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(71) Applicant: **ULKAR KIMYA SANAYII VE TICARET AS** [TR/TR]; Barbaros Bulvari 76-78, Besiktas, 34353 Istanbul (TR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ASLAN, Tuncer** [TR/TR]; Barbaros Bulvari 76-78, Besiktas, 34353 Istanbul (TR). **BICER, Tuba** [TR/TR]; Barbaros Bulvari 76-78, 34353 Besiktas, Istanbul (TR). **GULKOK, Yildiz** [TR/TR]; Barbaros Bulvari 76-78, Besiktas, 34353 Istanbul (TR). **TURHAN, Selda** [TR/TR]; Barbaros Bulvari 76-78, Besiktas, 34353 Istanbul (TR). **KOROGLU, Melek** [TR/TR]; Barbaros Bulvari 76-78, Besiktas, 34353 Istanbul (TR).

(74) Agent: **OZDEMIR, Sinem**; Barbaros Bulvari 76-78, Besiktas, 34353 Istanbul (TR).

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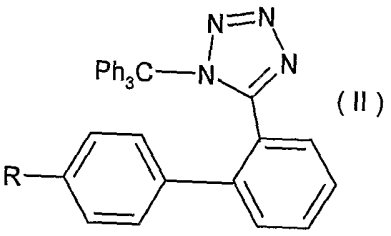
(54) Title: PROCESS FOR PRODUCING BIPHENYL-TETRAZOLE COMPOUNDS



(II)

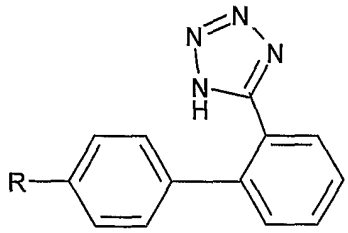
(57) Abstract: A process for producing biphenyl-tetrazole compounds in pure form by deprotecting compounds of the following formula (II): proposes to use acids in an alcohol-ketone-water mixture and/or a mixture of alcohol-alcohol-keton-water to remove the Ph_3C-protecting group.

WO 2006/098705 A1

DESCRIPTION

PROCESS FOR PRODUCING BIPHENYL-TETRAZOLE COMPOUNDS

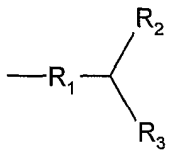
This invention relates to a method for producing biphenyl-tetrazole compounds of the general formula



(I)

Wherein

R is



with

R_1 being a straight chain or branched C_1-C_6-alkyl group; and R_2 and R_3 being the same or different and being selected from

-straight-chain or branched, saturated or unsaturated C_1-C_{20}-alkyl groups, which can optionally be substituted with halogen atoms;

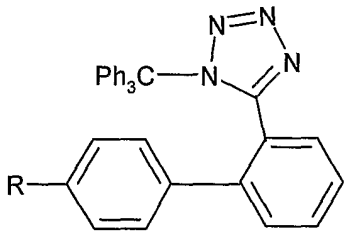
-straight-chain or branched, saturated or unsaturated C_1-C_{20}-heteroalkyl groups, which can optionally be substituted with halogen atoms;

-aromatic or aliphatic C_3-C_{18}-hydrocarbon rings, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings, and halogen atoms;

-aromatic or aliphatic C_3-C_{18}-heterocycles, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings, and halogen atoms;

whereby R_2 and R_3 together can form an aromatic or aliphatic C_3-C_{18}-heterocycle, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings, and halogen atoms;

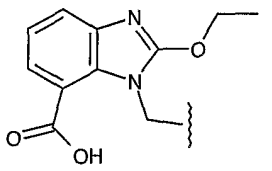
comprising reacting a compound of the following formula



(II)

Wherein R is the same as in Formula (I) with a deprotecting agent in a mixture of solvents in the presence of small amount of water.

