

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 December 2006 (21.12.2006)

PCT

(10) International Publication Number
WO 2006/134078 A1

- (51) International Patent Classification:
C07D 403/10 (2006.01) *C07D 235/26* (2006.01)
- (21) International Application Number:
PCT/EP2006/063062
- (22) International Filing Date: 9 June 2006 (09.06.2006)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
P-200501480 17 June 2005 (17.06.2005) ES
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR OBTAINING BENZIMIDAZOLE DERIVATIVES AND INTERMEDIATES THEREOF

(57) Abstract: The present invention relates to a method for obtaining benzimidazole derivatives and intermediates thereof, preferably, for obtaining Candesartan and Candesartan cilexetil. Said method allows the benzimidazole derivatives to be obtained with a higher yield.



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METHOD FOR OBTAINING BENZIMIDAZOLE DERIVATIVES AND
INTERMEDIATES THEREOF

5 **Field of the technique**

The present invention relates to a new method for
obtaining benzimidazole derivatives and intermediates
thereof.

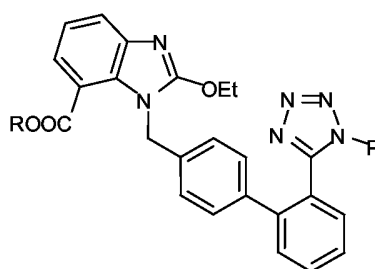
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State of the prior art

Candesartan and candesartan cilexetil are compounds
having an intense selective angiotensin II receptor
15 blocking activity which are useful in the treatment of
hypertension.

Candesartan is the international nonproprietary name
of 2-ethoxy-1-[[2'-(1H-tetrazole-5-yl)[1,1'-biphenyl]-4-
yl]methyl]-1H-benzimidazole-7-carboxylic acid of Formula
20 (I), finding application in medicine and used in the
treatment of hypertension.

25



(I)

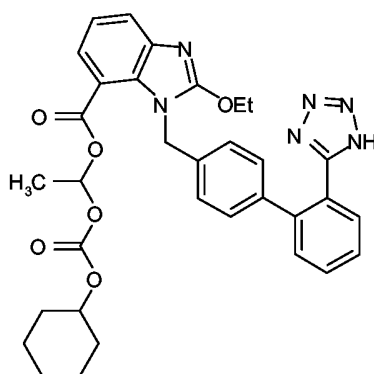
Candesartan: (I) when R and P = H

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Candesartan is normally used in the form of cilexetil
ester:

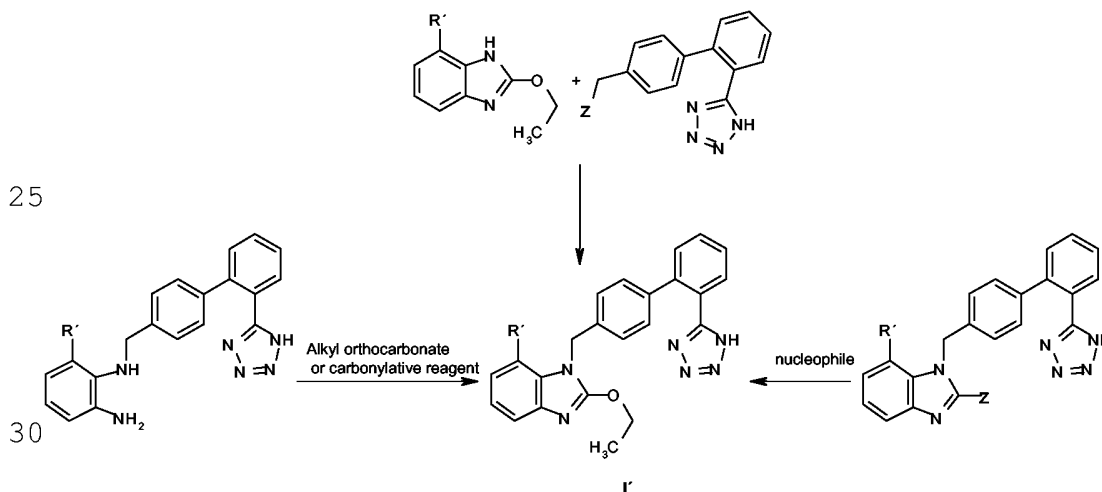
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**CANDESARTAN CILEXETIL**

European patent EP 459.136 B1 discloses candesartan and candesartan cilexetil for the first time, as well as several methods for preparing benzimidazole derivatives, among which are candesartan and its corresponding cilexetil ester.

Said methods are characterised in that in the final step of the synthesis the benzimidazole ring is generated, inserted or substituted from the biphenyltetrazolyl group, 20 as shown in the following schema:



25

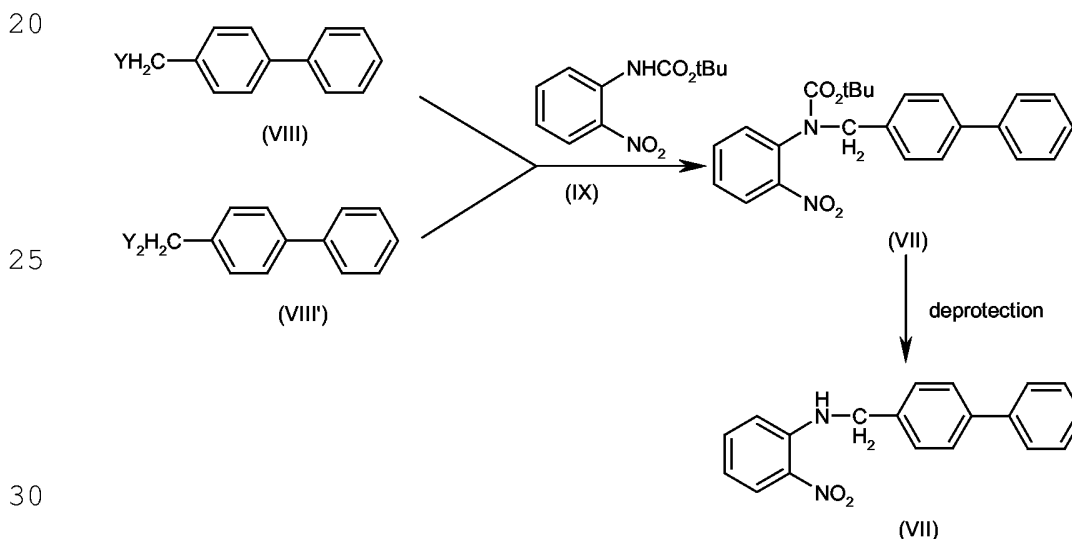
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One disadvantage of this method lies in the large number of reaction steps necessary for obtaining the

intermediates used, as well as the need to use azides to generate the tetrazole ring, which due to their high reactivity require particularly safe methods, especially when used on a large scale.

5 Patent EP 668.272 B1 describes a method for obtaining a number of compounds derived from tetrazole, among which methods are included candesartan and candesartan cilexetil, which method comprises deprotection of an N-tetrazolyl compound protected with a mineral acid in the
10 presence of an alcohol, with a concentration of water of up to 1 mole per mole of the aforesaid protected N-tetrazolyl compound.

