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(54) Title: PROCESSES FOR THE PREPARATION OF HIGHLY PURE IRBESARTAN

(57) Abstract: The present invention relates to processes for synthesis of highly pure irbesartan or pharmaceutically acceptable salts thereof.

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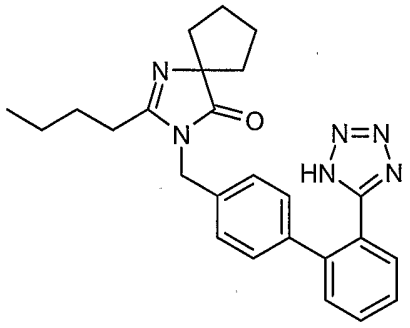
PROCESSES FOR THE PREPARATION OF HIGHLY PURE IRBESARTAN

Field of the Invention

The present invention relates to processes for the synthesis of highly pure irbesartan or pharmaceutically acceptable salts thereof.

Background of the Invention

Irbesartan, as shown in Formula I, belongs to the class of non-peptide angiotensin – II inhibitors. Irbesartan inhibits the action of angiotensin – II which prevents the increase in blood pressure produced by the hormone-receptor interaction. Irbesartan is traditionally used in the treatment of cardiovascular diseases, such as hypertension and heart failure.



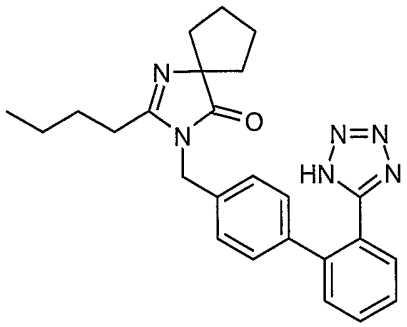
FORMULA I

U.S. Patent No. 5,270,317 describes a process for preparation of irbesartan which involves condensation of the spiro compound of Formula II with halomethyl-cyanobiphenyl compound of Formula III. This reaction is carried out in presence of N,N-dimethylformamide as a solvent and sodium hydride as base.

U.S. Patent No. 6,162,922 describes a process for preparation of irbesartan which involves treating the spiro intermediate of Formula II with halomethyl-cyanobiphenyl intermediate of Formula III in presence of a water immiscible solvent, a base and a phase transfer catalyst.

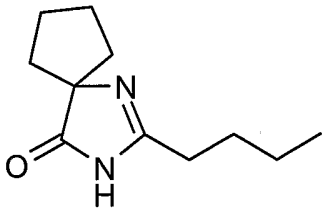
Summary of the Invention

In one general aspect there is provided a process for the preparation of irbesartan of Formula I.

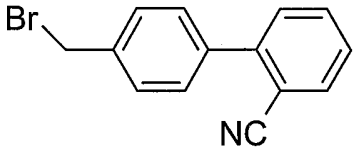


FORMULA I

The process includes condensing a spiro intermediate of Formula II with a halomethyl-cyanobiphenyl compound of Formula III



FORMULA II



FORMULA III

in the presence of a water miscible organic solvent and a base.

Embodiments of the process may include one or more of the following features. For example, the water miscible organic solvent may include one or more of water miscible lower alkanols, water miscible polar aprotic solvents and mixtures thereof. The lower alkanol may include one or more of methanol, ethanol, isopropanol and n-propanol.

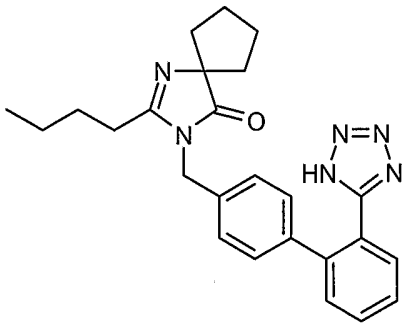
The polar aprotic solvent may include one or more of tetrahydrofuran, acetonitrile, 1,4-dioxane, N,N-dimethylacetamide, and dimethylsulphoxide.

The base may include one or more of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium methoxide, potassium t-butoxide or mixtures thereof.

The condensation may be carried out at a temperature of about 0 °C to about 150°C. The condensation may be carried out for about 2 to about 48 hours.

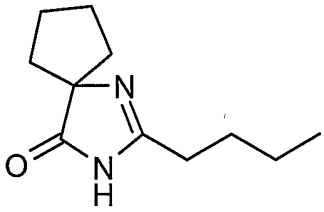
The irbesartan of Formula I obtained may have a purity greater than 99.5%.