The biphenyl-tetrazole compounds of Formula (I) form among others the backbone of a number of known antihypertensive agents, in which R is for example



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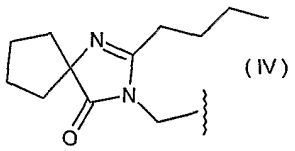

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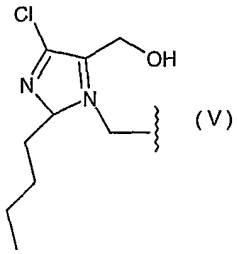

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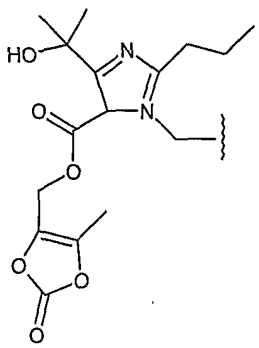

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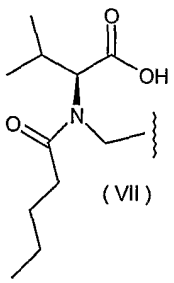
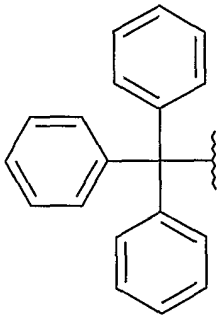


(VII)

Antihypertensive agents comprising such a biphenyl-tetrazole backbone belong to a group of angiotensin II-receptor antagonists which are generally referred to as ''sartans''. Sartans which show such a biphenyl-tetrazole backbone include Candesartan (R is III), Irbesartan (R is IV), Losartan (R is V), Olmesartan (R is VI) and Valsartan (R is VII).

These agents work by blocking the action of angiotensin II on its receptor. Angiotensin II mediates among others smooth muscle contraction especially in blood vessels. Angiotensin II receptor antagonists therefore act as powerful vasodilators.

The compounds of Formula (II) include precursors to the above sartans which are protected by a triphenylmethyl-protecting group. This group is commonly also referred to as a trityl-protecting group and has the following formula



It is generally represented in the above and below formulas as Ph_3C.

The compounds of Formula (II) are formed as intermediates in the synthesis of the corresponding sartans of Formula (I). In a further step, they need to be deprotected in order to form the desired active compounds.

EP 0 733 366 B1 describes the removal of the trityl-protecting group by treating the trityl-protected precursor of Losartan with hydrochloric acid (Example 316). The main problem with this patent is that the given process is very complicated due to the insolubility of the Tritiyl Losartan in methanol in the presence of the aqueous acid and the other sartans will show similar behavior.

It is further known from WO 03/093262 A2 with respect to Losartan that the trityl-

protecting group can be removed using an acid in a diluent comprising a liquid ketone. In this patent either purity of the losartan is low or the reaction time is long. In addition Losartan can react from tetrazole ring with ethyl acetate under acidic conditions to form acetyl losartan.

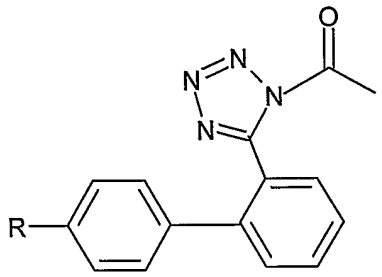
Both these methods have the problem that they use harsh reaction conditions. Larger organic compound further carries the risk of degrading some of the starting and/or target compounds leading impurities which is difficult to remove.

It is therefore an object of this invention to describe a new method for producing biphenyl-tetrazole compounds of Formula (I) from compounds of Formula (II) which can be affected by use a mixture of alcohol-ketone and/or alcohol-alcohol-ketone solvent in the presence of little amount of water.

It is now surprisingly found that if methanol-acetone is used during the deprotection reaction methoxytriphenylmethane is formed instead of triphenylmethanol. The isolation of methoxytriphenylmethane is much easier than former compound due to the polarity difference.

Another object is that formation of methoxytriphenylmethane is not acid depended and always forms in the methanol containing mixtures.

When the compound of the formula (I) is treated with ethyl acetate over a temperature of 40 °C, ethyl acetate can react from tetrazole ring of the compound (I) to form acetyl sartan which is an impurity difficult to separate. A third object of this invention is to treat the compound of the formula (I) with ethyl acetate at a temperature that is below 40 °C to prevent the reaction of the compound (I) with ethyl acetate and to minimize the formation of acetyl sartan. When sartans are treated with ethyl acetate according to the process of this invention; the amount of acetyl sartan impurity is below 0.1%. Treating process of this invention is carried out at a temperature that is below 40 °C, preferably at 20 to 30 °C due to the reaction of the tetrazole ring of the sartans with ethyl acetate to form acetyl sartans as shown in general formula.