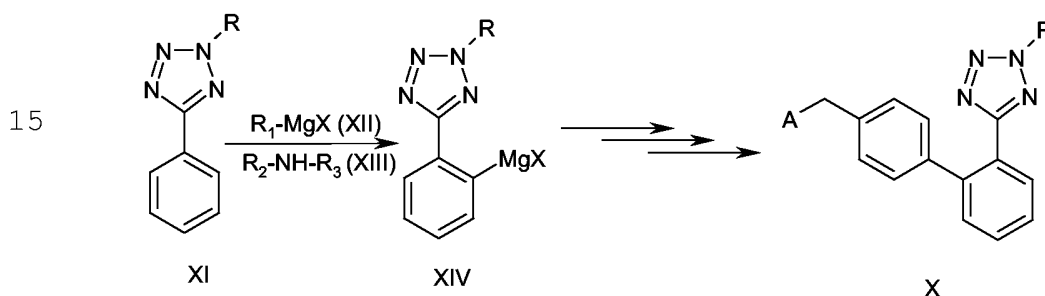
Patent EP 881.212 B1 claims a method for preparing a compound of formula (VII), which is an intermediate useful
15 in the synthesis of candesartan. The method comprises reacting a mixture that contains a monohalogenated compound of formula (VIII) or a dihalogenated compound of formula (VIII') or a salt thereof, with Y being a halogen atom, with a compound of formula (IX).



The known methods for the synthesis of benzimidazoles of formula I have been so far based on the reaction

between a suitable benzimidazole and a conveniently substituted derivative of the biphenyl group.

Known in the literature are palladium-catalysed coupling reactions for obtaining biphenyl derivatives, such as in EP 994.881 B1, which describes a method of ortho-metalation for preparing (tetrazole-5-yl)benzene compounds of general formula (X) that comprises treating a compound of general formula (XI) with a Grignard reagent of general formula (XII) R_1MgX , in the presence of a catalytic amount of a secondary amine of general formula (XIII) R_2-NH-R_3 , to form the compound of general formula (XIV).



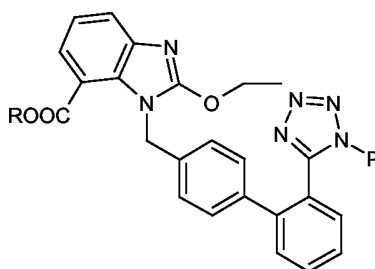
20 The authors of the present invention have discovered a new improved method for obtaining candesartan and candesartan cilexetil that allows the product to be prepared with higher yields and with a purity appropriate for the purpose for which it can be used, as an active ingredient in the preparation of pharmaceutical formulations.

Object of the invention

30 The object of the present invention is a method for obtaining derivatives of benzimidazole and intermediates thereof, in particular for obtaining Candesartan and Candesartan cilexetil.

Detailed description of the invention

In a first aspect, the present invention provides a method for obtaining the benzimidazole derivatives of general formula (I):

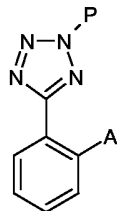


(I)

wherein:

R represents H, methyl, ethyl or cilexetil; and

P represents H, cumyl, diphenylmethyl or trityl, and pharmaceutically acceptable salts thereof, which comprises reacting the compound of general formula (II):



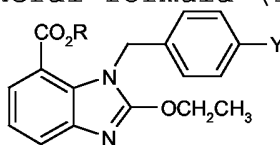
(II)

wherein:

A represents $B(OH)_2$ or ZnX ; where X represents a halogen group, and

P represents H, cumyl, diphenylmethyl or trityl;

with a compound of general formula (III):



(III)

wherein:

R represents H, methyl, ethyl or cilexetil; and
Y represents an halogen atom,
in the presence of a palladium catalyst, or in an organic solvent.

5 The method object of the invention is particularly suitable for obtaining candesartan and candesartan cilexetil, compounds that present an intense selective angiotensin II receptor blocking activity, and which are useful in the treatment of hypertension.

10 In a preferred embodiment of the first aspect of the invention, the coupling reaction is carried out in the presence of palladium catalysts such as trans-dichlorobis(triphenylphosphine) palladium (II), tetrakis(triphenylphosphine) palladium (0), tetrakis
15 (methyldiphenylphosphine) palladium (0). Preferably, the catalyst of the coupling reaction can be generated *in situ*, by carrying out the reaction in the presence of palladium acetate and triphenylphosphine.

In another preferred embodiment of the first aspect
20 of the invention, an inert organic solvent, preferably aprotic, such as toluene, acetonitrile, THF, dimethoxyethane, N,N-dimethylacetamide and the like can be used as a reaction solvent.

Advantageously, the reaction is carried out at a
25 temperature between 30 and 100°C, preferably between 60 and 70°C, for 1-20 hours.

Subsequently, the benzimidazole derivative of general formula (I) can be converted, if desired, by means of hydrolysis, esterification, protection and/or deprotection
30 to form another compound of formula (I), by means of methods known in the state of the art.

The starting compounds of general formula (II) can be synthesised according to methods known in the state of the art, such as those described in patent application DE

4313747, European patent EP 455.423, or application PCT/EP2004/008576 (application date: 30.07.04) and comprising the reaction of the corresponding phenyl tetrazole with BuLi and the subsequent transmetalation
5 reaction.

The benzimidazole derivatives of general formula (I) obtained in accordance with the first aspect of the invention can be isolated and/or purified from the reaction mixture in accordance with conventional methods,
10 such as recrystallisation and column chromatography, to obtain a crystalline product.

In a second aspect, the present invention provides an intermediate of general formula (III):



wherein

III

R is methyl; and

Y represents a halogen atom.

20 In a third aspect, the present invention provides a method for obtaining intermediates of general formula (III):



wherein:

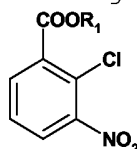
(III)

R represents hydrogen, methyl, ethyl or cilexetil;
and

Y represents a halogen atom;

which comprises:

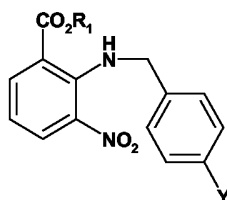
a) reacting a compound of general formula (IV):



(IV)

wherein R_1 is methyl or ethyl,

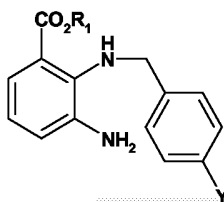
with a 4-halobenzylamine, in the presence of a base and an organic solvent, to obtain the compound of general formula (V):



(V)

with R_1 and Y being as defined above;

b) submitting the compound of general formula (V) to a reduction reaction in an organic solvent, for the purpose of obtaining a compound of general formula (VI):



(VI)

and

c) reacting the compound of general formula (VI) with ethyl orthocarbonate, in an acidic medium.

The compound of general formula (III) can be converted, if wished, by means of hydrolysis and/or esterification into another compound of formula (III), in

accordance with methods well-known to a skilled person in the art.