In another general aspect there is provided a process for the preparation of irbesartan of Formula I

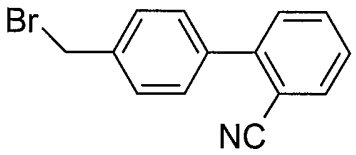


FORMULA I

The process includes condensing a spiro intermediate of Formula II with a halomethyl-cyanobiphenyl compound of Formula III

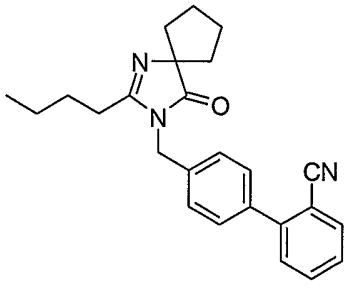


FORMULA II



FORMULA III

in presence of a water miscible organic solvent and a base; treating the product obtained of Formula IV with trialkyltin chloride and sodium azide; and



FORMULA IV

isolating irbesartan of Formula I.

Embodiments of the process may include one or more of the following features. For example, the process may also include adding a phase transfer catalyst to step (b) or protecting the tetrazolyl intermediate with a suitable protecting group and deprotecting the tetrazolyl protecting group prior to isolating the irbesartan of Formula I.

The trialkyltin chloride may include one or more tri C1-18 alkyltin chlorides. The trialkyltin chloride may include one or more of trimethyltin chloride, triethyltin chloride, tributyltin chloride and trioctyltin chloride.

The phase transfer catalyst may include one or more of crown ethers, quaternary ammonium salts, polyethylene glycols, diglyme and phosphoric acid derivatives.

The quaternary ammonium salts may include one or more of tetraalkyl ammonium halides or aryl and aralkyl trialkyl ammonium halides.

The quaternary ammonium salts may include one or more of tetrabutyl ammonium chloride, tetrabutyl ammonium bromide, tetrabutyl ammonium fluoride, tetrabutyl ammonium iodide, benzalkonium chloride, cetyl trimethyl ammonium chloride and benzyl trialkyl ammonium chloride.

The protecting group may include trityl, monomethoxytrityl, dimethoxytrityl, benzhydryl and acyl.

The irbesartan of Formula I obtained may have a purity greater than about 99.5%.

In another general aspect there is provided Irbesartan of Formula I with a purity of greater than about 99.5%. The irbesartan of Formula I may be Form A irbesartan.

Detailed Description of the Invention

The inventors have now developed processes for the preparation of highly pure irbesartan (Formula I) or pharmaceutically acceptable salts, polymorphs and geometric and optical enantiomers thereof. The process includes condensation of the spiro compound of Formula II with the halomethyl-cyanobiphenyl compound of

Formula III in presence of a water miscible organic solvent and a base. The product obtained (Formula IV) is treated with trialkyltin chloride and sodium azide, and optionally may include a phase transfer catalyst, to cyclize the aromatic cyano group to a tetrazole group to obtain highly pure irbesartan with or without protecting the tetrazolyl group.

The term Irbesartan of Formula I expressed herein means irbesartan and pharmaceutically acceptable salts, geometric and stereomeric isomers, polymorphic forms including the Form A, B and amorphous form thereof. The term highly pure irbesartan refers to irbesartan having purity greater than about 99.5%.

The condensation of the spiro intermediate with the halomethyl-cyanobiphenyl compound is carried out in the presence of a water miscible organic solvent and a base at temperature of about 0 °C to about 150°C for about 2 to about 48 hours.

Suitable water miscible organic solvents include one or more of water miscible lower alkanols, such as methanol, ethanol, isopropanol and n-propanol; water miscible polar aprotic solvents, such as tetrahydrofuran, acetonitrile, 1,4-dioxane, N,N-dimethylacetamide, and dimethylsulphoxide; and mixtures thereof.

Suitable bases include one or more of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium methoxide, potassium t-butoxide and mixtures thereof. A solution of base in water or a suitable organic solvent may also be employed in the reaction.

The condensation product (Formula IV) may also be treated with trialkyltin chloride and sodium azide, optionally in the presence of a phase transfer catalyst, to affect the cyclization of aromatic cyano group to tetrazolyl moiety.

The cyclization may be efficiently carried out in the presence of an organic solvent at a temperature of about 50 °C to about 250°C for about 10 to about 150 hours. For example, the reaction may be carried out at about 90 °C to 130°C for about 20 to about 50 hours.

