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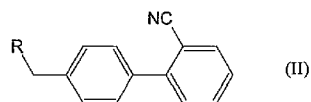
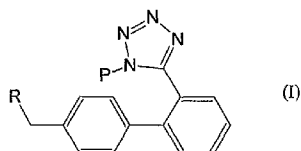
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(54) Title: PROCESS FOR PREPARATION OF TETRAZOLES FROM AROMATIC CYANO DERIVATIVES

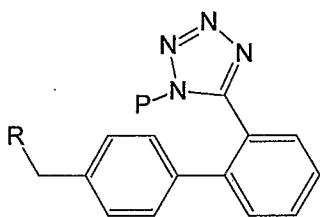


(57) Abstract: The present invention relates to process for preparation of tetrazoles of formula (I) from aromatic cyano derivatives of formula (II) comprising of treating the cyano compound of formula (II) with trialkyltin halide and metal azide in presence of base.

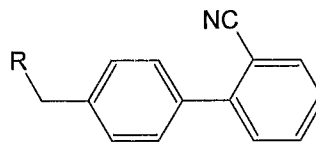
PROCESS FOR PREPARATION OF TETRAZOLES FROM AROMATIC CYANO DERIVATIVES

FIELD OF INVENTION

The present invention relates to process for preparation of tetrazoles of formula (I) from aromatic cyano derivatives of formula (II) comprising of treating the cyano compound of formula (II) with trialkyltin halide and metal azide in presence of base. This process is useful for preparation of various compounds belonging to the class of non-peptide angiotensin-II inhibitors such as Valsartan of formula (A), Candesartan of formula (B), Irbesartan of formula (C), Losartan of formula (D), Olmesartan of formula (E) and Tasosartan of formula (F).



Formula (I)

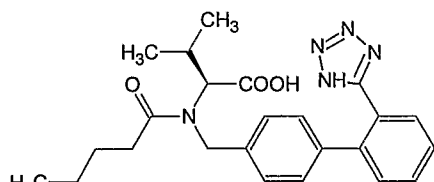


Formula (II)

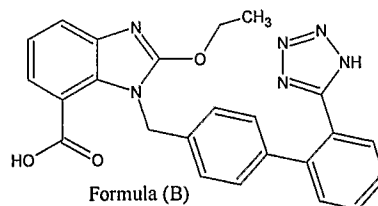
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BACKGROUND OF THE INVENTION AND PRIOR ART

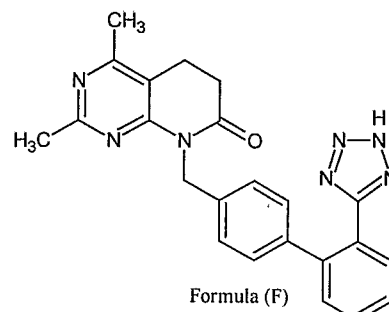
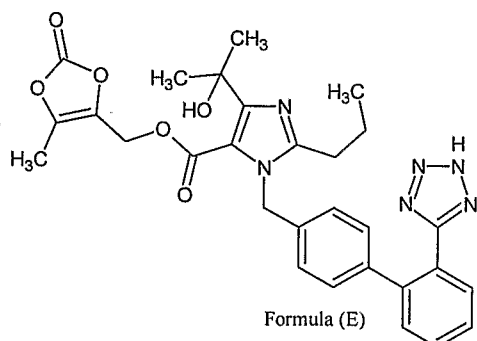
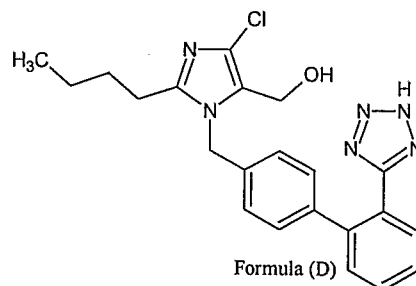
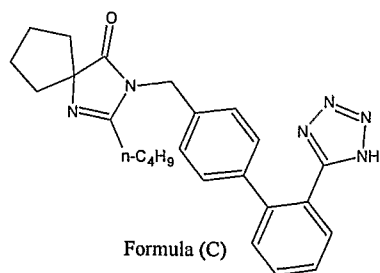
Valsartan of formula (A), Candesartan of formula (B), Irbesartan of formula (C), Losartan of formula (D), Olmesartan of formula (E) and Tasosartan of formula (F) are angiotensin II receptor antagonists also known as angiotensin receptor blockers (ARBs) and are useful for the treatment of hypertension and congestive heart failure. They act by inhibiting the action of angiotensin II on its receptors and prevent the increase in blood pressure produced by hormone-receptor interactions. These compounds contain a common structural feature – the 5-tetrazole group.



Formula (A)



Formula (B)



- Valsartan of formula (A), Candesartan of formula (B), Irbesartan of formula (C), Losartan of formula (D), Olmesartan of formula (E) and Tasosartan of formula (F) are reported in US Patent No. 5,399,578, US Patent No. 5,196,444, US Patent No. 5,270,317, US Patent No. 5,138,069, US patent No. 5,616,599 and US Patent No. 5,149,699 respectively. The route commonly followed for obtaining the 5-tetrazole moiety in the desired compound is by carrying out cyclization of the corresponding cyano derivative in presence of organotin azides. These compounds are purified by column chromatography and if desired further recrystallization can be carried out. But these processes generally suffer by giving low yields, longer reaction times and final purification by tedious chromatographic techniques.
- Hence there is a need to improvise the process for conversion of aromatic cyano derivatives to tetrazole compounds, thereby providing desired compound with high purity, better yields and shorter reaction times.

