ml of acetone at 50°C to 55°C and stirred for 30 minutes. The reaction mixture was cooled to 25°C to 35°C and gradually to 0°C to 5°C with stirring. The product was filtered and washed with acetone. The wet-cake approx. 120 g was treated with 800 ml of chilled water at 10°C to 15°C and stirred for 1 hour. The product was filtered and washed with water. The product was dried in a hot air oven at 50°C to 55°C for 15 hours to obtain 214 g (83%) of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III).

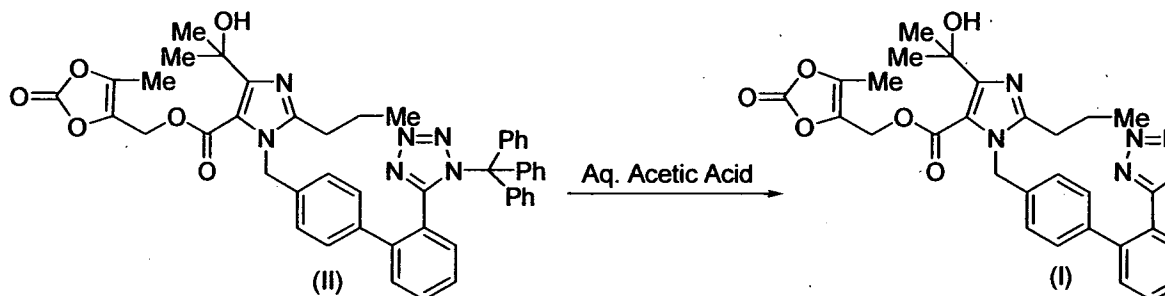
Example-2: Preparation of Trityl Olmesartan Medoxomil of Formula (II)



100 g of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III), 15.65 g of potassium hydroxide and 1 L of acetone were taken in a round bottom flask at 25°C to 30°C. The reaction mass was stirred for 4 hours till completion of the reaction by TLC. After the completion of reaction, the reaction mass was filtered through a hyflow bed and washed with acetone (Reaction Mass-A). In another round bottom flask, 500 ml acetone, 19.7 g of potassium carbonate and 5.78 g of potassium iodide were taken. 26.0 g of 4-chloromethyl-5-methyl-2-oxo-1,3-dioxolene was added to the reaction mixture above at 25°C to 30°C (Reaction Mass-B). The reaction mass B was heated at 35°C to 40°C and reaction mass -A was added drop wise during 2-3 hours. The reaction mixture was maintained for 6 hours. After the completion of the reaction, the reaction mass was cooled to 25°C and filtered through a hyflow and washed with

acetone. The reaction mixture was distilled under vacuum at 30°C to 40°C till thick mass was obtained. The residue was treated with 200 ml ethyl acetate and stirred for 45 minutes at 40°C to 45°C. The reaction mixture was cooled gradually to 0°C to 5°C and stirred. The reaction mass was filtered and wet-cake was washed with chilled ethyl acetate. The wet-cake was further purified in ethyl acetate followed by washing with chilled methanol to obtain 80 g (80%) of trityl olmesartan medoxomil (II).

Example-3: Preparation of olmesartan medoxomil (I)



400 ml of aqueous acetic acid obtained by mixing 412.5 ml acetic acid in 137.5 ml of water and 100 g of trityl olmesartan medoxomil were taken in a round bottom flask. The reaction mass was heated to 35°C to 40°C for 3 hours. After completion of the reaction, the reaction mass was cooled to 35°C and treated with 150 ml of water. The reaction mass was further cooled to 0°C to 5°C and stirred for 1 hour. The reaction mass was filtered and washed with 50 ml of aqueous acetic acid. The filtrate was extracted with 1 L of methylene dichloride. The separated aqueous layer was further washed with 500 ml of methylene dichloride. The combined organic layer was treated with 400 ml of water at 25°C to 30°C. The separated organic layer was treated with 250 ml of sodium bicarbonate solution and allowed to settle. The separated organic layer was again washed with 400 ml of water. The methylene dichloride layer was filtered and distilled under vacuum at 40°C to 50°C to get a residue. The residue was treated with 300 ml of ethyl acetate at 30°C to 35°C and cooled to 0°C to 5°C. The isolated product was filtered and washed with 100 ml of chilled ethyl acetate. The product was dried in hot air oven at 35°C to 40°C for 8 hours and at 50°C to 55°C for another 8 hours to obtain 56g (81%) of crystalline olmesartan medoxomil having the X-ray powder diffraction pattern as shown in Figure.-1.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

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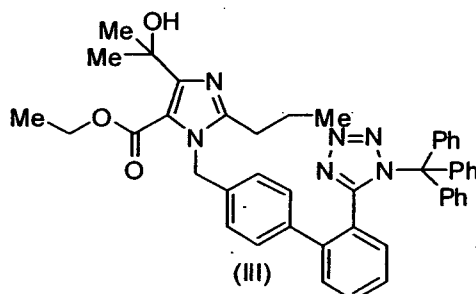
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Claims: -

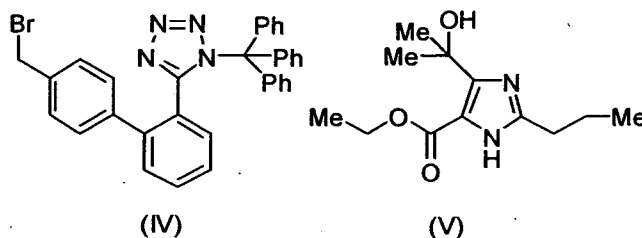
1. A process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III),



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the process comprising:

reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV),



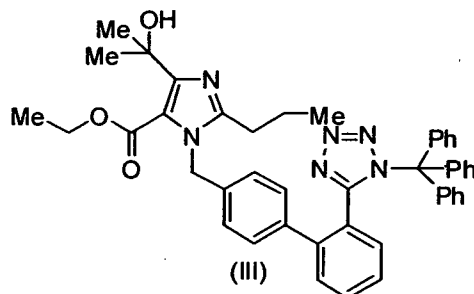
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in one or more solvents in the presence of one or more bases and absence of a phase transfer catalyst.

