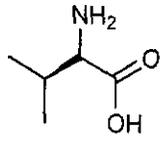
Abstract

The present invention relates to an improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl) biphenyl-4-yl) methyl] N-valeryl-(L)-valine benzylester. More particularly, the present invention relates to an improved, cost effective and industrially feasible in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl) biphenyl-4-yl) methyl] N-valeryl-(L)-valine benzylester from L-valine.

We claim,

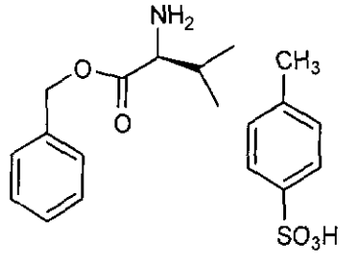
1. An improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester of Formula (I) ,comprising;

   a) reacting L-valine of Formula (II)



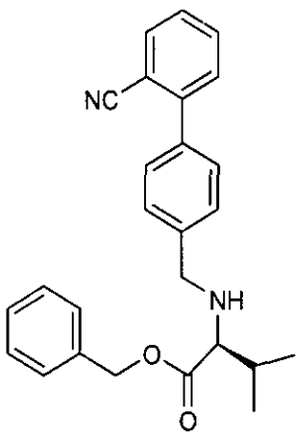
Formula II

with benzyl alcohol in presence of an organic acid such as para-toluene sulphonic acid and aromatic solvent selected from toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (III), which is further brought into aqueous layer



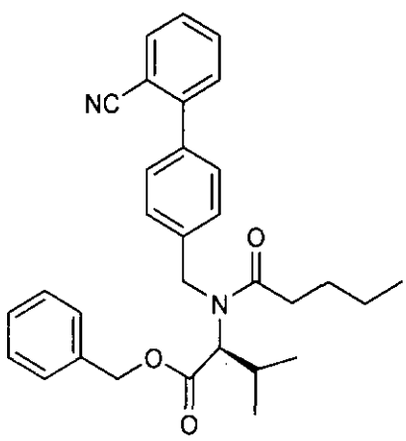
Formula III

   b) followed by reacting aqueous layer obtained in step a) containing compound of Formula (III) with 2-cyano-4'-bromomethylbiphenyl (herewith referring as Br-OTBN) in presence of a base and phase transfer catalyst in aromatic solvent selected from toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (IV)



Formula IV

c) followed by reacting organic layer obtain in step b) containing compound of Formula (IV) with valeroyl chloride in presence of base to obtain compound of Formula (V)



Formula V

d) followed by reacting the organic layer obtained in step c) containing compound of Formula (V) with sodium azide in presence of tributyl tin chloride to obtain Valsartan intermediate of Formula (I)

2. The process as claimed in claim 1, wherein intermediate compounds of Formula (III), (IV) and (V), obtained in step a), step b) and step c) respectively are not isolated

3. The process as claimed in claim 1, wherein step a), step b), step c) and step d) reactions are carried out in only one aromatic solvent such as toluene, o-xylene or mono-chlorobenzene, more preferably mono chlorobenzene is used

4. The process as claimed in claim 1, wherein the base used in step b) and step c) is selected from alkali metal hydroxides or alkali metal carbonates, wherein the alkali metal hydroxides such as sodium hydroxide, potassium hydroxide are used and the alkali metal carbonates such as potassium carbonate, sodium carbonate are used, preferably base used is potassium carbonate

5. The process as claimed in claim 1, wherein the phase transfer catalyst used in step b) is selected from quaternary ammonium salts selected from tetra butyl ammonium bromide (TBAB), triethyl benzyl ammonium chloride (TEBA) or PEG like PEG 400 , preferably it is TBAB

6. The process as claimed in claim 1, wherein in-situ process of the present invention is carried out at temperature ranging from 20 to 150°C

7. The process as claimed in claim 1, wherein molar ratio of Br-OTBN to compound of Formula (III) in step b) is in the range of 1: 1, preferably it is 0.91:1

8. The process as claimed in claim 1, wherein the molar ratio of valeroyl chloride to compound of Formula (IV) in step c) is in the range of 2: 1, preferably it is 1.6:1.