It was observed by the inventors of the present invention that use of base along with trialkyltin halide and metal azide results in improved yield, reduction in reaction time and high purity product.

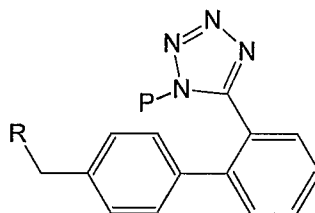
OBJECT OF THE INVENTION

The object of the present invention to provide a process of preparation of tetrazole of formula (I) from aromatic cyano derivatives of formula (II) which is high yielding, has shorter reaction times and gives desired compound with high purity.

Another object of the invention is to provide a process for preparing Valsartan, Candesartan, Irbesartan, Losartan, Olmesartan or Tesosartan, which is simple, easy to handle and cost effective.

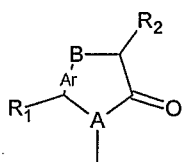
SUMMARY OF THE INVENTION

According to the object of the invention, there is provided a process for preparing compound of formula (I) or a stereoisomer or salt thereof,

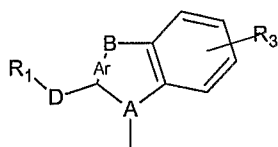


Formula (I)

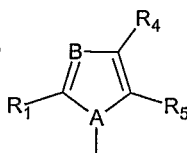
wherein R is selected from group comprising of formula (a), (b), (c), (d) or (e)



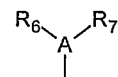
Formula (a)



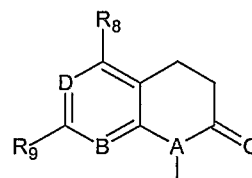
Formula (b)



Formula (c)



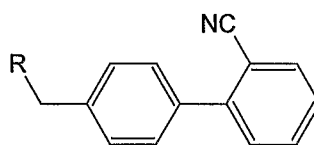
Formula (d)



Formula (e)

wherein A, B and D are independently C, O, N or S and the dotted line represents a single or a double bond; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are independently selected from hydrogen, C₁₋₆ alkyl, -CN, -NO₂, -COOH, -COOC₁₋₆ alkyl, -COOR_a (wherein R_a is benzyl, C₁₋₆ alkanoyloxy C₁₋₆ alkyl, C₆₋₇ cycloalkanoyloxy C₁₋₆ alkyl, C₁₋₆

- alkoxycarbonyloxy C₁₋₆ alkyl, C₅₋₆ cycloalkoxycarbonyloxy C₁₋₆ alkyl, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl group, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group, (5-ethyl-2-oxo-1,3-dioxolen-4-yl)methyl group or a phthalidyl group), -CRbRcRd (Rb, Rc and Rd are independently -H, C₁₋₆ alkyl, C₁₋₆ alkanoyl, -OH or C₁₋₆ alkoxy), -CONHR', -
- 5 OR'' (R' and R'' are independently C₁₋₆ alkyl, aryl, aralkyl, alkoxyalkyl or amino alkyl), -OH, C₁₋₆ alkoxyC₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, halo, halo C₁₋₆ alkyl, C₁₋₆ alkyl hydroxyl, C₁₋₆ alkylamino, C₃₋₈ cycloalkyl attached directly to the ring, C₃₋₈ heterocycloalkyl, C₁₋₆ alkoxy C₁₋₆ alkylamino, carboxy C₁₋₆ alkyl, C₁₋₆ alkyl-COO-Rx (Rx represents -H, C₁₋₆ alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, 2-methyl-
- 10 propyl or benzyl), pivaloyloxymethoxycarbonyl, 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl, acetoxymethyloxycarbonyl, propionyloxymethoxycarbonyl, n-butyryloxymethoxy-carbonyl, isobutyryloxymethoxycarbonyl, 1-(ethoxycarbonyloxy)ethoxycarbonyl, 1-(acetyloxy)ethoxycarbonyl, 1-(isobutyryloxy)ethoxycarbonyl,
- 15 cyclohexylcarbonyloxymethoxycarbonyl, benzoyloxymethoxycarbonyl, cinnamyloxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl; P is hydrogen or a tetrazole protecting group, comprising treating compound of formula (II)

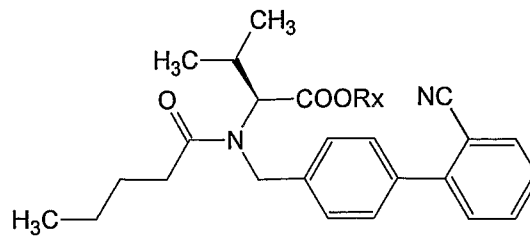


Formula (II)

wherein R is as defined above, with trialkyltin halide and metal azide in presence of base.

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According to another aspect of the present invention, there is provided a process of preparing Valsartan or a stereoisomer or a precursor thereof, comprising reacting compounds of formula (II) with trialkyltin halide and metal azide in presence of base

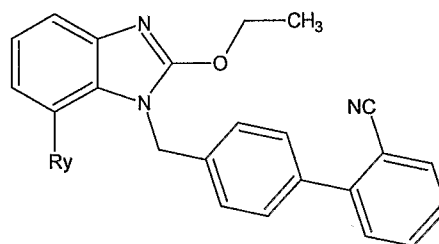


Formula (IIId)

wherein Rx represents hydrogen, C₁-C₆ alkyl selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, 2-methyl-propyl or benzyl to give Valsartan or a stereoisomer or a salt thereof.

