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(54) Title: PROCESS FOR PREPARING TELMISARTAN

(57) Abstract: Novel processes for preparing a telmisaitan nitrile intermediate (4'-[{2-n-propyl-4- methyI-6-f l-methyJbenzimidazol-2-yl)-benzimidazol- l -yl)-methyl]-biphenyl-2-nitrile) and further converting it to telmisaitan and/or salts thereof are disclosed.

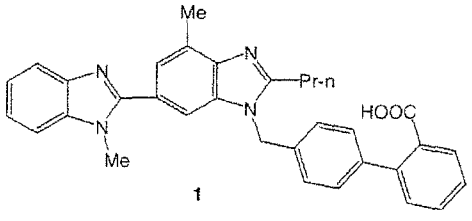
Process for Preparing Telmisartan

Field of the invention

The present invention is directed to processes for preparing a telmisartan intermediate substituted on position 2 of the biphenyl group of (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl) and further converting such an intermediate to telmisartan and/or salts thereof. The processes according to the invention are cost and time effective and produce telmisartan with high yield and quality.

Background of the invention

Telmisartan with its chemically name 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and formula 1



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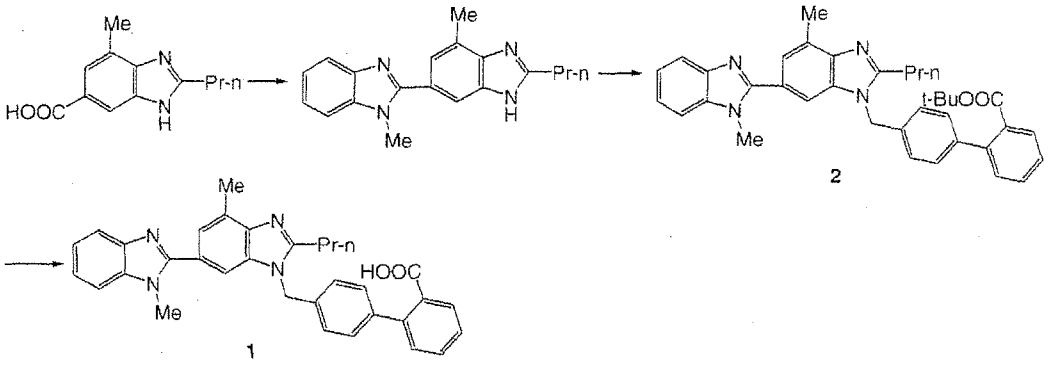
is a non-peptide antagonist of subtype 1 of the angiotensin II receptor (AT_1-antagonist) used for the treatment of hypertension. It can be used alone or in combination with another pharmaceutically active compound, e.g. hydrochlorothiazide.

Telmisartan is disclosed in **EP 0 502 314** as well as in J. Med. Chem., 36(25), 4040-4051 (1993). Its polymorphs are known from **EP 1 144 386** and J. Pharm. Sci, 89 (11), 1465-1479 (2000).

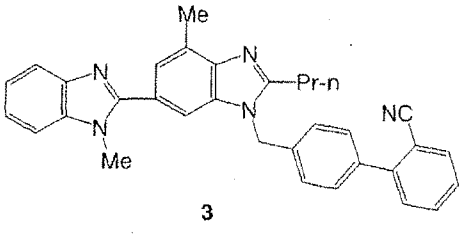
EP 0 502 314 A and J. Med. Chem., 36(25), 4040-4051 (1993), disclose a method for the preparation of telmisartan using its tert-butyl substituted intermediate (Scheme 1). The

final product of this method is difficult to be filtered, washed and isolated. These properties are an obstacle to an effective large-scale production.

Scheme 1



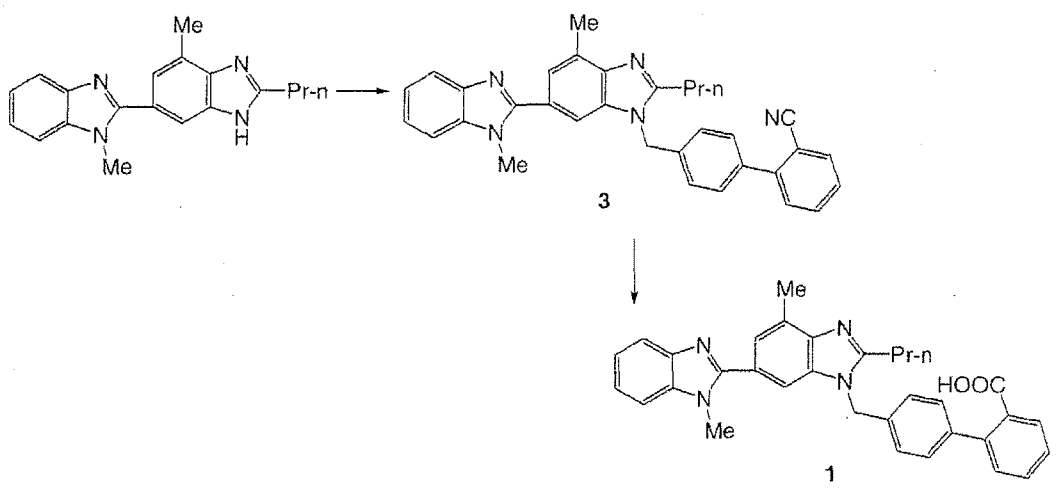
The synthesis of telmisartan from a compound with the chemical name 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile (further named as telmisartan nitrile) and represented by formula 3



is disclosed in EP 0 502 314A, WO 2004/087676, CN 1412183 and US 2006/264491.

In WO 2004/087676 and CN 1412183 telmisartan is prepared by hydrolyzing the compound of formula 3 (Scheme 2):

Scheme 2



The disclosed method can be used in the large-scale production of telmisartan and allows for a relatively easy purification thereof.

US 2006/0264491 discloses reacting 4'((1,4'-dimethyl-2'-propyl(2,6'-bi-1H-benzimidazol)-1'-yl)-methyl)-(1,1'-biphenyl)-2-carboxamide via hydrolysis into telmisartan, isolating crude telmisartan and optionally purifying the crude telmisartan via crystallization.

Amorphous telmisartan is disclosed in US 2006/111417 and WO 2006/050921, while crystalline forms of telmisartan are disclosed in WO 00/43370, IN 2005MU00164 and US 2006/0276525.

Various salts of telmisartan are known, for example from CN 1548421, WO 03/037876, WO 2006/044754, WO 2006/050509, WO 2006/050921, EP 1 719 766, WO 2006/136916, WO 2007/010558 and WO 2007/147889.

In addition to the above-discussed preparation processes of telmisartan, there still is a need for a yet further improved synthetic route to telmisartan.

Therefore, the object of the present invention is to provide new methods for the production of telmisartan intermediates substituted on position 2 of the biphenyl group of (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl) which methods are suitable for use on an industrial scale and which are economical, i.e. both cost and time effective and allow for the production of intermediates that can be converted into telmisartan and/or salts thereof with high quality and high yield.

Another object of the present invention is to provide novel intermediates of telmisartan and derivatives thereof that enable new, cost and time effective synthetic routes to such compounds.

Summary of the invention

In one aspect, the present invention provides processes for the preparation of the key intermediate of the synthesis of telmisartan, namely a telmisartan intermediate substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl.

In another aspect, the present invention provides novel intermediates useful for the synthesis of telmisartan intermediates substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl optionally in isolated and/or purified form and their use as intermediates in the preparation of telmisartan and/or its salts.

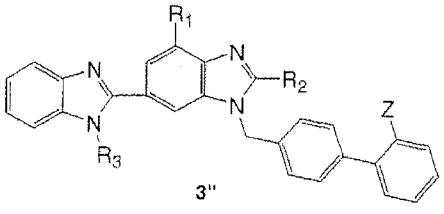
In another aspect, the present invention provides telmisartan intermediates substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl prepared by the processes according to the present invention having a purity of greater than 98%, preferably greater than 99%, wherein the amount of each individual impurity is less than 0.15%.

In another aspect, the present invention provides a pharmaceutical composition for administering an effective amount of telmisartan or salts thereof prepared by the processes

according to the present invention in a unit dosage form, either alone or in combination with another active ingredient.

Detailed description of the invention

The object of the present invention is to provide novel time- and cost-effective processes for the preparation of intermediates of telmisartan derivatives substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl. These derivatives are represented by formula 3"



3"

wherein

R_1 is C_1-C_6 alkyl,

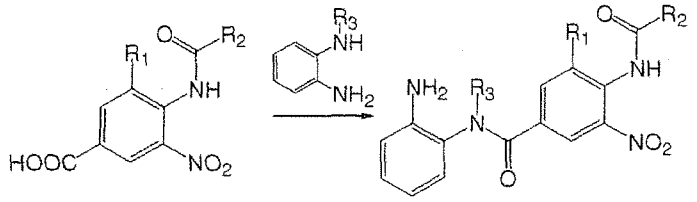
R_2 is C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl,

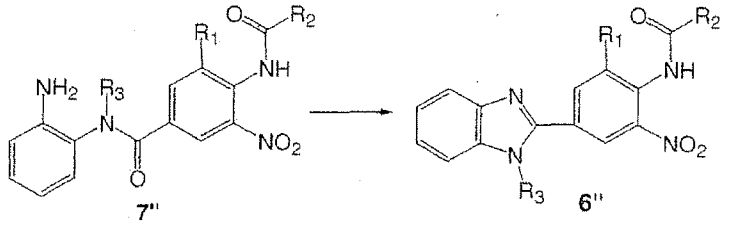
Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl. Preferably, Z is -CN, -COOMe, -COOEt, $-CONH_2$ or $-CONMe_2$.

The first of the inventive processes (Process A) comprises the steps of:

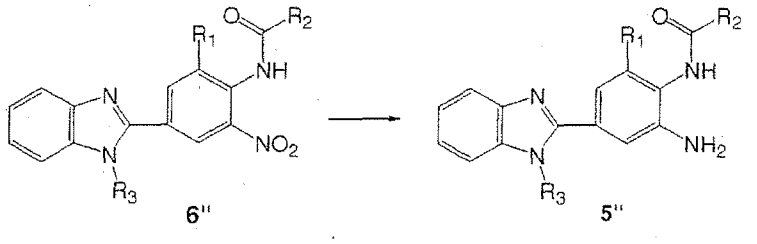
a) acylation of an N-alkyl-substituted diamino benzene with the starting compound 8" to form compound 7",



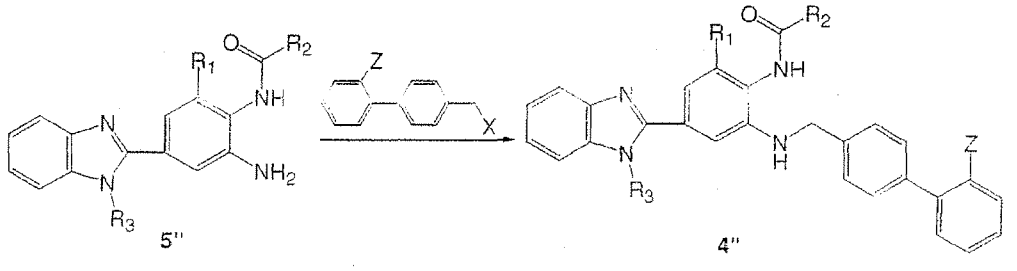
b) condensation to form compound 6",



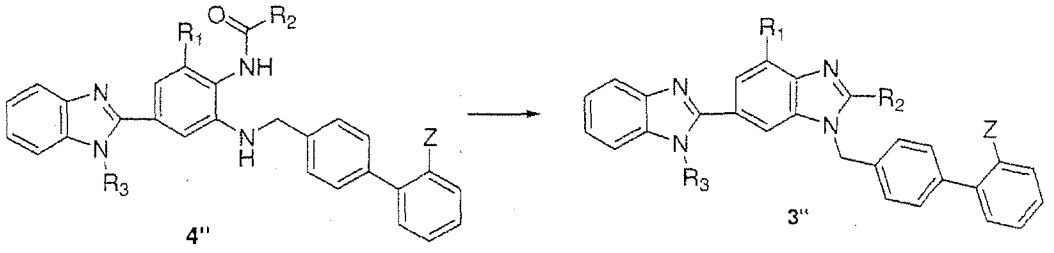
c) reduction to give compound 5",



d) aralkylation to give compound 4" and



e) condensation to prepare compound 3''



wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

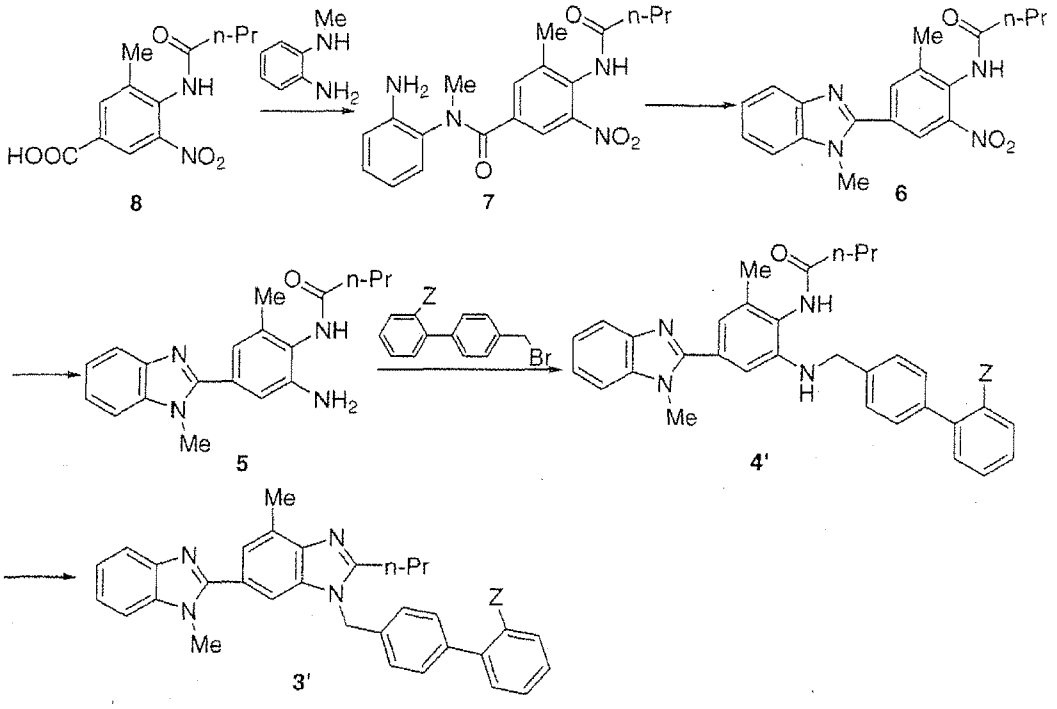
R_3 is C_1-C_6 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and

X is Cl, Br or I.