The first step of the reaction is an aromatic nucleophilic substitution of the general compound (IV) by
5 a 4-halobenzylamine in the presence of a base. The reaction is carried out in solvents such as toluene, THF, acetonitrile, DMF and the like. Examples of suitable bases include, but are not limited to, triethylamine, sodium hydride, potassium carbonate and sodium carbonate.

10 The second step of the method in accordance with the third aspect of the invention is a reduction reaction of the intermediate of general formula (V), which can be carried out by using, for example, tin chloride. The reaction solvent can be a protic organic solvent such as
15 EtOH. The reaction is normally carried out at a temperature between 30 and 100°C, for 1 to 4 hours.

The third step of the method in accordance with the third aspect of the invention comprises the reaction of the intermediate of general formula (VI) with ethyl
20 orthocarbonate, in the presence of an acid such as acetic acid or p-toluene sulphonic acid. As regards the reaction solvent, halogenated hydrocarbons and ethers can be used, although it is normally more convenient to carry out the reaction without solvent. The reaction is normally carried
25 out at a temperature between 30 and 100°C, preferably between 70 and 80°C, for 1 to 3 hours.

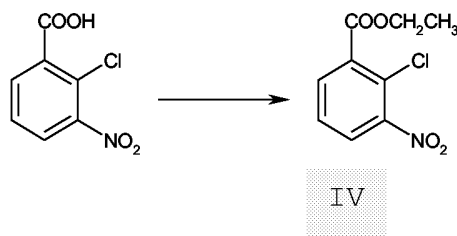
The reaction intermediates (V) and (VI) obtained as described above can easily be isolated and/or purified by means of, or in accordance with, conventional methods such
30 as, for example, evaporation of solvents, extraction by means of water or organic solvents, concentration, neutralisation, recrystallisation, distillation and column chromatography.

The compounds (I) and (III) obtained in the above-mentioned way can be in the form of solvates or salts (including addition salts) from pharmaceutically or physiologically acceptable acids or bases.

5 The following examples illustrate the invention but must not be considered as limiting the scope thereof.

Example 1. Obtaining ethyl 2-chloro-3-nitrobenzoate (IV)

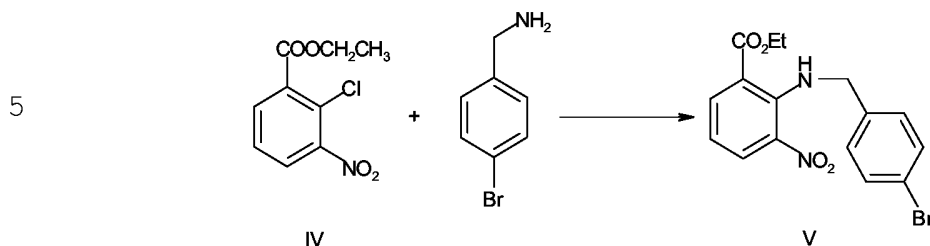
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In a 250 ml capacity flask, 5 g (1 equivalent) of 2-chloro-3-nitrobenzoic acid is dissolved in 50 ml of ethanol. 3.5 ml of sulphuric acid is then added to the solution, keeping the temperature of the reaction between 15 and 30°C.

The mixture is heated at reflux for 24 hours, following which the solvent is evaporated at reduced pressure and the residue is poured onto 120 ml of cold water. The mixture is extracted with toluene (3 x 50 ml) and the organic phase obtained is washed with 100 ml of water and with 100 ml of an aqueous solution of potassium carbonate. The organic phase is dried with MgSO₄, filtered and concentrated to dryness at reduced pressure. The resulting product, a pale yellow oil (5.1 g, 90%), is used without further purification in the following reaction.

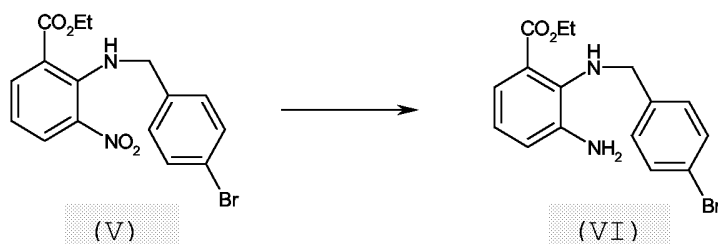
Example 2. Obtaining ethyl 2-(4-bromobenzylamine)-3-nitrobenzoate (V)



10 In a 100 ml capacity flask, 4.26 g of ethyl 2-chloro-3-nitrobenzoate is dissolved in 50 ml of toluene and 3.45 g of 4-bromobenzylamine, and 5.2 ml of triethylamine are added.

The mixture is heated at reflux for 12 hours, following which the solution is cooled at room temperature, washed twice with water and concentrated to dryness under vacuum in the rotary evaporator. The residue obtained is resuspended in ethyl alcohol and concentrated again to dryness at reduced pressure in the rotary evaporator. 6.7 g of a solid is obtained (yield: 95%) and is used without further purification in the following reaction.

Example 3. Obtaining ethyl (3-amino-2-(4-bromobenzylamine)benzoate (VI)

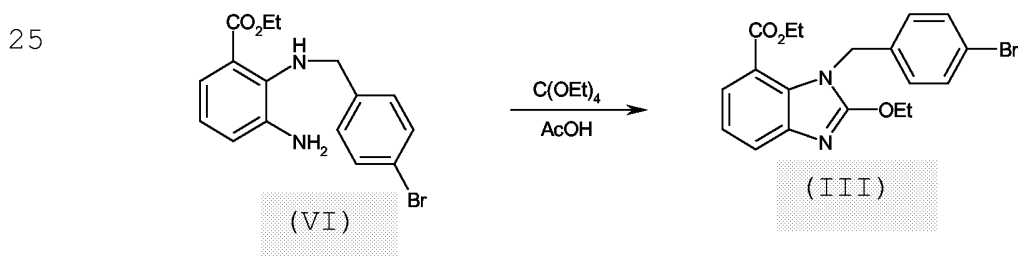


30 Tin (II) chloride dihydrate (14.87 g) is added to a solution of ethyl 2-(4-bromobenzylamine)-3-nitrobenzoate

(5.0 g) in ethyl alcohol (25 ml). The mixture is heated at reflux for 2 hours, following which the solvent is distilled at reduced pressure to dryness. The concentration residue is cooled with an ice bath and 5 sodium hydroxide 2 N (265 ml) is added dropwise. The aqueous phase is extracted with ethyl acetate (2 x 150 ml). The organic phases are combined, washed with water, dried over anhydrous sodium sulphate and filtered. The solvent is concentrated at reduced pressure to a final 10 volume of 100 ml, and a current of HCl gas (at least 1 equivalent) is passed over said solution, to obtain the ethyl 3-amino-2-(4-bromobenzylamine)benzoate hydrochloride.

The resulting solid is filtered, resuspended in a 15 solution of NaOH 2 N and extracted with ethyl acetate. The organic phase is dried with anhydrous magnesium sulphate and is concentrated in the rotary evaporator to dryness, to obtain 3.7 g of product (yield: 80%), which is used without further purification in the following step of 20 synthesis.