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Yet another embodiment of the present invention provides a process of preparing Candesartan or a stereoisomer or an ester or a precursor thereof comprising reacting compounds of formula (IIb) with trialkyltin halide and metal azide in presence of base

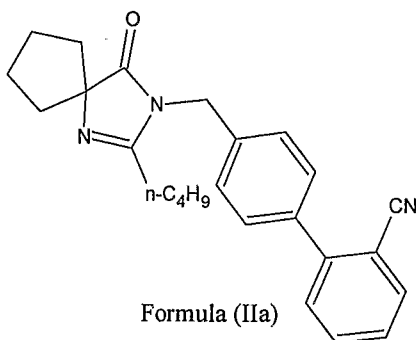


Formula (IIb)

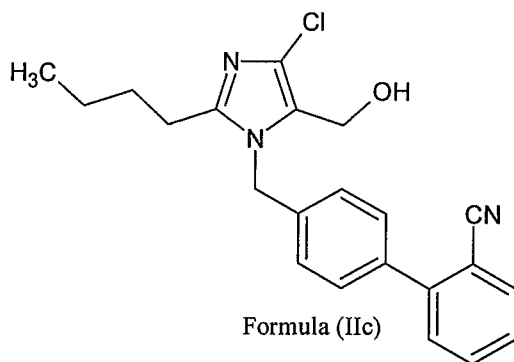
10 wherein Ry represents -COOH and salts thereof, -COOMe, -COOEt, -COOtBu, -COOPr, pivaloyloxymethoxycarbonyl, 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyloxycarbonyl, acetoxymethyloxycarbonyl, propionyloxymethoxycarbonyl, n-butyryloxymethoxy-carbonyl, isobutyryloxymethoxycarbonyl, 1-(ethoxycarbonyloxy)ethoxycarbonyl, 15 1-(acetyloxy)ethoxycarbonyl, 1-(isobutyryloxy)ethoxycarbonyl, cyclohexylcarbonyloxymethoxycarbonyl, benzoyloxymethoxycarbonyl, cinnamyloxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl or like to give Candesartan or a stereoisomer or a ester or a salt thereof.

20 According to yet another aspect of the present invention there is provided a process of preparing Irbesartan or a stereoisomer or a precursor thereof comprising reacting

compounds of formula (IIa) with trialkyltin halide and metal azide in presence of base to give Irbesartan or a stereoisomer or a salt thereof.

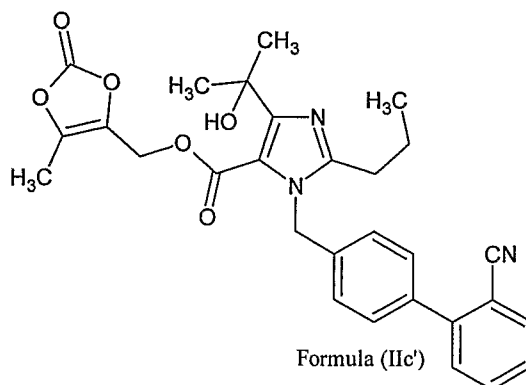


- 5 According to yet another aspect of the present invention there is provided a process of preparing Losartan or a stereoisomer or a precursor thereof comprising reacting compounds of formula (IIc) with trialkyltin halide and metal azide in presence of base to give Losartan or a stereoisomer or a salt thereof.

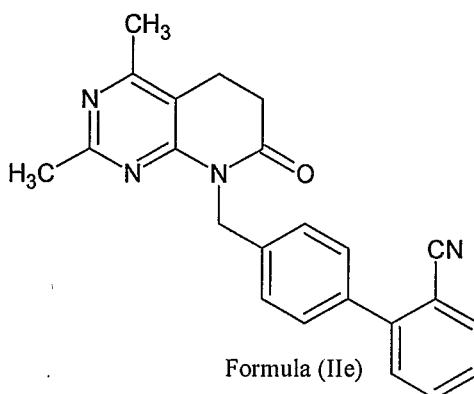


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According to yet another aspect of the present invention there is provided a process of preparing Olmesartan or a stereoisomer or a precursor thereof comprising reacting compounds of formula (IIc') with trialkyltin halide and metal azide in presence of base to give Olmesartan or a stereoisomer or a salt thereof.

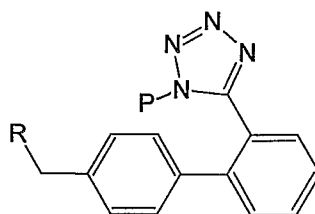


- According to yet another aspect of the present invention there is provided a process of preparing Tasosartan or a stereoisomer or a precursor thereof comprising reacting compounds of formula (IIe) with trialkyltin halide and metal azide in presence of base to
- 5 give Tasosartan or a stereoisomer or a salt thereof.



