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(54) **Title**: A NEW PROCESS FOR THE PREPARATION OF OLMESARTAN MEDOXOMIL

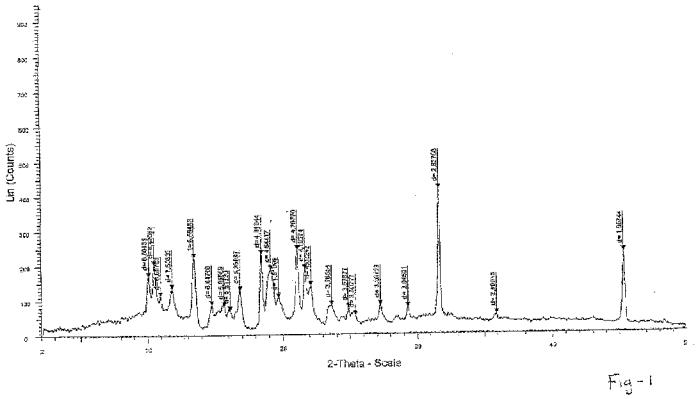


Fig - 1

(57) **Abstract**: This invention provides a new process for producing (5-methyl-2-oxo-1,3- dioxolen-4-yl)methyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-[2-(tetrazol-5- yl)phenyl] phenyl] methylimidaozle-5-carboxylate (olmesartan medoxomil) from alkaline salts of trityl olmesartan more preferably calcium salts of trityl olmesartan.

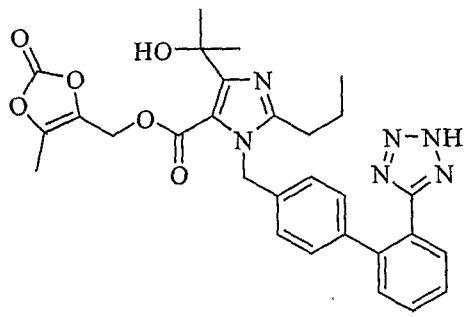
A NEW PROCESS FOR THE PREPARATION OF OLMESARTAN MEDOXOMIL

Field of the Invention

This invention, in general relates to process for producing (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-[2-(tetrazol-5-yl)phenyl]phenyl]methylimidaozle-5-carboxylate (olmesartan medoxomil). More particularly, the present invention provides a novel process for producing olmesartan medoxomil from alkaline salts of trityl olmesartan.

Background of the Invention

Olmesartan medoxomil, described chemically as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-phenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate and structurally as given below, is an antihypertensive agent. It is a selective AT1 subtype angiotensin II receptor antagonist. Olmesartan works by blocking the action of a substance in the body that causes blood vessels to tighten. As a result, olmesartan relaxes blood vessels thereby lowers blood pressure.



Olmesartan medoxomil

Various processes for the preparation of olmesartan medoxomil are known in prior art.

In *J.Med.Chem.*, 1996, 39, 323-338 by Yanagisawa et al, olmesartan medoxomil is prepared from trityl olmesartan medoxomil by hydrolysis employing 25% acetic acid at 60 °C to release triphenyl methanol. The isolation of the desired compound from the mixture is very tedious as large amount of impurities are formed during the process.