Dated this 8th day of July, 2013

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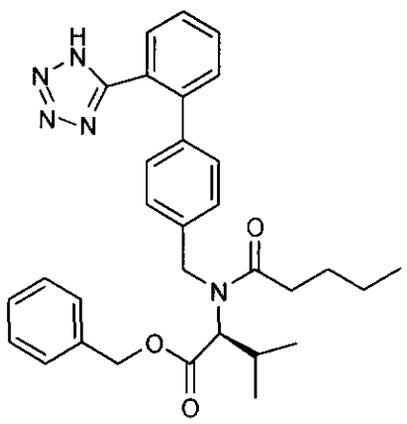
(Applicant)

FIELD OF THE INVENTION

The present invention relates to an improved, simple and cost-effective in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester (Formula I).

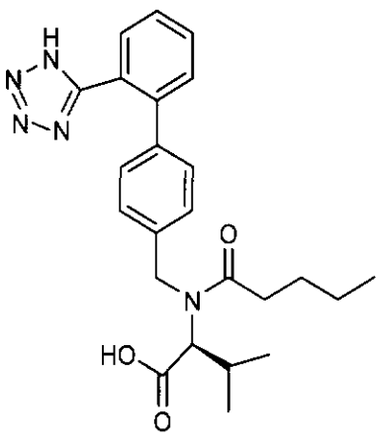


Formula I

More particularly, the present invention provides an improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester of Formula (I) from L-valine thereby avoiding isolation of intermediates.