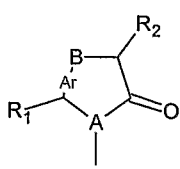
DETAILED DESCRIPTION OF THE INVENTION

- 10 The inventors of the following invention have surprisingly found that preparation of tetrazoles of formula (I) from aromatic cyano derivatives of formula (II) takes place conveniently by using trialkyltin halide and metal azide in presence of base, giving high yield, shorter duration of reaction and increased purity.
- 15 The compound of formula (I) or a stereoisomer or salt thereof,

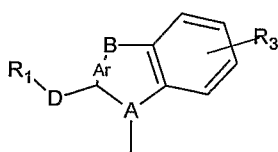


Formula (I)

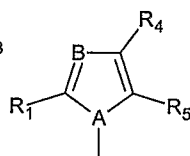
wherein R is selected from group comprising of formula (a), (b), (c), (d) or (e)



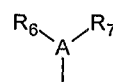
Formula (a)



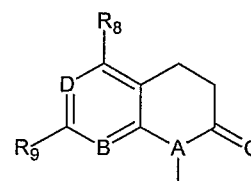
Formula (b)



Formula (c)



Formula (d)

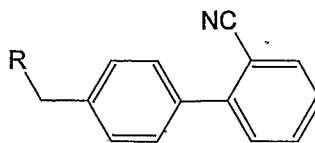


Formula (e)

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wherein A, B and D are independently C, O, N or S and the dotted line represents a single or a double bond; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are independently selected from hydrogen, C₁₋₆ alkyl, -CN, -NO₂, -COOH, -COOC₁₋₆ alkyl, -COOR_a (wherein R_a is benzyl, C₁₋₆ alkanoyloxy C₁₋₆ alkyl, C₆₋₇ cycloalkanoyloxy C₁₋₆ alkyl, C₁₋₆ alkoxy carbonyloxy C₁₋₆ alkyl, C₅₋₆ cycloalkoxy carbonyloxy C₁₋₆ alkyl, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl group, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group, (5-ethyl-2-oxo-1,3-dioxolen-4-yl)methyl group or a phthalidyl group), -CR_bR_cR_d (R_b, R_c and R_d are independently -H, C₁₋₆ alkyl, C₁₋₆ alkanoyl, -OH or C₁₋₆ alkoxy), -CONHR', -OR'' (R' and R'' are independently C₁₋₆ alkyl, aryl, aralkyl, alkoxyalkyl or amino alkyl), -OH, C₁₋₆ alkoxy C₁₋₆ alkyl, C₁₋₆ alkyl carbonyl, halo, halo C₁₋₆ alkyl, C₁₋₆ alkyl hydroxyl, C₁₋₆ alkyl amino, C₃₋₈ cycloalkyl attached directly to the ring, C₃₋₈ heterocycloalkyl, C₁₋₆ alkoxy C₁₋₆ alkyl amino, carboxy C₁₋₆ alkyl, C₁₋₆ alkyl-COO-R_x (R_x represents -H, C₁₋₆ alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, 2-methyl-propyl or benzyl), pivaloyloxymethoxycarbonyl, 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl, acetoxymethyloxycarbonyl, propionyloxymethoxycarbonyl, n-butyryloxymethoxy-carbonyl, isobutyryloxymethoxycarbonyl, 1-(ethoxycarbonyloxy)ethoxycarbonyl, 1-(acetyloxy)ethoxycarbonyl, 1-(isobutyryloxy)ethoxycarbonyl,

cyclohexylcarbonyloxymethoxycarbonyl, benzyloxymethoxycarbonyl, cinnamyloxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl; P is hydrogen or a tetrazole protecting group, comprising treating compound of formula (II)



Formula (II)

- 5 wherein R is as defined above, with trialkyltin halide and sodium azide in presence of base.

The reaction can be carried out in presence of suitable solvent selected from the group comprising of aliphatic, cycloaliphatic and aromatic hydrocarbon, such as an C₅-C₁₀
 10 alkane e. g. heptane, a cycloalkane such as cyclohexane ; an alkylated C₃-C₇ cycloalkane such as methyl-cyclohexane or 1, 3-dimethyl-cyclohexane, an alkylated benzene such as ethylbenzene, toluene, xylene, cumene, or mesitylene ; a halogenated aromatic solvent such as chlorobenzene, o-, m- or p-chlorotoluene, dichlorobenzene, and trifluoromethylbenzene which may be further substituted e.g. by C₁-C₇ alkyl or C₁-C₇
 15 alkoxy; an halogenated hydrocarbon like such as methylenedichloride, ethylenedichloride or chloroform; a halogenated aromatic compound, such as chlorobenzene; an ether, such as tetrahydrofuran, diisopropyl ether; an ketone, such as diisobutyl ketone, methyl isobutyl ketone; high boiling aprotic solvents such as dioxane, dimethylformamide, dimethylacetamide, dimethylsulphoxide; or mixtures thereof.

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The reaction is carried out at temperature ranging from about 0°C to about reflux temperature of the solvent, more preferably at about 20°C to about 250°C. The reaction time varies from about 1 hour to about 150 hours, more preferably from about 10 hours to about 50 hours.

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The trialkyltin halide can be trialkyltin chloride selected from group of trimethyltin chloride, triethyltin chloride, tributyltin chloride and like. The metal azide can be selected from inorganic azide like sodium, potassium or lithium azide.

The base is a nitrogeneous base selected from group of primary, secondary or tertiary amines for e.g. isopropyl amine, diethyl amine, triethyl amine, tributyl amine, diisopropyl ethyl amine and like.

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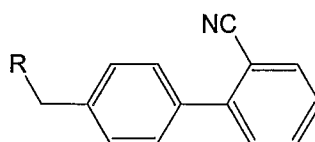
After the completion of the reaction the compound can be isolated by conventional methods or by methods known to person skilled in art.