More particularly, the object of the present invention is to provide a process for the preparation of telmisartan intermediates represented by formula 3' (Scheme 3, wherein Z is as defined above):

Scheme 3



Even more particularly, the object of the present invention is to provide a process for the preparation of telmisartan nitrile (Scheme 3, wherein Z is CN) comprising the following steps:

Step a) Acylation of N-methylbenzene-1,2-diamine with compound 8 in the presence of a suitable solvent and a suitable catalyst, to form compound 7 (N-(2- aminophenyl)-4-(butyramido)-N,3-dimethyl-5-nitrobenzamide).

Suitable catalysts that can be used include, but are not limited to, pyridine, triethylamine and similar. Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, dioxane, dichloromethane, chloroform, toluene, dimethylformamide and similar and any mixtures thereof.

The temperature for conducting the acylation can be in the range from about 0 to about 100 °C, particularly from about 20 to about 60 °C and more particularly at the reflux temperature of the solvent(s) used.

The above preferred reaction conditions, catalysts and solvents are also the preferred embodiments to carry out the acylation step (a) according to the broader aspects of this invention. The same applies in the following *mutatis mutandis*.

Step b) Condensation of compound 7 in the presence of a suitable solvent and a suitable catalyst, to form compound 6 (N-(2-methyl-4-(1-methyl-1H-benzo[d]imidazol- 2-yl)-6-nitrophenyl)butyramide).

Suitable catalysts that can be used include, but are not limited to, pyridine, p-toluene sulphonic acid, acetic acid and similar organic and inorganic compounds that assist intramolecular condensation.

Suitable solvents that can be used in step b) include, but are not limited to, tetrahydrofuran, dioxane, pyridine, acetic acid, toluene and similar solvents; and any mixtures thereof. The temperature for conducting the condensation can be in the range from about 0 to about 130 °C, particularly from about 20 to about 60 °C and more particularly at the reflux temperature of the solvent(s) used.

Step c) Reduction of compound 6 by hydrogenation in the presence of a suitable solvent and a suitable catalyst to give compound 5 (N-(2-amino-6-methyl-4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl)butyramide).

Suitable catalysts that can be used in step c) include, but are not limited to, palladium on charcoal, Raney-Ni and similar hydrogenation catalysts.

Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, methanol, ethanol, propanol and other lower alcohols and ethers having less than 6 carbon atoms; water; and any mixtures thereof.

The temperature for conducting the reduction can be in the range from about 0 about 100 °C, particularly from about 20 to about 50 °C and more particularly at the reflux temperature of the solvent(s) used.

Step d) Alkylation of compound 5 with 4'-(bromomethyl) biphenyl-2-nitrile in the presence of a suitable solvent and a suitable catalyst to form compound 4 (N-((2-nitrile-biphenyl-4'-methyl)amino-6-methyl-4-(1-methyl-1H-benzo [d] imidazol -2-yl) phenyl) butyramide).

Suitable catalysts for step d) can be inorganic basic catalysts including, but not limited to, hydroxides of alkaline metals such as lithium hydroxide, sodium hydroxide, potassium hydroxide and other alkaline hydroxides; carbonates of alkaline metals such as for example sodium carbonate, potassium carbonate and other basic carbonates; and bicarbonates of alkaline metals such as for example sodium bicarbonate, potassium bicarbonate and similar hydrogen carbonates. Mixtures of these compounds may also be used as may be alkaline phosphates such as trisodium phosphate.

Suitable solvents that can be used in step d) include, but are not limited to, tetrahydrofuran, acetonitrile, toluene, N,N-dimethylformamide and similar; and any mixtures thereof. The temperature for conducting the alkylation can be in the range from about 0 to about 100 °C, particularly from about 20 to about 50 °C and more particularly at the reflux temperature of the solvent(s) used.

Step e) Condensation of compound 4 in the presence of a suitable solvent and a suitable catalyst to form compound 3 (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile).

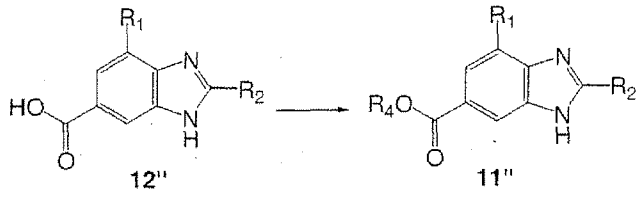
Suitable catalysts that can be used in this step (including step e according to the broader aspects of the invention, as mentioned above) include, but not limited to, pyridine, p-toluene sulphonic acid, acetic acid and similar. Suitable solvents include, but are not limited to, tetrahydrofuran, dioxane, pyridine, acetic acid, toluene and similar; and any mixtures thereof.

The temperature for conducting the condensation can be in the range from about 0 to about 130°C, particularly from about 20 to about 60°C and more particularly at the reflux temperature of the solvent(s) used.

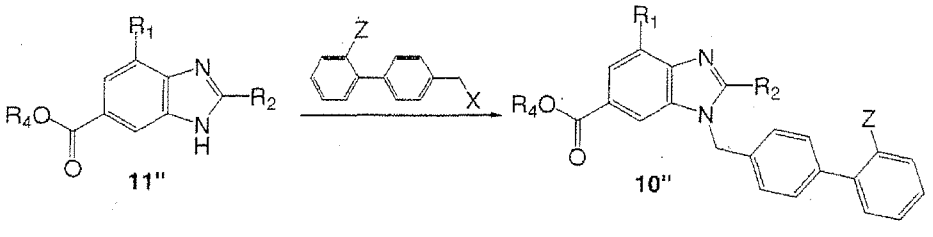
The starting compound 8'' or 8 (4-(butyramido)-3-methyl-5-nitrobenzoic acid) can be prepared as disclosed in J. Med. Chem., 36(25), 4040-4051 (1993), or by acylation of 4-amino-5-methyl-3-nitrobenzoic acid, which is disclosed in US 3691166, US 7220862, WO 2005/065779 and WO 2007/056155. For the acylation reaction processes those known in the art for the acylation of amino groups such as activation with chlorides, mixed anhydrides and coupling reagents can be employed.

Another aspect of the present invention is Process B. This process is again directed at the preparation of intermediate telmisartan derivatives substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl as represented by formula 3'', and comprises the steps of:

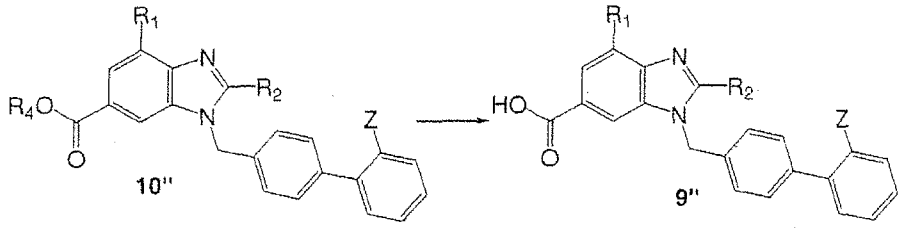
a) esterification of starting compound 12'' to form compound 11'',



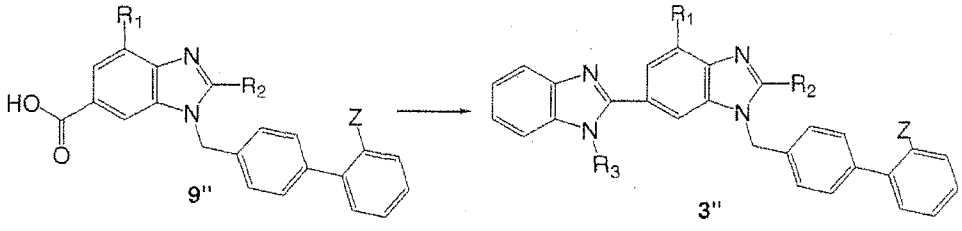
b) alkylation to form compound 10'',



c) hydrolysis to form compound 9'' and



d) condensation to form compound 3''



wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl,

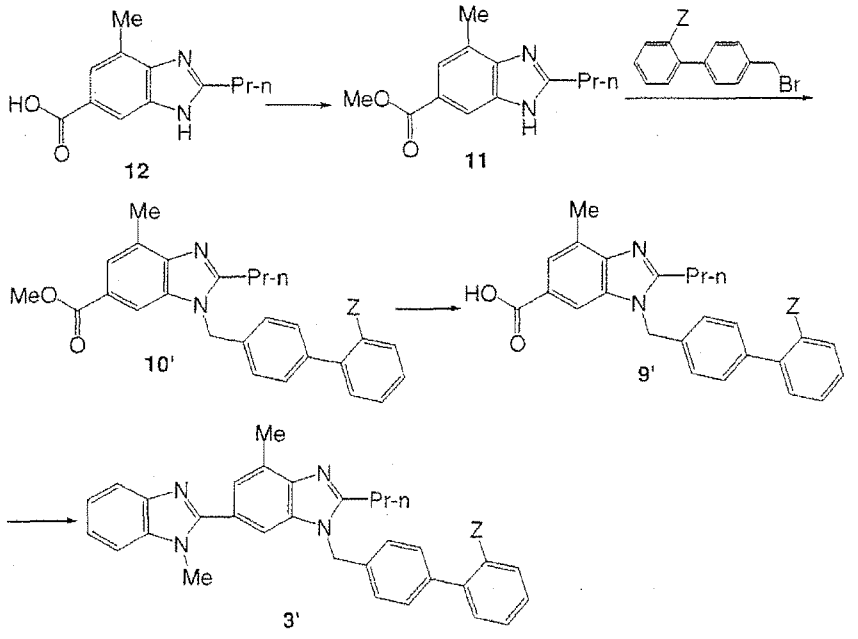
R_4 is $CONR_5$, wherein R_5 is H or C_1-C_3 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and

X is Cl, Br or I.

A preferred aspect of the present invention is a shortened process for the preparation of telmisartan intermediates with formula 3'' (Scheme 4, wherein Z is defined above):

Scheme 4



Another preferred aspect of this embodiment of the present invention is a process for the preparation of telmisartan nitrile (Scheme 4, wherein Z is CN) comprising the steps of:

a) esterification of the carboxyl group of compound 12 (7-methyl-2-propyl- 3H-benzo[d] imidazole-5-carboxylic acid) to form compound 11 (methyl 7-methyl-2-propyl-3H-benzo[d] imidazole-5-carboxylate),

b) alkylation of compound 11 with 4'-(bromomethyl)biphenyl-2-nitrile to form compound 10 (4'-((7-methyl -2-propyl-3H-benzo[d]imidazole-5-methoxycarbonyl-3-yl)-methyl)-biphenyl-2- nitrile),

c) hydrolysis of compound 10 to form compound 9 (4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxyl-3-yl)-methyl)-biphenyl -2-nitrile) and

d) condensation of compound 9 with N-methylbenzene-1,2-diamine to form compound 3 (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2- nitrile).

Step a) involves the esterification of carboxyl group of compound 12 in the presence of a suitable solvent and a suitable catalyst, to form compound 11 (methyl 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylate).

Suitable catalysts can be inorganic acid catalysts including, but not limited to, hydrochloric acid, sulfuric acid and similar strong inorganic acids. Suitable solvents that can be used include, but are not limited to, methanol, tetrahydrofuran, acetonitrile, toluene and similar organic solvents; and any mixtures thereof.

The temperature for conducting the esterification can be in the range from about 0 to about 100 °C, particularly from about 20 to about 50 °C and more particularly at the reflux temperature of the solvent(s) used.

Step b) involves the alkylation of compound 11 with 4'-(bromomethyl)biphenyl-2-nitrile, in the presence of a suitable solvent and a suitable catalyst to form compound 10 (4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-methoxycarbonyl-3-yl)-methyl)-biphenyl-2-nitrile).

Suitable catalysts can be inorganic basic catalysts including, but not limited to, hydroxides of alkaline metals such as for example lithium hydroxide, sodium hydroxide, potassium hydroxide and similar alkaline oxides and hydroxides; carbonates of alkaline metals such as for example sodium carbonate, potassium carbonate and similar carbonates such as ammonium carbonate; and bicarbonates of alkaline metals such as for example sodium bicarbonate, potassium bicarbonate and similar bicarbonates such as ammonium hydrogen carbonate.

Suitable solvents that can be used include, but are not limited to, acetone, tetrahydrofuran, acetonitrile, toluene, N,N-dimethylformamide and similar organic solvents; and any mixtures thereof.

The temperature for conducting the alkylation can be in the range from about 0 to about 100 °C, particularly from about 20 to about 50 °C and more particularly at the reflux

temperature of the solvent(s) used.

Step c) involves the hydrolysis of compound 10 in the presence of a suitable solvent and a suitable catalyst, to form compound 9 (4'-((7-methyl-2-propyl-3H-benzo[d]imidazole- 5-carboxyl-3-yl)-methyl)-biphenyl-2-nitrile).

Suitable catalysts can be inorganic basic catalysts including, but not limited to, hydroxides of alkaline metals such as for example lithium hydroxide, sodium hydroxide, potassium hydroxide and similar; carbonates of alkaline metals such as for example sodium carbonate, potassium carbonate and similar carbonates such as ammonium carbonate.

Suitable solvents that can be used include, but are not limited to, methanol, ethanol, propanol and similar, water; and any mixtures thereof.

The temperature for conducting the hydrolysis can be in the range from about 0 to about 80 °C, particularly from about 20 to about 50 °C and more particularly at the reflux temperature of the solvents used.

Step d) involves the condensation of compound 9 with, N-methylbenzene-1,2-diamine in the presence of a suitable solvent and a suitable catalyst, to form compound 3 (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile).

Suitable catalysts that can be used include, but are not limited to, $SOCl_2$ and similar compounds that assist the removal of water.

Suitable solvents that can be used include, but are not limited to, methylene chloride, toluene, chlorobenzene and the like; and their mixtures.