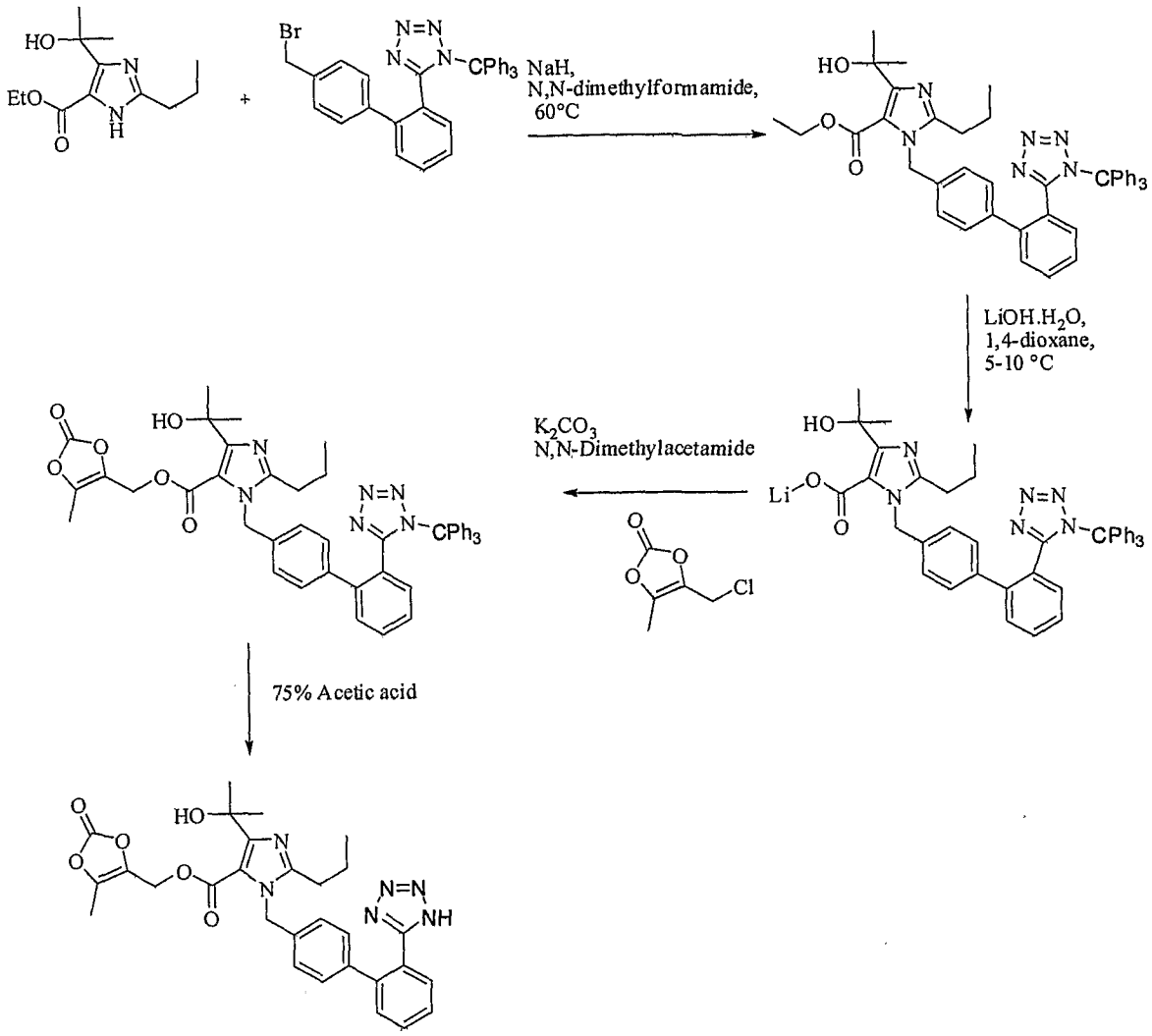
The product patent, US 5616599 discloses a process for the preparation of olmesartan medoxomil comprising

-reacting ethyl-4-(1-hydroxyl-1-methylethyl)-2-propyl imidazole-5-carboxylate with N-(triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole using NaH as base in N,N-dimethylformamide at 60°C to give ethyl-4-(1-hydroxyl-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate

-the above product is hydrolysed with lithium hydroxide monohydrate as base in 1,4-dioxane at 5-10 °C to give lithium salt of 4-(1-hydroxyl-1-methylethyl)-2-propyl-1-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylic acid

-coupling the product of the previous step with 5-methyl-2-oxo-1,3-dioxolene-4-yl)methyl chloride using K_2CO_3 as base in N,N-dimethylacetamide at 50 °C to give trityl Olmesartan medoxomil

-Trityl Olmesartan medoxomil on deprotection using 75% acetic acid give Olmesartan medoxomil as given in scheme-I.



OLMESARTAN MEDOXOMIL

Scheme-I

The lithium intermediate so formed in the above process is difficult to handle and isolate as it involves use of hazardous reagents, formation of impurities and numerous extractive workup in the final stage.

US 200600069141 discloses a process for preparing olmesartan medoxomil comprising contacting trityl olmesartan medoxomil with an acid in a water miscible organic solvent, with or without water, to obtain a solution of olmesartan medoxomil and a precipitate of triphenyl carbinol followed by separating the precipitate of triphenyl carbinol from the solution of olmesartan medoxomil and contacting the solution of olmesartan medoxomil with a base to obtain a precipitate of olmesartan medoxomil. Olmesartan medoxomil isolated from acidic conditions contains about 2.2% olmesartan acid impurity

WO 2007017135 A2 covers a one-pot process, comprising hydrolysis of the olmesartan ethyl ester, subsequent esterification with 4-chloromethyl-5-methyl-1,2-oxo-1,3-dioxolene, and deprotection of the trityl protection without any isolation during the process also in addition, it discloses a method of preparing olmesartan medoxomil, wherein the trityl olmesartan medoxomil is dissolved in acidic solution resulting in deprotection. The solution is neutralized and crude olmesartan medoxomil is precipitated, and requires careful recrystallizatio for purification, as the trityl alcohol is the potential impurity during this process.

WO2007148344 A2 discloses a process for hydrolysis of trityl olmesartan ester to obtain trityl Olmesartan dihydrate, which is esterified with 4-chloromethyl-5-methyl-2-oxo-1,3-dioxolene in the presence of a base and catalyst to obtain trityl olmesartan medoxomil.

The process for the preparation of olmesartan medoxomil which comprising contacting trityl olmesartan medoxomil with an acid in water and water immiscible organic solvent, separating aqueous and organic layers, adjusting the pH of the aqueous layer with base, extracting the resulting solution with water-miscible organic solvents and isolating Olmesartan medoxomil.