It is also possible to prepare 5-tetrazole protected compound protected with suitable protecting group selected from trityl, monomethoxytrityl, dimethoxytrityl, benzhydryl, acyl, benzyl which is unsubstituted or substituted, for example by nitro, such as 4-nitrobenzyl, lower alkoxymethyl, such as methoxy- and ethoxymethyl, lower alkylthiomethyl, such as methylthiomethyl, silyl, such as tri-lower alkylsilyl, for example dimethyl-tert-butyl- and triisopropylsilyl, and 2-cyanoethyl, also lower alkoxy-lower
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alkoxymethyl, such as 2-methoxyethoxymethyl, benzyloxymethyl, phenacyl or like by process known to person skilled in general art.

It is also possible to carry out reaction in presence of organo-tin azides or any cyclizing agent known in art for conversion of cyano group to tetrazole group.

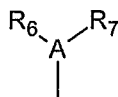
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According to the present invention process for the preparation of Valsartan of formula (A) or a stereoisomer or a precursor thereof, comprises treating compound of formula (II)



Formula (II)

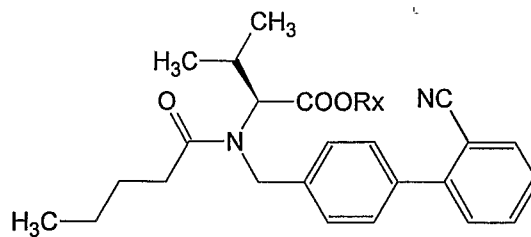
wherein R is selected from compound of formula (d)



Formula (d)

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wherein A is N; R₆ is valeroyl and R₇ is L-valine or its ester derivative, with trialkyltin halide and metal azide in presence of base, to give Valsartan or a stereoisomer or a salt thereof. Thus compound of formula (II) can be represented by compound of formula (IIId)



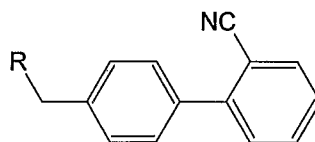
Formula (IIId)

- 5 wherein Rx represents -H, C₁-C₆ alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, 2-methyl-propyl or benzyl.

The reaction conditions and the reagents used for this reaction are such as herein described above in the preparation of compound of formula (I).

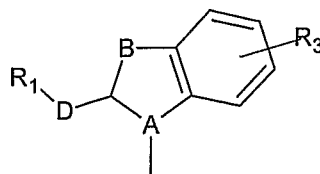
10

Moreover, in accordance with the present invention, there is given process of preparing Candesartan of formula (B) or a stereoisomer or a ester or a precursor thereof, comprising treating compound of formula (II)



Formula (II)

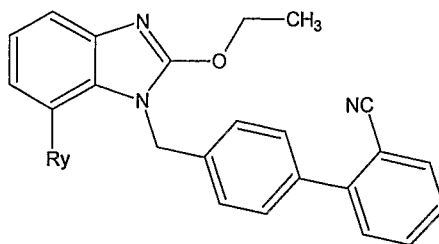
- 15 wherein R is selected from compound of formula (b)



Formula (b)

wherein A and B are N; C is O; the dotted line represents a double bond; R₃ is a carboxyl group or its ester and R₁ is ethyl, with trialkyltin halide and metal azide in presence of

base, to give Candesartan or a stereoisomer or a salt or an ester thereof. Thus compound of formula (II) can be represented by compound of formula (IIb)



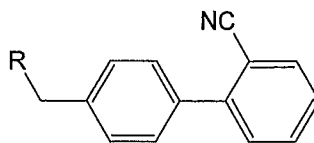
Formula (IIb)

- wherein Ry represents -COOH and salts thereof, -COOMe, -COOEt, -COOtBu, -COOPr, 5-methyl-
 5 pivaloyloxymethoxycarbonyl, 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl, 2-oxo-1,3-dioxolen-4-ylmethyloxycarbonyl, acetoxymethyloxycarbonyl, propionyloxymethoxycarbonyl, n-butyryloxymethoxy-carbonyl, isobutyryloxymethoxycarbonyl, 1-(ethoxycarbonyloxy)ethoxycarbonyl, 1-(acetyloxy)ethoxycarbonyl, 1-(isobutyryloxy)ethoxycarbonyl,
 10 cyclohexylcarbonyloxymethoxycarbonyl, benzoyloxymethoxycarbonyl, cinnamyloxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl or like.

The reaction conditions and the reagents used for this reaction are such as herein described above in the preparation of compound of formula (I).

15

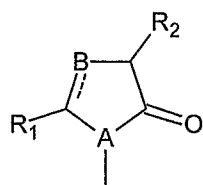
According to present invention, there is further provided a process for preparation of Irbesartan of formula (C) or a stereoisomer or a precursor thereof, comprising treating compound of formula (II)



Formula (II)

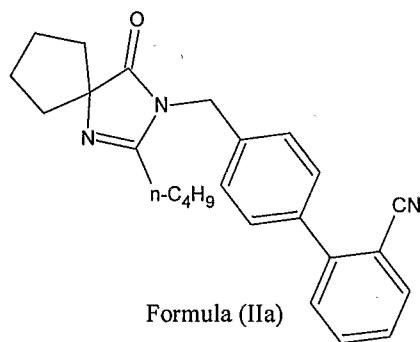
- 20 wherein R is selected from compound of formula (a)

13



Formula (a)

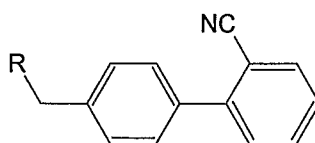
wherein A and B are N; the dotted line represents a double bond; R₁ is n-butyl and R₂ is a cyclopentyl ring directly attached to the imidazole ring, forming a spiro compound, with trialkyltin halide and metal azide in presence of base, to give Irbesartan or a stereoisomer or a salt thereof. Thus compound of formula (II) can be represented by compound of formula (IIa)



Formula (IIa)

The reaction conditions and the reagents used for this reaction are such as herein described above in the preparation of compound of formula (I).