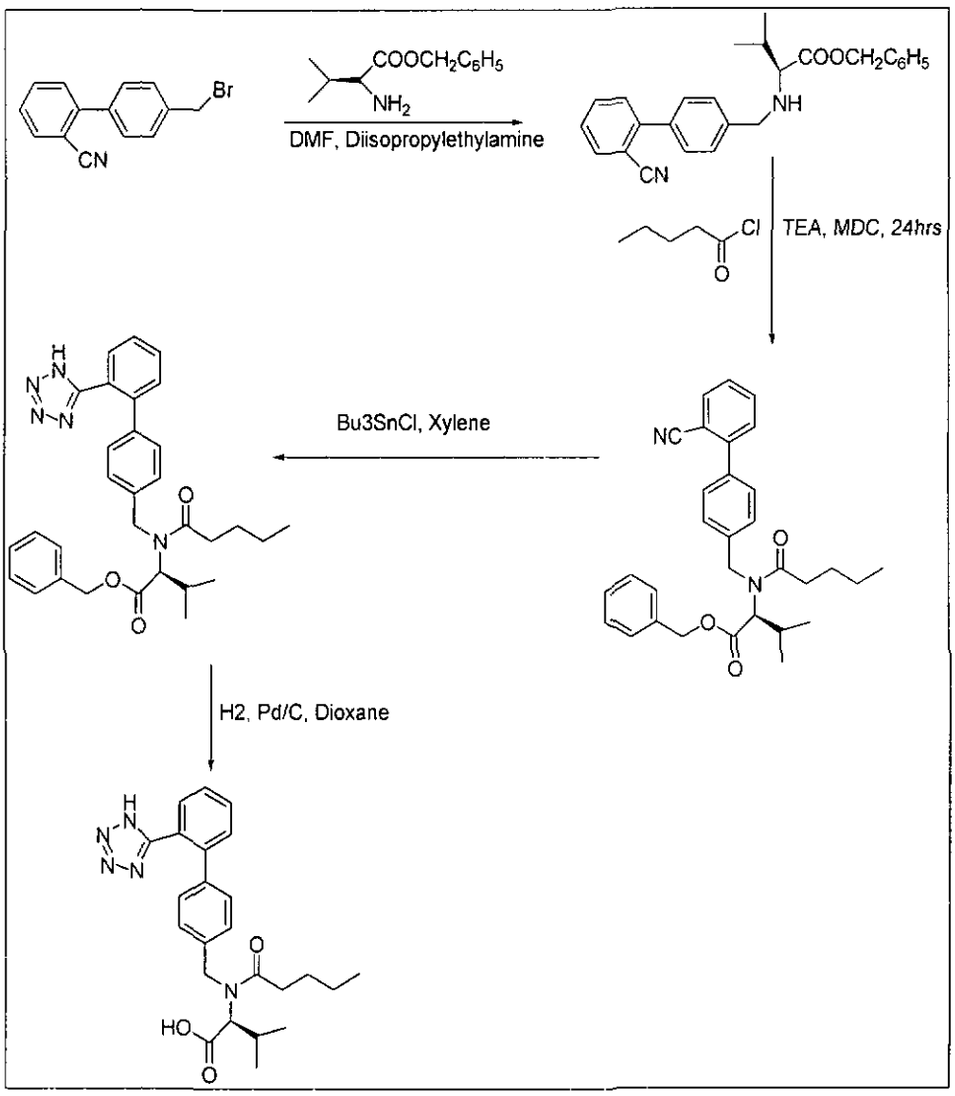
BACKGROUND OF THE INVENTION

Valsartan also known as (*S*)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentonyl-N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]amine (Formula VI) is an orally active specific angiostenin II antagonist acting on the AT1 receptor subtype. Valsartan is prescribed for the treatment of hypertension and related conditions.



Formula VI

Valsartan (Formula VI) was first disclosed in US 5399578. The synthesis of Valsartan and its intermediates as reported in patent US 5399578 and Bioorganic and Medicinal Chemistry Letters, (4), 29-34, 1994 is as shown in Scheme I below



Scheme I

The drawbacks of the process disclosed above includes

i) the crude form of intermediate obtained in most of steps was carried forward in next step without purification. Hence, the final product i.e. Valsartan was therefore strongly contaminated and required multiple crystallization.

ii) the processes described are time consuming and industrially less feasible.

iii) hazardous chemicals like THF and pyridine are used.

iv) use of diisopropylethylamine, which is reported to lead to the formation of impurities.

WO 2009125416 describes the preparation of N-[2'-cyano [1,1biphenyl]-4-yl)methyl](L)-valine benzylester or its acid salt. The process comprises of reacting L-valine benzyl ester and 4-bromomethyl-2-cyanobiphenyl in presence of base in organic solvent and further maintaining the reaction mass for at least 3h at about 40-140°C followed by isolating the compound obtained or converting it into its acid salt. Thus the process includes a tedious and additional salt formation step, thereby making the process industrially less feasible.

Organic Process Research and Development, 2007, 11, 892-898 discloses the new synthesis process for Valsartan. The first two steps of the process are mainly modified. The alkylation of L-valine benzyl ester with 4-bromomethyl-2-cyanobiphenyl is performed under homogenous condition. The reaction is carried out in xylene in presence of aqueous sodium hydroxide as a base. The product is then acylated with valeroyl chloride in xylene in presence of aqueous sodium hydroxide acting as a base.

EP 1714963 describes a process for the preparation of Valsartan by reacting 4-bromomethyl-2-cyanobiphenyl with tosylate salts of L-valine benzyl ester in the presence of solvent system containing toluene or xylene and water. The reaction is carried out by heating the reaction mixture to 50°C -55°C for 24 hr in the presence of potassium carbonate and tetrabutylammonium bromide followed by acidification with hydrochloric acid to obtain N-[2'-cyano [1,1biphenyl]-4-yl)methyl](L)-valine benzylester as a hydrochloric salt with 97% purity. The salt is further treated to aqueous sodium bicarbonate in toluene. The free base obtained is subjected to acylation with valeroyl chloride to obtain benzyl Valsartan. The compound is isolated with 96% purity and further treated with tributyl tin chloride followed by deprotection of benzyl group to get Valsartan. The patent also emphasis on the purification of benzyl Valsartan in order to obtain pure Valsartan free from its organo tin impurities.