Existing process require a large quantity of acid during hydrolysis and further isolation to obtain olmesartan medoxomil involves neutralization of large quantity of acidic solution and exhaustive work up to isolate the material. In addition, the aforementioned process, employs large volume of the solvent, thereby making the process uneconomic. The large usage of hydrochloric acid (more then 6 volume) and neutralization of the same, requires large quantity of base. Moreover, the handling of the large quantity of acid during the neutralization stage is not amenable in large scale production and invites safety risks too.

US 20060258727A1 discloses an alternate process for preparing olmesartan medoxomil containing less than about 0.1% of one or more of its impurities, OLM-Me, OLM-Cl and OLM-eliminate.

In light of the foregoing discussion, there exists a need to develop an efficient, robust, cost effective and environment-friendly process for large scale production of olmesartan medoxomil. Further, the process should involve minimal use of acid and other solvents that is easier to handle during large scale production.

Object and Summary of the Invention

It is a principal object of the present invention to provide a process for large scale production of olmesartan medoxomil.

It is another object of the present invention to provide a process for producing olmesartan medoxomil employing alkaline earth metal salts of trityl olmesartan like magnesium, calcium and barium, preferably calcium salt of trityl olmesartan.

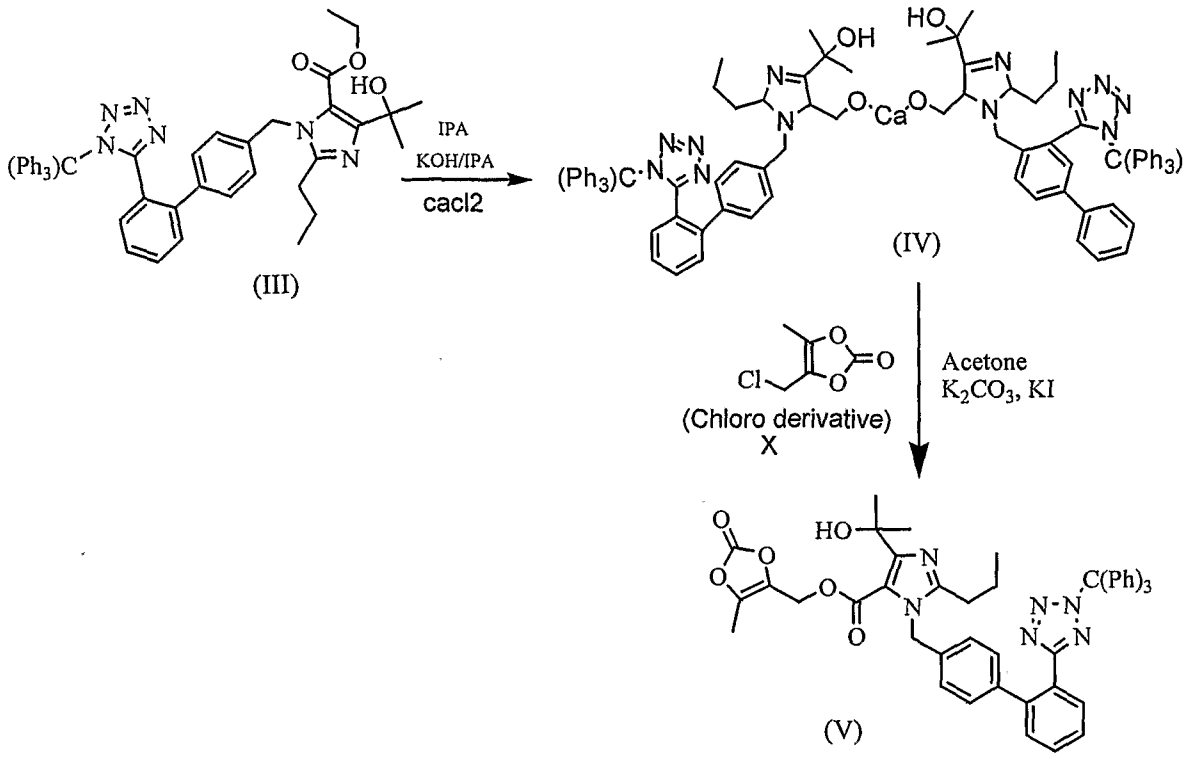
It is a further object of the present invention to provide an economical process for producing olmesartan medoxomil, wherein the process involves minimal extractive workups and impurities employing alkaline earth metal salts of olmesartan medoxomil, preferably calcium salt.

It is yet another object of the present invention to provide a process for producing olmesartan medoxomil, wherein the process requires less amount of acid consumption as well as isolation procedure is minimized. This provides for better control for the process related impurities also.

