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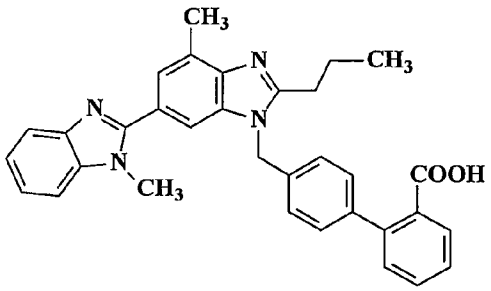
(54) Title: PROCESS FOR THE PREPARATION OF PURE 4'-[4-METHYL-6-(l-METHYL-2-BENZIMIDAZOLYL)-2-PROPYL-I -BENZIMID AZOL YL]METHYL]-2-BIPHENYLCARBOXYLIC ACID



Formula I

(57) Abstract: The present invention relates to the purification of Telmisartan (I) from a mixture of water immiscible solvent and polar aprotic solvent, which results in the Telmisartan with the purity of above 99.5% by HPLC. Further, the precipitation process of the present invention improves flowability of crystallized product, ease of filtration from the crystalline medium, thereby increasing the yield, decreasing the cost and avoiding the drying problems.

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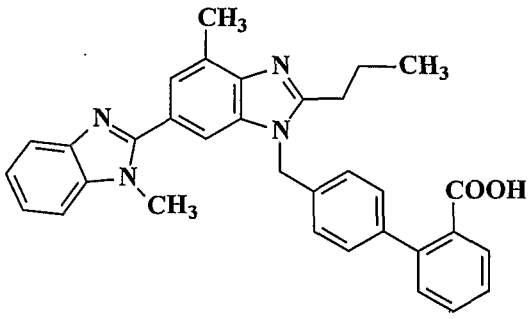
PROCESS FOR THE PREPARATION OF PURE 4'-[[4-METHYL-6-(1-METHYL-I-BENZIMIDAZOLYL)^-PROPYL-I-BENZIMIDAZOLYL]METHYL]^-BIPHENYLCARBOXYLIC ACID

FIELD OF INVENTION

The present invention relates to an improved process for the preparation of pure 4'-[[4-methyl-6-(1-methyl-2-benzimidazolyl)-2 -propyl- 1-benzimidazolyl]methyl] -2-biphenylcarboxylic acid (I) (Telmisartan):

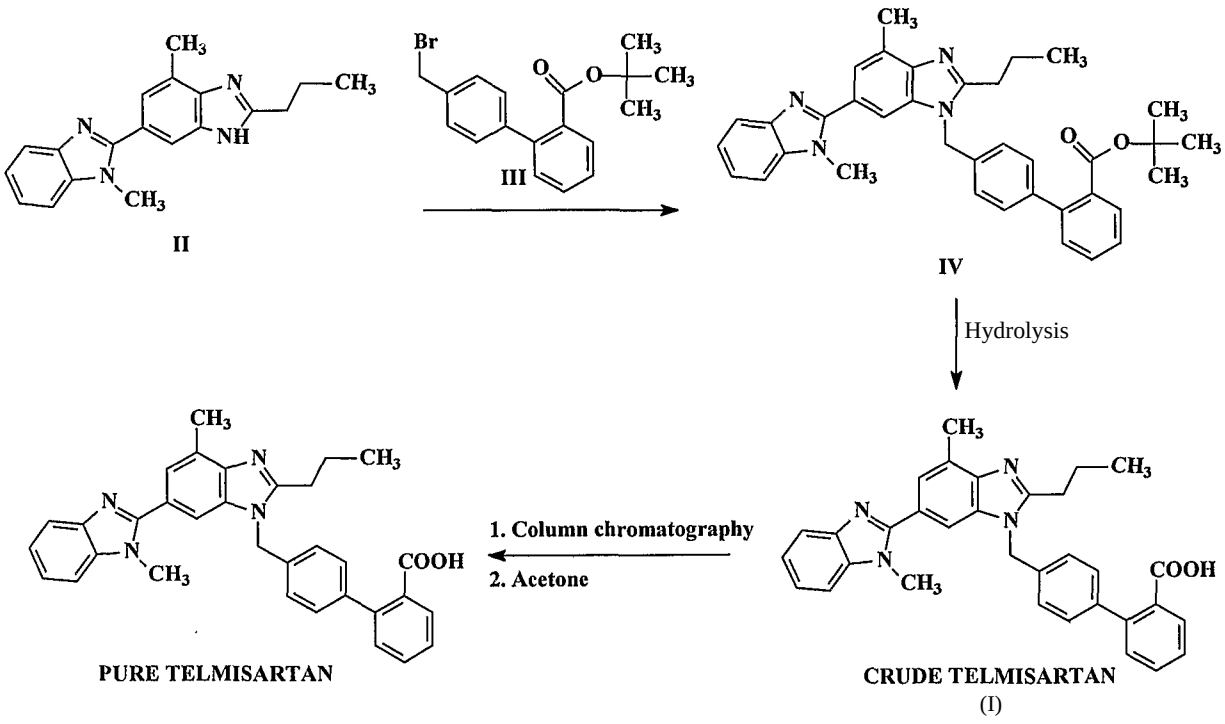


Formula I

BACKGROUND OF THE INVENTION

Telmisartan chemically known as 4'-[[4-methyl-6-(l-methyl-2-benzimidazolyl)-2-propyl-l-benzimidazolyl]methyl]-2-biphenylcarboxylic acid, is a non-peptide AT_1-subtype angiotensin II receptor antagonist. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE kininase **II).** Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the ATi receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. Telmisartan is indicated for the treatment of hypertension. Telmisartan is sold under the trade name MICARDIS® by Boehringer Ingelheim.