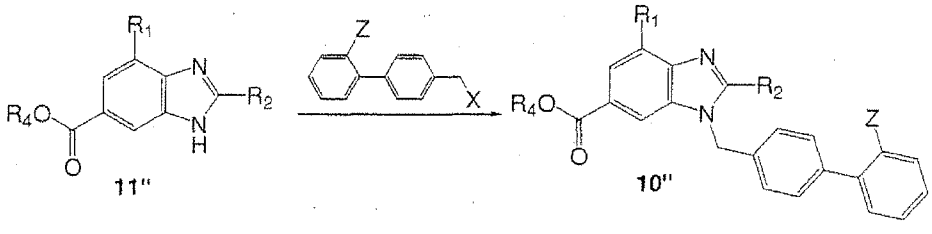
The temperature for conducting the condensation can be in the range from about 0 about 130 °C particularly from about 20 to about 100 °C and more particularly at the reflux temperature of the solvents used.

As mentioned above, these preferred conditions apply to process B in general and are not limited to the particular embodiment of preparing telmisartan nitrile by process B.

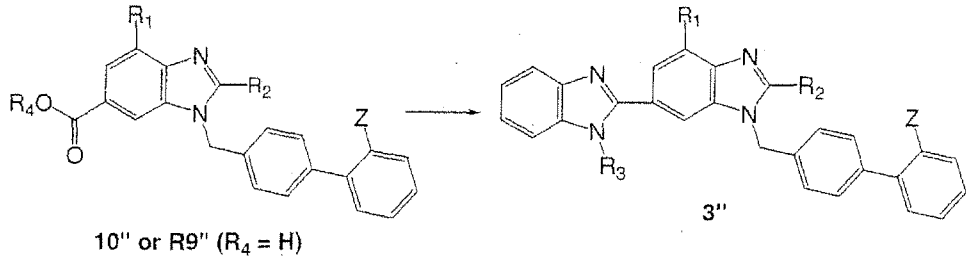
The starting compound 12" or 12 (7-methyl-2-propyl-3H-benzo[d] imidazole-5-carboxylic acid), can be prepared by any method known from the prior art as for example from J. Med. Chem., 36(25), 4040-4051 (1993), WO 97/19911, CN 1623992, Youji Huaxue 26(3), 318-323 (2006) and WO 2006/044754.

Yet a further preferred aspect of the present invention is the following process for the preparation of intermediates of telmisartan derivatives substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl) with formula 3". This process comprises the steps of:

a) alkylation of compound 11" to form compound 10" and



b) condensation to form compound 3"



wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl,

R_4 is $CONR_5$, wherein R_5 is H or C_1-C_3 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and

X is Cl, Br or I.

Step a) involves the alkylation of compound 11" in the presence of a suitable solvent and a suitable catalyst to form compound 10" and optionally the hydrolysis of compound 10" in the presence of a suitable solvent and a suitable catalyst to form compound 9".

Suitable catalysts can be inorganic basic catalysts including, but not limited to, hydroxides of alkaline metals such as for example lithium hydroxide, sodium hydroxide, potassium hydroxide and similar alkaline oxides and hydroxides; carbonates of alkaline metals such as for example sodium carbonate, potassium carbonate and similar carbonates such as ammonium carbonate; and bicarbonates of alkaline metals such as for example sodium bicarbonate, potassium bicarbonate and similar bicarbonates such as ammonium hydrogen carbonate.

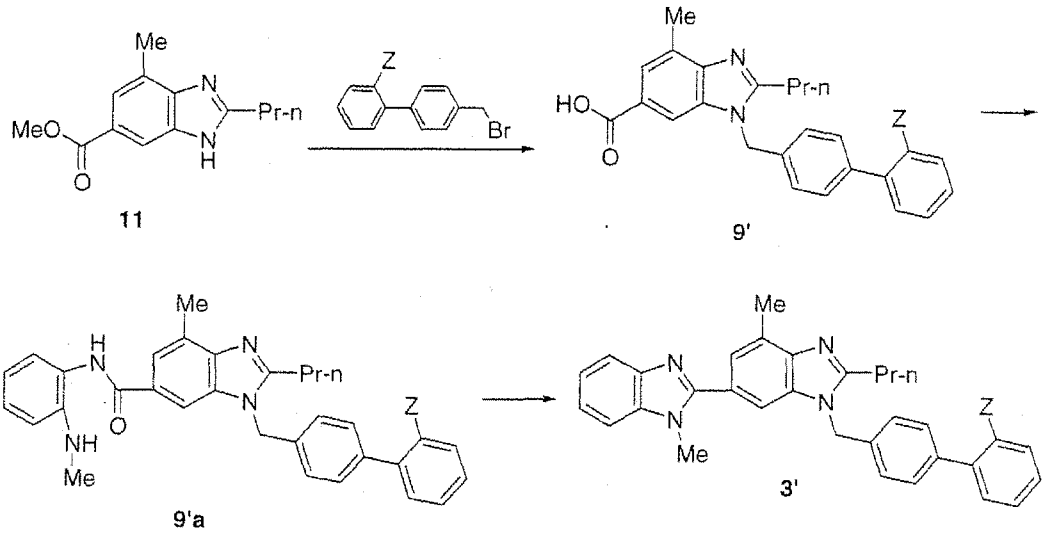
Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, acetonitrile, toluene, N,N-dimethylformamide and similar; and any mixtures thereof.

The temperature for conducting the alkylation can be in the range from about 0 to about 100 °C, particularly from about 20 to about 50 °C and more particularly at the reflux temperature of the solvent(s) used.

Step b) involves the condensation of compound 9" or compound 10" with N-methylbenzene-1,2-diamine in the presence in the presence of a suitable solvent and a suitable catalyst, to form compound 3".

Even more particularly, the object of the present invention is to provide a process for the preparation of the telmisartan intermediates with formula 3' (Scheme 5, wherein Z is as defined above), comprising:

Scheme 5



wherein

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and R_1 is C_1-C_6 alkyl.

Even more particularly, the object of the present invention is to provide a process for the preparation of telmisartan nitrile (Scheme 5, wherein Z is CN) comprising the steps of:

a) alkylation of compound 11 (methyl 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylate) with 4'-(bromomethyl)biphenyl-2-nitrile followed by hydrolysis of the ester group to form compound 9 (4'-((7-methyl -2-propyl-3H-benzo[d]imidazole-5-methoxycarbonyl-3-yl)-methyl)-biphenyl-2- nitrile),

b) condensation of compound 9 with N-methylbenzene-1,2-diamine to form compound 9a (1-((2'-cyanobiphenyl-4-yl)methyl)-4-methyl-N-(2-(methylamino)phenyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide) and

c) cyclization of compound 9a to form compound 3 (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl) -methyl]-biphenyl-2-nitrile).

Step a) involves the alkylation of compound 11 (methyl 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylat) with 4'-(bromomethyl)biphenyl-2-nitrile in the presence of a suitable solvent and a suitable catalyst to form after hydrolysis compound 9 (4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-methoxycarbonyl-3-yl)-methyl)-biphenyl-2-nitrile) without the isolation of the ester.

Suitable catalysts can be inorganic basic catalysts including, but not limited to, hydroxides of alkaline metals such as for example lithium hydroxide, sodium hydroxide, potassium hydroxide and similar alkaline oxides and hydroxides; carbonates of alkaline metals such as for example sodium carbonate, potassium carbonate, sodium phosphate, potassium phosphate and similar strongly alkaline salts; and bicarbonates of alkaline metals such as for example sodium bicarbonate, potassium bicarbonate and similar bicarbonates such as ammonium hydrogen carbonate.

Additional catalysts can be used such as iodides, including sodium iodide, potassium iodide and lithium iodide. Preferably potassium iodide is used.

Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, acetonitrile, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, DMSO, acetone, 2-butanone, 3-pentanone and similar; and any mixtures thereof.

The temperature for conducting the alkylation can be in the range from about 0 to about 120 °C particularly from about 20 to about 60 °C and more particularly at the reflux temperature of the solvent(s) used.

After the alkylation step, the solvent is removed and the hydrolysis of the ester group is carried out without the isolation of the ester intermediate. To the residue another solvent is added. Suitable solvents that can be used include, but are not limited to, methanol, ethanol, propanol and similar alcohols; water, and any mixtures thereof.

Suitable catalysts can be inorganic basic catalysts including, but not limited to, hydroxides of alkaline metals such as for example lithium hydroxide, sodium hydroxide, potassium hydroxide and similar alkaline oxides and hydroxides; and carbonates of alkaline metals such as for example sodium carbonate, potassium carbonate and similar carbonates such as ammonium carbonate.

The temperature for conducting the hydrolysis can be in the range from about 0 to about 80 °C, particularly from about 20 to about 50 °C and more particularly at the reflux temperature of the solvents used.

After the reaction is completed (after 1 to 10 h) the mixture is cooled and the pH of the mixture is adjusted to a value of 2-7, preferably to 5-6, by adding an acid such as a mineral acid, for example aqueous HCl, H_2SO_4 or H_3PO_4; preferably aqueous HCl is added.

Step b) involves the condensation of compound 9 with N-methylbenzene-1,2-diamine in the presence of a suitable solvent and a suitable reagent to form compound 9a (1-((2'-cyanobiphenyl-4-yl)methyl)-4-methyl-N-(2-(methylamino)phenyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide).

N-methylbenzene-1,2-diamine can be used in form of a salt with an inorganic acid such as HCl, H_3PO_4 and H_2SO_4.

Suitable reagents for amide bond formation that can be used include, but are not limited to, $SOCl_2$ and similar. The amount of the catalyst(s) is from 1 to 7 equivalents, preferably 3 to 5 equivalents.

Suitable solvents that can be used include, but are not limited to, pyridine, N-methylpyrrolidone, toluene, dichloromethane, chloroform, 1,2-dimethoxyethane, THF, 2-methyl-THF, 1,4-dioxane, pentane and similar polar aprotic organic solvents; and their mixtures.

The temperature for conducting the condensation can be in the range from about 0 about 130°C, particularly from about 20 to about 100°C and more particularly at the reflux temperature of the solvent used. After an isolation step (extraction) from the residue, the product (compound 9a) is precipitated by adding an organic solvent such as a nonpolar solvent, preferably hexane, heptane, petroleum ether, cyclohexane, ethers (diethyl ether, diisopropyl ether, tert-butyl methyl ether), benzene, toluene, xylenes and similar.

Step c) involves the cyclization of compound 9a to form compound 3 (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2- nitrile). To compound 9a an organic solvent is added. As organic solvent the following solvents can be used: toluene, xylenes, benzene, cyclohexane, 1,4-dioxane, THF, 2-methyl-THF, 1,2-dimethoxyethane, diisopropyl ether, tert-butyl methyl ether and similar. To this mixture a catalytic amount of an acid catalyst is added. A Lewis acid, preferably H_3BO_3 is used. The acidic catalyst is present in an amount from 1 to 50 mol%, preferably from 1 to 10 mol%.

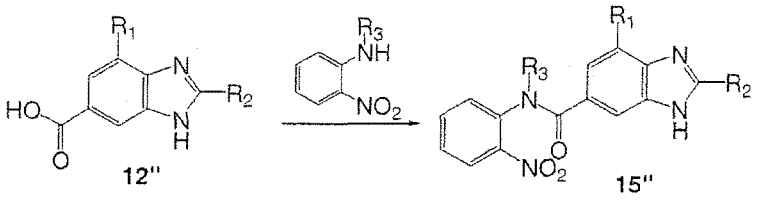
The temperature for conducting the cyclization can be in the range from about 0 about 140 °C and particularly at the reflux temperature of the solvents used. Water formed during the reaction can be separated and removed.

After the cyclization is completed, the reaction mixture can optionally be worked up with activated charcoal. Finally, the product solution is cooled to a temperature between -10 and 30 °C, preferably between 15 and 25 °C, and the product is separated and dried.

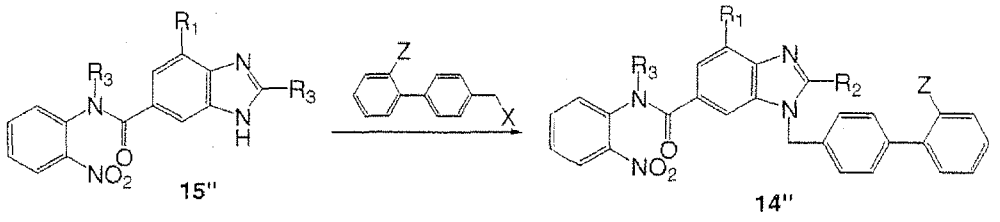
The starting compound 11" or 11 (methyl 7-methyl-2-propyl- 3H-benzo[d] imidazole-5-carboxylate) can be prepared by any method known from the prior art as for example from J. Med. Chem., 36(25), 4040-4051 (1993), WO 97/19911, CN 1623992, Youji Huaxue 26(3), 318-323 (2006) and WO 2006/044754.