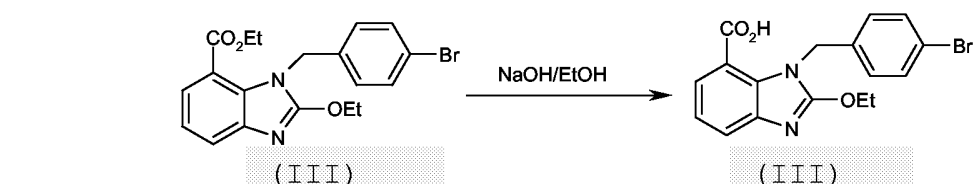
Example 4. Obtaining ethyl 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylate (III)



Acetic acid (1 g) is added to a solution of ethyl 3-amino-2-(4-bromobenzylamine)benzoate (5.0 g) in ethyl orthocarbonate (25 ml) and is heated at 80°C for 1 hour.

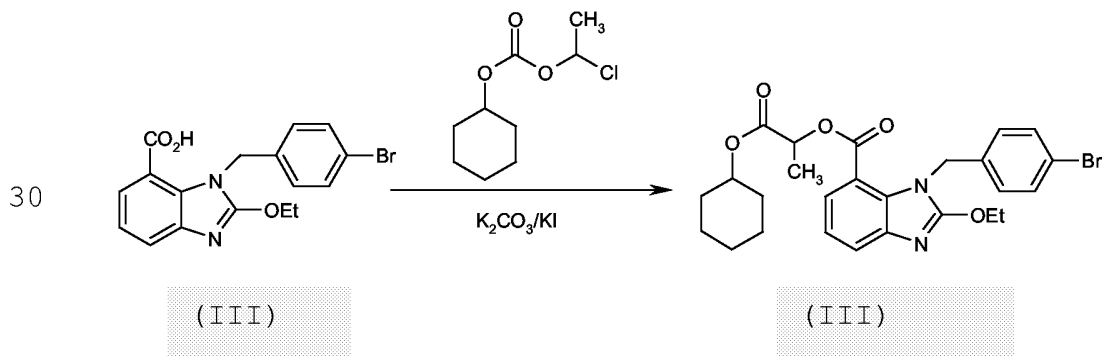
The reaction is concentrated and the residue is dissolved in ethyl acetate. The so obtained solution is washed with a sodium bicarbonate solution in water and afterwards with water. The organic phase is dried over anhydrous magnesium sulphate and is concentrated, to obtain a residue which is recrystallised in ethyl acetate and heptane (1:5). A yellow solid (4.33 g, 75%) is obtained in the form of needles.

Example 5. Obtaining 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylic acid (III)



Solid soda (0.24 g, 1.2 equivalents) is added to a solution of ethyl 3-amino-2-(4-bromobenzylamine)benzoate (2 g, 1 equivalent) in ethanol (15 ml). The mixture is heated at reflux for 10 hours. Water is then added to the crude reaction product and concentrated hydrochloric acid is added to achieve a pH of 4-4.5. The formed solid is filtered and washed with water. Yield: 98%.

Example 6. Obtaining cilexetil 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylate (III)

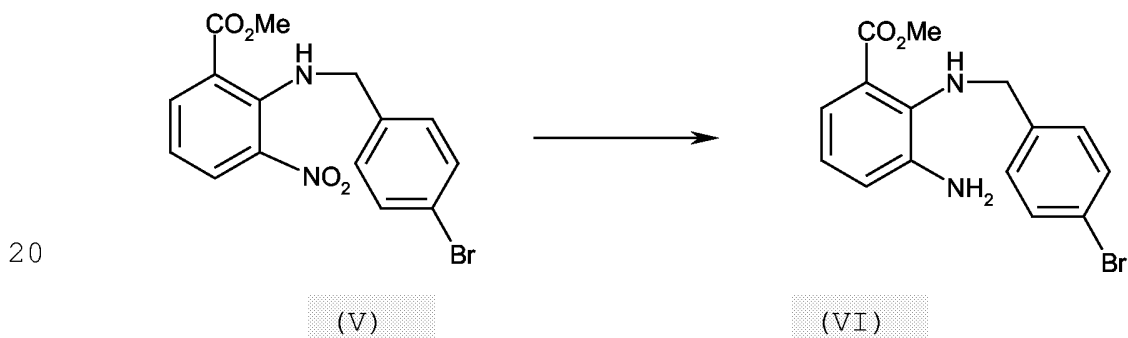


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To a solution made of 1.8 g of 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylic acid in dimethylformamide potassium iodide (0.44 g) and anhydrous potassium carbonate (0.89 g) are added. (+/-)1-chloroethyl cyclohexyl carbonate (6.43 g) is added to the resulting mixture and stirred at 60-70°C for approximately 10 hours. Ethyl acetate (20 ml) and water (30 ml) are then added successively. The organic phase is separated, washed with water and concentrated at reduced pressure. This provides 2.05 g of dry product in the form of an oil (79% yield).

Example 7. Obtaining methyl (3-amino-2-(4-bromobenzylamine)benzoate (VI)

15

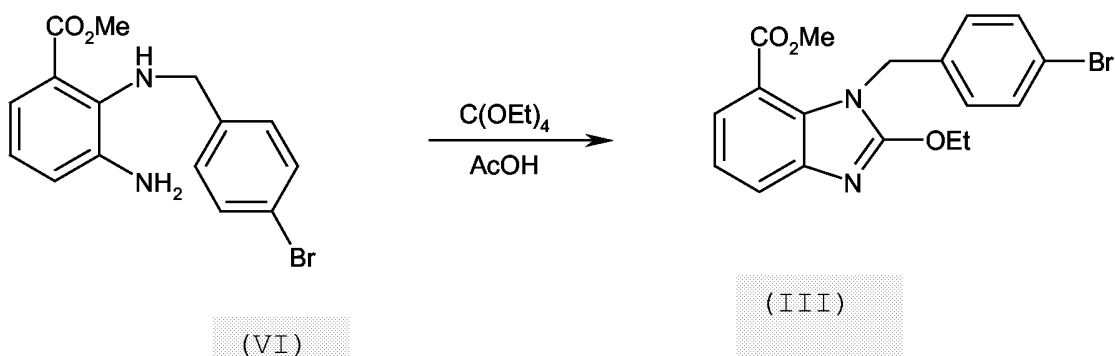


Tin (II) chloride dihydrate (244.1 g) in a mixture of 35% hydrochloric acid (307.5 g) and water (93 ml) is added to a suspension of methyl 2-(4-bromobenzylamine)-3-nitrobenzoate (123.0 g) in toluene/THF (3:2 v/v) (615 ml). The mixture is heated at 55°C for 2 hours, following which the mixture is cooled to room temperature and the phases are separated. The organic phase is washed with water and to the resulting organic phases, sodium hydroxide 30% (175 ml) is added dropwise. Once the addition is finished, water is added (900 ml) and phases are separated. The

aqueous phase is extracted with toluene (2 x 300 ml). The organic phases are combined, washed with water, dried over anhydrous sodium sulphate and filtered. The solvent is concentrated at reduced pressure to yield 144 g of an orange oily mixture of methyl 3-amino-2-(4-bromobenzylamine)benzoate (113 g) and toluene (31 g).