Telmisartan was first disclosed in US 5,591,762. US 5,591,762 also discloses a process for the preparation of Telmisartan by reacting l,4'-dimethyl-2'-propyl[2,6'-bi-l *H*-benzimidazole (II) with 4'-(bromomethyl)[l,r-biphenyl]-2-carboxylic acid 1,1-dimethylethyl ester (III) in a solvent optionally in the presence of an acid binding agent to produce the intermediate 4'-[(l,4'-dimethyl-2'-propyl[2,6l-bi-l*H*-benzimidazol]-l-yl)methyl]-[l,l'-biphenyl]-2-carboxylic acid 1,1-dimethylethyl ester (IV), which is further hydrolysed to produce crude Telmisartan. The crude product obtained is purified over a silica gel column and finally crystallized from acetone. The process is shown in Scheme 1:



The disadvantage with the above process is the use of column chromatography in the purification of Telmisartan. Employing column chromatography technique is tedious and laborious and also involves use of large quantities of solvents, and hence is not suitable for industrial scale operations.

US 6,358,986 describes two crystalline forms of Telmisartan donated as Form A, Form B. In US 6,358,986, the process for preparing crystalline Telmisartan Form A comprises mixing the Telmisartan with ethanol, adding activated charcoal and aqueous ammonia

and mixing for one hour, then filtering to another stirring apparatus and washing with ethanol. Resulting solution is heated to 70~80°C, adding glacial acetic acid and stirring for further 1.5-2 hours at the same temperature, cooling to 0-10°C, stirring for further 2 hours, isolating the product by centrifugation, washing with ethanol then with water and drying at 70-90°C. According to the detailed description given in the US '986 patent, in addition to the disadvantageously prolonged drying process of the Telmisartan Form A, very hard particles are obtained. The grinding process of these particles produces a dry powder, which has strong tendency to electrostatic charging and which is virtually impossible to pour and manipulate for pharmaceutical preparations. On the other hand, Telmisartan Form B is free from the above-mentioned limitations. However, the inventors of the US '986 patent could not obtain pure, dry Form B because upon drying, some of Form B transformed into Form A. According to the teachings of the US '986 patent, mixtures of Telmisartan Form A and Form B ranging from 90:10 to 60:40 are suitable for industrial scaling-up, and even a content of 10% of Form B is sufficient to ensure that the product will have the positive qualities required for large-scale production.

US 2006/0276525 Al describes a process for the preparation of crystalline solid of Telmisartan Form A by dissolving Telmisartan in a polar solvent such as dimethylsulfoxide (DMSO), *N,N*-dimethylformamide (DMF), ʌ/,iV-dimethylacetamide (DMA)$_5$ iV-methyl-2-pyrrolidone (NMP) and cooling the solution for sufficient time to produce Telmisartan Form A crystals, which are filtered and dried.

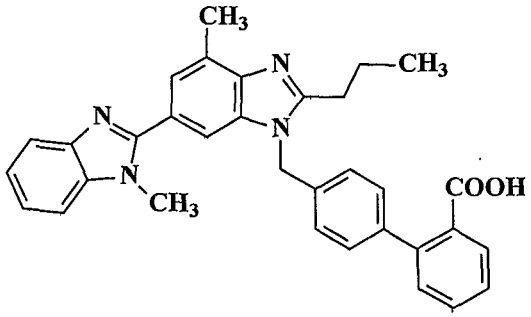
The present invention is specifically directed towards the purification of Telmisartan (I) from a mixture of water immiscible solvent and polar aprotic solvent, which results in the Telmisartan with the purity of above 99.5% by HPLC. Further, the precipitation process of the present invention improves flowability of crystallized product, ease of filtration from the crystalline medium, thereby increasing the yield, decreasing the cost and avoiding the drying problems.

OBJECTIVE OF THE INVENTION

The main objective of the present invention is to provide a simple and cost effective process for the preparation of Telmisartan Form A with high purity and good yields on a commercial scale.

SUMMARY OF THE INVENTION

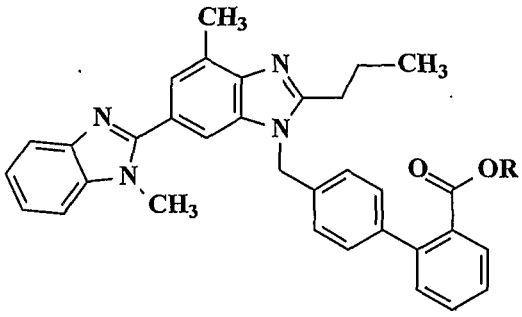
The present invention provides a process for the preparation of pure 4'-[[4-methyl-6-(l-methyl-2-benzimidazolyl)-2-propyl- 1-benzimidazolyl]methyl] -2-biphenylcarboxylic acid of Formula (I),



FormulaI

which comprises :

(i) treating Telmisartan alkyl ester (IV),



FormulaI V

wherein R represents methyl, ethyl, tertiary butyl;

with an aqueous solution of base in a water miscible solvent, optionally containing up to 25% water by volume, under heating to produce a solution of Telmisartan;

(ii) isolating pure Telmisartan from the solution using the solvent mixture selected from water immiscible solvent and polar aprotic solvent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of pure 4'-[[4-methyl-6-(l-methyl-2-benzimidazolyl)-2-propyl-l-benzimidazolyl]methyl]-2-biphenylcarboxylic acid (I) (Telmisartan).