Suitable organic solvents for this cyclization include one or more of aromatic hydrocarbons, non-polar aprotic solvents, high boiling polar aprotic solvents and

mixtures thereof. Suitable aromatic hydrocarbons include one or more of benzene, toluene, mono, di or tri-substituted benzenes and xylene. Suitable non-polar aprotic solvents include one or more of diisopropyl ether, methyl isobutyl ketone, diisobutyl ketone and substituted 2-pyrrolidones. Suitable high boiling polar aprotic solvent include one or more of dioxane, dimethylformamide, dimethylacetamide and dimethylsulphoxide.

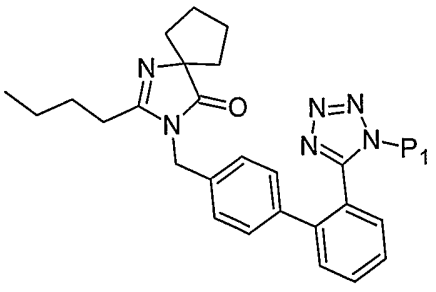
The trialkyltin chloride include tri C_{1-18} alkyltin chlorides, such as trimethyltin chloride, triethyltin chloride, tributyltin chloride and trioctyltin chloride.

Suitable phase transfer catalysts include one or more of crown ethers, quaternary ammonium salts, polyethylene glycols, diglyme and phosphoric acid derivatives.

Suitable quaternary ammonium salts include one or more of tetraalkyl ammonium halides or aryl and aralkyl trialkyl ammonium bromides, such as tetrabutyl ammonium chloride, tetrabutyl ammonium bromide, tetrabutyl ammonium fluoride, tetrabutyl ammonium iodide, benzalkonium chloride, cetyl trimethyl ammonium chloride and benzyl trialkyl ammonium chloride or mixtures thereof.

Irbesartan obtained by the above process may also be treated with a conventional protecting agent capable of protecting the tetrazole group. Suitable protecting agents include one or more of trityl, monomethoxytrityl, dimethoxytrityl, benzhydryl and acyl.

The protection may be carried out in a conventional manner in an organic solvent. The protected tetrazole derivative of Formula V, wherein P_1 stands for a conventional protecting group, is illustrated below.



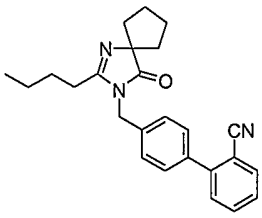
FORMULA V

The protected tetrazole compound is then deprotected in the presence of an organic solvent and deprotecting agent. Suitable organic solvents include one or more of methanol, ethanol, isopropanol, n-butanol, isobutanol, ethyl acetate, tetrahydrofuran, acetone, acetonitrile, N,N-dimethylformamide, dimethylsulphoxide or mixtures thereof. Suitable deprotecting agents include mineral acid or organic acid. Suitable organic acids include one or more of hydrochloric acid, nitric acid, sulphuric acid, phosphoric acid, formic acid, acetic acid, propionic acid and mixtures thereof.

After completion of the reaction, the reaction mass is then cooled to an ambient temperature and diluted with water and acetic acid. Irbesartan (Formula I) is isolated by adding a non-solvent and water to the reaction mass sufficient to precipitate the product completely. To enhance the precipitation the reaction mass may be cooled. Seeding with the product crystals may also be used wherever applicable. The purification of the irbesartan (Formula I) may be carried out by treating it with a base in the presence of water and converting it to the salt. Next, the salt is washed with an organic solvent to remove the impurities. The aqueous solution of the salt is then acidified to liberate irbesartan. The irbesartan may then be crystallized from the organic solvent to get the desired polymorphic form in a high purity. Form A of irbesartan may be prepared by crystallizing the highly pure irbesartan (Formula I) from absolute ethanol or from denatured spirit.