According to present invention, there is given a process of preparing Losartan of formula (D) or a stereoisomer or a precursor thereof, comprising treating compound of formula (II)

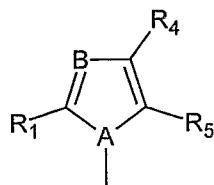


Formula (II)

15

wherein R is selected from compound of formula (c)

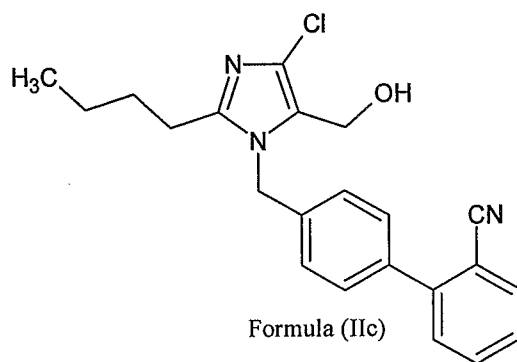
14



Formula (c)

wherein A and B are N; R₁ is n-butyl and R₅ is hydroxymethyl and R₄ is chloro, with trialkyltin halide and metal azide in presence of base, to give Losartan or a stereoisomer or a salt thereof. Thus compound of formula (II) can be represented by compound of

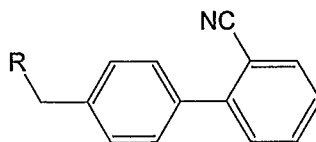
5 formula (IIc)



Formula (IIc)

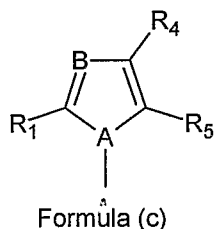
The reaction conditions and the reagents used for this reaction are such as herein described above in the preparation of compound of formula (I).

- 10 According to present invention, there is given a process of preparing Olmesartan of formula (E) or a stereoisomer or a precursor thereof, comprising treating compound of formula (II)

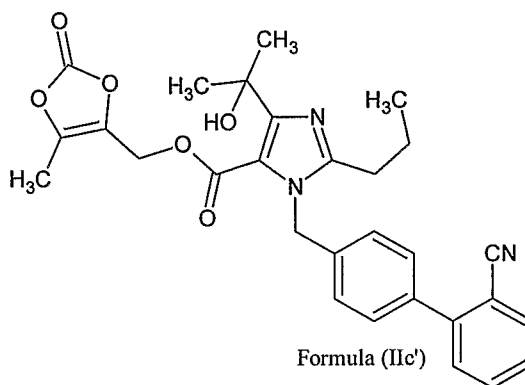


Formula (II)

wherein R is selected from compound of formula (c)

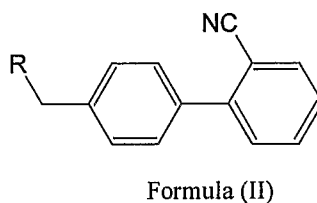


- wherein A and B are N; R₁ is n-propyl and R₅ is (5-methyl-2-oxo-1,3-dioxol-4-yl)carboxylate and R₄ is 1-hydroxy-1-methylethyl, with trialkyltin halide and metal azide in presence of base, to give Olmesartan or a stereoisomer or a salt thereof. Thus
- 5 compound of formula (II) can be represented by compound of formula (IIc')



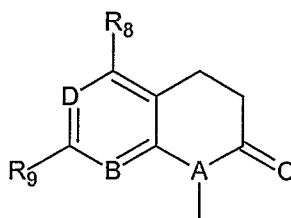
The reaction conditions and the reagents used for this reaction are such as herein described above in the preparation of compound of formula (I).

- 10 According to present invention, there is given a process of preparing Tasosartan of formula (F) or a stereoisomer or a precursor thereof, comprising treating compound of formula (II)



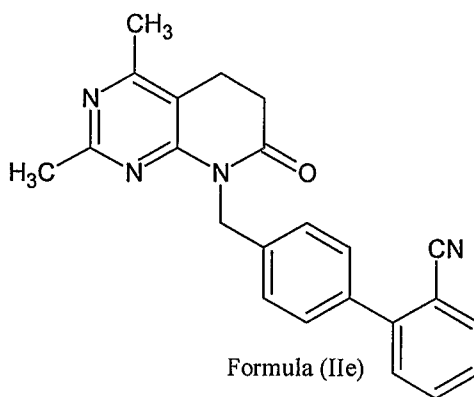
wherein R is selected from compound of formula (e)

16



Formula (e)

wherein A, B and D are N; R₈ and R₉ is methyl, with trialkyltin halide and metal azide in presence of base, to give Tasosartan or a stereoisomer or a salt thereof. Thus compound of formula (II) can be represented by compound of formula (IIe)



Formula (IIe)

5

The reaction conditions and the reagents used for this reaction are such as herein described above in the preparation of compound of formula (I).