Telmisartan alky ester (IV) used in the present invention may be prepared by the procedures provided in US 5,591,762, which is either isolated or directly proceeded further for hydrolysis.

Telmisartan alkyl ester (IV) is suspended in water miscible organic solvent selected from methanol, ethanol, isopropanol, ethylene glycol, diethylene glycol and treating with aqueous solution of base at a temperature of about 45-50°C and rising to the reflux temperature, preferably to 65-75^{0}C and agitating the reaction mass at same temperature for the complete conversion of Telmisartan methyl ester (IV) to Telmisartan. The base used is inorganic base selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, and potassium hydroxide. The solution containing Telmisartan is concentrated at atmospheric pressure till the reaction mass temperature reaches 80 ± 2°C. Adding water and water immiscible solvent selected from methylene chloride, ethylene chloride, chloroform to the above reaction mass followed by treating with acid selected from mineral acid such as hydrochloric acid, acetic acid, phosphoric acid, sulfuric acid or perchloric acid, at a temperature of about 25-30^{0}C. the organic and aqueous layers separated and the organic layer containing Telmisartan is washed with water and diluted with polar aprotic solvent selected from dimethylsulfoxide (DMSO), *N,N*-dimethylformamide (DMF), iV.*N*-dimethylacetamide (DMA), iV-methyl-2-pyrrolidone (NMP), at a temperature of about 25-30^{0}C, followed by seeding with Telmisartan Form A and agitating the resulting solution for at least 30 minutes. Concentrated the slurry containing Telmisartan at atmospheric pressure till the reaction mass temperature reaches 84 ± 2°C. Cooling the slurry to 0-2^{0}C and agitating for at least about 1 hour and filtered the pure Telmisartan.

4'-[[4-Methyl-6-(l-methyl-2-benzoimidazolyl)-2-propyl-l-benzoimidazolyl]methyl]-2-biphenylcarboxylic acid (Telmisartan) product produced by the above process is Telmisartan Form A and having a HPLC purity of about 99.7%. The major advantage

realized with the process of the present invention is that the removal of unwanted impurities without the use of tedious techniques such as column chromatography. The present technique improves flowability of crystallized product, ease of filtration from the crystalline medium, thereby increasing the yield, decreasing the cost and avoiding the drying problems.

The following examples illustrate the nature of the invention and are provided for illustrative purposes only and should not be construed to limit the scope of the invention.

EXAMPLE - 1

PREPARATION OF 4'-[[4-METHYL-O-(I-METHYL-Z-BENZIMIDAZOLYL) -2-PROPYL-I-BENZIMIDAZOLYL]METHYL]-Z-BIPHENYLCARBOXYLIC ACID **[TELMISARTAN]** :

l-Methyl-2-[4'-(bromomethylphenyl)]benzoate (148.68 g) was dissolved in *N*,*N*-dimethylformamide at 2 ± 2^{0}C and 2-n-propyl-4-methyl-6-(r-methylbenzimidazol-2'-yl) benzimidazole (150 g) was added at 2 ± 2^{0}C followed by sodium hydroxide (20.49 g). Thereafter, stirring was continued at 2 ± 2^{0}C till completion of the reaction. Methylene chloride (750 ml) was added at 2 ± 2^{0}C followed by DM water (150 ml, 22 ± 2^{0}C) and stirring was continued at 22 ± 2^{0}C for 15 min. The layers were separated and the aqueous layer was extracted with methylene chloride (150 ml) at 22 ± 2^{0}C. The combined organic extract was washed with DM water (750 ml) at 22 ± 2^{0}C and concentrated the organic layer (~ 1050 ml) till the mass temperature reaches to 54 ± 2^{0}C at atmospheric pressure. Methanol (450 ml) was added to the concentrated mass at 53 ± 2^{0}C. The concentration was continued till the vapor temperature reaches to 63 ± 2^{0}C. The concentrated mass was cooled to 45 ± 5^{0}C and diluted with methanol (600 ml). Aqueous sodium hydroxide (prepared by dissolving 65.22 g of sodium hydroxide in 150 ml DM water) was added at 45 ± 5^{0}C in 15 ± 5 min. The reaction mixture was heated to reflux at 68 ± I^{0}C. Thereafter, stirring was continued at reflux temperature (68 ± I^{0}C) till completion of the reaction. The reaction mass was concentrated at atmospheric pressure till the mass temperature reaches to 80 ± 2^{0}C. DM water (2250 ml, 28 ± 2^{0}C) was added to the residue followed by methylene chloride (300 ml) and stirred for 10 min