Another aspect of the present invention is Process C for the preparation of intermediate telmisartan derivatives substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl represented by formula 3". This process comprises the steps of:

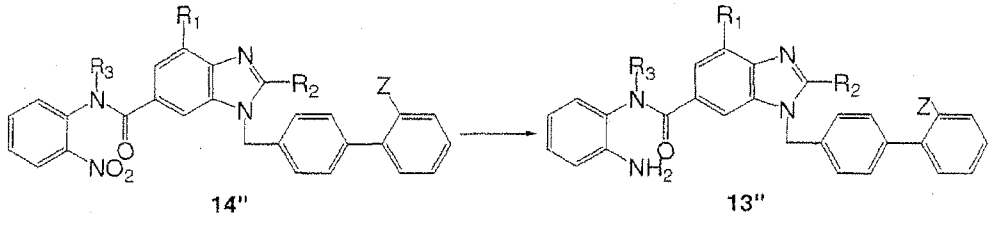
a) acylation of alkyldiaminobenzene of compound 12" to form compound 15",



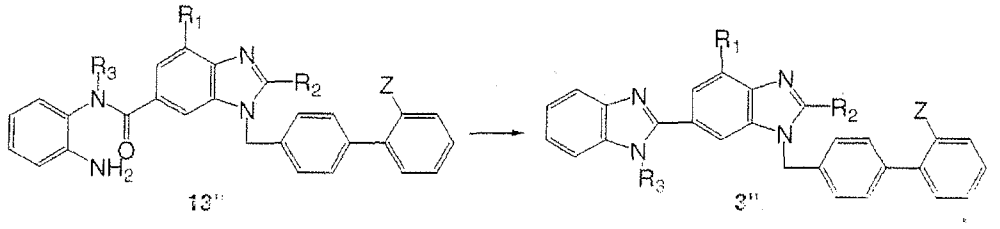
b) alkylation to form compound 14",



c) reduction to form compound 13" and



d) condensation to form compound 3"



wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

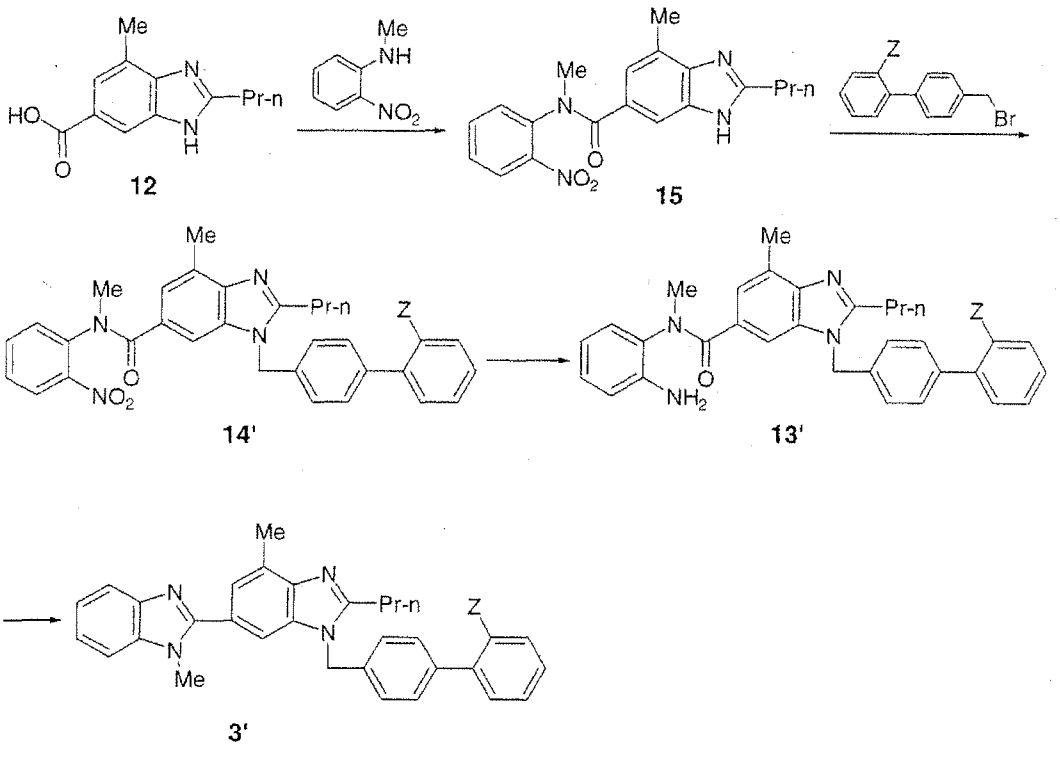
R_3 is C_1-C_6 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and

X is Cl, Br or I.

A particular aspect of the present invention is a process for the preparation of the telmisartan intermediates with formula 3' (Scheme 6, wherein Z is as defined above):

Scheme 6



wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is

H, C_1-C_6 alkyl or benzyl.

A preferred aspect of the present invention is a process for the preparation of telmisartan nitrile (Scheme 6, wherein Z is CN) comprising the steps of:

a) acylation of N-methyl-2-nitrobenzenamine with compound 12 (7-methyl-2-propyl-3H-benzo[d] imidazole-5-carboxylic acid) to form compound 15 (N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide),

b) alkylation of compound 15 with 4'-(bromomethyl)biphenyl-2-nitrile to form compound 14 (4'-((N,7-dimethyl-N-(2-nitrophenyl)-2-propyl -3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile),

c) reduction of compound 14 to form compound 13 (4'-((N,7-dimethyl-N-(2-aminophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile) and

d) condensation of compound 13 to form compound 3 (4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)- benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile).

Step a) involves the treatment of compound 12 with thionyl chloride or oxalyl chloride and the subsequent acylation of N-methyl-2-nitrobenzenamine in the presence of a suitable solvent and catalyst to form compound 15 (N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5- carboxamide).

Suitable catalysts that can be used include, but are not limited to, pyridine, triethylamine and similar basic catalysts. Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, dioxane, dichloromethane, chloroform, toluene, dimethylformamide and similar; and any mixtures thereof.

The temperature for conducting the acylation can be in the range from about 0 about 100 °C, particularly from about 20 to about 60 °C and more particularly at the reflux

temperature of the solvent(s) used.

Step b) involves the alkylation of compound 15 with 4'-(bromomethyl)biphenyl-2-nitrile, in the presence of a suitable solvent and a suitable catalyst, to form compound 14 (4'-((N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile).

Suitable catalysts can be inorganic basic catalysts including, but not limited to, hydroxides of alkali metals such as for example lithium hydroxide, sodium hydroxide, potassium hydroxide and similar; carbonates of alkaline metals such as for example sodium carbonate, potassium carbonate and similar; and bicarbonates of alkaline metals such as for example sodium bicarbonate, potassium bicarbonate and similar. In this context the expression "and similar" may particularly include the corresponding ammonium hydroxide, carbonate and hydrogen carbonate; the same applies throughout this application.

Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, acetonitrile, toluene, N,N-dimethylformamide and similar polar aprotic solvents; and any mixtures thereof.

The temperature for conducting the alkylation can be in the range from about 0 to about 100 °C, particularly from about 20 to about 50 °C and more particularly at the reflux temperature of the solvent(s) used.

Step c) involves the reduction of compound 14 in the presence of a suitable solvent and a suitable catalyst to form compound 13 (4'-((N,7-dimethyl-N-(2-aminophenyl) -2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile).

Suitable catalysts that can be used include, but are not limited to, palladium on charcoal, Raney-Ni and similar hydrogenation catalysts.

Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, methanol, ethanol, propanol and similar protic solvents; water; and any mixtures thereof.

The temperature for conducting the reduction can be in the range from about 0 to about 100 °C, particularly from about 20 to about 50 °C and more particularly at the reflux

temperature of the solvent(s) used.

Step d) involves the condensation of compound 13 in the presence of a suitable solvent and a suitable catalyst to form compound 3 (4'-[(2-n- propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl] -biphenyl-2-nitrile).

Suitable catalysts that can be used include, but are not limited to, pyridine, p-toluene sulphonic acid, acetic acid and similar compounds (see above). Suitable solvents that can be used include, but are not limited to, tetrahydrofuran, dioxane, pyridine, acetic acid, toluene and similar compounds (see above); and any mixtures thereof.

The temperature for conducting the condensation can be in the range from about 0 to about 130 °C, particularly from about 20 to about 60 °C and more particularly at the reflux temperature of the solvent(s) used.

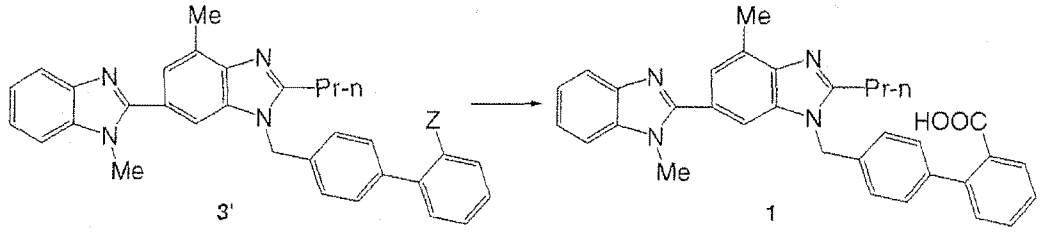
The starting compound 12'' or 12 (7-methyl-2-propyl- 3H-benzo[d]imidazole-5-carboxylic acid) can be prepared according to any method known from the prior art as for example from J. Med. Chem., 36(25), 4040-4051 (1993), WO 97/19911, CN 1623992, Youji Huaxue 26(3), 318-323 (2006) and WO 2006/044754.

Another embodiment of the present invention are the telmisartan intermediate substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl with formula 3 as well as the derivatives thereof represented by formulae 3' and 3'' prepared by the processes according to the present invention having a purity of greater than 98%, preferably greater than 99%, wherein the amount of each individual impurity is less than 0.15%.

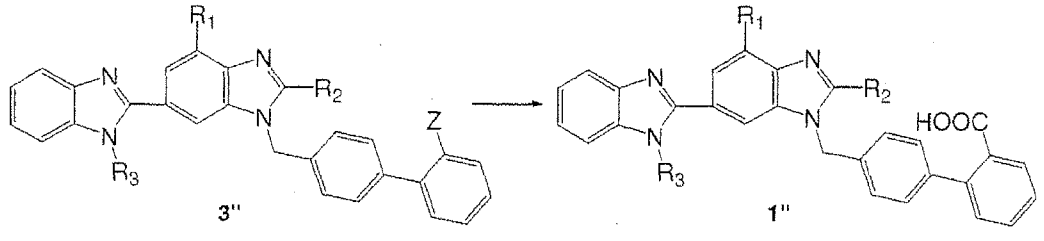
We surprisingly found out that the chemical purity of the compound with formula 3 or 3' or 3'' plays an important role in the manufacturing process of telmisartan or telmisartan derivatives and/or salts thereof. If, for example, the chemical purity of the compound with formula 3 is less than 98%, the telmisartan substance further prepared from the compound with formula 3 does not comply with the pharmacopoeia requirements.

The intermediates of telmisartan and of the telmisartan derivatives substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl with formulae 3' and 3" prepared by the processes according to the present invention are converted to telmisartan and the telmisartan derivatives with formulae 1 and 1", respectively, by a hydrolysis process (Scheme 7a and Scheme 7b). Suitable hydrolysis processes are known from the prior art and are for example disclosed in EP 0 502 314, CN 1412183, WO 2004/087676 and the co-pending application WO 2007/147889.

Scheme 7a



Scheme 7b



wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

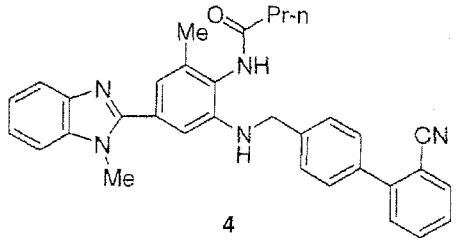
R_3 is C_1-C_6 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl.

The obtained telmisartan is preferably converted to a pharmaceutically acceptable salt, such as the sodium, potassium, meglumine, erbumine or any other salt known from the prior art as for example from the co-pending application WO 2007/147889.

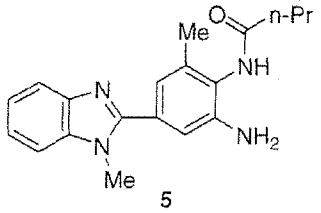
In another aspect, the present invention provides novel intermediates of the synthesis of telmisartan nitrile, optionally in isolated and/or purified form selected from the group consisting of:

Compound 4 with the chemical name
N-((2-cyano-biphenyl-4'-methyl)amino-6-methyl-4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl) butyramide



4

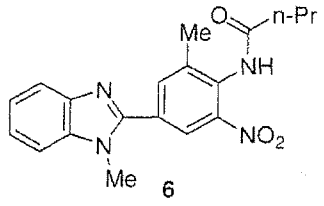
Compound 5 with the chemical name
N-(2-amino-6-methyl-4-(1-methyl-1H -benzo[d] imidazol-2-yl)phenyl)butyramide



5

Compound 6 with the chemical name

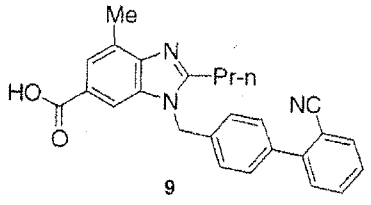
N-(2-methyl-4-(1-methyl-1H-benzo[d] imidazol-2-yl)-6-nitrophenyl)butyramide



6

Compound 9 with the chemical name

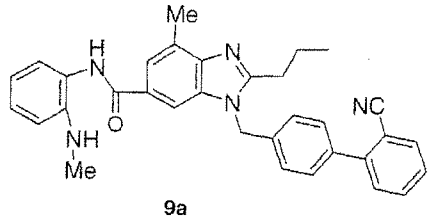
4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxyl-3-yl)-methyl)-biphenyl-2-nitrile



9

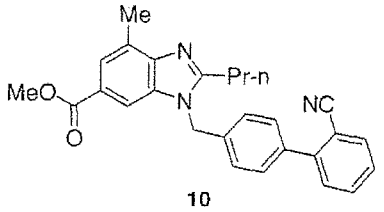
Compound 9a with the chemical name

1-((2'-cyanobiphenyl-4-yl)methyl)-4-methyl-N-(2-(methylamino)phenyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide



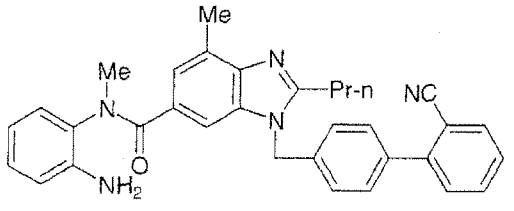
9a

Compound 10 with the chemical name
4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-methoxycarbonyl-3-yl)-methyl)-biphenyl-2-nitrile



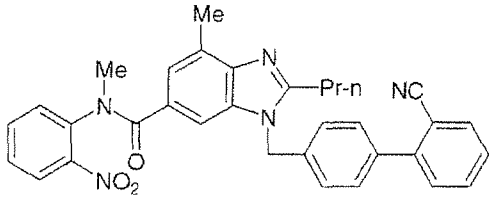
10

Compound 13 with the chemical name
4'-((N,7-dimethyl-N-(2-aminophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile



13

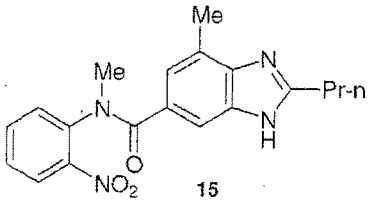
Compound 14 with the chemical name
4'-((N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitril



14

Compound 15 with the chemical name

N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide



15

In another aspect, the present invention provides the use of the novel intermediates in the preparation of telmisartan and/or its salts.

The processes according to the present invention avoid the use of 1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-bibenzo[d]imidazole, which is the key intermediate of the art known syntheses of telmisartan (cf. Scheme 1) and which is difficult to prepare (processes disclosed in the prior art use polyphosphoric acid at temperature 150 °C for 20 hours).