EXAMPLE 1: Preparation of 2-n-butyl-3-[[2'(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Irbesartan of Formula I)

Step A) 2-n-butyl-3-[[2'-cyanobiphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Formula IV)

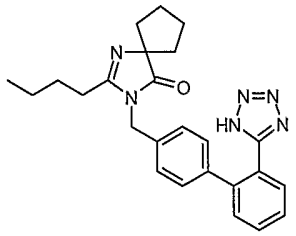


FORMULA IV

A mixture of 2-n-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one hydrochloride of Formula I (100 g), ethyl acetate (500 ml), water (300 ml) and aqueous ammonia solution (60 ml) was stirred at 25-30°C for 15 min. The layers were separated. After concentration of the organic layer, the residue was taken up in acetonitrile (1000 ml) and to the solution was added potassium carbonate (119.7 g) and 4'-bromomethyl[1,1'-biphenyl]-2-carbonitrile of Formula III (118 g). The mixture was refluxed for 10 hrs. After completion of the reaction, the reaction mass was concentrated under reduced pressure and the residue was dissolved in a mixture of dichloromethane (500 ml) and water (500 ml). The layers were separated and the organic phase was concentrated under reduced pressure to give an oily residue which was crystallized in methyl-tertiary butyl ether to yield the title compound of Formula IV

Yield: 120 gm

Step B) 2-n-butyl-3-[[2'(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Irbesartan of Formula I)



FORMULA I

A mixture of 2-n-butyl-3-[[2'-cyanobiphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one of Formula II as obtained in example 1 step A) (25 g), tributyltin chloride (63.4 g), sodium azide (12.7 g) and tetrabutyl ammonium bromide (2.5 g) in toluene (75 ml) was refluxed for 20 hrs. The reaction mixture was cooled to room temperature and to it was added water (100 ml) and acetic acid (12.5 ml). The mixture was stirred at room temperature for 15 min. To it was added methanol (100 ml), water (100 ml) and toluene (100 ml) and the entire mass was filtered. After washing the wet solid with toluene and water, the solids were dissolved in a mixture of water (250 ml) and 1N sodium hydroxide solution (100 ml). The aqueous phase was washed with ethyl acetate (2 x 100 ml). To the resulting aqueous phase was added 6N HCl slowly

to adjust the pH of the solution to about 4.8 – 5.3. After stirring at room temperature for 30 min, the crystals were filtered, washed with water (200 ml) and dried at 50°C to yield the compound of Formula I in 99.7% purity (24 g) which was purified, although this purification is optional.

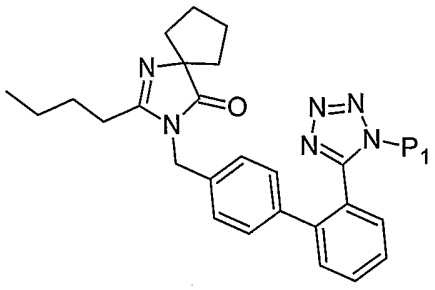
To this was added ethanol (96%, 250 ml) and the resulting mixture was heated to reflux until the product completely dissolved. The mixture was cooled to 15°C and stirred at 15 – 20°C for 30 min. The separated crystals were filtered and washed with 96% ethanol and dried at 50°C under reduced pressure to yield Irbesartan.

Yield: 23 g (86%)

HPLC Purity: 99.95%

EXAMPLE 2: Preparation of 2-n-butyl-3-[[2'(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Irbesartan of Formula I)

Step A) 2-n-butyl-3-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Trityl-Irbesartan of Formula V)



FORMULA V

A mixture of 2-n-butyl-3-[[2'-cyanobiphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one of Formula II as obtained in example 1 step A) (25 g), tributyltin chloride (63.4 g), sodium azide (12.7 g) and tetrabutyl ammonium bromide (2.5 g) in toluene (75 ml) was refluxed for 20 hrs. The reaction mixture was cooled to room temperature and to it was added water (100 ml) and acetic acid (12.5 ml). The mixture was stirred at room temperature for 15 min. To it was added methanol (100 ml), water (100 ml) and toluene (100 ml) and the entire mass was filtered. The wet solid was dissolved in methylene chloride (150 ml) and to it was added triethylamine

(8 gm) followed by triphenylmethyl chloride (18.2 gm). The resultant reaction mass was stirred at 25-30°C for about 2 hours. After the completion of the reaction water (125 ml) was added and the biphasic mass was stirred for 30 minutes. Next, the layers were separated and the methylene chloride was layer was concentrated under a vacuum. The crude residue was used as such in the next step.