at 22 ± 2^{0}C. The aqueous layer was separated, methylene chloride (900 ml) was added to the aqueous layer at 22 ± 2^{0}C and adjusted the pH to 4.1 ± 0.1 with hydrochloric acid (-84 ml, 30% w/w) and stirred for 10 min at 22 ± 2^{0}C. The aqueous layer was separated from methylene chloride (150 ml) at 22 ± 2^{0}C. The organic layer was washed with DM water (300 ml) at 28 ± 2^{0}C. The organic layer (-1200 ml) was diluted with JVjJV-dimethylformamide (750 ml) at 28 ± 2^{0}C and seeded with Telmisartan Form A. The solution was kept standing for 30 mins and Telmisartan Form A crystallized out at 28 ± 2^{0}C. The resulting slurry was concentrated at atmospheric pressure till the mass temperature reaches to 82 ± 2^{0}C. The slurry was cooled to 2 ± 2^{0}C and stirred for Ih at this temperature. The product was filtered and washed with pre-cooled DMF followed by pre-cooled ethanol to obtain Telmisartan (~275g-wet) having more than 99.7% HPLC purity.

EXAMPLE - 2

PREPARATION OF 4'-[[4-METHYL-O-(I-METHYL-Z-BENZIMIDAZOLYL)-Z-PROPYL-I-BENZIMIDAZOLYL]METHYL]-Z-BIPHENYLCARBOXYLIC ACID **[TELMISARTAN] FROM ISOLATED TELMISARTAN METHYL ESTER**

Telmisartan methyl ester 10 g, was suspended in methanol (50 ml) at 25-3O^{0}C. Aqueous sodium hydroxide (prepared by dissolving 2.65 g of sodium hydroxide in 10 ml of DM water) was added at 25-3O^{0}C in 20 min and heated the contents to reflux at 68 ± I^{0}C. Thereafter, continued the stirring at reflux temperature (68 ± I^{0}C) till completion of the reaction. The reaction mass was concentrated at atmospheric pressure till the mass temperature reaches to 80 ± 2^{0}C. DM water (150 ml, 28 ± 2^{0}C) was added to the residue followed by methylene chloride (20 ml) and stirred for 10 min at 22 ± 2^{0}C and the layers were separate. Methylene chloride (80 ml) was added to the aqueous layer at 22 ± 2^{0}C and the pH was adjusted to 4.1 ± 0.1 with hydrochloric acid (5.5 ml, 30%w/w) and continued stirring for 10 min at 18 - 22^{0}C. The combined organic layer was washed with DM water (20 ml) at 18 - 22^{0}C and diluted the organic layer (-1200 ml) with JV,JV-dimethylformamide (50 ml) followed by seeding with Telmisartan Form A. Thereafter, the reaction mass was kept on standing at 28 ± 2^{0}C for 30 min. The resulting slurry was concentrated at atmospheric pressure till the mass temperature reaches to 84 ± 2^{0}C and

thereafter the slurry was cooled to 2 ± 2^{0}C and stirred for Ih at this temperature. The product was filtered and washed with pre-cooled iV,*N*~dimethylformamide (10 ml, 0 ± 2^{0}C) followed by pre-cooled ethanol and dried at 90-95^{0}C to produce pure Telmisartan (7.9 g).

EXAMPLE - 3

PREPARATION OF TELMISARTAN FROM 1-ETH YL-2- [4'-(BROMO-METHYLPHENYL)]BENZOATE

l-Ethyl-2-[4'-(bromomethylphenyl)]benzoate (30.30 g, 85.5%) was dissolved in *N*,*N*-dimethylformamide (100 ml) at 2 ± 2^{0}C and 4-methyl-6-(l -methyl- 1-benzimidazolyl)-2-propyl-l-benzimidazole (25 g) at 2 ± 2^{0}C was added to the above solution followed by sodium hydroxide (3.42 g). Thereafter, stirring was continued at 2 ± 2^{0}C till the completion of the reaction. Methylene chloride (125 ml) was added to the above reaction mass followed by DM water (250 ml, 22 ± 2^{0}C) at 2 ± 2^{0}C. Stirring was continued at 22 ± 2^{0}C for 15 min and the layers were separated and the aqueous layer was extracted with methylene chloride (25 ml) at 22 ± 2^{0}C. The combined organic extract was washed with DM water (125 ml) at 22 ± 2^{0}C and the organic layer was concentrated till the mass temperature reaches to 6O^{0}C at atmospheric pressure. Ethanol (75 ml) was added to the concentrated mass (Contains Telmisartan ethyl ester) at 60^{0}C and the concentration was continued till the vapor temperature reaches to 82^{0}C. The concentrated mass was cooled to 45 ± 5° and diluted with ethanol (100 ml) followed by aqueous sodium hydroxide (prepared by dissolving 10.87 g of sodium hydroxide in 25 ml of DM water) at 45 ± 5^{0}C in 15 ± 5 min was added and the contents were heated to reflux at 78 ± I^{0}C. Thereafter, stirring was continued at reflux temperature (78 ± I^{0}C) till completion of the reaction. The reaction mass was concentrated at atmospheric pressure till the mass temperature reaches to 80 ± 2^{0}C and DM water (375 ml, 28 ± 2^{0}C) was added to the residue followed by methylene chloride (50 ml) and stirred for 10 min at 22 ± 2^{0}C. The layers were separated and methylene chloride (200 ml) was added to the aqueous layer at 22 ± 2^{0}C and pH was adjusted to 4.1 ± 0.1 with hydrochloric acid (-17 ml, 30%w/w) and stirring was continued for 10 min at 22 ± 2^{0}C. The layers were separated and the organic layer