According to the first aspect, the present invention provides a process for the preparation of trityl olmesartan medoxomil, comprising the steps of:

a) Alkylating 4-(1-Hydroxy-1-methyl)-2-propyl-1H-imidazole-5-carboxylic acid ethyl ester with N-(triphenylmethyl)-5-(4-bromomethyl biphenyl-2-yl) tetrazole in an organic solvent, in presence of a base and a phase transfer catalyst to give trityl olmesartan ethyl ester.

b) Hydrolyzing the trityl Olmesartan ethyl ester with alkaline chlorides more preferably calcium chloride in an organic solvent in presence of a base to give trityl olmesartan calcium, which is further treated with 4-chloromethyl-5-methyl-1,2-oxo-1,3-dioxolene (X) to produce trityl olmesartan medoxomil of formula (V).



c). The final detritylation process involves using little quantity (~0.5T of batch size) of acid with water immiscible solvent to precipitate the product completely. The crude product thus isolated by filtration is purified to get the pure olmesartan medoxomil. The triphenyl methanol impurity is very much soluble and is not present in the final product. The less quantity of acid used leads to less degradation of product to form the olmesartan medoxomil. The olmesartan acid impurity in the final product is less then 0.1%.

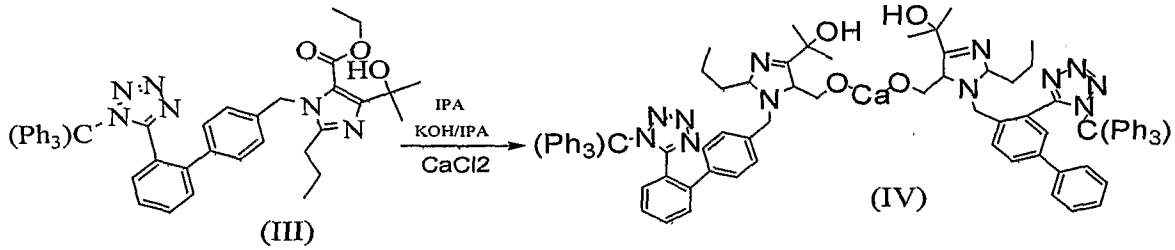
Detailed description of the Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

According to the present invention, trityl olmesartan ethyl ester (III) is hydrolyzed to obtain trityl olmesartan calcium (IV), which is isolated and esterified with 4-chloromethyl-5-methyl-2-oxo-1,3-dioxolene (X) in organic solvent in presence of base to isolate trityl olmesartan medoxomil (V).

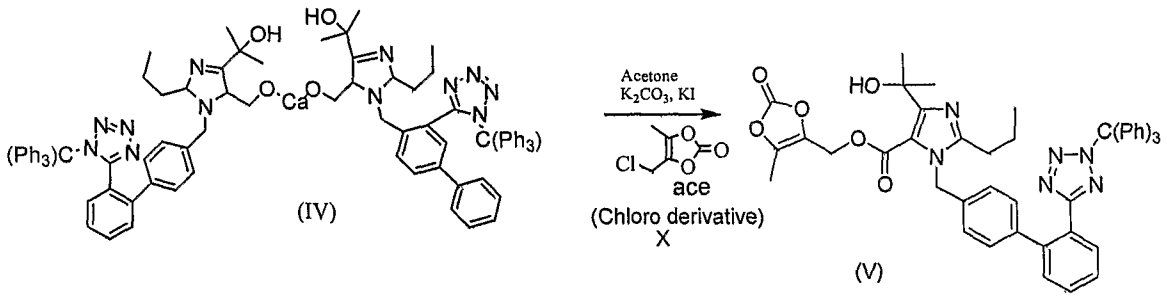
The hydrolysis is carried out in presence of an organic solvent selected from alcohols, such as methanol, ethanol, isopropyl alcohol, preferably isopropyl alcohol

and the base selected such as lithium carbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide and lithium hydroxide, more preferably, potassium hydroxide.



(III) (IV)

The esterification is carried out in organic solvent selected from ketones, more preferably acetone and the base is selected from lithium carbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide and lithium hydroxide more preferably, potassium carbonate in presence of alkali iodide, which is selected from sodium iodide, lithium iodide, most preferably potassium iodide.



(IV) (V)