2. The process according to claim 1, wherein the solvent comprises one or more of C₃-C₈ ketones, amides, or mixtures thereof.
3. The process according to claim 2, wherein the C₃-C₈ ketone comprises one or more of acetone, methyl isobutyl ketone, and methyl ethyl ketone.
4. The process according to claim 2, wherein the amide comprises one or both of N,N-dimethylacetamide, and N,N-dimethylformamide.
5. The process according to claim 2, wherein the solvent comprises a mixture of acetone and N,N-dimethylformamide.
6. The process according to claim 1, wherein the base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, sodium methoxide, and potassium tert-butoxide.

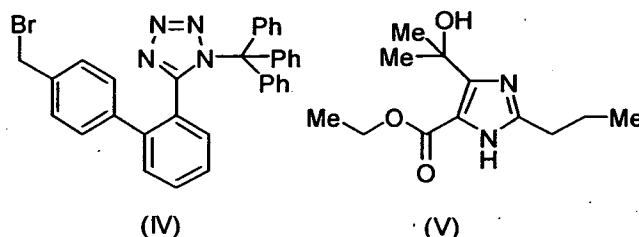
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7. The process according to claim 1, further comprising heating reaction mixture from about 40°C to about 80°C.
8. A process for the preparation of ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III),



the process comprising:

- (a) reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV),



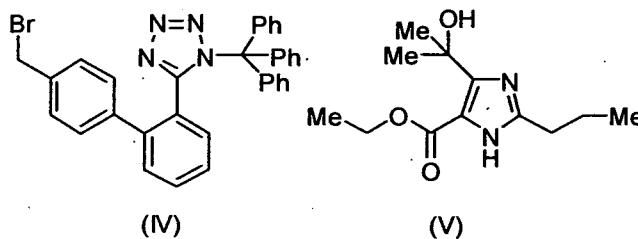
in one or more solvents in the presence of a base and absence of a phase transfer catalyst;

(b) removing the solvent; and

(c) isolating the compound of Formula (III).

9. The process according to claim 8, wherein the solvent comprises one or more of C₃-C₈ ketones, amides, or mixtures thereof.
10. The process according to claim 9, wherein the C₃-C₈ ketone comprises one or more of acetone, methyl isobutyl ketone, and methyl ethyl ketone.
11. The process according to claim 9, wherein the amide comprises one or both of N,N-dimethylacetamide, and N,N-dimethylformamide.
12. The process according to claim 8, wherein the base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, sodium methoxide, and potassium tert-butoxide.

13. The process according to claim 8, wherein removing the solvent comprises one or more of filtration, evaporation, distillation, distillation under vacuum, decantation and centrifugation.
14. The process according to claim 8, wherein the isolating comprises one or more of
5 filtration, filtration under vacuum, decantation and centrifugation.
15. The process according to claim 8, further comprising heating reaction mixture from about 40°C to about 80°C.
16. The process according to claim 8, further comprising adding additional solvent after removing the solvent.
- 10 17. The process according to claim 8, further comprising cooling before isolating the compound of Formula (III).
18. The process according to claim 8, further comprising additional drying of the product obtained.
19. The process according to claim 8, further comprising converting the compound of
15 Formula (III) to olmesartan medoximil.
20. A process for the preparation of olmesartan medoximil, the process comprising:
- (a) reacting ethyl-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate of Formula (V) with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of Formula (IV),



- 20 in one or more solvents in the presence of a base and absence of a phase transfer catalyst;
- (b) removing the solvent;
- (c) isolating the compound of Formula (III); and
- 25 (d) converting the compound of Formula (III) to olmesartan medoximil.
21. A process for the preparation of olmesartan medoximil, the process comprising:
- (a) hydrolyzing ethyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate of Formula (III) prepared according to claim 1,



(IIa)

- (11)

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25. The process according to claim 21, wherein the deprotection of the trityl protective group is carried out with aqueous acetic acid.
26. The process according to claim 21, wherein the olmesartan medoxomil obtained is crystalline.
- 5 27. The process according to claim 21, wherein the olmesartan medoximil has the X-ray diffraction pattern of Figure 1.
28. The process according to claim 21, further comprising forming the product obtained into a finished dosage form.
29. Crystalline olmesartan medoxomil characterized by X-ray diffraction pattern having
10 characteristic peaks at 2-theta values 7.3, 9.2, 12.7 and $16.6 \pm 0.2^\circ$.
30. Crystalline olmesartan medoxomil of claim 29, further characterized by X-ray diffraction pattern having characteristic peaks at 2-theta values 10.7, 11.7, 14.6, 14.9, 19.7, 20.6, 21.9, 23.4, 24.8, 25.3 and $27.6 \pm 0.2^\circ$.
31. A pharmaceutical composition comprising a therapeutically effective amount of
15 crystalline olmesartan medoximil characterized by X-ray diffraction pattern having characteristic peaks at 2-theta values 7.3, 9.2, 12.7 and $16.6 \pm 0.2^\circ$, and one or more pharmaceutically acceptable carriers, excipients or diluents.
32. Crystalline olmesartan medoxomil of Formula (I) substantially as herein described with reference to any of the embodiments of the invention illustrated in the
20 accompanying drawings and/or examples.

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Figure 1