Wherin R is the same as in Formula I.

Acetyl sartans is appear as an impurity in the final product and difficult to separate from the final compound by using common purification method like crystallization or extraction.

Any compound act as a source of H^+-ions to remove the trityl-protecting group can be used for the deprotection reaction such as mineral acid like hydrochloric acid, sulfuric acid or hydroxylammonium salts, like hydroxylamine hydrochloride or sulfate. Only one or two equivalent of mineral acid or ammonium salts is used during the deprotection reaction. Because of the low water content of the reaction mixture the reaction proceeds at a more moderate pH value than the agents used in previous examples and results in high yields with easily purified product. Preferably, R_2 and R_3 either together form an imidazole ring, which can be substituted or unsubstituted, part of a fused ring system and partially or fully hydrogenated, or R_2 and R_3 are alkyl residues comprising at least one carboxy or alkoxy group.

R_1 is preferably $-CH_2-$.

Compounds of such a structure are known to show biological activity and therefore are of interest in the synthesis of active ingredients for various pharmaceuticals.

In an embodiment of the invention, the compound of Formula (I) is a compound that shows angiotensin II –receptor antagonistic activity. Preferably, it is selected from the group consisting of Candesartan, Irbesartan, Losartan, Olmesartan and Valsartan, whereby Irbesartan and Losartan are particularly preferred.

Such compounds are powerful vasodilators and antihypertensive agents and therefore are of high commercial interest.

In an embodiment of the invention, the reaction is carried in a mixture of solvents in the presence of small amount of water, the solvents are protic solvents, preferably an alcohol-ketone mixture and/or alcohol-alcohol-ketone mixture, more preferably C_1-C_6 alcohols and C_3-C_6 ketone mixture and especially alcohol selected from the group consisting of methanol, ethanol and isopropanol and especially a ketone selected from the group consisting of acetone, methylisobutylketone and *tert*-butylmethylketone.

It has been shown that for this kind of reaction, protic solvent mixtures, particularly alcohols and ketones, especially mixture of C_1-C_6 alcohols and C_3-C_6 ketones give the best results with regard to yield as well as solubility of all agents involved. Mixtures of methanol/acetone and methanol/isoprapanol/acetone have thereby been shown to be the most suitable solvents.

The use of alcohol-ketone and/or alcohol-alcohol-ketone mixtures as solvent further has the advantage that methoxytriphenylmethane (the compound is characterized by ^{1}H-NMR, ^{13}C-NMR, DEPT and MS) which is formed during the deprotection reaction readily precipitates from such solvent mixtures, further facilitating the purification of the desired product.

In a further embodiment of the invention, the method further comprises isolating formed methoxytriphenylmethane from the solvent preferably by precipitation.

The trityl-protecting group is removed from the biphenyltetrazole compound of the formula (II) in form of methoxytriphenylmethane. The methoxytriphenylmethane is formed by the reaction of the trityl cation formed during the deprotection with methanol present. The isolation of the formed methoxytriphenylmethane from the solvent thereby serves two purposes.

First of all, it helps the purification of the desired deprotected compound of the formula (I) and second it provides a source of methoxytriphenylmethane. The so obtained methoxytriphenylmethane can be easily converted to the tritylchloride and used again in the synthesis of the trityl protected compounds of the formula (II), saving resources and

thus making the process more economical as well as more environmentally friendly.

Precipitation is a particularly preferred method for isolating the formed methoxytriphenylmethane since it can be affected by simply stirring the mixture at room temperature without the need for more complex purification technique such as column chromatography.

In a further embodiment of the invention, an acid is reacted with the compound of formula (II) at a temperature from 20 to 40 °C, preferably from 20 to 25 °C

In an embodiment of the invention, the solvent is a mixture of protic solvents, particularly, alcohols and ketones, preferably a C_1-C_6 alcohol and a C_3-C_6 ketone, and especially an alcohol selected from the group consisting of methanol, ethanol and isopropanol, a ketone selected from the group consisting of acetone, methylisobutylketone, and tert-butylmethylketone.

It has been shown that for this kind of reaction, mixture of protic solvents, particularly alcohol-ketone-water and/or alcohol-alcohol-ketone-water mixture, especially the mixture of C_1-C_6 alcohols and C_3-C_6 ketones, give the best results with regard to yield as well as solubility of all agents involved.