was washed with DM water (50 ml) at 28 ± 2^{0}C. The organic layer was diluted with Λ^I,*N*-dimethylformamide (125 ml) at 28 ± 2^{0}C and seeded with Telmisaratn Form A. Thereafter, the solution was kept on standing at 28 ± 2^{0}C for 30 min and Telmisartan Form A crystallizes out. The resulting slurry was concentrated at atmospheric pressure till the mass temperature reaches to 84 ± 2^{0}C. The slurry was cooled to 2 ± 2^{0}C and stirred for Ih at this temperature. The product was filtered and washed with pre-cooled *N*,iV-dimethylformamide (25 ml, 0 ± 2^{0}C) followed by pre-cooled ethanol (50 ml, O^{0}C) and dried to obtain Telmisartan (30 g) was having more than 99.7 % of HPLC purity.

EXAMPLE-4

REMOVAL OF RESIDUAL SOLVENTS FROM WET TELMISARTAN:

Telmisartan wet, as obtained above, was suspended in 20% v/v aqueous ethanol (1125 ml at 28 ± 2^{0}C) and aqueous ammonia (37.20 g, 20% w/w) was added at 28 ± 2^{0}C and stirred to get a clear solution. The solution was filtered through hyflo and washed with aqueous ethanol (20% v/v, 375 ml, 28 ± 2^{0}C). The filtrate was heated to 60 ± 2^{0}C; Acetic acid (30.75 g) was added at 60 ± 2^{0}C over a period of about Ih. Thereafter, the contents were heated to reflux at 76 ± 2^{0}C and stirring was continued at this temperature for Ih. The resulting slurry was cooled to 0 ± 2^{0}C and stirred at this temperature for Ih. The product was filtered and washed with aqueous ethanol (20% v/v, 187.5 ml 0 ± 2^{0}C). The product was dried at 90-95^{0}C under reduced pressure (~ 10 mmHg) to yield Telmisartan Form A (172.5 g) having more than 99.9% of HPLC purity and about 1500 ppm of ethanol as residual solvent.

EXAMPLE-5

PREPARATION OF 4'-[[4-METHYL-O-(I-METHYL-I-BENZIMIDAZOLYL)-I-**PROPYL-1-BENZIMIDAZOLYL] METHYL]-2-BIPHENYLCARBOXYLIC ACID [TELMISARTAN]**

Powdered sodium hydroxide (3.41 g) was added in dimethyl sulfoxide (75 ml) followed by 4-methyl-6-(l-methyl-2-benzimidazolyl)-2-propyl-l-benzimidazole monohydrate (25 g) at 25-26^{0}C and the contents were stirred at this temperature for 10 min. Thereafter,

methyl-2-[4'-(bromomethylphenyl)]benzoate (26.70 g) was added and stirred at 25-30^{0}C till completion of the reaction. Methylene chloride (125 ml) was added, followed by water (250 ml) and separated the layers. The aqueous layer was extracted with methylene chloride (25 ml). The combined organic layer was washed with water (50 ml). The organic layer was concentrated under reduced pressure to a volume of 50 ml. Methanol (50 ml) was added to the concentrated mass and redistilled to collect the 50 ml of the distillate. Thereafter, the concentrated mass was diluted with methanol (125 ml). Aqueous sodium hydroxide solution (9.3 g of NaOH in 12.5 ml of water) was added at 30-35°C and heated to reflux till completion of the hydrolysis reaction. After completion of the reaction, the reaction mass was filtered through hyflo and the filtrate was concentrated at 55-60^{0}C under reduced pressure. The oily mass obtained was dissolved in water (400 ml) and washed with methylene chloride (50 ml). Methylene chloride (125 ml) was added to the aqueous layer and pH was adjusted to 4.9 with hydrochloric acid (17 ml, 35% w/w) at 25-3O^{0}C and stirred for 15 min at this temperature. The aqueous layer was separated and extracted with methylene chloride (25 ml). The combined organic layer was washed with water (50 ml). N,N-dimethylformamide (125 ml) was added to the organic layer followed by Telmisartan Form-A seed and left on standing without stirring for 30 min. The resulting slurry was concentrated under reduced pressure at 60-65°C to collect 80 ml of the distillate. Thereafter, the slurry was stirred at 25-30^{0}C for 30 min and cooled to 0-5°C. Solid was filtered, washed with precooled N,N-dimethylformamide (40 ml, 0^{0}C) followed by precooled ethanol (10 ml, -2°C) and dried at 80-85^{0}C under reduced pressure to afford Telmisartan (26 g).

EXAMPLE-6

PREPARATION OF 4'-[[4-METHYL-O-(I-METHYL-Z-BENZIMIDAZOLYL)-Z-PROPYL-1-BENZIMIDAZOLYL] METHYL]-Z-BIPHENYLCARBOXYLIC ACID **[TELMISARTAN]**

Powdered sodium hydroxide (3.41 g) was added in N,N-dimethylformamide (75 ml) followed by 4-methyl-6-(l-methyl-2-benzimidazolyl)-2-propyl-l-benzimidazole monohydrate (25 g) at 25-26°C and stirred the contents at this temperature for 10 min.