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

Example 1

Preparation of Irbesartan

In a 3 necked 250 ml round bottom flask equipped with mechanical stirrer, was charged with 2-(n-Butyl)-3-(2'-cyanobiphenyl-4-ylmethyl)-4-oxo-1,3-diazaspiro [4.4] non-1-ene (5.0 g), o-xylene (25.0 ml) and tri n.butyltin chloride (12.7g), sodium azide (2.5g) and diisopropylethyl amine (0.5g) and stir it. The reaction mixture was heated to reflux under stirring for 12 hours. The reaction mixture was cooled to ambient temperature and 2N sodium hydroxide (50ml) was added and stirred for 30 minutes. The mixture was filtered

through hyflo bed and the phases were separated and aqueous phase was washed with o-xylene and isopropyl ether. The aqueous phase was treated with activated charcoal and filtered through hyflo bed. The filtrate was cooled 5-10°C and pH was adjusted to 4-5 by 3N hydrochloric acid on pH meter. The product was filtered, washed, dried under vacuum at 60°C and crystallized in rectified spirit.

Example 2

Preparation of Valsartan

Step (a): Preparation of N-[(2'-cyanobiphenyl-4-yl)methyl]-N-pentanoyl-(L)-valine methyl ester

A solution of N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester oxalate salt (25g) in xylene (125ml) and water (100 ml), was treated with potassium carbonate (29.8g) and valeroyl chloride (11.2g) at 0-5°C for 2 hours. The layers were separated and the organic layer was washed with bicarbonate solution and brine successively. The organic layer was then concentrated to obtain the title compound as yellow coloured liquid or it can be used as such for the next step.

Step (b): Preparation of S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl]-amine (Valsartan)

To a solution of N-[(2'-cyanobiphenyl-4-yl)methyl]-N-pentanoyl-(L)-valine methyl ester obtained in step (a), tri n.butyltin chloride (60.1 g), sodium azide (11.85g) and triethylamine (2.5g) was refluxed for 8-12 hours. It was cooled and stirred with 10% sodium hydroxide solution for 20-24 hours to complete hydrolysis of Valsartan methyl ester. The aqueous layer was separated, washed with dichloromethane, acidified with acetic acid and extracted with dichloromethane. The dichloromethane layer was washed with water, concentrated and the material was isolated using cyclohexane.

Example 3

Preparation of Candesartan acid

In a 3 necked 250 ml round bottom flask equipped with mechanical stirrer, was charged with methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxy-benzimidazole-7-carboxylate (5.0 g), o-xylene (25.0 ml) and tri n.butyltin chloride (11.7g, sodium azide (2.3g) and diisopropylethyl amine (0.5g) and stir it. The reaction mixture was heated to reflux under

stirring for 12 hours. The reaction mixture was cooled to ambient temperature and 2N sodium hydroxide (50ml) was added and the reaction mixture was heated to reflux under stirring for 12 hours. The reaction mixture was cooled to ambient temperature. The mixture was filtered through hyflo bed and the phases were separated and aqueous phase was washed with o-xylene and isopropyl ether. The aqueous phase was treated with activated charcoal and filtered through hyflo bed. The filtrate was cooled 5-10°C and pH was adjusted to 4-5 by 3N hydrochloric acid on pH meter. The product was filtered, washed, dried under vacuum at 60°C to give product i.e. 2-ethoxy- 1-[(2'-{1H-tetrazole-5-yl}biphenyl-4-yl)-methyl] benzimidazole-7-carboxylic acid.

Example 4

Preparation of Candesartan cilexetil

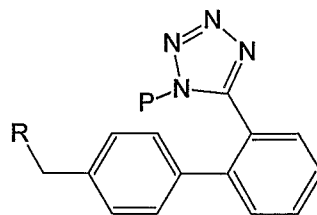
In a 3 necked 250 ml round bottom flask equipped with mechanical stirrer, was charged with (±) 2-ethoxy-1-[(2'-cyanobiphenyl-4-yl)-methyl]-1H-benzimidazole-7-carboxylic acid, 1{[(Cyclohexyl-oxy)carbonyl]oxyl} ethyl ester (5.67g), o-xylene (25.0 ml) and tri n.butyltin chloride (9.76g), sodium azide (1.95g) and diisopropylethyl amine (0.56g) and stir it. The reaction mixture was heated to reflux under stirring for 12 hours. The reaction mixture was distilled at reduced pressure and remaining product dissolved by alcohol (20 ml). Then (6M, 10 ml) HCl is added and extract with ethyl acetate (2 X 30 ml) and combine organic layer and wash it with water. Distilled out organic layer and residue dissolve in alcohol (15 ml) and water (5 ml) and stir for 7 hour at 20°C to 30°C and filter it and dry it reduced pressure at 50°C.

Recrystallised by alcohol/water (4/1) to give product i.e. (±)-1-(cyclohexyloxycarbonyloxy) ethyl-2-ethoxy- 1-[(2'-{1H- tetrazole-5-yl} biphenyl-4-yl)-methyl] benzimidazole-7-carboxylate.