The use of mixture of alcohols and ketones as solvent further has the advantage that methoxytriphenylmethane which is formed during the deprotection reaction readily precipitates from such solvents, further facilitating the purification of the desired product.

In a further embodiment of the invention, the compound of formula (II) is reacted with the any acid like hydrochloric acid, sulfuric acid, hydroxyammonium chloride and sulfate or ammonium salts at a temperature from 20 to 40 °C, preferably from 20 to 25 °C.

When deprotecting larger and potentially unstable organic compounds such as those of formula (II), a balance must be found between the fact that at higher temperatures these compounds have the tendency to degrade, resulting in a lower yield, and the necessity that the temperature is high enough so that the deprotection reaction proceeds within a

reasonable period of time.

It has been found that in the above-named temperature ranges, the reactions can be performed in 1.0 to 4.5 hours while obtaining a good yield.

In a further embodiment of the invention, the compound of formula (II) is reacted with the acids for 1.0 to 4.5 hours, preferably for 1,5 to 3.5 hours.

Since the deprotection reaction involves heating a larger organic compound in the presence of a reactive agent, a longer reaction time is always connected with the risk of degrading large amounts of the starting or the target compound. Too short a reaction time on the other hand will result in an incomplete deprotection.

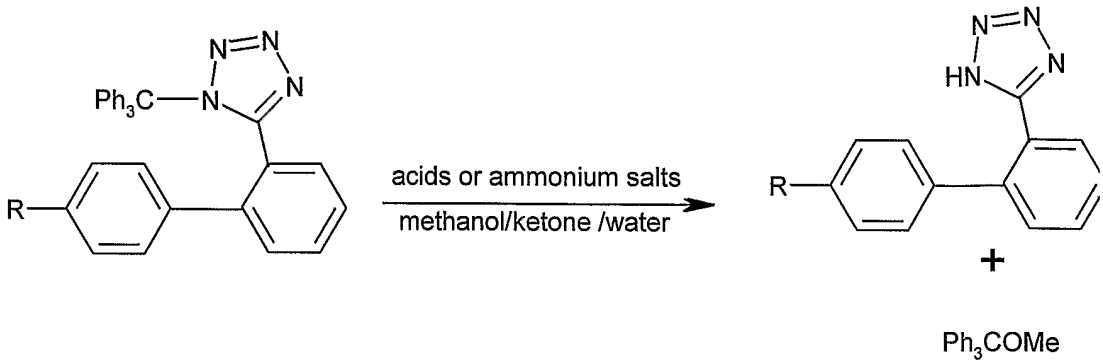
It has been found that in the above-named time ranges a virtually complete deprotection can be achieved while only small quantities of the desired compound are degraded, leading to good yields.

It is understood that the above features and the features described below can be used not only in their described combination but also in other combinations or in isolation without departing from the scope of the invention.

The invention is now further illustrated by means of examples. These examples are not intended to limit the scope of the invention any way.

EXAMPLE 1

General Procedure for the Deprotection of Trityl-Protected Biphenyl-Tetrazole Compounds



A trityl-protected biphenyl-tetrazole compounds of the formula (II) is stirred together with one to four equivalent of mineral acid or ammonium salts in a mixture of methanol/ketone mixture in the presence of little amount of water at 20-40°C. The progress of the reaction is monitored by HPLC and/or TLC. After most of the starting compound with formula (II) is consumed, usually after 1.0 to 4.5 hours, the stirring is stopped: The formed methoxytriphenylmethane is removed by filtration. The pH of the solution is raised by addition of base to a value of 3.5 to 12.5 depending on the molecule. The mixture is concentrated under reduced pressure. For further purification either it is extracted with an apolar solvent or directly precipitated by adding water. The crude product is treated with ethyl acetate to remove trace amount of methoxytriphenylmethanol and help to drying of the final product.