Thereafter, methyl-2-[4'-(bromomethylphenyl)]benzoate (26.70 g) was added and stirred at 25-30°C till completion of the reaction. Methylene chloride (125 ml) was added, followed by water (250 ml) and separated the layers. The aqueous layer was extracted with methylene chloride (25 ml). The combined organic layer was washed with water (50 ml). The organic layer was concentrated under reduced pressure to a volume of 50 ml. Methanol (50 ml) was added to the concentrated mass and redistilled to collect the 50 ml of the distillate. Thereafter, the concentrated mass was diluted with methanol (125 ml). Aqueous sodium hydroxide solution (9.3 g of NaOH in 12.5 ml of water) was added at 30-35°C and heated to reflux till completion of the hydrolysis reaction. After completion of the reaction, the reaction mass was filtered through hyflo and the filtrate was concentrated at 55-60°C under reduced pressure. The oily mass obtained was dissolved in water (400 ml) and washed with methylene chloride (50 ml). Methylene chloride (125 ml) was added to the aqueous layer and pH adjusted to 4.9 with hydrochloric acid (13 ml, 35% w/w) at 25-30°C and stirred for 15 min at this temperature. The aqueous layer was separated and extracted with methylene chloride (50 ml). The combined organic layer was washed with water (50 ml). N,N-dimethylformamide (125 ml) was added to the organic layer followed by Telmisartan Form-A seed and left on standing without stirring for 30 min. The resulting slurry was concentrated under reduced pressure at 60-65°C to collect 80 ml of the distillate. Thereafter, the slurry was stirred at 25-30°C for 30 min and cooled to 0-5°C. Solid was filtered, washed with precooled N,N-dimethylformamide (40 ml, 0°C) followed by precooled ethanol (10 ml, -2°C) and dried at 80-85°C under reduced pressure to afford Telmisartan (26 g).

EXAMPLE-7

PREPARATION OF 4'-[[4-METHYL-O-(I-METHYL^-BENZIMIDAZOLYL)-Z-PROPYL-1-BENZIMIDAZOLYL] METHYL]-Z-BIPHENYLCARBOXYLIC ACID [TELMISARTAN]

Powdered sodium hydroxide (3.41 g) was added in dimethyl acetamide (75 ml) followed by 4-methyl-6-(l-methyl-2-benzimidazolyl)-2-propyl-l-benzimidazole monohydrate (25 g) at 25-26°C and stirred the contents at this temperature for 10 min. Thereafter,

methyl-2-[4'-(bromomethylphenyl)]benzoate (26.70 g) was added and stirred at 25-30°C till completion of the reaction. Methylene chloride (125 ml) was added, followed by water (250 ml) and separated the layers. The aqueous layer was extracted with methylene chloride (25 ml). The combined organic layer was washed with water (50 ml). The organic layer was concentrated under reduced pressure to a volume of 50 ml. Methanol (50 ml) was added to the concentrated mass and redistilled to collect the 50 ml of the distillate. Thereafter, the concentrated mass was diluted with methanol (125 ml). Aqueous sodium hydroxide solution (9.3 g of NaOH in 12.5 ml of water) was added at 30-35°C and heated to reflux till completion of the hydrolysis reaction. After completion of the reaction, the reaction mass was filtered through hyflo and the filtrate was concentrated at 55-60°C under reduced pressure. The oily mass obtained was dissolved in water (400 ml) and washed with methylene chloride (50 ml). Methylene chloride (125 ml) was added to the aqueous layer and pH adjusted to 4.9 with hydrochloric acid (13 ml, 35% w/w) at 25-30°C and stirred for 15 min at this temperature. The aqueous layer was separated and extracted with methylene chloride (50 ml). The combined organic layer was washed with water (50 ml). N,N-dimethylformamide (125 ml) was added to the organic layer followed by Telmisartan Form-A seed and left on standing without stirring for 30 min. The resulting slurry was concentrated under reduced pressure at 60-65°C to collect 80 ml of the distillate. Thereafter, the slurry was stirred at 25-30°C for 30 min and cooled to 0-5°C. Solid was filtered, washed with precooled N,N~dimethylformamide (40 ml, 0°C) followed by precooled ethanol (10 ml, -2°C) and dried at 80-85°C under reduced pressure to afford Telmisartan (26 g).

EXAMPLE-8

PREPARATION OF 4'-[[4-METHYL-O-(I-METHYL-Z-BENZIMIDAZOLYL) -2-PROPYL-1-BENZIMIDAZOLYL] METHYL]-Z-BIPHENYLCARBOXYLIC ACID [TELMISARTAN]

Powdered sodium hydroxide (6.83 g) was added in N,N~dimethylformamide (175 ml) at 4°C followed by 4-methyl-6-(l-methyl-2-benzimidazolyl)-2 -propyl- 1-benzimidazole monohydrate (50 g) and stirred for 5 min. Thereafter, methyl-2-[4'-