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

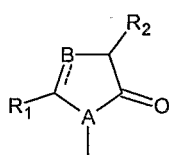
CLAIMS

1. A process for preparation of compound of formula (I) or a stereoisomer or salt thereof,

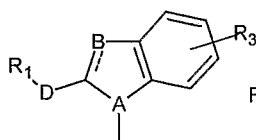


Formula (I)

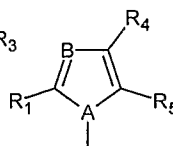
wherein R is selected from group comprising of formula (a), (b), (c), (d) or (e)



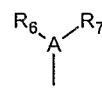
Formula (a)



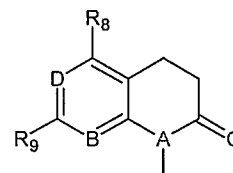
Formula (b)



Formula (c)



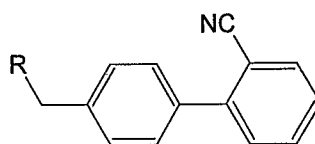
Formula (d)



Formula (e)

- wherein A, B and D are independently C, O, N or S and the dotted line represents a single or a double bond; R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are independently selected from hydrogen, C₁₋₆ alkyl, -CN, -NO₂, -COOH, -COOC₁₋₆ alkyl, -COOR_a (wherein R_a is benzyl, C₁₋₆ alkanoyloxy C₁₋₆ alkyl, C₆₋₇ cycloalkanoyloxy C₁₋₆ alkyl, C₁₋₆ alkoxy carbonyloxy C₁₋₆ alkyl, C₅₋₆ cycloalkoxy carbonyloxy C₁₋₆ alkyl, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl group, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group, (5-ethyl-2-oxo-1,3-dioxolen-4-yl)methyl group or a phthalidyl group), -CR_bR_cR_d (R_b, R_c and R_d are independently -H, C₁₋₆ alkyl, C₁₋₆ alkanoyl, -OH, C₁₋₆ alkoxy or C₁₋₆ alkoxy carbonyl), -CONHR', -OR'' (R' and R'' are independently C₁₋₆ alkyl, aryl, aralkyl, alkoxyalkyl or amino alkyl), -OH, C₁₋₆ alkoxy C₁₋₆ alkyl, C₁₋₆ alkyl carbonyl, halo, halo C₁₋₆ alkyl, C₁₋₆ alkyl hydroxyl, C₁₋₆ alkyl amino, C₃₋₈ cycloalkyl attached directly to the ring, C₃₋₈ heterocycloalkyl, C₁₋₆ alkoxy C₁₋₆ alkyl amino, carboxy C₁₋₆ alkyl, C₁₋₆ alkyl-COO-R_x (R_x represents -H, C₁₋₆ alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, 2-methyl-propyl or benzyl), pivaloyloxymethoxycarbonyl, 1-

(cyclohexyloxycarbonyloxy)ethoxycarbonyl, acetoxymethyloxycarbonyl,
 propionyloxymethoxycarbonyl, n-butyryloxymethoxy-carbonyl,
 isobutyryloxymethoxycarbonyl, 1-(ethoxycarbonyloxy)ethoxycarbonyl,
 1-(acetyloxy)ethoxycarbonyl, 1-(isobutyryloxy)ethoxycarbonyl,
 5 cyclohexylcarbonyloxymethoxycarbonyl, benzoyloxymethoxycarbonyl,
 cinnamyloxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl; P is hydrogen or
 a tetrazole protecting group,
 comprising treating compound of formula (II)



Formula (II)

- 10 wherein R is as defined above, with trialkyltin halide and metal azide in presence
 of base.
2. A process according to claim 1, wherein base is a nitrogeneous base.
 3. A process according to claim 2, wherein nitrogeneous base is selected from the
 15 group comprising primary, secondary or tertiary amines for e.g. isopropyl amine,
 diethyl amine, triethyl amine, tributyl amine, diisopropyl ethyl amine or mixture
 thereof.
 4. A process according to claim 1, wherein solvent is selected from the group
 comprising aliphatic, cycloaliphatic and aromatic hydrocarbon, such as an C₅-C₁₀
 20 alkane e. g. heptane, a cycloalkane such as cyclohexane ; an alkylated C₃-C₇
 cycloalkane such as methyl-cyclohexane or 1, 3-dimethyl-cyclohexane, an
 alkylated benzene such as ethylbenzene, toluene, xylene, cumene, or mesitylene; a
 halogenated aromatic solvent such as chlorobenzene, o-, m- or p-chlorotoluene,
 dichlorobenzene, and trifluoromethylbenzene which may be further substituted
 25 e.g. by C₁-C₇ alkyl or C₁-C₇ alkoxy; an halogenated hydrocarbon like such as
 methylenedichloride, ethylenedichloride or chloroform; a halogenated aromatic
 compound, such as chlorobenzene; an ether, such as tetrahydrofuran, diisopropyl
 ether; an ketone, such as diisobutyl ketone, methyl isobutyl ketone; high boiling

aprotic solvents such as dioxane, dimethylformamide, dimethylacetamide, dimethylsulphoxide; or mixtures thereof.

5. A process according to claim 1, wherein trialkyltin halide is a trialkyltin chloride.
6. A process according to claim 5, wherein trialkyltin chloride selected from group comprising trimethyltin chloride, triethyltin chloride, tributyltin chloride or mixture thereof.
7. A process according to claim 1, wherein metal azide is inorganic azide.
8. A process according to claim 7, wherein inorganic azide is selected from group comprising sodium azide, potassium azide or lithium azide.