EXAMPLE 2

Preparation of Losartan from Trityl-Protected Losartan by using Hydroxylammonium Chloride

A 2 l 3-necked flask equipped with a reflux condenser and thermometer was charged with 380 g of methanol, 120 g of trityl- losartan, 95 g of acetone, 12 g of water, and 28.8 g of hydroxylammonium chloride at room temperature. The mixture was stirred for 2 hours at this temperature. HPLC analysis showed that 99.5 of trityl protected losartan had been consumed. The resulting slurry was filtered and the filter cake containing precipitated methoxytriphenylmethane was washed with 20 g of methanol and sucked to dryness. Wet methoxytriphenylmethane (70 g) were obtained. The pH of the mixture was adjusted to 3.8-4.2 by adding 50% NaOH solution with external cooling to keep the temperature between 20-25°C.

To remove the salt and precipitate losartan, 80 g of water was added and the mixture was stirred for 1 hour at room temperature and crude losartan was isolated by filtration. For further purification crude losartan was suspended into 290 g of ethyl acetate and the mixture was stirred for 1 hour at 25 to 30 °C. A homogeneous precipitate was obtained, filtered and washed with 20 g ethyl acetate. After drying losartan (72 g) was obtained as a white powder (95 % yield).

^{1}H-NMR (DMSO) δ 7.55 (d, 1H), 7.36 (m, 2H), 7.31 (d, 1H), 7.15 (d, 2H), 6.95 (d, 2H), 5.72 (m, OH), 5.26 (m, 2H), 4.38 (s, 2H), 2.53 (m, 2H), 1.52 (m, 2H), 1.29 (m, 2H), 0.84 (t, 3H). **^{13}C-NMR** (DMSO) δ 161, 147, 141, 140, 135, 132, 131, 130 (2C), 129, 128, 127, 126 (2C), 125, 51, 47, 29, 26, 22, 14.

Proton and Carbon NMR of Methoxytriphenylmethane

^{1}H-NMR (DMSO) δ 7.67 (m, 6H), 7.58 (m, 6H), 7.54 (m, 3), 2.95 (s, 3H). **^{13}C-NMR** (DMSO) δ 144.1 (3C), 128.7 (6C), 128.3 (6C), 127.4 (3C), 86.9, 52.2

Proton and Carbon NMR of Acetyl Losartan

If last purification step in ethyl acetate is carried out over 40°C acetyl losartan is formed as a side product. **^{1}H-NMR** (DMSO) δ 7.62 (d, 2H), 7.56 (m, 1H), 7.50 (d, 1H), 7.06 (d,2H),

6.94 (d, 2H), 5.21 (m, 2H), 4.95 (s, 2H), 2.53 (m, 2H), 1.72 (s, 3H), 1.47 (m, 2H), 1.24 (m, 2H), 0.79 (t, 3H). **^{13}C-NMR** (DMSO) δ 170.6, 149.0, 141.6, 139.3, 136.5, 131.5, 131.3, 131.2, 129.8 (2C), 128.7, 128.4, 126.5, 124.7 (2C), 121.4, 51, 47, 29, 26, 22, 20.9, 14.

EXAMPLE 3

Preparation of Losartan from Trityl-Protected Losartan by using Hydrochloric Acid

A 2 l 3-necked flask equipped with a reflux condenser and thermometer was charged with 380 g of methanol, 120 g of trityl- losartan, 95 g of acetone, and 38.4 g of hydrochloric acid (31 %) at room temperature. The mixture was stirred for 2 hours at this temperature. The mixture was analyzed by HPLC. The analysis showed that 99.2 of trityl protected losartan had been consumed. The resulting slurry was filtered and the filter cake containing precipitated methoxytriphenylmethane was washed with 20 g of methanol and sucked to dryness. Wet methoxytriphenylmethane (73 g) were obtained. The pH of the mixture was adjusted to 3.8-4.2 by adding 50% NaOH solution with external cooling to keep the temperature between 20-25°C. The mixture was concentrated under reduced pressure.

To remove the salt and precipitate losartan 80 g of water was added, the mixture was stirred for 1 hour at room temperature and crude losartan was isolated by filtration. Crude losartan was suspended into 290 g of ethyl acetate and the mixture was stirred for 1 hour at 25 to 30 °C. A homogeneous precipitate was obtained, filtered and washed with 20 g ethyl acetate. After drying losartan (70.5 g) was obtained as a white powder (93 % yield).