(bromomethylphenyl)]benzoate (54.76 g) was added at 0°C and stirred to the reaction mass till completion of the reaction. Methylene chloride (250 ml) was added, followed by water (500 ml) at 2^{0}C and stirred for 10 min. The aqueous layer was separated and extracted with methylene chloride (50 ml). The combined organic extract was washed with water (250 ml) to obtain 380 ml of the organic solution containing Telmisartan methyl ester. 320 ml of this organic layer was concentrated at ambient pressure to collect 210 ml of the distillate. Methanol (120 ml) was added to the concentrated mass and distilled to collect 96 ml of the distillate. The concentrated mass was diluted with 160 ml of methanol at 5O^{0}C. Thereafter, aqueous sodium hydroxide solution (17.4 g of NaOH in 40 ml of water) was added at 5O^{0}C and heated to reflux at 69-7O^{0}C and stirred at reflux temperature till completion of hydrolysis reaction. Thereafter, the reaction mass was concentrated under reduced pressure at 60-65^{0}C till no more solvent distils. Water (600 ml) and methylene chloride (200 ml) was added to this solution. pH was adjusted to 4 with hydrochloric acid (22 ml, 35% w/w) at 27-28°C. The aqueous layer was separated and extracted with methylene chloride (40 ml). The combined organic layer was washed with water (80 ml) to obtain 280 ml of the organic solution. This is divided in to four parts and taken for isolation of Telmisartan as given below.

Part-1

The organic layer (70 ml) as obtained above was diluted with N,N-dimethylformamide (500 ml) at 27°C and seeded with Telmisartan form-A. The solution was left on standing without stirring for 30 min. The resulting suspension was stirred at 27-28°C for 30 min at this temperature. Solid was filtered, washed with precooled N,N-dimethylformamide (15 ml, -5°C) followed by precooled ethanol (10 ml, -2°C) and dried at 85-90^{0}C under reduced pressure to afford 10.1 g of Telmisartan.

Part-2

The organic layer (70 ml) as obtained above was diluted with N,N-dimethylformamide (50 ml) at 27°C and seeded with Telmisartan form-A. The solution was left on standing without stirring for 30 min. The resulting suspension was concentrated under reduced pressure at 65-70^{0}C to collect 30 ml of the distillate. Thereafter, the concentrated mass was cooled to -5°C and stirred for 30 min at this temperature. Product was filtered,

washed with precooled N,N-dimethylformamide (15 **ml,** -3°C) followed by precooled ethanol (10 ml, -2°C) and dried at 85-90^{0}C under reduced pressure to afford **11.4** g of Telmisartan.

Part-3

The organic layer (70 ml) as obtained above was diluted with N,N-dimethylformamide (60 ml) at 27°C and seeded with Telmisartan form-A. The solution was left on standing without stirring for 30 min. The resulting suspension was concentrated under reduced pressure at 65-70°C to collect 50 ml of the distillate. Thereafter, stirred at 30°C for 15 min, cooled to -5°C and stirred for 30 min at this temperature. Product was filtered, washed with precooled N,N-dimethylformamide (15 ml, -5°C) followed by precooled ethanol (10 **ml,** -2^{0}C) and dried at 85-90^{0}C under reduced pressure to afford 11.7 g of Telmisartan.

Part-4

The organic layer (70 ml) as obtained above was diluted with N,N-dimethylformamide (40 ml) at 27°C arid seeded with Telmisartan form-A. The solution was left on standing without stirring for 30 min. The resulting suspension was concentrated under reduced pressure at 65-70^{0}C to collect 45 ml of the distillate. Thereafter, stirred at 30^{0}C for 15 min, cooled to -5°C and stirred for 30 min at this temperature. Product was filtered, washed with precooled N,N-dimethylformamide (15 ml, -5°C) followed by precooled ethanol (10 ml, -2^{0}C) and dried at 85-90^{0}C under reduced pressure to afford 12.3 g of Telmisartan.

REFERANCE EXAMPLE I

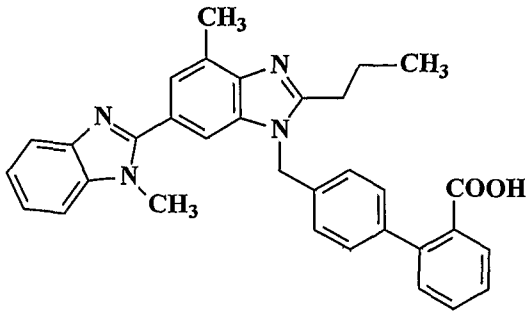
PREPARATION OF 4'-[[4-METHYL-O-(I-METHYL^-BENZIMIDAZOLYL)-I-PROPYL-1-BENZIMIDAZOLYL] METHYL]-2-BIPHENYLCARBOXYLIC **ACID [TELMISARTAN]**

l-Methyl-2-[4'-(bromomethylphenyl)]benzoate (26.22 g) was dissolved in *N,N*-dimethylformamide (100 ml) at 2 ± 2^{0}C and 4-methyl-6-(l -methyl- 1-benzimidazolyl)-2-propyl-1-benzimidazole (25 g) was added at 2 ± 2^{0}C followed by sodium hydroxide