Example 8. Obtaining methyl 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylate (III)

10

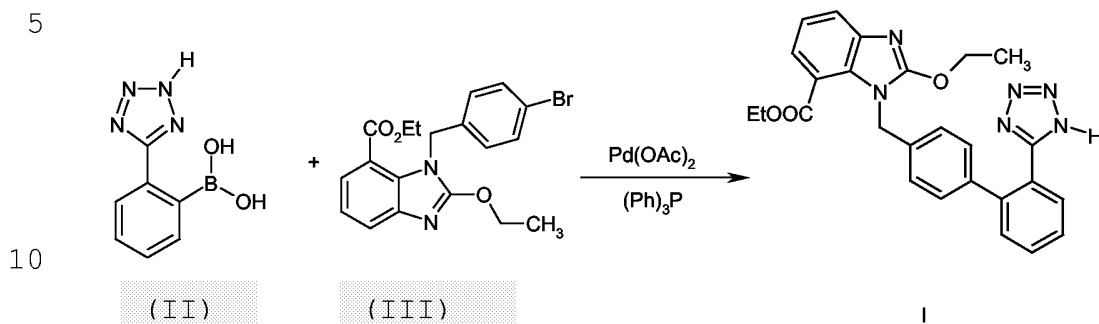


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Acetic acid (22.6 g) is added to the oily mixture obtained in the previous example in ethyl orthocarbonate (162.46 ml) and is heated at 80°C for 1 hour. The resulting mixture is suspended in heptane (225 ml) and is let to stand to room temperature for 3 hours. The resulting solid is filtered and washed with heptane (30 ml) affording the desired compound (75.8 g) as a yellow solid.

25

Example 9. Obtaining ethyl 2-ethoxy-1-[[2'-(1H-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate (I)

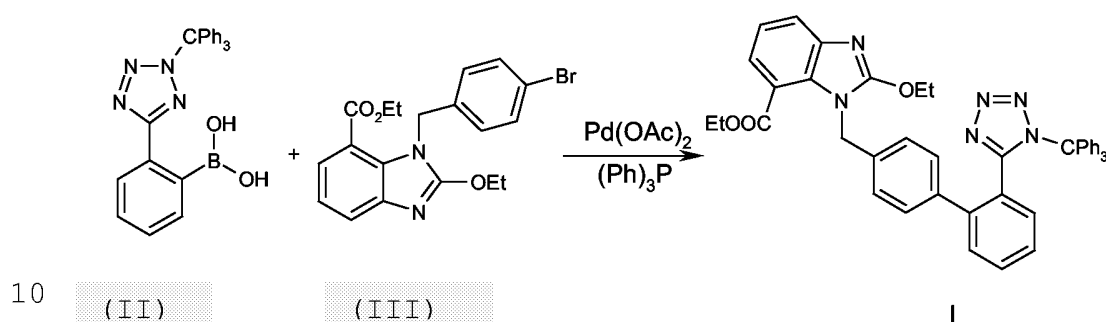


In a 50 ml capacity flask under nitrogen atmosphere 1.99 g of 2H-(tetrazole-5-yl)phenyl boronic acid, 4.03 g of ethyl 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylate, 2.9 g of potassium carbonate, 0.04 g of triphenylphosphine, 0.011 g of palladium acetate, 10 ml of toluene and 0.1 ml of water are introduced.

The reaction mixture is heated between 60 and 70°C and stirred for approximately 16 hours at that temperature. When the reaction is completed, the mixture is washed with 100 ml of water and the organic phase is dried with magnesium sulphate and concentrated in the rotary evaporator to dryness to obtain a solid residue, which is purified by column chromatography (eluent: 25 AcOEt/Heptane 1:1). A white solid is obtained (1.87 g, 39.9%).

Example 10. Obtaining ethyl 2-ethoxy-1-[[2'-(1-triphenyltetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate

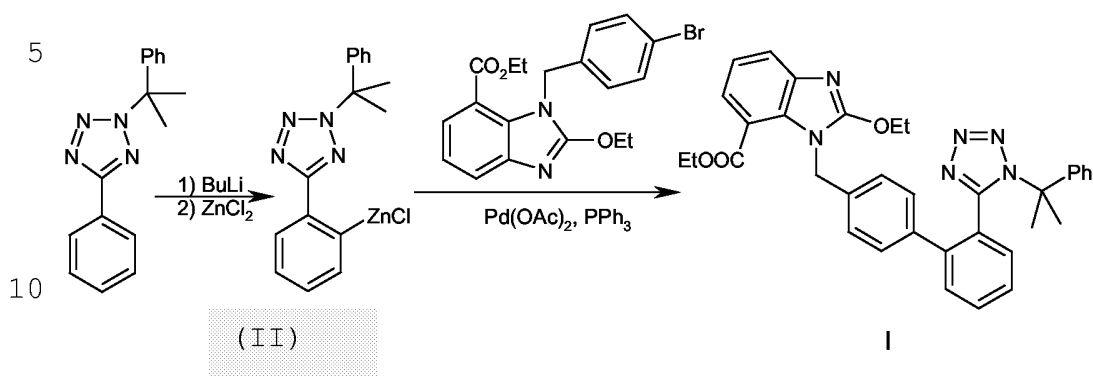
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In a 50 ml capacity flask under nitrogen atmosphere 4.54 g of 2-trityl-2H-tetrazole-5-yl)phenyl boronic acid, 4.03 g of ethyl 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylate, 2.9 g of potassium carbonate, 20 ml of toluene, 0.04 g of triphenylphosphine, 0.011 g of palladium acetate and 0.1 ml of water are introduced.

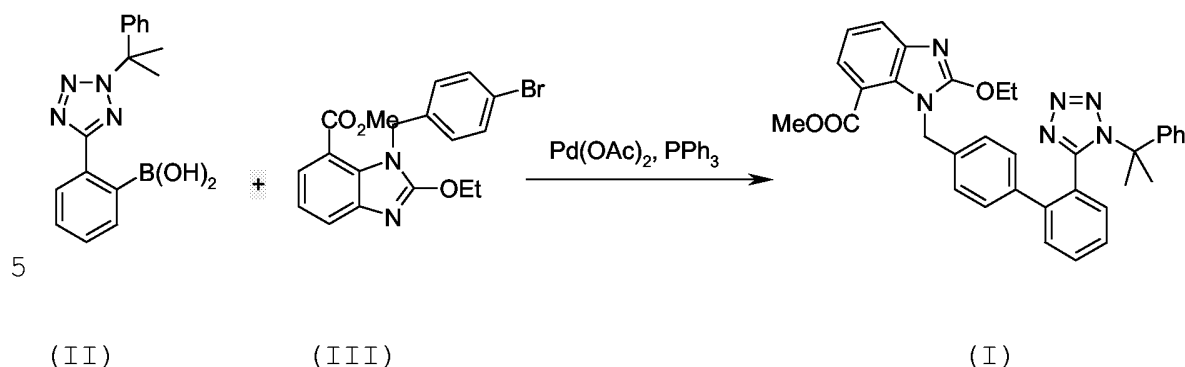
The reaction mixture is heated between 60 and 70°C and stirred for approximately 16 hours at that temperature. When the reaction is completed, the mixture is washed with 100 ml of water and the organic phase is dried with magnesium sulphate. It is then concentrated in the rotary evaporator to dryness to yield a solid residue. This provides 5.07g (71%) of ethyl 2-ethoxy-1-[[2'-(1-triphenyl-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate.