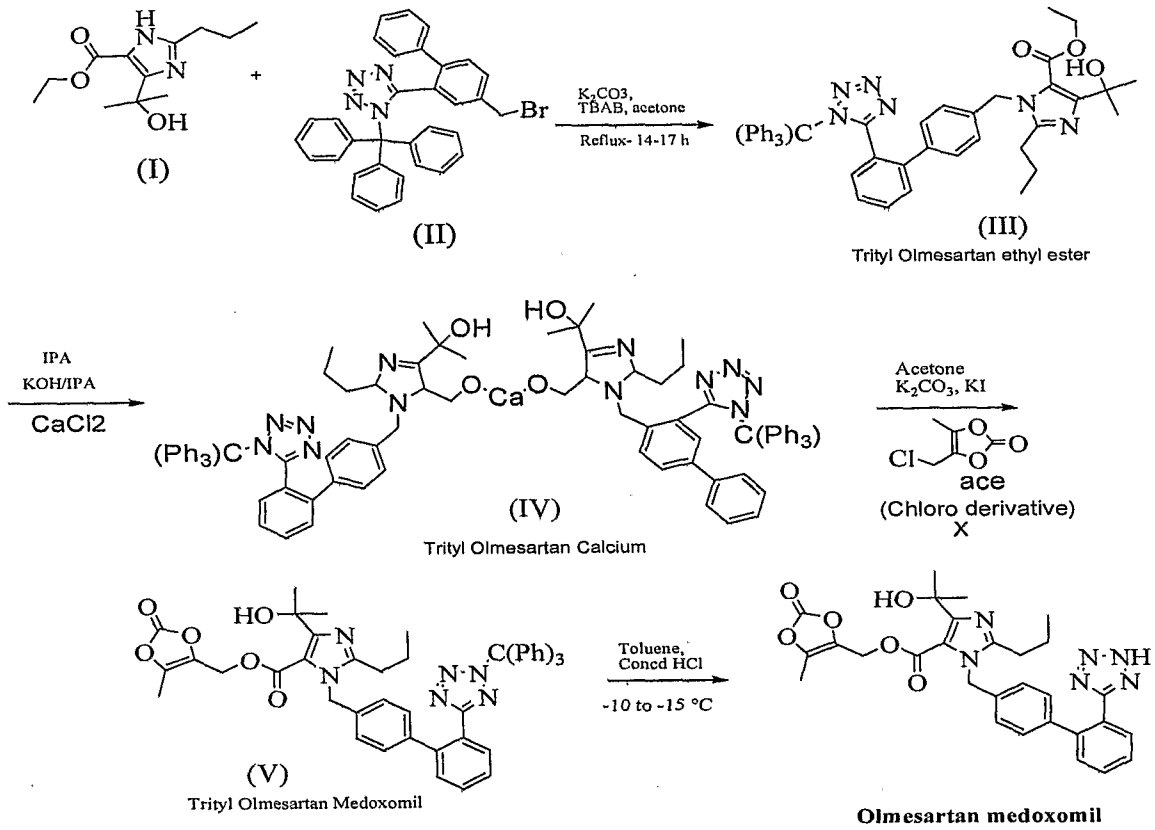
Olmesartan medoxomil is prepared from trityl Olmesartan medoxomil (V) in water/ water immiscible organic solvent in presence of minimum amount of acid and at low temperature to ambient temperature.

The organic solvent used is selected from aromatic hydrocarbons such as toluene or xylene, most preferably toluene.

The acid is selected from organic acids such as acetic acid, oxalic acid, formic acid, p-toluenesulfonic acid or inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, most preferably hydrochloric acid.

The reaction is carried out at a temperature in the range of -10 to 25 °C, most preferably below 0 °C.

Thus, in accordance with the present invention, the preparation of Olmesartan medoxomil follows the steps as given in the scheme below:



The olmesartan acid impurity is not more then 0.1% and the process waste is low in the present invention.

The invention also relates to a crystalline form of trityl olmesartan calcium based on which the following X-Ray diffraction pattern (in Fig. 1) has given as peaks at degrees 2 Theta: 10.486, 13.416, 18.394, 21.097, and 31.6.

The innovators have optimized the process and surprisingly found that by using little quantity (~0.5T of batch size) of acid with water immiscible solvent, the product precipitated completely. The crude product, thus isolated by filtration is purified to get the pure olmesartan medoxomil. The triphenyl methanol impurity is highly soluble in water and is not present in the final product. The less quantity of acid used leads to less degradation of product to form the olmesartan medoxomil.

The invention is further explained in detail in the following examples which is provided by way of illustrations only and should not be construed to limit the scope of the invention.

EXAMPLES:

Experiment-1: Preparation of ethy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityl tetrazole-5-yl) phenyl] phenyl} methylimidazole-5-carboxylate

N-(triphenylmethyl)-5-(4-bromomethyl biphenyl-2-yl) tetrazole (100 g), 4-(1-Hydroxy-1-methyl)-2-propyl-1H-imidazole-5-carboxylic acid ethyl ester(45g), potassium carbonate (50g) & tetrbutyl ammonium bromide (4 g) in acetone (800 ml) were refluxed for 14-17hr. Progress of reaction was monitor by HPLC. After completion of reaction, distilled the solvents and added water to the residual material. Filtered the material and dried to obtain ethy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityl tetrazole-5-yl) phenyl] phenyl} methylimidazole-5-carboxylate (120 g).Chromatographic purity 97%.

Experiment-2: Preparation of Trityl Olmesartan Calcium

Ethy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityltetrazole-5-yl)phenyl] phenyl} methylimidazole-5-carboxylate (100g) was suspended in isopropyl alcohol (800ml)and added potassium hydroxide (15g). Reaction mass was stirred, after completion of reaction, isopropyl alcohol was distilled under reduced pressure. The reaction residue is added brine solution and extracted with ethyl acetate, the ethyl acetate layer is washed with saturated sodium bicarbonate solution. Partially recovered the ethyl acetate and added Calcium chloride (20gm). The reaction mass is stirred over night, the precipitated material is filtered and washed with ethyl acetate. After drying the 89 gm Trityl Olmesartan Calcium obtained as white powder, purity 98% by HPLC. X-Ray diffraction pattern (in Fig. 1) given as peaks at degrees 2Theta: 10.486, 13.416, 18.394, 21.097, and 31.6.