(3.41 g). Thereafter, stirring was continued at 2 ± 2^{0}C till completion of the reaction. Methylene chloride (125 ml) was added at 2 ± 2^{0}C followed by DM water (1500 ml, 22 ± 2^{0}C) and stirring was continued at 22 ± 2^{0}C for 15 min. The layers were separated and the aqueous layer was extracted with methylene chloride (25 ml) at 22 ± 2^{0}C. The combined organic extract was washed with DM water (250 ml) at 22 ± 2^{0}C and concentrated till the mass temperature reaches to 54 ± 2^{0}C at atmospheric pressure. Methanol (75 ml) was added to the concentrated mass at 53 ± 2^{0}C and the concentration was continued till the vapor temperature reaches to 63 ± 2^{0}C. The concentrated mass was cooled to 45 ± 5^{0}C and diluted with methanol (100 ml). Aqueous sodium hydroxide (prepared by dissolving 10.86 g of sodium hydroxide in 25 ml of DM water) was added at 45 ± 5^{0}C in 15 ± 5 min. The reaction mixture was heated to reflux at 68 ± I^{0}C. Thereafter, stirring was continued at reflux temperature (68 ± I^{0}C) till completion of the reaction. The reaction mass was concentrated at atmospheric pressure till the mass temperature reaches to 80 ± 2^{0}C. DM water (375 ml, 28 ± 2^{0}C) was added to the residue followed by methylene chloride (50 ml) and stirred for 10 min at 22 ± 2^{0}C. The aqueous layer was separated. Methylene chloride (200 ml) was added to the aqueous layer at 22 ± 2^{0}C and adjusted its pH to 4.1 ± 0.1 with hydrochloric acid (15 ml, 30%w/w) and stirred for 10 min at 22 ± 2^{0}C. The organic layer was washed with DM water (50 ml) at 28 ± 2^{0}C and concentrated to dryness. The solid obtained was dried to yield 36.50 g of Telmisartan. Thereafter, the solid (3Og) was dissolved in *N*,vV-dimethylformamide (125 ml) and heated to 110^{0}C to get a clear solution. The solution was cooled to 0-2^{0}C and stirred for Ih at this temperature. Product was filtered and washed with chilled *N*,*N*-dimethylformamide. The wet solid was dried at 90-95^{0}C for 12h to afford crude Telmisartan (20.5Og) having more than 99.5 % of HPLC purity.

WE CLAIM

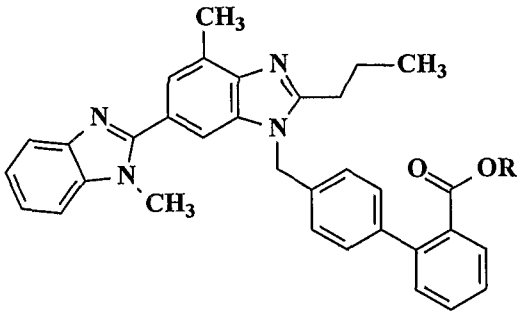
1. A process for the preparation of pure 4'-[2-n-propyl-4-methyl-6-(l-methylbenzimidazol-2-yl)benzimidazol-l -ylmethyl]biphenyl-2-carboxylic acid of Formula (I),



Formula I

which comprises :

(i) treating Telmisartan alkyl ester (IV),



Formula IV

wherein R represents methyl, ethyl, tertiary butyl;

with an aqueous solution of base in a water miscible solvent, optionally containing up to 25% water by volume, under heating to produce a solution of Telmisartan;

(ii) isolating Telmisartan from the solution using the solvent mixture selected from water immiscible solvent and polar aprotic solvent.

2. A process according to claim 1, wherein the base used in step (i) is inorganic base selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide.

3. A process according to claim 1, wherein the water miscible solvent used in step (i) is selected from methanol, ethanol, and isopropanol, ethylene glycol and diethylene glycol.

4. A process according to claim 1, isolation of Telmisartan, comprises:

(i) adding water and water immiscible solvent and adding acid to the resulting solution in an amount sufficient to adjust the pH to 4-4.5;

(ii) separating the organic layer and washing with water;

(iii) adding polar aprotic solvent to the above organic layer containing Telmisartan;

(iv) optionally seeding the solution with Telmisartan Form A;

(v) keep on standing the contents at 28 ± 2°C for at least 30 minutes;

(vi) concentrating the resulting Telmisartan slurry at atmospheric pressure till the mass temperature reaches to 84 ± 2°C;

(vii) cooling the Telmisartan slurry in the range of 0-2°C; for at least 1 hour;

(viii) isolating the pure Telmisartan by filtration and optionally washing the crystals with organic solvents.

5. A process according to claim 4, wherein the water immiscible solvent used in step (i) is selected from methylene chloride, ethylene chloride, and chloroform.

6. A process according to claim 4, wherein the polar aprotic solvent used in step (iii) is selected from dimethylsulfoxide (DMSO), Λ/,JV-dimethylformamide (DMF), ΛfJV-dimethylacetamide (DMA), JV-methyl-2-pyrrolidone (NMP).

7. A process according to claim 1-6, wherein the pure Telmisartan produced by any of the proceeding claims is Telmisartan Form A.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/005934

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D235/20 A61K31/4184 A61P9/00

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)
C07D A61K A61P

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

Electronic data base consulted during the International search (name of dala base and, where practical, search terms used)

EPO-Internal , CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No
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X	EP 0 502 314 A (THOMAE GMBH DR K [DE]) 9 September 1992 (1992-09-09) claim 5 ; example 9	1-7

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[X] Further documents are **listed** in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents

1A" document defining lhe general state of the art which is not considered to be of particular relevance

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Date of lhe actual completion of the international search	Date of mailing of the international search report
2 October 2009	13/10/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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