Step B) 2-n-butyl-3-[[2'(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Irbesartan of Formula I)

Methanol (65 ml) and formic acid (16 gm) was added to the crude residue obtained in Example 2 step A). The resultant solution was stirred at 25-30°C for 4 hours. After completion of the reaction, ethyl acetate (100 ml) and water (100 ml) were added and stirred for 30 minutes. The resulting layers were separated and the ethyl acetate layer was washed with sodium carbonate solution twice (10%, 50 ml). The ethyl acetate was concentrated under vacuum to get the residue, which was then dissolved in a mixture of water (250 ml) and 1N sodium hydroxide solution (100 ml). The aqueous phase was washed with ethyl acetate (2 x 100 ml). To the resulting aqueous phase was added 6N HCl slowly to adjust the pH of the solution to about 4.8 – 5.3. After stirring at room temperature for 30 min, the crystals were filtered, washed with water (200 ml) and dried at 50°C to yield the compound of Formula I in 99.7% purity (24 g) which was purified, although the purification is optional.

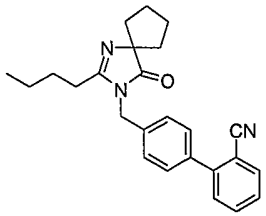
To this purified compound ethanol (96%, 250 ml) was added and the resulting mixture was heated to reflux until the product completely dissolves. The mixture was cooled to 15°C and stirred at 15 – 20°C for 30 min. The separated crystals were filtered and washed with 96% ethanol and dried at 50°C under reduced pressure to yield Irbesartan.

Yield: 23 g (86%)

HPLC Purity: 99.95%.

Example 3: Preparation of 2-n-butyl-3-[[2'(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Irbesartan of Formula I)

Step A) 2-n-butyl-3-[[2'-cyanobiphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Formula IV)



FORMULA IV

A mixture of 2-n-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one hydrochloride (25 g), aqueous sodium hydroxide solution (35%, 125 ml), 2-cyano-4'-bromomethylbiphenyl (29.5 g), and tetrabutyl ammonium bromide (2.5 g) in acetonitrile (375 ml) was stirred at room temperature for 3 hrs. After completion of reaction, the two layers were separated and the organic layer was concentrated under reduced pressure. The residue was dissolved in methylene chloride (125 ml) and washed with water (2 x 125 ml). The organic layer was concentrated under reduced pressure. The residue was crystallized in methyl tert-butyl ether to get 2-n-butyl-3-[2'-cyanobiphenyl-4-yl] methyl-1,3-diazaspiro[4.4]non-1-ene-4-one.

Step B) 2-n-butyl-3-[[2'(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro-[4.4]non-1-ene-4-one (Irbesartan of Formula I)

The product obtained in Example 3, step A) was converted to irbesartan by the process described in Example 1, step B).

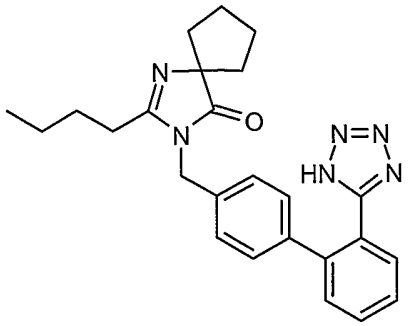
Yield: 35 g

HPLC Purity: 99.85%.

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 included within the scope of the present invention.

We Claim:

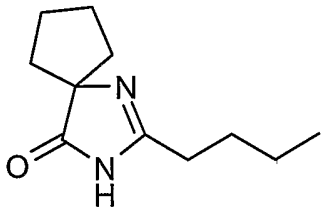
1. A process for preparation of irbesartan of Formula I,

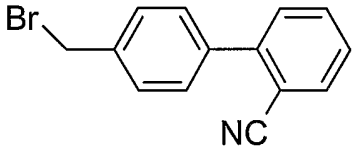


FORMULA I

the process comprising:

condensing a spiro intermediate of Formula II with a halomethyl-cyanobiphenyl compound of Formula III





FORMULA II **FORMULA III**

in the presence of a water miscible organic solvent and a base.

2. The process according to claim 1, wherein the water miscible organic solvent comprises one or more of water miscible lower alkanols, water miscible polar aprotic solvents and mixtures thereof.

3. The process according to claim 2, wherein the lower alkanol comprises one or more of methanol, ethanol, isopropanol and n-propanol.

4. The process according to claim 2, wherein the polar aprotic solvent comprises one or more of tetrahydrofuran, acetonitrile, 1,4-dioxane, N,N-dimethylacetamide, and dimethylsulphoxide.