EXAMPLE 4

Preparation of Losartan from Trityl-Protected Losartan by using Sulfuric Acid

A 2 l 3-necked flask equipped with a reflux condenser and thermometer was charged with 380 g of methanol, 120 g of trityl- losartan, 95 g of acetone, 12 g of water, and 19.68 g of sulfuric acid (96.5%) at room temperature. The mixture was stirred for 2 hours at this temperature. The mixture was analyzed by HPLC. The analysis showed that 99.1 of trityl

protected losartan had been consumed. The resulting slurry was filtered and the filter cake containing precipitated methoxytriphenylmethane was washed with 20 g methanol and sucked to dryness. Wet methoxytriphenylmethane (71 g) were obtained. The pH of the mixture was adjusted to 3.8-4.2 by adding 50% NaOH solution with external cooling to keep the temperature between 20-25°C. The mixture was concentrated under reduced pressure.

To remove the salt and precipitate losartan 80 g of water was added, the mixture was stirred for 1 hour at room temperature and crude losartan was isolated by filtration. Crude losartan was suspended into 290 g of ethyl acetate and the mixture was stirred for 1 hour at 25 to 30 °C. A homogeneous precipitate was obtained, filtered and washed with 20 g ethyl acetate. After drying losartan (69.2 g) was obtained as a white powder (91.3 % yield).

EXAMPLE 5

Preparation of Irbesartan from Trityl-Protected Irbesartan by using Hydroxylammonium Chloride

A 2 l 3-necked flask equipped with a reflux condenser and thermometer was charged with 380 g of methanol, 120 g of trityl-irbesartan, 95 g of acetone, 12 g of water, and 25.0 g of hydroxylammonium chloride at room temperature. The mixture was stirred for 2 hours at this temperature. The mixture was analyzed by HPLC. The analysis showed that 99.4 of trityl protected irbesartan had been consumed. The resulting slurry was filtered and the filter cake containing precipitated methoxytriphenylmethane was washed with 20 g methanol and sucked to dryness. Wet methoxytriphenylmethane (70 g) were obtained. The pH of the mixture was adjusted to 12.0-12.5 by adding 50% NaOH solution with external cooling to keep the temperature between 20-25°C and then concentrated under reduced pressure.

To remove the salt and precipitate irbesartan, 80 g of water was added and the mixture was stirred for 1 hour at room temperature. Crude irbesartan was suspended into 290 g of ethyl acetate and the mixture was stirred for 1 hour at 25 to 30 °C. A homogeneous precipitate was obtained, filtered and washed with 20 g ethyl acetate. After drying irbesartan (72 g)

was obtained as a white powder (95% yield).

^{1}H-NMR (DMSO) δ 7.65 (m, 2H), 7.55 (m, 2H), 7.05 (s, 4H), 4.64 (s, 1H), 2.25 (m, 2H), 1.80 (s, 4H), 1.62 (m, 4H), 1.42 (m, 2H), 1.23 (m, 2H), 0.76 (m, 3H). **^{13}C-NMR** (DMSO) δ 186.32, 161.92, 155.67, 141.67, 139.06, 136.92, 131.28, 129.93 (2C), 129.10 (2C), 128.51, 126.92 (2C), 124.14, 76.47, 42.87, 37.46, 28.13, 27.21, 26.11 (3C), 22.18, 14.30.

EXAMPLE 6

Preparation of Irbesartan from Trityl-Protected Irbesartan by using Hydrochloric Acid

A 2 l 3-necked flask equipped with a reflux condenser and thermometer was charged with 300 g of methanol, 80 g of isoprapanol, 120 g of trityl- irbesartan, 95 g of acetone, 12 g of water, and 28.8 g of hydroxylammonium chloride at room temperature. The mixture was stirred for 2 hours at this temperature. The mixture was analyzed by HPLC. The analysis showed that 99.5 of trityl protected irbesartan had been consumed. The resulting slurry was filtered and the filter cake containing precipitated methoxytriphenylmethane was washed with 20 g methanol and sucked to dryness. Wet methoxytriphenylmethane (70 g) were obtained. The pH of the mixture was adjusted to 12.0-12.5 by adding 50% NaOH solution with external cooling to keep the temperature between 20-25°C and then concentrated under reduced pressure.