Another aspect of the present invention is a pharmaceutical composition for administering an effective amount of telmisartan and/or its salts prepared by one of the processes according to the present invention, alone or in combination with another active ingredient and at least one pharmaceutically acceptable excipient selected from the group consisting of, but not limited to, basic agents, diluents, binders, disintegrants, surfactants, crystallization retarders, lubricants and glidants. The term "pharmaceutically acceptable excipient" denotes the additives used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients.

The solid pharmaceutical composition according to the present invention is preferably formulated in a unit dosage form, each dosage containing from about 10 to 160 mg, preferably from about 20 to 80 mg of telmisartan and/or its salts. When one or more other active ingredients are present in the stable solid pharmaceutical composition according to the present invention, said other active ingredient can be present in an amount of 6.25 to 50 mg, preferably in an amount of 12.5 to 25 mg. The term „unit dosage form" refers to physically discrete units suitable as unitary dosages for human objects and other mammals,

each unit containing a predetermined quantity of telmisartan and/or its salts calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical acceptable excipient.

The term basic agent denotes such agents that maintain the pH of the pharmaceutical composition at a value of least 7, preferably at least 8. The pH of the pharmaceutical composition is measured by dissolving an appropriate amount thereof in neutral water and preparing a 20% [w/w] solution. Any standard pH meter can be used for the pH measurement. The basic agents used in the pharmaceutical composition according to the present invention may be selected from, but not restricted to, the group consisting of ammonia, choline, tert-butylamine, ethanolamine, NaOH, KOH, $Ca(OH)_2$, Na- and K-carbonates, hydrogen carbonates and phosphates, meglumine, piperazine, diethylamine, L-arginine and any mixtures thereof. Preferred are ammonia, NaOH, KOH and meglumine.

The diluent used in the pharmaceutical composition according to the present invention may be selected from, but not restricted to, the group consisting of microcrystalline cellulose, powdered cellulose, lactose (anhydrous and monohydrate), compressible sugar, fructose, dextrates, sugar alcohols such as mannitol, sorbitol, maltitol, xylitol, lactitol, or other sugars such as saccharose, raffinose, trehalose, fructose or any mixtures thereof, siliconised microcrystalline cellulose, calcium hydrogen phosphate, calcium carbonate, calcium lactate and any mixtures thereof. Preferred are water-soluble fillers like mannitol, sorbitol, xylitol and lactose other sugars.

The binder used in the pharmaceutical composition according to the present invention may be selected from, but not restricted to, the group consisting of polyvinylpyrrolidone, microcrystalline cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose or other cellulose ethers, starch, pregelatinized starch, or polymethacrylate and any mixtures thereof.

The disintegrant used in the pharmaceutical composition according to the present invention may be selected from, but not restricted to, the group consisting of crospovidone, starch, pregelatinized starch, sodium starch glycolate, microcrystalline cellulose,

carboxymethylcellulose sodium (CMC-Na) or calcium (CMC-Ca), cross-linked CMC-Na, polacrilin potassium, low-substituted hydroxypropylcellulose and any mixtures thereof. Preferably, at least one disintegrant is selected from cross-linked CMC-Na, starch and low-substituted hydroxypropylcellulose.

The surfactant used in the pharmaceutical composition according to the present invention may be selected from, but not restricted to, the group consisting of anionic, cationic, ampholytic and nonionic surfactants. Anionic surfactants are those where the hydrophilic group carries a negative charge are such as for example carbonyl ($RCOO^-$), sulphonate (RSO_3^-) or sulphate ($ROSO_3^-$); examples include potassium laurate ($CH_3(CH_2)_{10}COO^-K^+$) and sodium lauryl sulphate ($CH_3(CH_2)_{11}SO_4^-Na^+$). Cationic surfactants are those where the hydrophilic group carries a positive charge (e.g., quaternary ammonium halides, $R_4N^+Cl^-$); examples include cetrimide, a mixture mainly consisting of tetradecyl (ca. 68%), dodecyl (ca. 22%), and hexadecyltrimethylammonium bromides (ca. 7%), as well as benzalkonium chloride, a mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5CH_2N^+(CH_3)_2R]Cl^-$, where R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$. Ampholytic surfactants (also called zwitterionic surfactants) are those where the molecule contains, or can potentially contain, both a negative and a positive charge (e.g., the sulfobetaines: $RN^+(CH_3)_2CH_2CH_2SO_3^-$); examples include N-Dodecyl-N,N-Dimethylbetaine ($C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$). Nonionic surfactants are a group of surfactants where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene groups ($(-CH_2CH_2O-)_n$); examples include polyoxyethylated glycol monoethers (e.g. cetomacrogol), sorbitan esters (Spans®) and polysorbates (Tweens®), polyoxyethylene-polyoxypropylene copolymers and any mixtures thereof. Preferred are nonionic surfactants.

The crystallization retarder used in the pharmaceutical composition according to the present invention may be selected from, but not restricted to the group consisting of povidone, copovidone, crospovidone, carboxymethylcellulose sodium, hydroxypropylcellulose, hydroxypropylmethylcellulose and any mixtures thereof. Preferred are povidone and copovidone.

The lubricant and the glidant used in the pharmaceutical composition according to the present invention may be selected from, but not restricted to, the group consisting of stearic acid or stearic acid salts, such as for example magnesium stearate, magnesium palmitate, magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols, silicon dioxide and any mixtures thereof. Preferably at least one lubricant is selected from the group consisting of stearic acid, magnesium stearate and hydrogenated vegetable oil.

In a preferred embodiment, the pharmaceutical composition according to the present invention may comprise one or more excipients selected from the group consisting of meglumine, Poloxamer 188, Povidone K30, KOH, NaOH, sorbitol, microcrystalline cellulose, lactose, mannitol, maltose and magnesium stearate.

In a more preferred embodiment, the pharmaceutical composition according to the present invention comprises meglumine, Povidone K30, NaOH, sorbitol, lactose and magnesium stearate as excipients.

In a particular preferred embodiment, the pharmaceutical composition according to the present invention is characterized in that it is composed of telmisartan or a pharmaceutically acceptable salt thereof, meglumine, Povidone K30, NaOH, sorbitol, lactose, magnesium stearate.

In the pharmaceutical composition according to the present invention meglumine may be present in an amount of 1 to 30mg, Povidone K30 may be present in an amount of 5 to 30mg, NaOH and magnesium stearate may each be present in an amount of 2 to 10mg and sorbitol and lactose may each be present in an amount of 50 to 300mg.

The pharmaceutical composition according to the present invention can be prepared by any method known from the state of the art such as for example spray-drying, fluid-bed granulation and lyophilization. If the pharmaceutical composition is prepared by a spray-drying method, telmisartan and/or its salts optionally together with a basic agent and/or optionally a crystallization retarder is dissolved in an appropriate solvent such as for

example water or an organic solvent and spray-dried. The spray-dried granulate is further mixed with other pharmaceutically acceptable excipients to form the final composition. In case of fluid-bed granulation, telmisartan and/or its salts optionally together with a basic agent and/or a crystallization retarder is dissolved in an appropriate solvent such as for example water or an organic solvent to form a granulation liquid. Other pharmaceutically acceptable excipients are placed in the fluid-bed granulating machine and sprayed with the granulation liquid. When the granulation process is completed, the obtained granulate is dried and optionally mixed with additional pharmaceutically acceptable excipients to form the final composition.

The pharmaceutical composition according to the present invention can further contain at least one other active pharmaceutical ingredient. Any combinations of therapeutic doses of telmisartan and/or its salts and at least one other active pharmaceutical ingredient can be used in the pharmaceutical composition according to the present invention. The other active pharmaceutical ingredient can be selected from the group consisting of, but not limited to, diuretics such as for example hydrochlorothiazide or indapamide; antihypertensives such as for example angiotensin converting enzyme (ACE) inhibitors such as for example captopril, enalapril, lisinopril, trandolapril, cilazapril, ramipril, fosinopril, perindopril or any pharmaceutically acceptable salt thereof; angiotensin receptor blockers (ARBs); AT_1-receptor antagonists such as for example candesartan, irbesartan, losartan, olmesartan, valsartan or any pharmaceutically acceptable salts thereof; calcium-channel blockers (CCBs) such as for example amlodipine, diltiazem, felodipine, nifedipine, nitrendipine and verapamil or any pharmaceutically acceptable salts thereof; β-adrenergic blockers such as for example acebutol, atenolol betaxolol, bisoprolol, metoprolol or any pharmaceutically acceptable salts thereof; as mixed α- and β-adrenergic blocker carvedilol may be included; lipid regulators such as for example 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors such as for example lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin or any pharmaceutically acceptable salts thereof and antidiabetics such as for example sulfonyl urea, meglitinides (such as nateglinide and repaglinide) or any pharmaceutically acceptable salts thereof, thiazolidinediones (such as pioglitazone and rosiglitazone) or any pharmaceutically acceptable salts thereof, alpha glucosidase inhibitors, incretin mimetics or biguanides such as for

example metformin or the like and the pharmaceutically acceptable salts thereof.

Diuretics such as hydrochlorothiazide or indapamide can be present exclusively within the granulate or they can be added exclusively as extragranular phase after granulation or they can be divided between the granulate and the extragranular phase. The amount of the diuretic can be between 5 and 50 mg, preferably between 10 and 30 mg, per dosage unit. Any combinations of telmisartan and/or its salts with a diuretic of any of these amounts are possible; for example, the ratio of telmisartan and/or its salts to hydrochlorothiazide [mg:mg] may be 40:12.5, 80:12.5 and 80:25. In case indapamide is used as diuretic, 0.5 to 3 mg, preferably 1.25 mg of indapamide is combined with 20, 40, or 80 mg of telmisartan (free acid).

The pharmaceutical composition according to the present invention comprising telmisartan and/or its salts and at least one other active pharmaceutical ingredient such as for example hydrochlorothiazide can be prepared by any method known from the state of the art. For example telmisartan and/or its salts can be granulated by spray-drying or by a fluid-bed method to form a telmisartan-containing granulate. The granulate is then mixed with at least one other active pharmaceutical ingredient and compressed into tablets. Another possibility is that telmisartan and/or its salts can be granulated and the other active pharmaceutical ingredient can be granulated as well. Two separate granulates are then mixed together to form a final composition. Another possibility is that at least one other active pharmaceutical ingredient can be granulated and the obtained granulate is then mixed with telmisartan and/or its salts and then formed into a final composition. Still another possibility is that telmisartan and/or its salts are granulated and the obtained granulate is then coated with any particle-separating agent. The coated granulate is then mixed with the other active agent and then the final composition is formed. Yet another possibility is that at least one other active pharmaceutical ingredient can be granulated and coated by any particle-separating agent. This coated granulate is then mixed with a telmisartan and/or its salts containing granulate and then the final composition is formed. In another possibility, a bilayer tablet can be prepared. One layer contains a granulate of telmisartan and/or its salts and the other layer contains at least one other active pharmaceutical ingredient. In yet another possibility, a bilayer tablet can be prepared

according to the previous method, where the two layers are additionally separated by a third layer that assures separation of particles. In still another possibility, a bilayer tablet having a central core and an outer layer surrounding the core can be prepared. Optionally, the two layers can be separated by an additional particle separating layer. Either telmisartan and/or its salts can be present in the core layer and the other active pharmaceutical ingredient is present in the outer layer or vice-versa.

The pharmaceutical composition according to the present invention may be administered to a patient in any dosage form, such as for example tablet, pill, troche, lozenge, capsule, powder, liquid, suppository, sachet, elixir, solution, syrup, suspension etc., preferably in form of tablets or capsules. Dosage forms may be adapted for administration to the patient by for example oral, buccal, parenteral, ophthalmic, rectal as well as transdermal route and preferably for oral route.

A telmisartan salt prepared according to the present invention can be included in the pharmaceutical composition or it can be formed in-situ during the preparation of the pharmaceutical composition according to the present invention. In the latter case telmisartan is placed in a solvent together with a corresponding basic agent and mixed together. Thereby, a dissolved salt form of telmisartan is obtained. The telmisartan salt can be used directly either in a spray-drying or in a fluid-bed process.

Finally, the present invention provides a method of treating a disease state, which is prevented, ameliorated or eliminated by the administration of telmisartan and/or its salts prepared by the processes according to the present invention to a patient in need of such treatment.

The present invention also provides the use of telmisartan and/or its salts prepared by the processes according to the present invention for the preparation of a medicament comprising a pharmaceutical composition as described hereinabove for treating a disease state, which is prevented, ameliorated or eliminated by the administration of telmisartan and/or its salts.

The present invention furthermore provides the use of telmisartan and/or its salts prepared by the processes according to the present invention for treating a disease state, which is prevented, ameliorated or eliminated by the administration of telmisartan and/or its salts.

The following examples are provided to illustrate certain aspects of the invention in greater detail, and are not to be construed as limiting the invention in any manner.

Example 1

Preparation of N-(2-aminophenyl)-4-(butyramido)-N,3-dimethyl-5-nitrobenzamide (compound 7):

To the mixture of 3.9 g (20 mmol) N-methylbenzene-1,2-diamine dihydrochloride and 10 ml CH_2Cl_2, 1.6 ml pyridine (20 mmol) was added and stirred at room temperature to obtain free N-methylbenzene-1,2-diamine solution. The resulted solution was added to the mixture of 2.66 g (10 mmol) of **compound 8**, 3.24 g (20 mmol) CDI and 60 ml THF, stirred for 3 h and filtered off. The wet cake was dried in an oven to obtain 2.26 g solid of **compound 7** (yield: 61%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.33(s, 1H), 8.19(s, 1H), 7.11(d, 2H, J=6.9 Hz), 6.63(d, 2H, J=7.8 Hz), 2.70(s, 3H), 2.30~2.36(m, 5H), 1.60(m, 2H), 0.93(t, 3H, J=7.5 Hz); ESI-MS: 369 $[M-1]^-$.

Example 2

Preparation of N-(2-methyl-4-(1-methyl-1H-benzo[d]imidazol-2-yl)-6-nitrophenyl)butyramide (compound 6):

The mixture of 370 mg (1 mmol) of **compound 7** and 5 ml pyridine was heated to reflux and stirred for 5 h. The mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and filtrated and the solvent was removed under vacuum to obtain 0.3 g of **compound 6** (yield 85%).