Example 11. Obtaining ethyl 2-ethoxy-1-[[2'-(1-methyl-1-phenyl-ethyl)]-2H-tetrazole-5-yl] [1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate



In a 50 ml capacity flask under nitrogen atmosphere 1.95 g of 2-[(1-methyl-1-phenyl-ethyl)]-5-phenyl-2H-tetrazole is dissolved in 30 ml of THF. The resulting solution is cooled at a temperature between -10 and -5°C and 4.45 ml of a commercial solution of n-BuLi 2.5 M in hexane is added slowly, preventing the temperature rising above 5°C. The resulting solution is maintained at -5°C for 30 minutes, following which a solution of 2.22g of ZnCl₂ in 15 ml of THF is added slowly without exceeding -5°C. The reaction mixture is kept at -5°C for 1 hour. After this time, it is left to attain room temperature steadily. After 4 hours at room temperature, 2.14 g of ethyl 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylate, 0.021 g of palladium acetate and 0.071 g of triphenylphosphine are added to the crude reaction product and heated at THF reflux. Following 12 hours at reflux, the mixture is washed with 20 ml of water and is extracted with 2 x 15 ml of ethyl acetate. The organic phase is dried over magnesium sulphate and concentrated in the rotary evaporator to dryness to provide an oil that contains the desired product in a ratio to the starting product of (1:1).

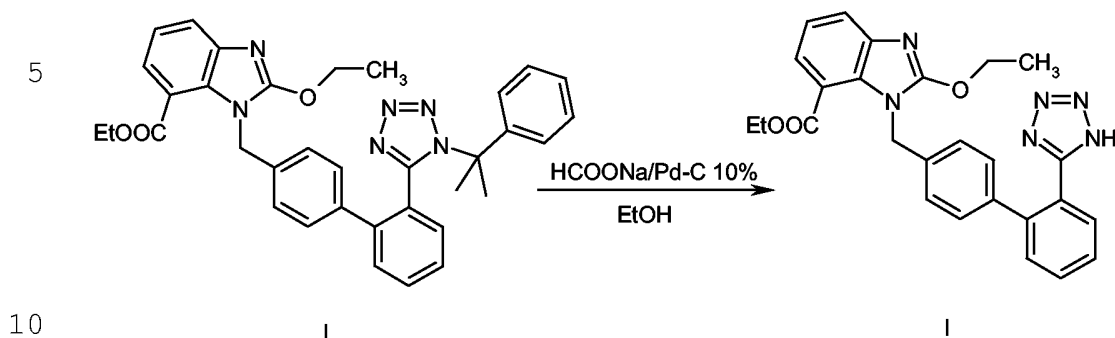
Example 12. Obtaining methyl 2-ethoxy-1-[[2'-(1-methyl-1-phenyl-ethyl)]-2H-tetrazole-5-yl][1,1'-biphenyl]-4-yl)methyl]-1H-benzimidazole-7-carboxylate



In a 250 ml capacity flask under nitrogen atmosphere
 10 14.92 g of 2-[(1-methyl-1-phenyl-ethyl)]-2H-tetrazole-5-yl)phenyl boronic acid, 17.96 g of methyl 1-(4-bromobenzylamine)-2-ethoxybenzimidazole-7-carboxylate, 13.37 g of potassium carbonate, 75 ml of toluene, 0.193 g of triphenylphosphine, 0.052 g of palladium acetate and
 15 1.2 ml of water are introduced.

The reaction mixture is heated between 60 and 75°C and stirred for approximately 18 hours at that temperature. When the reaction is completed, the mixture is washed with 100 ml of water and the organic phase is dried with
 20 magnesium sulphate. It is then concentrated in the rotary evaporator to dryness to yield a brownish oily residue. This provides 26.42 g of methyl 2-ethoxy-1-[[2'-(1-methyl-1-phenyl-ethyl)]-2H-tetrazole-5-yl][1,1'-biphenyl]-4-yl)methyl]-1H-benzimidazole-7-carboxylate.

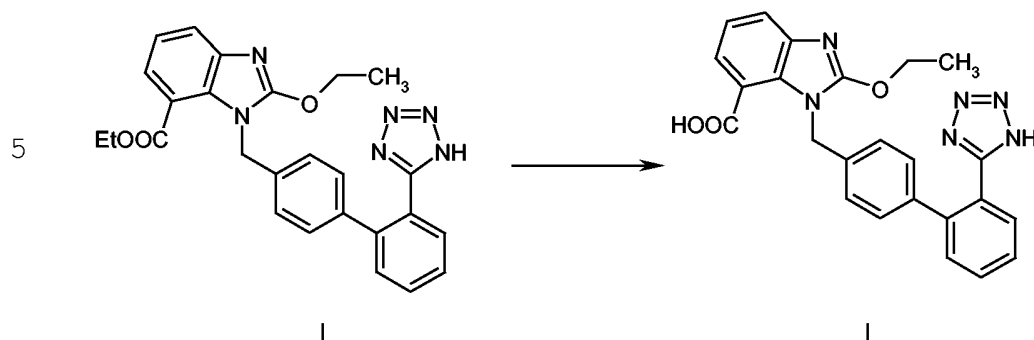
Example 13. Obtaining ethyl 2-ethoxy-1-(2H-tetrazole-5-yl) [1,1'-biphenyl]-4-yl)methyl]-1H-benzimidazole-7-carboxylate



To a solution of 1.2 g of ethyl 2-ethoxy-1-[[2'-(1-methyl-1-phenyl-ethyl)]-2H-tetrazole-5-yl] [1,1'-biphenyl]-4-yl)methyl]-1H-benzimidazole-7-carboxylate in 18 ml of ethanol under nitrogen atmosphere 0.82 g of sodium formate and 0.38 g of Pd-C 10% are added. The resulting reaction mixture is heated at reflux for 3 days, adding 0.41 g of sodium formate every 24 h. The crude product obtained is filtered through cellite and concentrated to dryness in the rotary evaporator to provide an oil. The so

20 obtained oil is suspended in water and washed with ethyl acetate. The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 4-4.5. In the reaction medium a solid is precipitated and filtered, washed with water and dried in a vacuum oven at 40°C,

25 obtaining 0.58 g (60%) of a white solid.