Experiment-3: Preparation of Trityl Olmesartan Calcium

Ethy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityltetrazole-5-yl)phenyl] phenyl} methylimidazole-5-carboxylate (50g) was suspended in isopropyl alcohol (300ml) and added potassium hydroxide (8g). Reaction mass was stirred, after completion of reaction, isopropyl alcohol was distilled under reduced pressure. The reaction residue is added brine solution and extracted with ethyl acetate, the ethyl acetate layer is washed with saturated sodium bicarbonate solution. Partially recovered the ethyl acetate and added Calcium chloride (20gm). The reaction mass is stirred over night, the precipitated material is filtered and washed with ethyl acetate.

After drying the 46 gm Trityl Olmesartan Calcium obtained as white powder, purity 97% by HPLC.

Experiment-4: Preparation of Trityl Olmesartan Calcium

Ethy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityltetrazole-5-yl)phenyl] phenyl} methylimidazole-5-carboxylate (500g) was suspended in isopropyl alcohol (2500mland added potassium hydroxide (80g). Reaction mass was stirred, after completion of reaction, isopropyl alcohol was distilled under reduced pressure. The reaction residue is added brine solution and extracted with ethyl acetate, the ethyl acetate layer is washed with saturated sodium bicarbonate solution. Partially recovered the ethyl acetate and added Calcium chloride (100gm). The reaction mass is stirred over night, the precipitated material is filtered and washed with ethyl acetate. After drying the 475 gm Trityl Olmesartan Calcium obtained as white powder, purity 97.5% by HPLC.

Experiment-5: Preparation of Trityl Olmesartan Calcium

Ethy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityltetrazole-5-yl)phenyl] phenyl} methylimidazole-5-carboxylate (500g) was suspended in isopropyl alcohol (2500mland added potassium hydroxide (80g). Reaction mass was stirred, after completion of reaction, isopropyl alcohol was distilled under reduced pressure. The residual mass is diluted with ethyl acetate and Calcium chloride (100gm) is added. The reaction mass is stirred for 10hr, the precipitated material is filtered and washed with ethyl acetate. After drying the 475 gm Trityl Olmesartan Calcium obtained as white powder, purity 97.5% by HPLC.

Experiment-6: Preparation of Olmesartan medoxomil

The trityl olmesartan Calcium salt (100gm), acetone (1000ml), potassium carbonate (50g) and potassium iodide (5g) is subjected for reflux then 4-chloromethyl-5-methyl-1,3-dioxol-2-one(30g) solution in acetone is added at 50-55°C. After completion of reaction, reaction mass was cooled and filtered to remove the salts. Filtered acetone is recovered and thus residue obtained is dissolved in toluene and conc hydrochloric acid (55ml) is added at -10 to -15^{0}C and monitored the reaction with TLC . After completion of reaction, filtered the reaction mass and wash with toluene. The residual material is suspended in ethyl acetate and washed the resulted suspension with sodium bicarbonate solution. The ethyl acetate is partially distilled under reduced pressure to obtain the crude olmesartan medoxomil. The crude

olmesartan medoxomil is purified with acetone to yield pure olmesartan medoxomil (45 g). Chromatographic purity 99.89%.