ESI-MS: 353 $[M+1]^+$

Example 3

Preparation of N-(2-amino-6-methyl-4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl)butyramide (compound 5):

The mixture of 0.21 g (0.6 mmol) of **compound 6,** 8 ml methanol and 3.5 mg (0.06 mmol) Raney-Ni was stirred for 2 h under H_2 at room temperature. A white solid was formed and methanol was added to dissolve the white solid. The resulting mixture was filtrated and the filtrate was evaporated under vacuum to obtain 0.183 g of a white solid (yield: 94.8%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61(d, 1H, J=4.5 Hz), 7.57(d, 1H, J=7.2 Hz), 7.24(m, 2H), 7.05(s, 1H), 6.90(s, 1H), 3.86(s, 3H), 2.34 (t, 2H, J=7.2 Hz), 1.65(m, 2H), 0.97(t, 3H, J=4.5 Hz); ESI-MS: 323 $[M+1]^+$

Example 4

Preparation of N-((2-cyano-biphenyl-4'-methyl)amino-6-methyl-4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl) butyramide (compound 4):

To the mixture of 0.13 g (0.4 mmol) of **compound 5**, 0.11 g K_2CO_3 (0.8 mmol) and 5 ml DMF 0.115 g (0.42 mmol) 4'-bromomethyl-biphenyl-2-carbonitrile was added and stirred for 22 h at room temperature. The mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over Na_2SO_4 and filtrated and the solvent was removed under reduced pressure to obtain a solid. Methanol was used to wash the solid to obtain 81 mg of **compound 4** (yield: 40%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93(d, 1H, J=8.1 Hz), 7.79(m, 1H), 7.45~7.62(m, 8H, J=7.2 Hz), 7.21(m, 2H), 6.90(s, 1H), 6.62(s, 1H), 4.52(s, 2H), 3.49(s, 3H), 2.42 (t, 2H, J=7.2 Hz), 1.69(m, 2H), 0.96(t, 3H, J=4.5 Hz); ESI-MS: 514 $[M+1]^+$

Example 5

Preparation of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile (compound 3) from compound 4:

To the mixture of 45 mg (0.08 mmol) of **compound 4** and 5 ml toluene 15 mg (0.42 mmol) p-TsOH was added, heated to reflux and stirred for 5 h. The mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over Na_2SO_4 and filtrated and the solvent was removed under vacuum to obtain 37 mg of **compound 3** (yield: 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75(m, 2H), 7.62(m, 1H), 7.16~7.51(m, 11H), 5.48(s, 2H),

3.80(s, 3H), 2.94 (t, 2H, J=7.2 Hz), 2.77(s, 3H), 1.85(m, 2H), 1.06(t, 3H, J=4.5 Hz); EI-MS: 495 $[M]^+$

Example 6

Preparation of methyl 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylate (compound 11):

5 g (23 mmol) 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylic acid was added to 100 ml methanol, stirred and 3 ml concentrated hydrochloric acid (37%) was added and heated to 70 °C for 20 h. Another 3 ml concentrated hydrochloric acid was added and heated to reflux for 4 h. 4 ml concentrated hydrochloric acid was added and heated to reflux for 3 h. The solvent was removed under vacuum to give 6.6 g of crude **compound 11**.

Example 7

Preparation of 4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-methoxycarbonyl-3-yl)-methyl)-biphenyl-2-nitrile (compound 10):

6.6 g crude **compound 11** and 5.48 g (20 mmol) 4'-bromomethyl-biphenyl-2-carbonitril were dissolved in 100 ml DMF, then 13.8 g (100 mmol) K_2CO_3 was added and stirred for 18 h at room temperature. 150 ml water was added to the mixture and a white solid formed. Then it was filtrated to obtain a cake and dried to obtain 8 g of crude **compound 10** (yield: 82.5%) in two crops.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.97(m, 2H), 7.74(t, 1H, J=6.3 Hz), 7.53~7.67(m, 5H), 7.19(d, 2H, J=8.1 Hz), 5.68(s, 2H), 3.83(s, 3H), 2.88 (t, 2H, J=7.2 Hz), 2.58(s, 3H), 1.76(m, 2H), 0.94(t, 3H, J=4.5 Hz).

Example 8

Preparation of 4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxyl-3-yl)-methyl)-biphenyl-2-nitrile (compound 9):

To the mixture of 7.2 g of **compound 10** and 180 ml methanol, 30 ml 10% NaOH was added and heated to reflux for 5 h. The solvent was removed under vacuum. 50 ml water was added to the mixture and 1 M HCl was used to adjust the pH value to 5-6. The mixture was filtrated to obtain a wet cake, which was washed with water and dried to obtain 4.5 g

of **compound 9** (yield: 65%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.94(m, 2H), 7.75(t, 1H, J=6.3 Hz), 7.54~7.65(m, 5H), 7.20(d, 2H, J=8.1 Hz), 5.68(s, 2H), 2.88 (t, 2H, J=7.5 Hz), 2.58(s, 3H), 1.77(m, 2H), 0.96(t, 3H, J=4.5 Hz).

Example 9

Preparation of 4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxyl-3-yl)-methyl)-biphenyl-2-nitrile (compound 9):

400 g of **compound 11** (1.72 mol, HPLC purity: 98.9%), 480g of K_2CO_3 and 1.7g of KI were added to 2.0 L of acetone. Then 440 g (1.72 mol) of 4'-bromomethyl-biphenyl-2-carbonitril was added and the mixture was stirred at reflux temperature for 18 h. The solvent was removed by evaporation under reduced pressure and then 2 L of methanol and 1.72 L of 2M NaOH were added and the mixture was stirred at reflux temperature for 4 h. The mixture was cooled and 720 ml of 12M HCl was used to adjust the pH value to 5-6 at 30 to 40 °C. The formed solid precipitate was filtrated, washed with water and dried to obtain 600 g of **compound 9** (yield: 85 %, HPLC purity: 97.5 %).

Example 10

Preparation of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile (compound 3) from compound 9:

200 mg of **compound 9** was added in 1ml $SOCl_2$. The mixture was heated to reflux. After 2 hours, $SOCl_2$ was evaporated at 45 °C under reduced pressure to obtain a light-yellow foamy residue. The residue was dissolved in 2 ml dry pyridine and 100 mg N-methylbenzene-1,2-diamine was added. The mixture was heated to reflux for 24 h.

Pyridine was evaporated in vacuum. The residue was extracted with ethyl acetate, washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and then filtered and concentrated to give 188 mg (yield: 78%) of crude **compound 3**.

EI-MS: 496$[M+1]^+$

Example 11

Preparation of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile (compound 3) from compound 9:

445g (1.09 mol) of **compound 9** was added into 1.5 L of CH_2Cl_2 and then 513g (4.35 mol) of $SOCl_2$ was added. The mixture was heated under reflux temperature for 5h and the mixture was evaporated under reduced pressure to obtain a light-yellow foamy residue. The residue was dissolved in 5.5 L of CH_2Cl_2 and added dropwise during a period of 10 h to a mixture consisting of 425 g (2.18 mol) of N-methylbenzene-1,2-diamine dihydrochloride, 916 g of $NaHCO_3$, 3 L of water and 2 L of CH_2Cl_2 at 10 to 15 °C. The mixture was stirred at this temperature for 1h. Then stirring was stopped and the layers were separated. The organic layer was washed with water (2×5 L) and evaporated under reduced pressure to a residue volume of about 3-4 L. To this residue 3L of petroleum ether was added dropwise during a period of 1h at 30 °C. The formed solid was filtered and dried to obtain 560g (yield: 90%, HPLC purity: 90%) of 1-((2'-cyanobiphenyl-4-yl)methyl)-4-methyl-N-(2-(methylamino)phenyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide.

To this product (560g, 0.98mol) 5 L of toluene and 3g (0.048 mol) of H_3BO_3 were added. The mixture was heated to reflux temperature and water formed during the reaction was separated. After the reaction was completed (about 2 h), 50 g of charcoal was added into the reaction mixture and the mixture was refluxed for 0.5 h. After hot filtration, the filtrate was cooled to 15-25 °C and stirred at this temperature for 5h.

The formed precipitate was filtered and dried to obtain 303 g of **compound 3** (HPLC purity: 99.9%).

The filtrate was concentrated to a volume about 2L and the concentrate was stirred at 15-25 °C for 5h. The formed solid was filtered and dried to obtain 150 g of **compound 3** (HPLC purity: 98.4%, total yield: 90%).

Example 12

Preparation of N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide (compound 15):

To the mixture of 1.09 g (5 mmol) 2-propyl-3H-benzo[d]imidazole-5-carboxylic acid and 50 ml CH_2Cl_2, 7.26 ml (100 mmol) $SOCl_2$ was added. The mixture was stirred for 18 h and evaporated under reduced pressure.

The residue was dissolved in 30 ml DMF and 1.6 g (10.5 mmol) N-methyl-2-nitroaniline was added. The mixture was stirred at room temperature for 48 h. Saturated $NaHCO_3$ was added to adjust the pH value to 8. The resulting mixture was extracted with ethyl acetate two times. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and then filtered and concentrated to give a residue, which was purified by silica gel chromatography to obtain 0.69 g (yield: 39%) of **compound 15**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70~7.83(m, 3H), 7.44(m, 1H), 6.84~7.07(m, 2H), 3.47(s, 3H), 3.37(s, 3H), 2.29(m, 2H), 1.775(m, 2H), 0.93(t, 3H, J=4.5 Hz); ESI-MS: 353 $[M+1]^+$; 351$[M-1]^-$.

Example 13

Preparation of 4'-((N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile (compound 14):

0.7 g of **compound 15** (2 mmol) and 0.82 g (3 mmol) 4'-bromomethyl-biphenyl-2-carbonitril were dissolved in 30 ml acetonitrile. Then 0.55 g (4 mmol) K_2CO_3 was added and stirred for 22 h at room temperature. Methanol was added to dilute the reaction mixture. Then it was filtrated and the filtrate was concentrated under vacuum to obtain a residue. Ethyl acetate was used to dissolve the residue. Then it was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated to obtain 0.84 g of crude **compound 14** (yield: 77%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95(d, 1H, J=4.8 Hz), 7.52~7.81(m, 8H), 7.32(m, 1H), 6.88~6.99(m, 4H), 5.38(s, 3H), 3.37(s, 3H), 2.71(m, 2H), 2.39(s, 3H), 1.66(m, 2H), 0.91(t, 3H, J=4.5 Hz); EI-MS: 543 $[M]^+$.

Example 14

Preparation of 4'-((N,7-dimethyl-N-(2-aminophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile (compound 13):

100 mg (0.2 mmol) of **compound 14** was dissolved in 35 ml methanol and then 40 mg Pd/C (10%) was added and stirred for 2 h under H_2 at room temperature. The reaction mixture was filtrated to remove Pd/C and the filtrate was evaporated under vacuum to obtain 63 mg of **compound 13** as a white solid (yield: 67%).

ESI-MS: 514 $[M+1]^+$.

Example 15

Preparation of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-nitrile (compound 3) from compound 13

The mixture of 100 mg (0.2 mmol) of **compound 13** and 5 ml pyridine was heated to reflux for 22 h (TLC monitor the reaction) and cooled to room temperature. Then ethyl acetate was added to dilute the reaction mixture. The organic phase was washed in sequence with water, a saturated NH_4Cl solution and brine, dried over Na_2SO_4, filtrated and concentrated to obtain 74 mg of a residue. The residue was purified by silica gel chromatography to give 45 mg of **compound 3** (yield: 47%).

^1H NMR (300 MHz, $CDCl_3$): δ 7.77(m, 2H), 7.59(m, 1H), 7.51~7.26(m, 9H), 5.47(s, 3H), 3.78(s, 3H), 2.94(t, 2H, J=7.8 Hz), 2.77(s, 3H), 1.88(m, 2H), 1.06(t, 3H, J=4.5 Hz); EI-MS: 495 $[M]^+$

Example 16

Preparation of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid (compound 1)

A mixture of 2.5 g of **compound 3** (5 mmol), 1.0 g sodium hydroxide (25 mmol), 0.18 g water (10 mmol) and 30 ml ethyleneglycol was refluxed for 8 h. After the reaction was completed, the reaction mixture was cooled to room temperature and H_2O (250 ml) was added. After the pH value of this solution was adjusted to 4 with HOAc (12 ml), the product precipitated and was extracted three times with CH_2Cl_2. The combined organic

layers were washed with brine, dried over $NaSO_4$ and filtered and the filtrate was concentrated to give 2.55 g of crude **compound 1** (yield: 98%).

Example 17

Preparation of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid (compound 1):

A mixture of 15 g of **compound 3** (30 mmol), 6.0 g potassium hydroxide (91 mmol), 1.6 g water and 54 ml propylene glycol was refluxed for 19 h. After the reaction was completed, the reaction mixture was cooled to room temperature and H_2O (120 ml) was added. After the pH value of this solution was adjusted to 4.9 with 6M HCl (17 ml), the product was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried over $NaSO_4$ and filtered and the filtrate was concentrated. To the residue acetone was added. The suspension was filtered to give 12.55 g of crude **compound 1**.

Example 18

Crystallization of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid (compound 1):

A mixture of 3 g of telmisartan and 20 ml of N,N-dimethylformamide was heated to a temperature of about 100 °C until telmisartan was dissolved. Then the solution was filtered and cooled to room temperature. The solution was stirred at this temperature for 3h and then 2h at 0 °C. The product was filtered, washed with DMF and dried under reduced pressure at 70-90 °C to give 2.7 g of telmisartan (HPLC purity: 99.5%).

Example 19

Crystallization of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid (compound 1):

A mixture of 21.4 g of telmisartan, 107 ml of ethanol and 1.1 g of charcoal was stirred at room temperature for 15 min. Then 4.7 ml of 25% NH_3 was added and the mixture was stirred for another 1.5h. The mixture was then filtered and the filtrate was heated to 80 °C.

At this temperature, 4.76 ml of acetic acid was slowly added and the mixture was cooled to room temperature. The mixture was stirred at this temperature for 1h, then the product was filtered, washed with water and ethanol and dried under reduced pressure at 70-90 °C to give 19.7 g of telmisartan (HPLC purity: 99.6%)

Example 20

Preparation of telmisartan and/or its pharmaceutically acceptable salts

The mixture of 1.0 g (2.0 mmol) of **compound 3**, 5 ml of isopropanol, 5 ml of water and 1.03 g (18.4 mmol) of KOH was heated to 120 °C for approximately 48 h. Then the solution was cooled to room temperature and 10 ml of water was added. The mixture was neutralized by adding 3M HCl until a pH value of about 7 was reached. The product (telmisartan) was filtered, washed and dried.