To remove the trace of impurity and precipitate irbesartan, 80 g of water and 80 g of toluene was added and the mixture was stirred for 1 hour at room temperature. The phases were separated and the pH of the aqueous phase is adjusted to 3.8-4.2 by adding HCl. The mixture was stirred for 1 hour at room temperature and crude irbesartan was isolated by filtration. Crude irbesartan was suspended into 290 g of ethyl acetate and the mixture was stirred for 1 hour at 25 to 30 °C. A homogeneous precipitate was obtained, filtered and washed with 20 g ethyl acetate. After drying irbesartan (67 g) was obtained as a white powder (89% yield).

EXAMPLE 7

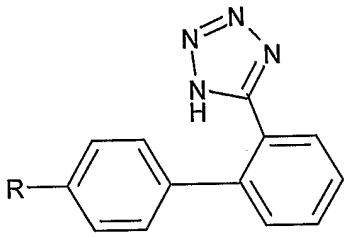
Preparation of Irbesartan from Trityl-Protected Irbesartan by using Sulfuric Acid

A 2 l 3-necked flask equipped with a reflux condenser and thermometer was charged with 380 g of methanol, 120 g of trityl- irbesartan, 95 g of acetone, 12 g of water, and 28.8 g of hydroxylammonium chloride at room temperature. The mixture was stirred for 2 hours at this temperature. The mixture was analyzed by HPLC. The analysis showed that 99.5 of trityl protected irbesartan had been consumed. The resulting slurry was filtered and the filter cake containing precipitated methoxytriphenylmethane was washed with 20 g methanol and sucked to dryness. Wet methoxytriphenylmethane (70 g) were obtained. The pH of the mixture was adjusted to 3.8-4.2 by adding 50% NaOH solution with external cooling to keep the temperature between 20-25°C and then concentrated under reduced pressure.

To remove the trace of impurity and precipitate irbesartan, 80 g of water and 80 g of eter was added and the mixture was stirred for 1 hour at room temperature. The phases were separated and the pH of the aqueous phase is adjusted to 3.8-4.2 by adding sulfuric acid. The mixture was stirred for 1 hour at room temperature and crude irbesartan was isolated by filtration. Crude irbesartan was suspended into 290 g of ethyl acetate and the mixture was stirred for 1 hour at 25 to 30 °C. A homogeneous precipitate was obtained, filtered and washed with 20 g ethyl acetate. After drying irbesartan (68.5 g) was obtained as a white powder (91% yield).

CLAIMS

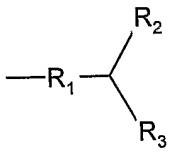
1. Method for producing biphenyl-tetrazole compounds of the general formula



(I)

Wherein

R is



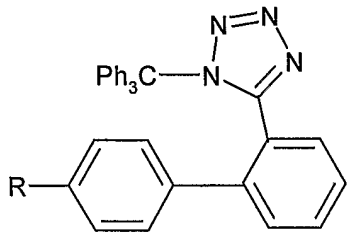
with

R_1 being a straight chain or branched C_1-C_6-alkyl group; and R_2 and R_3 being the same or different and being selected from

- straight-chain or branched, saturated or unsaturated C_1-C_{20}-alkyl groups, which can optionally be substituted with halogen atoms;
- straight-chain or branched, saturated or unsaturated C_1-C_{20}-heteroalkyl groups, which can optionally be substituted with halogen atoms;
- aromatic or aliphatic C_3-C_{18}-hydrocarbon rings, which can optionally be substituted with one or more selected from the group consisting of alkyl,alkenyl,alkynyl, carboxy, hydroxy,amine, nitro, thiol,sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings, and halogen atoms;
- aromatic or aliphatic C_3-C_{18}-heterocycles, which can optionally be substituted with one or more selected from the group consisting of alkyl,alkenyl,alkynyl, carboxy, hydroxy,amine, nitro, thiol,sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings, and halogen atoms;

whereby R_2 and R_3 together can form an aromatic or aliphatic C_3-C_{18}-heterocycle, which can optionally be substituted with one or more selected from the group consisting of alkyl,alkenyl,alkynyl, carboxy, hydroxy,amine, nitro, thiol,sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings, and halogen atoms;

comprising reacting a compound of the following formula



(II)

wherein R is the same as in formula (I), with an acidic deprotecting agent in a mixture of solvents in the presence of small amount of water.