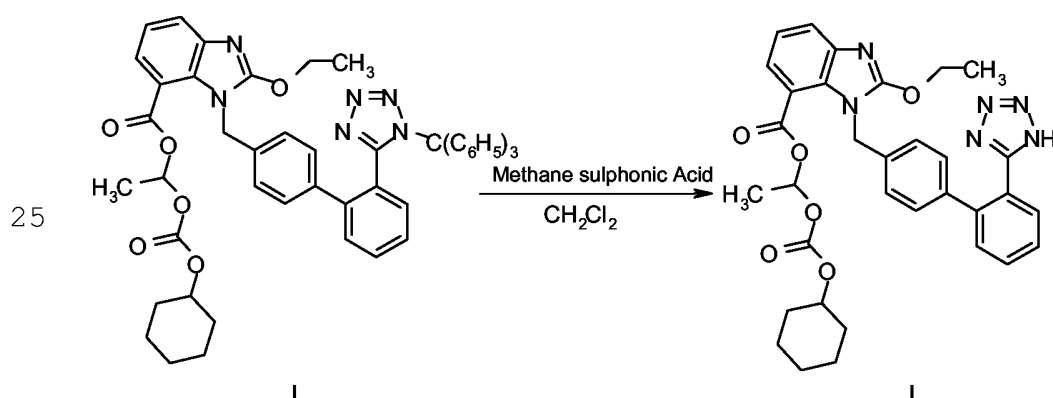
Example 14. Obtaining candesartan

10 3.5 ml of a 2M soda solution is added to a solution of 0.24 g of ethyl 2-ethoxy-1-(2H-tetrazole-5-yl)[1,1'-biphenyl]-4-ylmethyl-1H-benzimidazole-7-carboxylate in 4 ml of ethanol and is heated at reflux for 24 hours. The crude reaction product is adjusted to pH 4-4.5 with

15 concentrated HCl. A solid is precipitated in the reaction medium and then filtered, washed with water and dried in a vacuum oven at 40°C, to obtain 0.18 g (80%) of dry product.

Example 15. Obtaining candesartan cilexetil

20



30 Methane sulphonic acid (62 mg) is added to a solution of cilexetil 2-ethoxy-1-[2'-(trityl)-2H-tetrazole-5-yl][1,1'-biphenyl]-4-ylmethyl-1H-benzimidazole-7-carboxylate (0.42 g), which can be obtained from candesartan according to the method described in examples

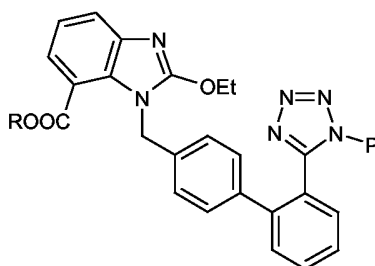
7 and 8 of European patent EP 459.136 B1, in methylene chloride, keeping the temperature between -5 and 0°C. Once the acid has been added, the ice bath is removed and the mixture is stirred for 2 hours at room temperature. When
5 the reaction is completed, cold water and methylene chloride are added and the pH of the resulting mixture is adjusted to approximately 6.3 with a solution of sodium bicarbonate in water 7% (p/v). The aqueous phase is separated and extracted with methylene chloride. The
10 organic phases are combined, washed with water and concentrated at reduced pressure. Acetone is added to the concentration residue and it is concentrated again at reduced pressure. The so obtained solid is recrystallised with ethanol/hexane, filtered and dried under vacuum at
15 40°C. (80% yield).

1

Claims

1. A method for obtaining benzimidazole derivatives of general formula (I):

5



10 wherein:

I

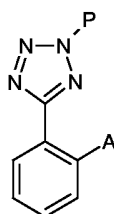
R represents H, methyl, ethyl or cilexetil; and

P represents H, cumyl, diphenylmethyl or trityl;

and pharmaceutically acceptable salts thereof characterised in that

15 a compound of general formula (II):

20



II

wherein:

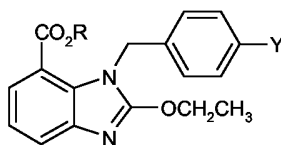
A represents $B(OH)_2$ or ZnX ;

P represents H, cumyl, diphenylmethyl or trityl; and

25 X represents a halogen group,

is reacted with a compound of formula (III):

30



III

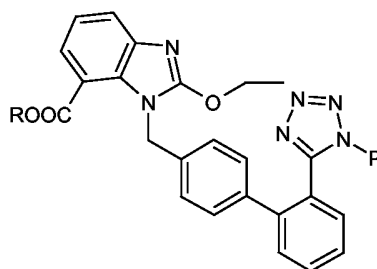
wherein

R represents H, methyl, ethyl or cilexetil; and

Y represents a halogen atom,

in the presence of a palladium catalyst, in an organic solvent to lead to a compound of formula (I):

5



(I)

10 and, if wished or necessary, to convert the product obtained by means of the preceding method into another compound of formula (I) by means of a hydrolysis, esterification, protection and/or deprotection reaction, and, if wished, to convert the compound of formula (I)
15 into a pharmaceutically acceptable salt thereof.

2. A method according to claim 1, characterised in that said palladium catalyst is selected from trans-dichlorobis(triphenylphosphine) palladium (II), tetrakis(triphenylphosphine) palladium (0) and tetrakis
20 (methyldiphenylphosphine) palladium (0).

3. A method according to claim 1, characterised in that said catalyst is generated *in situ* by carrying out the reaction in the presence of palladium acetate and triphenylphosphine.

25 4. A method according to claim 1, characterised in that the organic solvent is an inert aprotic organic solvent.

5. A method according to claim 4 characterised in that said inert aprotic organic solvent is toluene, acetonitrile, THF, dimethoxyethane and N,N-
30 dimethylacetamide.

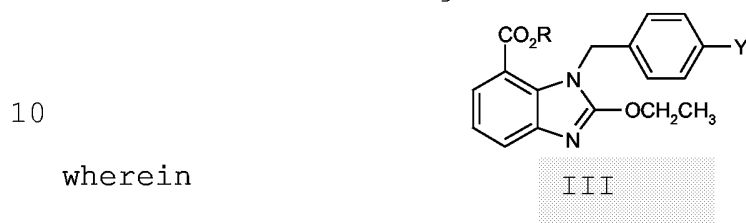
6. A method according to claims 1 to 5, characterised in that the reaction is carried out at a temperature between 30 and 100°C.

7. A method according to claim 6, characterised in that the reaction is carried out at a temperature between 60 and 70°C.

8. A method according to claims 1-7, characterised in that the derivative obtained is candesartan.

9. A method according to claims 1-8, characterised in that the derivative obtained is candesartan cilexetil.

10. Intermediate of general formula (III):



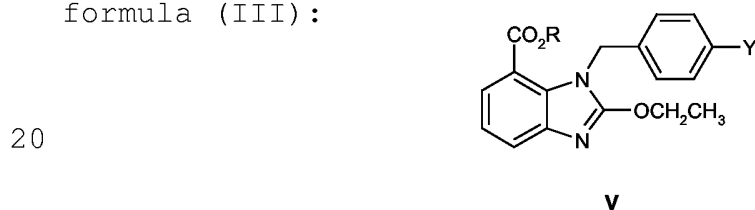
wherein

R is methyl; and

Y represents a halogen atom.