The obtained telmisartan was converted to its salts by adding a corresponding acid or base and subsequent isolation.

Example 21

Pharmaceutical formulations comprising telmisartan or salts thereof prepared by the processes according to the present invention or by any known processes

	mg	mg	mg	mg	mg	mg
Telmisartan meglumine salt	54	54	54	54	54	54
Meglumine	10	10				
KOH			4	4		
NaOH					3	3
Poloxamer 188		8		8		8
Sorbitol	120	120	120	120	120	120
Microcrystalline cellulose	53.6	45.6	59.6	51.6	60.6	52.6
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4

	mg	mg	mg	mg	mg	mg
Telmisartan	40	40	40	40	40	40
Meglumine	20	20	20	20	2	20
Povidone K30	12	12	12	12	12	12
Sorbitol	225				168.75	112.5
Lactose agglomerated		225			56.25	112.5
Mannitol			225			
Maltose				225		
Magnesium stearate	3	3	3	3	3	3

	mg	mg	mg	mg	mg	mg
Telmisartan	40	40	40	40	40	40
Meglumine	12	12	12	12	12	12
Povidone K30	12	12	12	12	12	12
KOH	4.7		4.7		4.7	
NaOH		3.36		3.36		3.36
Sorbitol	148.3	149.64				
Lactose agglomerated	60	60	80	80	100	100
Mannitol			128.3	129.64		
Maltose					108.3	109.64
Magnesium stearate	3	3	3	3	3	3

The above mentioned compositions containing telmisartan can be prepared by various methods. Two appropriate methods are spray-drying and fluid-bed granulation. If telmisartan and/or its salts are prepared by a spray-drying method, telmisartan and/or its salts together with a basic agent and optionally a crystallization retarder are dissolved in an appropriate (water or organic) solvent and spray-dried. The spray-dried granulate is mixed further with other excipients to form a final composition ready for tabletting. In case of fluid-bed granulation, telmisartan and/or its salts together with a basic agent and optionally a crystallization retarder are dissolved in an appropriate (water or organic) solvent to form a granulation liquid. Other excipients are placed in the fluid-bed granulating machine and sprayed with the granulation liquid. When granulation is completed, the granulate is dried and optionally mixed with additional excipients like flow control agents and/or lubricants to form a final composition ready for tabletting.

Example 22

Pharmaceutical formulations comprising a combination product containing telmisartan and/or its salts prepared by the processes according to the present invention or by any known processes and hydrochlorothiazide

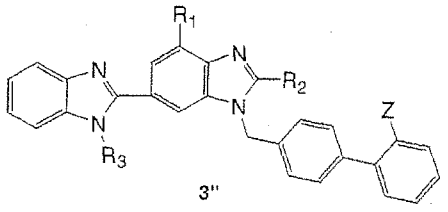
	mg	mg	mg	mg	mg	mg
Telmisartan-containing granulate						
Telmisartan	40	40	40	40	40	40
Meglumine	12	12	12	12	12	12
Povidone K30	12	12	12	12	12	12
KOH	4.7		4.7		4.7	
NaOH		3.36		3.36		3.36
Sorbitol	148.3	149.64				
Lactose agglomerated	60	60	80	80	100	100
Mannitol			128.3	129.64		
Maltose					108.3	109.64
Magnesium stearate	3	3	3	3	3	3
Hydrochlorothiazide-containing granulate						
Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5
Povidone K30	12.5		12.5		12.5	
PEG8000		12.5		12.5		12.5
Lactose monohydrate	150		150		150	
Mannitol		150		150		150
Croscarmellose sodium	4	4	4	4	4	4
Magnesium stearate	1	1	1	1	1	1

The telmisartan-containing granulate can, for instance, be prepared according to example 21. The hydrochlorothiazide-containing granulate can be prepared by any known method, for instance by wet or dry granulation, spray-drying etc. The final composition is then prepared by mixing the two granulates together. Another possibility is that telmisartan and/or its salts are granulated and the obtained granulate is then coated with any particle-separating agent. The coated granulate is then mixed with the hydrochlorothiazide-containing granulate in order to prepare the final composition. Another possibility is that the hydrochlorothiazide-containing granulate is coated by any particle-separating agent.

This coated granulate is then mixed with the telmisartan and/or its salts containing granulate and then the final composition is formed. In still another possibility, a bilayer tablet can be prepared. One layer contains a granulate of telmisartan and/or its salts and the other layer contains a hydrochlorothiazide-containing granulate. In yet another possibility, a bilayer tablet can be prepared according to the previous method, where the two layers are additionally separated by a third layer that assures separation of particles. In still another possibility, a bilayer tablet having a central core and an outer layer surrounding the core can be prepared. Optionally, the two layers can be separated by an additional particle separating layer. Either telmisartan and/or its salts can be present in the core layer and hydrochlorothiazide is present in the outer layer or vice-versa.

Claims

1. Process for the preparation of intermediates of telmisartan derivatives represented by formula 3''



3''

wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

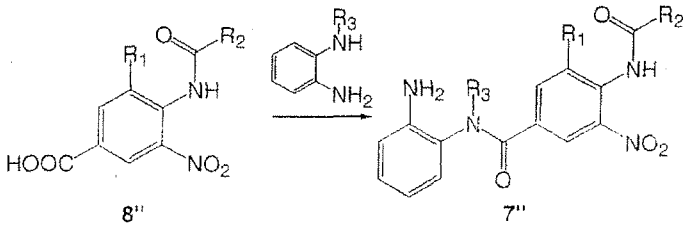
R_3 is C_1-C_6 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 is $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl,

the process being selected from any one of the following Processes A, B, and C:

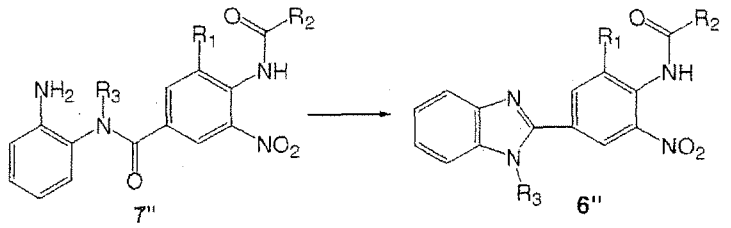
Process A comprising the steps of:

a) acylation of an alkyl-unsubstituted diamino benzene with a compound represented by formula 8'' to form a compound of formula 7'',

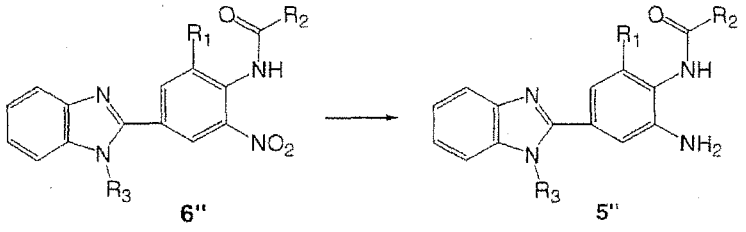


8'' 7''

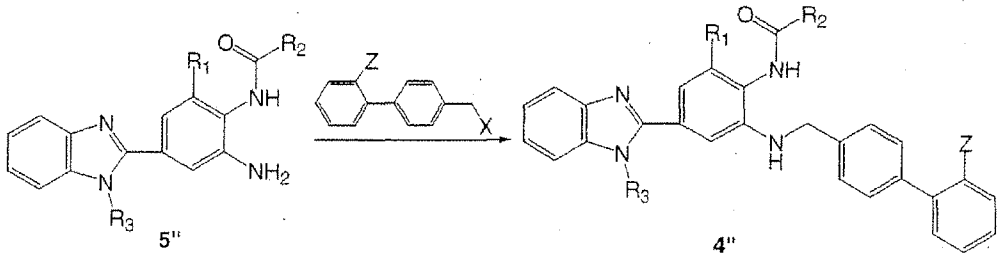
b) condensation to form a compound of formula 6'',



c) reduction to form a compound of formula 5'',

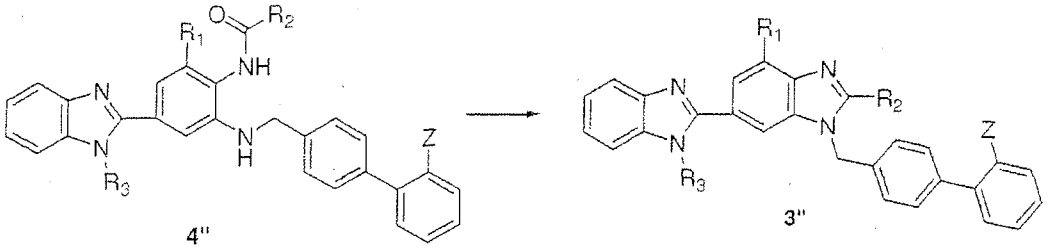


d) alkylation of the amino group in the compound of formula 5'' to form a compound of formula 4''



wherein X is Br, Cl, I, and

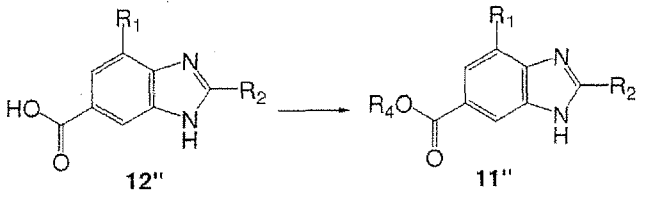
e) condensation of the compound of formula 4'' to prepare a compound of formula 3''



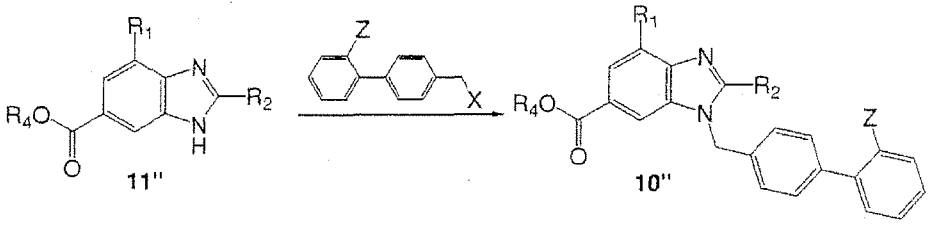
wherein the substituents are as defined above;

Process B comprising the steps of:

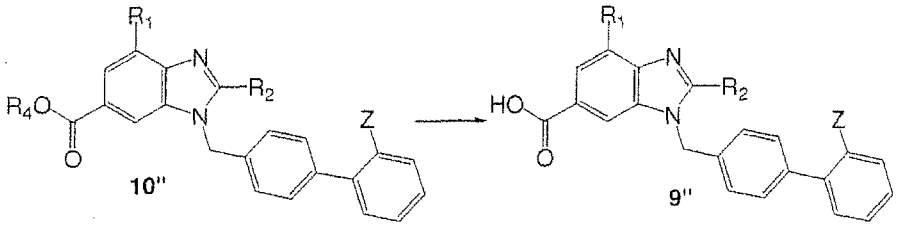
a) esterification of a compound of formula 12" to form a compound of formula 11",



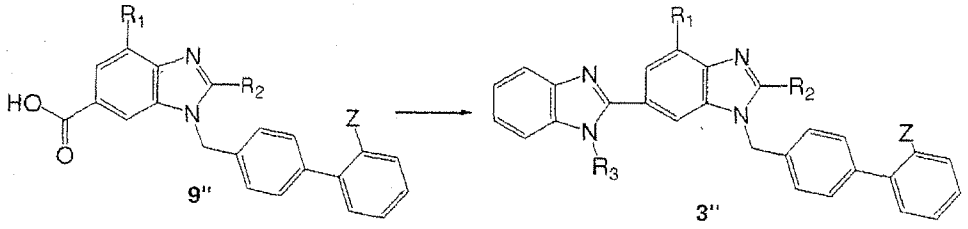
b) alkylation to form a compound of formula 10",



c) hydrolysis to form a compound of formula 9" and



d) condensation to form a compound of formula 3''



wherein in the above formulae of Process B:

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl,

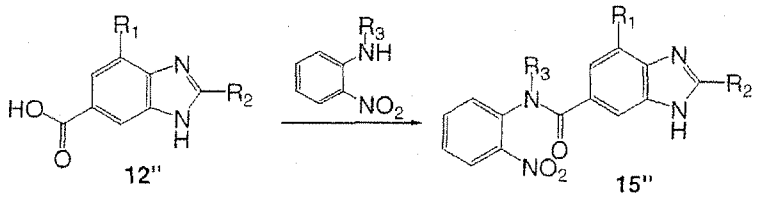
R_4 is $CONR_5$, wherein R_5 is H or C_1-C_3 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and

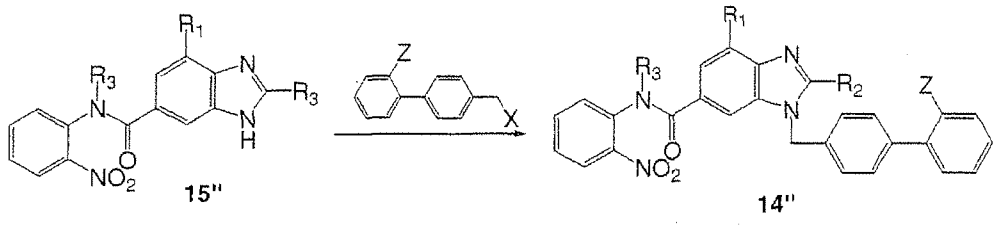
X is Cl, Br or I;

Process C comprising the steps of:

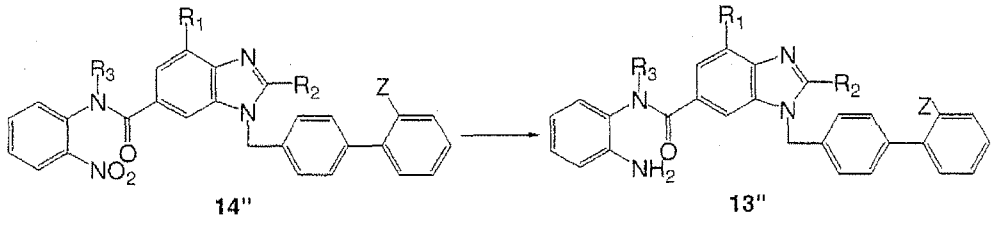
a) acylation of an o-nitrophenyl-C_{1-6}-alkylamine with a compound of formula 12'' to form a compound of formula 15'',



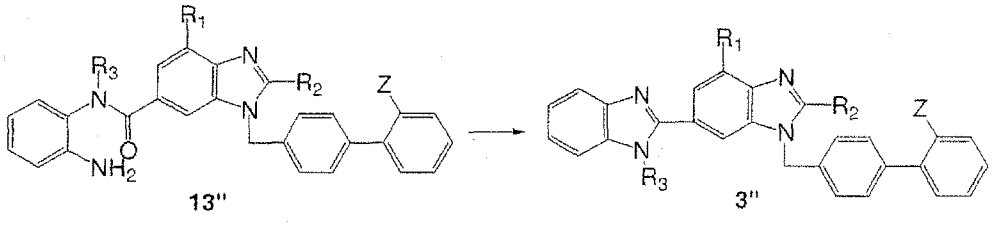
b) alkylation to form a compound of formula 14",



c) reduction to form a compound of formula 13" and



d) condensation to form a compound of formula 3"



wherein in the above formulae of Process C

R_1 is C_1-C_6 alkyl,

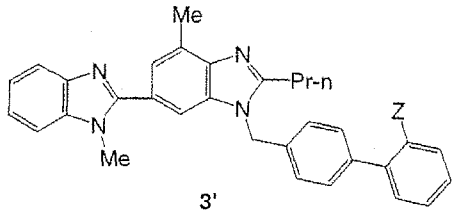
R_2 is C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and

X is Cl, Br or I.