5. The process according to claim 1, wherein the base comprises one or more of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium

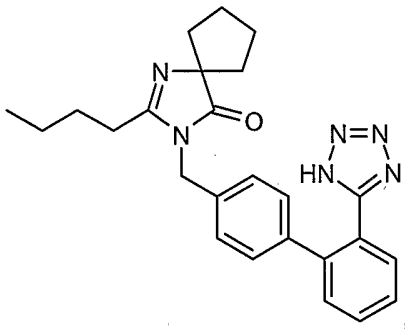
carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium methoxide, potassium t-butoxide or mixtures thereof.

6. The process according to claim 1, wherein the condensation is carried out at a temperature of about 0 °C to about 150°C.

7. The process according to claim 1, wherein the condensation is carried out for about 2 to about 48 hours.

8. The process according to claim 1, wherein the irbesartan of Formula I obtained has a purity greater than 99.5%.

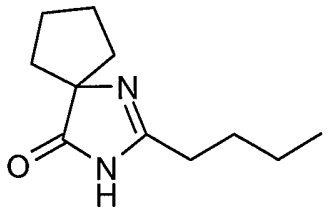
9. A process for preparation of irbesartan of Formula I



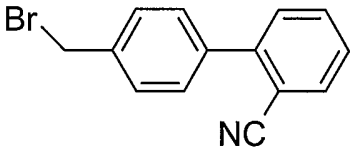
FORMULA I

the process comprising:

a) condensing a spiro intermediate of Formula II with a halomethyl-cyanobiphenyl compound of Formula III



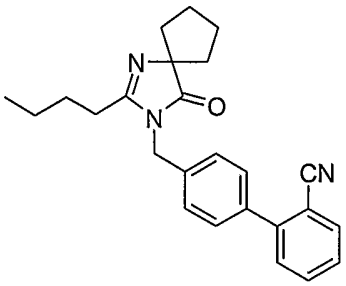
FORMULA II



FORMULA III

in presence of a water miscible organic solvent and a base;

b) treating the product obtained of Formula IV with trialkyltin chloride and sodium azide; and



FORMULA IV

c) isolating irbesartan of Formula I.

10. The process according to claim 9, further comprising adding a phase transfer catalyst to step (b).

11. The process according to claim 9, further comprising the steps of protecting the tetrazolyl intermediate with a suitable protecting group and deprotecting the tetrazolyl protecting group prior to isolating the irbesartan of Formula I.

12. The process according to claim 9, wherein the trialkyltin chloride comprises one or more tri C_{1-18} alkyltin chlorides.

13. The process according to claim 12, wherein the trialkyltin chloride comprises one or more of trimethyltin chloride, triethyltin chloride, tributyltin chloride and trioctyltin chloride.

14. The process according to claim 10, wherein the phase transfer catalyst comprises one or more of crown ethers, quaternary ammonium salts, polyethylene glycols, diglyme and phosphoric acid derivatives.

15. The process according to claim 14, wherein the quaternary ammonium salts comprise one or more of tetraalkyl ammonium halides or aryl and aralkyl trialkyl ammonium halides.

16. The process according to claim 15, wherein the quaternary ammonium salts comprise one or more of tetrabutyl ammonium chloride, tetrabutyl ammonium bromide, tetrabutyl ammonium fluoride, tetrabutyl ammonium iodide, benzalkonium chloride, cetyl trimethyl ammonium chloride and benzyl trialkyl ammonium chloride.

17. The process according to claim 11, wherein the protecting group comprises trityl, monomethoxytrityl, dimethoxytrityl, benzhydryl and acyl.

18. The process according to claim 9, wherein the irbesartan of Formula I has a purity greater than about 99.5%.

19. Irbesartan of Formula I with a purity of greater than about 99.5%.

20. The irbesartan of Formula I of claim 19, wherein the irbesartan of Formula I is Form A irbesartan.

INTERNATIONAL SEARCH REPORT

IB2004/003777

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/10

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)
IPC 7 C07D

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, CHEM ABS Data, WPI 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.
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Y	column 12; example 5	1-20
X	BERNHART G A ET AL: "A NEW SERIES OF IMIDAZOLONES: HIGHLY SPECIFIC AND POTENT NONPEPTIDEAT1 ANTIOTENSIN II RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, no. 22, 1993, pages 3371-3380, XP002064391 ISSN: 0022-2623	1,2,6-8, 19,20
Y	page 3373, column 2, paragraph 2 Scheme VI on page 3373; compound 21 in Table V on page 3375 page 3379, column 1, paragraphs 3,4	1-20
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2005	04/03/2005

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	Guspanova, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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