Experiment-7: Preparation of Olmesartan medoxomil

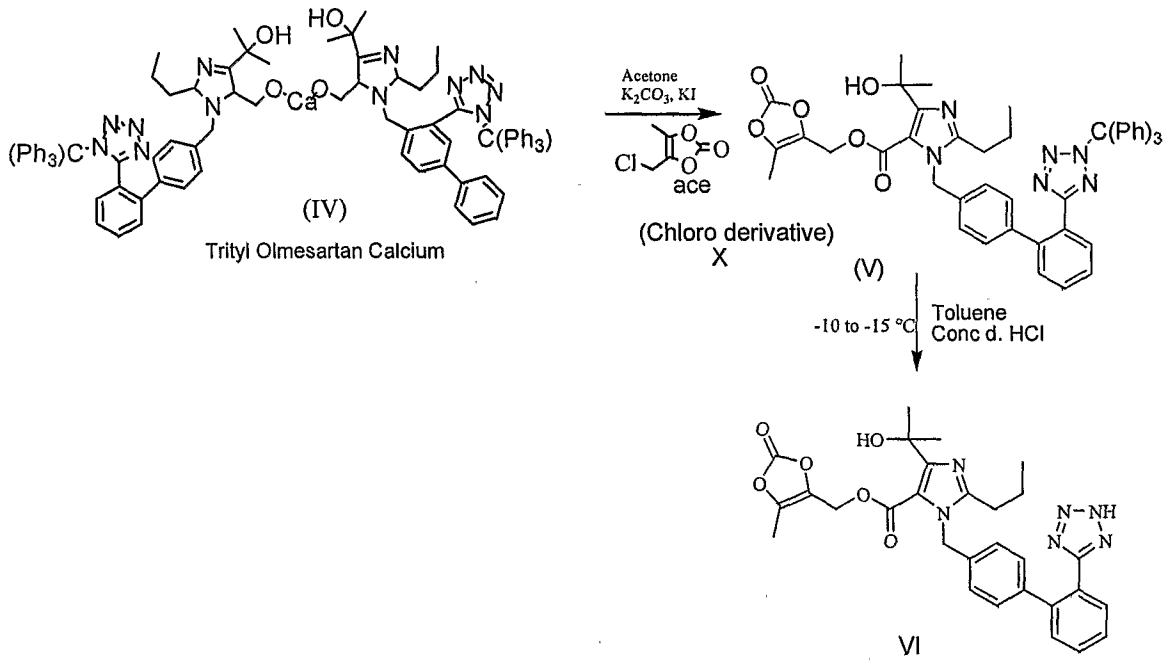
The trityl olmesartan Calcium salt (100gm), acetone (1000ml), potassium carbonate (50g) and potassium iodide (5g) is subjected for reflux then 4-chloromethyl-5-methyl-1,3-dioxol-2-one(40g) solution in acetone is added at 50-55°C. After completion of reaction, reaction mass was cooled and filtered to remove the salts. Filtered acetone is recovered and thus residue obtained is dissolved in toluene and conc hydrochloric acid (55ml) is added at -10 to -15^{0}C and monitored the reaction with TLC . After completion of reaction, filtered the reaction mass and wash with toluene. The residual material is suspended in methylene dichloride and washed the resulted suspension with sodium bicarbonate solution. The methylene dichloride is distilled under reduced pressure and residue crystallized with ethyl acetate to obtain the crude olmesartan medoxomil. The crude olmesartan medoxomil is purified with acetone to yield pure olmesartan medoxomil (42 g). Chromatographic purity 99.79%.

Experiment-8: Preparation of Olmesartan medoxomil

The trityl olmesartan Calcium salt (200gm), acetone (1800ml), potassium carbonate (200g) and potassium iodide (10g) is subjected for reflux then 4-chloromethyl-5-methyl-1,3-dioxol-2-one(80g) solution in acetone is added at 50-55°C. After completion of reaction, reaction mass was cooled and filtered to remove the salts. Filtered acetone is recovered and thus residue obtained is dissolved in toluene and conc hydrochloric acid (55ml) is added at -10 to -15^{0}C and monitored the reaction with TLC . After completion of reaction, filtered the reaction mass and wash with toluene. The residual material is suspended in methylene dichloride and washed the resulted suspension with sodium bicarbonate solution. The methylene dichloride is distilled under reduced pressure and residue crystallized with ethyl acetate to obtain the crude olmesartan medoxomil. The crude olmesartan medoxomil is purified with acetone to yield pure olmesartan medoxomil (42 g). Chromatographic purity 99.75%.

We Claim:

1. A process for the preparation of (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-[2-(tetrazol-5-yl)phenyl]phenyl] methylimidaozle-5-carboxylate (olmesartan medoxomil (VI)) from alkaline earth metal salts of trityl olmesartan, process comprising reacting alkaline earth metal salts of trityl olmesartan and 4-chloromethyl-5-methyl-2-oxo-1,3-dioxolene (formula X) in water miscible organic solvent in the presence of base followed by extraction in water immiscible solvent and treatment with an acid to obtain a precipitate, where in the precipitated product is isolated by filtration, washing and slurring to obtain olmesartan medoxomil.



2. The process according to claim 1, wherein the crystalline forms of the trityl olmesartan calcium is characterized by X-Ray diffraction pattern (in Fig. 1) given as peaks at degrees 2Theta: 10.486, 13.416, 18.394, 21.097, and 31.6.

3. The process according to claim 1, wherein the alkaline earth metal is selected from magnesium, calcium and barium to form trityl olmesartan calcium (IV), trityl olmesartan magnesium and trityl olmesartan barium.

4. The process according to claim 1, wherein the organic solvent is selected from acetone, acetonitrile, methyl isobutyl ketone and ethyl methyl ketone.

5. The process according to claim 1, wherein the base is selected from lithium carbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide and lithium hydroxide.

6. A process according to claim 1, wherein the detritylation reaction is carried out with acid in the presence of immiscible solvents at a temperature in the range of -10 to 30°C.