2. Process according to claim 1 for the preparation of telmisartan intermediates of formula 3'



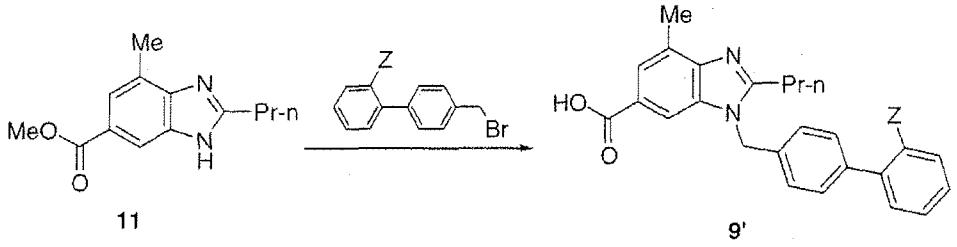
3'

wherein

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and R_1 is C_1-C_6 alkyl.

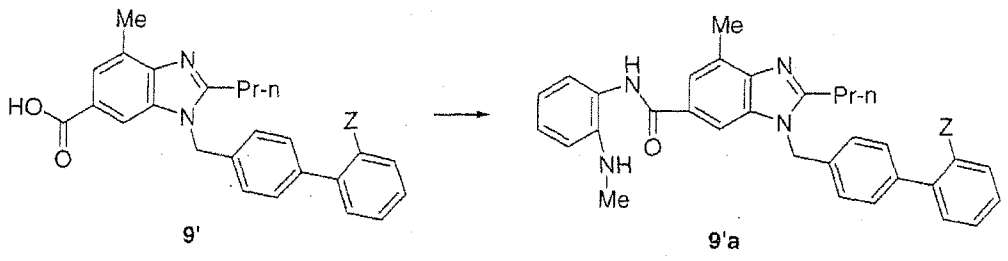
3. Process for the preparation of intermediates of telmisartan derivatives substituted on position 2 of the biphenyl group of 4'-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl)-methyl]-biphenyl and represented by formula 3' comprising the steps of:

a) N-alkylation of compound 11 followed by hydrolysis to form compound 9',

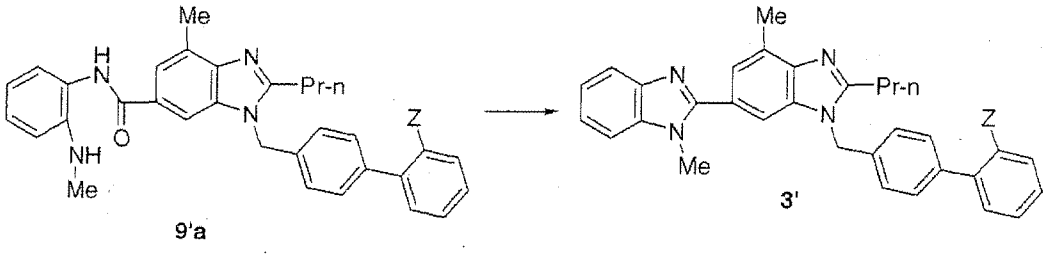


11 9'

b) condensation of compound 9' with N-methylbenzene-1,2-diamine to form compound 9'a and



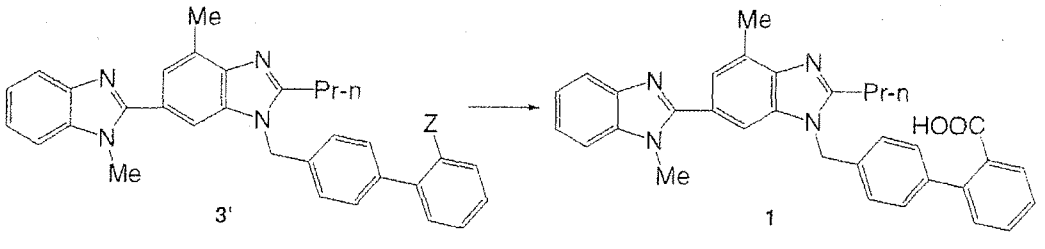
c) cyclization to form compound 3'

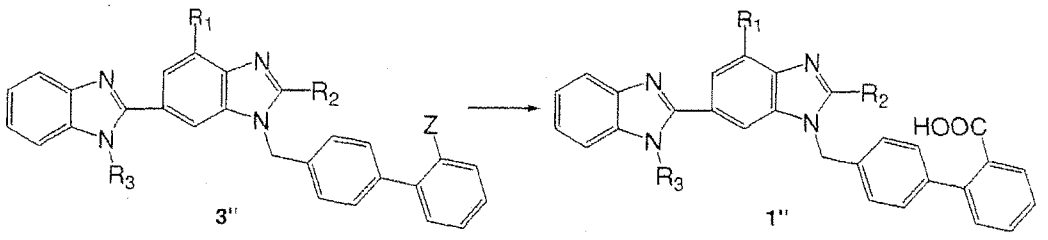


wherein

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl and R_1 is C_1-C_6 alkyl.

4. A process according to any of claims 1-3 for the preparation of telmisartan or telmisartan derivatives represented by formulae 1 or 1'', respectively, further comprising the step of converting the group Z in a compound of formulae 3' or 3'' into a carboxyl group:





wherein

R_1 is C_1-C_6 alkyl,

R_2 is C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl,

Z is a group which can be converted to a tetrazolyl or a carboxyl group and can be selected from the group consisting of CN and COR_6, wherein R_6 can be $N(R)_2$ or OR_1, wherein R is H, C_1-C_6 alkyl or benzyl.

5. A process according to claim 4, wherein the conversion of Z into a carboxyl group is carried out by hydrolysis.

6. A process according to any of claims 4 or 5, further comprising the step of converting telmisartan or its derivative of formula 1'' into a pharmaceutically acceptable salt thereof.

7. A process according to any of claims 4-6, further comprising the step of formulating telmisartan or its derivative or a pharmaceutically acceptable salt of either of them with pharmaceutically acceptable excipients to provide a medicament.

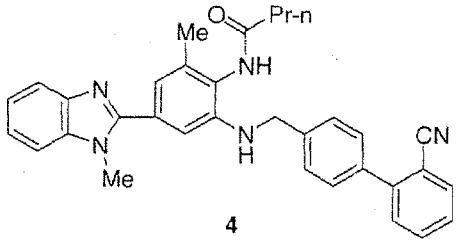
8. A process according to claim 7, wherein telmisartan or its derivative or a pharmaceutically acceptable salt of either of them is formulated with pharmaceutically acceptable excipients and another active pharmaceutical ingredient to provide a medicament.

9. A process according to claim 8 wherein the further active pharmaceutical ingredient is a diuretic, preferably hydrochlorothiazide.

10. A process according to any of claims 7-9, wherein the medicament is for oral use, particularly in the form of tablets or capsules.

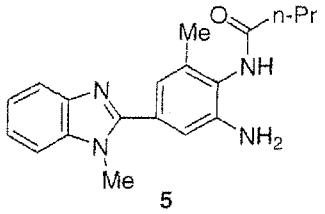
11. A compound selected from

(i) N-((2-cyano-biphenyl-4'-methyl)amino-6-methyl-4-(1-methyl-1H-benzo[d] imidazol-2-yl)phenyl)butyramide represented by formula 4:



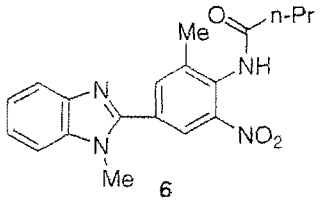
4

(ii) N-(2-amino-6-methyl-4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl) butyramide represented by formula 5:



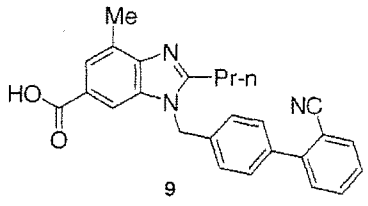
5

(iii) N-(2-methyl-4-(1-methyl-1H-benzo[d] imidazol-2-yl)-6-nitrophenyl)butyramide represented by formula 6



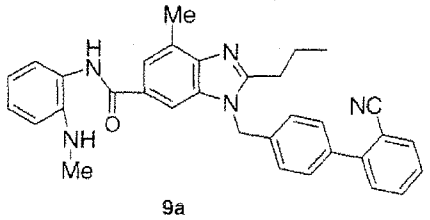
6

(iv) 4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxyl-3-yl)-methyl)-biphenyl-2-nitrile represented by formula 9



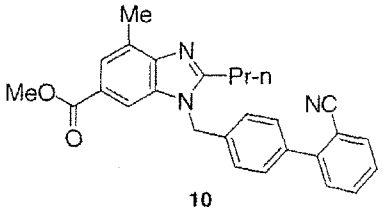
9

(v) 1-((2'-cyanobiphenyl-4-yl)methyl)-4-methyl-N-(2-(methylamino)phenyl)-2-propyl-1H-benzo[d]imidazole-6-carboxamide represented by formula 9a



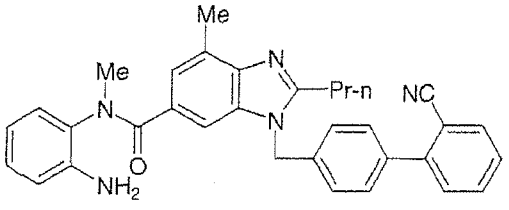
9a

(vi) 4'-((7-methyl-2-propyl-3H-benzo[d]imidazole-5-methoxycarbonyl-3-yl)-methyl)-biphenyl-2-nitrile represented by formula 10



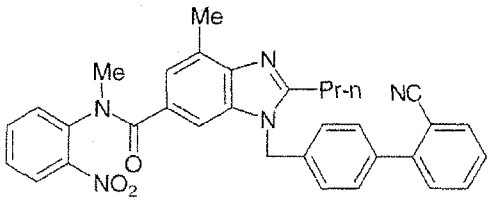
10

(vii) 4'-((N,7-dimethyl-N-(2-aminophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile represented by formula 13



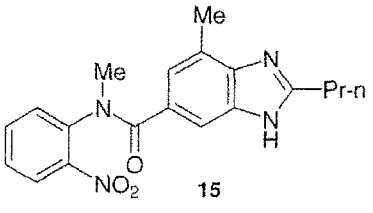
13

(viii) 4'-((N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide-3-yl)-methyl)-biphenyl-2-nitrile represented by formula 14



14

(ix) N,7-dimethyl-N-(2-nitrophenyl)-2-propyl-3H-benzo[d]imidazole-5-carboxamide represented by formula 15



15

and salts thereof.

12. Use of a compound according to claim 11 as an intermediate in the preparation of telmisartan or a derivative thereof having formula 1" as defined in claim 4 or a pharmaceutically acceptable salt of either of them

13. Use of a compound according to claim 11 as an intermediate for the preparation of a medicament containing telmisartan or a derivative thereof having formula 1" as defined in claim 4 or a pharmaceutically acceptable salt of either of them.

14. A pharmaceutical composition containing telmisartan or a derivative thereof having formula 1" as defined in claim 4 or a pharmaceutically acceptable salt of either of them, wherein the telmisartan or derivative or salt thereof has been obtained or is obtainable according to a process according to any of claims 4-6.

15. The pharmaceutical composition according to claim 14 further comprising a basic agent and a water soluble diluent in an amount of greater than 70% per weight of the total composition, wherein the formulation does neither comprise a surfactant nor a water insoluble diluent.

16. The pharmaceutical composition according to claim 15, characterized in that it is composed of telmisartan or a pharmaceutically acceptable salt thereof, meglumine, Povidone K30, NaOH, sorbitol, lactose, magnesium stearate.

17. The pharmaceutical composition according to any of claims 14-16 for use in the treatment of a disease state, which is prevented, ameliorated or eliminated by the administration of telmisartan and/or its salts, particularly hypertension.

18. A telmisartan intermediate of formula 3' or 3" as defined in claims 1 or 2, which has been prepared by a process according to any of claims 1-3 and which has a purity of greater than 98%, preferably greater than 99%, wherein the amount of each individual impurity is less than 0.15%.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/058616

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D235/08 C07D235/18 C07D235/20 A61K31/4184 A61P9/12

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"TELMISARTAN" DRUGS OF THE FUTURE, PROUS SCIENCE, ES, vol. 22, no. 10, 1 January 1997 (1997-01-01), pages 1112-1116, XP009008343 ISSN: 0377-8282 scheme 1	1-13
X	the whole document	14-18
A	EP 0 502 314 A (THOMAE GMBH DR K [DE]) 9 September 1992 (1992-09-09) cited in the application claim 10	1-13
X	claims 1,5-9	14-18
P,X	CN 101 024 631 A (SHENGMEI MEDICINE SCIENCE TECH [CN]) 29 August 2007 (2007-08-29) schemata 3 and 4	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2008	01/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, Irmgard

INTERNATIONAL SEARCH REPORT

Information on patent family members

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