2. Method according to claim1, characterized in that R_2 and R_3 together form an imidazole ring, which can be substituted or unsubstituted, part of a fused ring system and partially or fully hydrogenated.

3. Method according to claim1, characterized in that R_2 and R_3 are alkyl groups comprising at least one carboxy or alkoxy group.

4. Method according to any one of claims 1 to 3, characterized in that R_1 is $-CH_2-$.

5. Method according to any one of claims 1 to 4, characterized in that the compound of formula (I) is a compound that shows angiotensin II-receptor antagonistic activity.

6. Method according to claim 5, characterized in that the compound of formula (I) is selected from the group of consisting of Candesartan, Irbesartan, Losartan, Olmesartan and Valsartan.

7. Method according to claim 6, characterized in that the compound of the formula (I) is selected from the group consisting of Losartan and Irbesartan.

8. Method according to any one of the claims1 to 7, characterized in that the deprotecting agent is an acid.

9. Method according to claims 8, characterized in that the acid is selected from the consisting of hydrogen chloride, hydrogen bromide, sulfuric acid, hydroxylammonium sulfate, hydroxylammonium chloride, ammonium chloride and ammonium sulfate.

10. Method according to any one of the claim 1 to 9, characterized in that the solvent is a mixture of alcohol-keton-water and/or alcohol-alcohol-keton-water.

11. Method according to claim 10, characterized in that the alcohol/alcohols is/are C_1-C_6-alcohols and the ketone is a C_3-C_6 ketone.

12. Method according to claim 11, characterized in that the alcohol/alcohols selected from the group consisting of methanol, ethanol, isopropanol and the ketone is selected from the group consisting of acetone, methylisobutylketone and *tert*-butylmethylketone.

13. Method according to claim 12, characterized in that the alcohol is methanol and/or methanol/isopropanol and the ketone is acetone.

14. Method according to any one of the claims 1 to 13, characterized in that further compressing isolating formed methoxytriphenylmethane from the solvent.

15. Method according to claim 14, the methoxytriphenylmethane is isolated by precipitation.

16. Method according to any one of the claims 1 to 15, characterized in that the compound of formula (II) is reacted with any one of the acid in claim 9 at a temperature from 20 to 40 °C.

17. Method according to any one of the claims 1 to 16, characterized in that the compound of formula (II) is reacted with acid at a temperature from 20 to 25 °C.

18. Method according to any one of claim 1 to 17, characterized in that the compound of formula (II) is reacted with acids for 1 to 4,5 hours.

19. Method according to claim 18, characterized in that the compound of formula (II) is reacted with acids for 1,5 to 3.5 hours.

20. Method according to any one of the claims 1 to 19, characterized in that treating the compound of the formula (I) with ethyl acetate at a temperature that is below 40 °C to prevent the reaction of the compound (I) with ethyl acetate to minimize the formation of acetyl sartan which is an impurity difficult to separate.

21. Method according to claim 20, characterized in that the compound of formula (I) is treated with ethyl acetate at a temperature from 20 to 30 °C.

22. Method according to any one of the claims 1 to 21, characterized in that the amount of acetyl sartan impurity is below 0.1%.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2006/000007

A. CLASSIFICATION OF SUBJECT MATTER
INV. 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)
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, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 733 366 A (DU PONT) 25 September 1996 (1996-09-25) cited in the application examples 92C,315C,316C	1-22
A	WO 03/093262 A (TEVA PHARMACEUTICAL INDUSTRIES) 13 November 2003 (2003-11-13) cited in the application claims; examples	1-22
A	US 2004/224998 A1 (KUMAR ET. AL.) 11 November 2004 (2004-11-11) claims; examples	1-22
A	WO 2004/007482 A (TEVA PHARMACEUTICAL INDUSTRIES) 22 January 2004 (2004-01-22) claims; examples	1-22

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

[X] See patent family annex.

* Special categories of cited documents :

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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
19 June 2006	26/06/2006

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	Helps, I

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INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2006/000007

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/111021 A (TEVA PHARMACEUTICAL INDUSTRIES) 24 November 2005 (2005-11-24) page 4, line 16 - line 24; claims; examples	1-22
E	WO 2006/050922 A (LEK PHARMACEUTICALS) 18 May 2006 (2006-05-18) claims; examples	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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