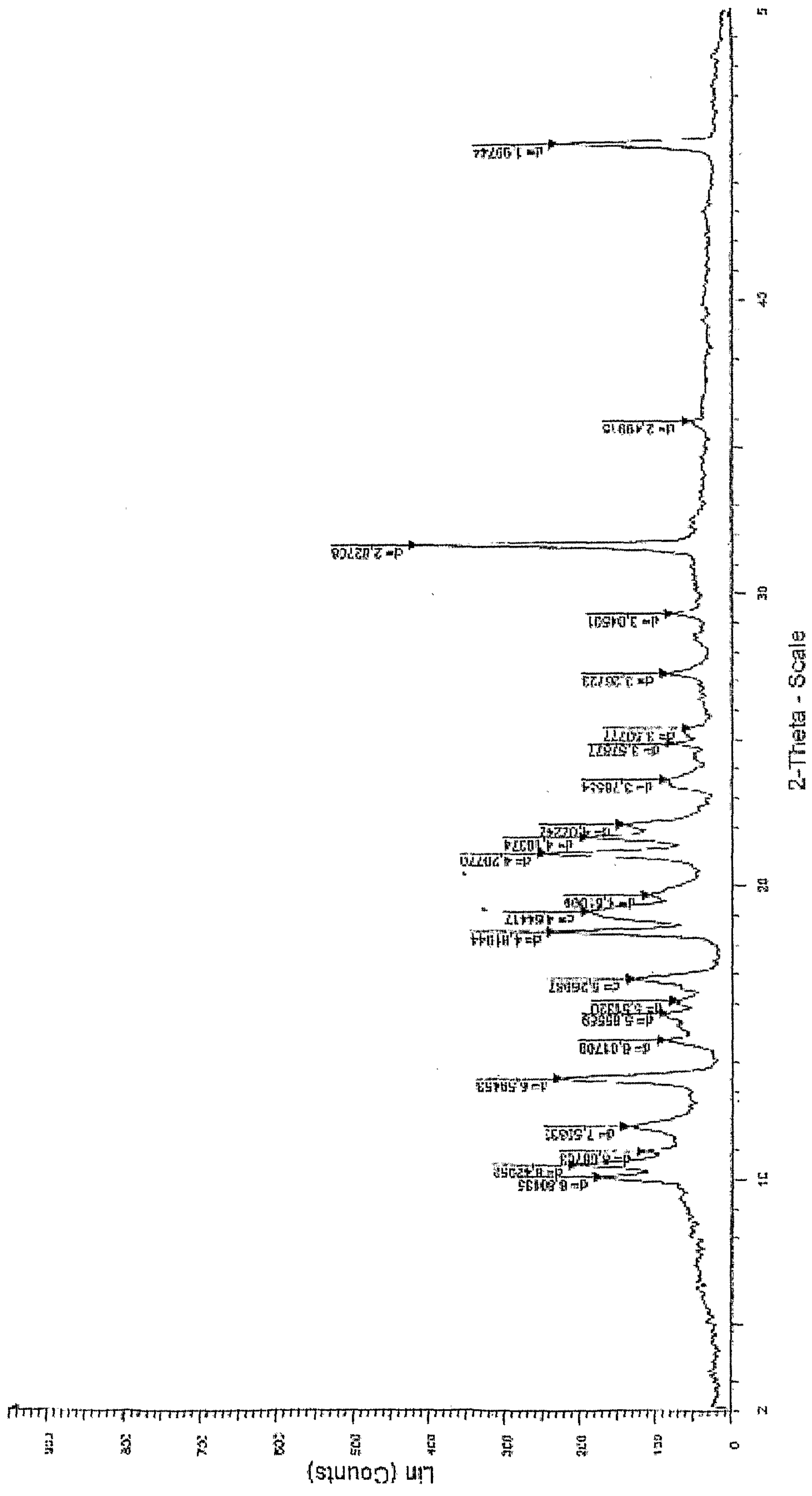
7. A process according to claim 6, wherein filteration of olmesartan medoxomil is carried out after detritylation.

8. The process according to claim 1, wherein the olmesartan acid impurity in the final product is not more then 0.3%.

9. A process according to claim 8, wherein the resultant product is purified by recrystallization employing an organic solvent.

10. A process according to claim 9, wherein the olmesartan Medoxomil (VI) obtained contains less then 0.1% of the olmesartan acid impurity.

Fig - 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 09/00721

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 257/04 (2010.01)
USPC - 548/254
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)
USPC - 548/254 (see search terms below)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 548/253; 514/381 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: olmesartan medoxomil, process, preparation, purification, trityl olmesartan, antihypertensive, trityl olmesartan salt, 4-chloromethyl-5-methyl-1,3-dioxolene-2-one, organic solvent, base, detritylation reaction, calcium, magnesium, toluene. INTERNET search - Google - same

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 2 036 904 A1 (LEK Pharmaceuticals) 18 March 2009 (18.03.2009), para [0002]; [0011]; [0013]; [0015]; [0017] - [0029].	1-10
Y	WO 2008/076862 A2 (HU et al.) 26 June 2008 (26.06.2008), pg 1 - pg 2; pg 9; pg 16 - pg 18.	1-10
Y	WO 02/06279 A1 (SEYEDI et al.) 24 January 2002 (24.01.2002), pg 18 - pg 19.	6-7

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Date of the actual completion of the international search	Date of mailing of the international search report
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