11. Compound methyl 1-(4-bromobenzylamine)-2-ethoxybenzimidazole -7-carboxylate.

12. Method for obtaining an intermediate of general formula (III):



wherein

(III)

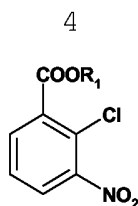
R represents hydrogen, methyl, ethyl or cilexetil;

25 and

Y represents a halogen atom;

characterised in that

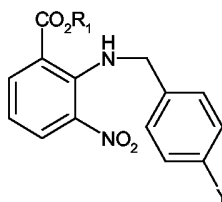
a) a compound of formula (IV):



(IV)

wherein R_1 is methyl or ethyl,

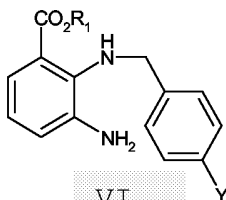
5 is reacted with a 4-halobenzylamine in the presence of a base and an organic solvent, to obtain the compound of general formula V:



V

wherein Y represents a halogen atom,

b) the compound of general formula (V) is submitted to a reduction reaction in an organic solvent to obtain a compound of general formula VI:



VI

and

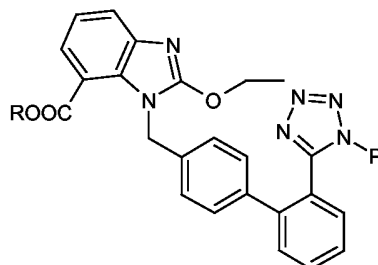
c) the compound of general formula (VI) is reacted with ethyl orthocarbonate in an acid medium to obtain the compound of general formula (III) and, if wished or necessary, convert the product obtained by means of the preceding method into a compound of formula III by means of a hydrolysis and/or esterification reaction.

13. A method according to claim 12, characterised in that in step (a) the solvent is selected from toluene, THF, acetonitrile, DMF, and the base is selected from triethylamine, sodium hydride, potassium carbonate and sodium carbonate.

14. A method according to claim 12 characterised in that step (b) is carried out in the presence of tin chloride as reducing agent, the solvent used is a protic organic solvent, preferably ethanol, and the reaction temperature ranges between 30 and 100°C.

15. A method according to claim 12, characterised in that in step (c) the acid is selected from acetic acid or p-toluene sulphonic acid, the reaction takes place in the absence of solvent or in the presence of solvent, preferably, halogenated hydrocarbons and ethers, at a temperature between 30 and 100°C, preferably between 70 and 80°C.

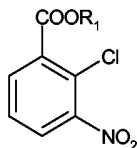
16. A method for obtaining benzimidazole derivatives of formula (I) where R represents H, methyl, ethyl or cilexetil and P represents H, cumyl, diphenylmethyl or trityl;



(I)

and pharmaceutically acceptable salts thereof, characterised in that

a) a compound of formula IV:

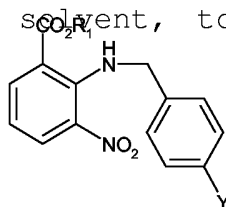


IV

wherein R₁ is methyl or ethyl,

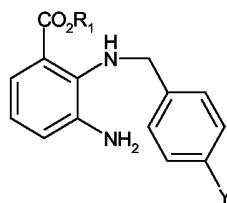
6

is reacted with a 4-halobenzylamine in the presence of a base and of organic solvent, to obtain the compound of formula V:

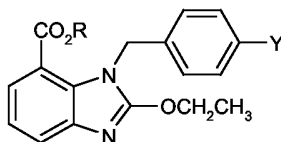
**V**

wherein Y represents a halogen atom,

b) the compound of general formula (V) is submitted to a reduction reaction in an organic solvent to obtain a compound of general formula VI

**VI**

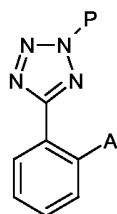
c) the compound of general formula (VI) is reacted with ethyl orthocarbonate in an acid medium to obtain the compound of general formula (III) and, if wished or necessary, convert the product obtained by means of the preceding method into a compound of formula III by means of a hydrolysis and/or esterification reaction;

**III**

wherein R represents hydrogen, methyl, ethyl or cilexetil and Y represents a halogen atom,

d) the compound of general formula (III) is reacted with a compound of formula (II):

7

**II**

5

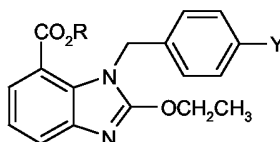
wherein:

A represents $B(OH)_2$ or ZnX , wherein X represents a halogen group, and

10 P represents H, cumyl, diphenylmethyl or trityl, in the presence of a palladium catalyst, in an organic solvent, to lead to a compound of formula (I), and, if wished or necessary, convert the product obtained by the preceding method into another compound of formula (I) by
15 means of a hydrolysis, esterification, protection and/or deprotection reaction, and, if wished, convert the compound of formula (I) into a pharmaceutically acceptable salt thereof.

17. Use of the compound of formula III:

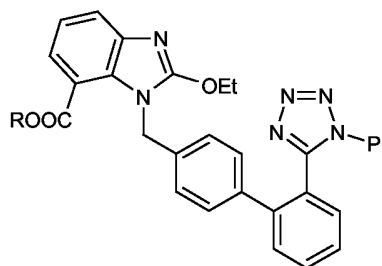
20

**III**

25 where R represents hydrogen, methyl, ethyl or cilexetil and Y represents a halogen atom, for obtaining a benzimidazole derivative of formula (I), according to claims 1-9 or 16,

30

5



I

10 wherein R represents H, methyl, ethyl or cilexetil and P represents H, cumyl, diphenylmethyl or trityl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/063062

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/10 C07D235/26

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

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, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CN 1 510 031 A (SHENHUAXI PHARMACEUTICAL CO., LTD., CHONGQING; CHONGQING SHENGHUAXI PH) 7 July 2004 (2004-07-07) page 9; claims 2,3,5,6	1-11,17
Y	claims 3,6	12-16
Y	EP 0 455 423 A (MERCK & CO. INC; MERCK & CO., INC) 6 November 1991 (1991-11-06) page 2, line 51 - line 56; claim 7; examples 1-12	1-11,17
E	WO 2006/063578 A (RATIOPHARM GMBH; WANG, YAPING; LI, YONGGANG; LI, YULIN; ZHENG, GUOJUN;) 22 June 2006 (2006-06-22) page 1, paragraph 5; claims 1-15,32-36; example 1	1-11,17
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☒ 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

13 October 2006

Date of mailing of the international search report

24/10/2006

Name and mailing address of the ISA/

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Authorized officer

Rufet, Jacques

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/063062

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 459 136 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 4 December 1991 (1991-12-04) cited in the application claims 45-49	1
Y	scheme D, M'; page 17, lines 50-58 -----	12-16
Y	WO 91/16313 A (SMITHKLINE BEECHAM CORP [US]) 31 October 1991 (1991-10-31) scheme 1; pages 10-11; example 3, step (i) -----	12-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/063062

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11,17

Provision of an improved process for the preparation of candesartan and candesartan cilexetil and intermediate compounds of formula (III) thereof

2. claims: 12-16

Alternative process for the preparation of intermediate compounds of formula (III)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/063062

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/063062

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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