Thus, it has been seen in the prior art, all processes explained above suffers from several drawbacks. The processes involve tedious isolation practices, longer reaction time. The processes also involve many disadvantages from the point of view of its yield and purity. Major problem arising from these processes is the contamination of Valsartan with a number of impurity or starting material/intermediates.

Thus, there is a necessity for an improved process for the production of Valsartan and its intermediate which can be economical and industrially beneficial thereby avoiding tedious workup procedure, isolation of intermediates and long reaction time. In other words, the known processes are lengthy and involve tedious isolation process which makes them costly and difficult to handle on large scale and environment unfriendly.

The inventors of the present invention have developed an in-situ process for the preparation of an intermediate of Valsartan, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester of Formula (I) from L-valine whereby the problems associated with the prior art methods are avoided. Also, the process of the present invention is simple, cost effective, avoiding tedious isolation and crystallization of intermediates, less time consuming and environmental friendly.

OBJECT OF THE INVENTION

a) An object of the present invention is to provide an improved, simple and cost-effective in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzyl ester of Formula (I) from L-valine thereby avoiding isolation of intermediates.

b) An object of the present invention is to provide an improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-

yl)methyl]N-valeryl-(L)-valine benzylester of Formula (I) with reduced parameters and utility simplification.

c) Another object of the present invention is to provide an improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester of Formula (I) with good yield and purity.

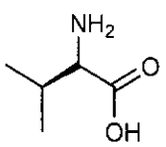
d) Another object of the present invention is to provide a simple, economic, environment friendly and industrially viable in-situ processes for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl- (L)-valine benzylester of Formula (I).

SUMMARY OF THE INVENTION

According to an aspect of the present invention there is provided an improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester of Formula (I) from L-valine

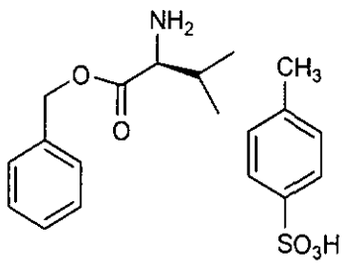
comprising;

a) reacting L-valine of Formula (II)



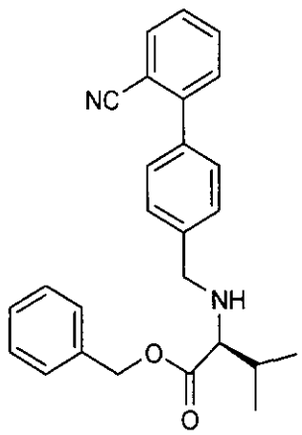
Formula II

with benzyl alcohol in presence of an organic acid such as para-toluene sulphonic acid and aromatic solvent such as toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (III), which is further brought into the aqueous layer



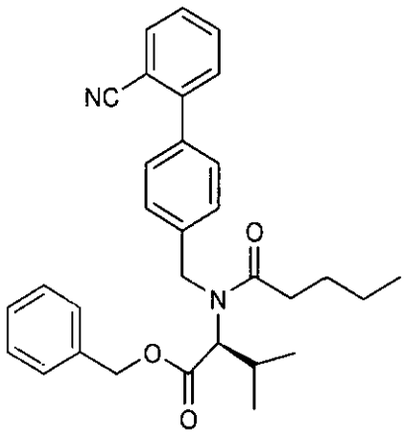
Formula III

b) followed by reacting aqueous layer obtained in step (a) containing compound of Formula (III) with 2-cyano-4'-bromomethyl biphenyl (herewith referring as Br-OTBN) in presence of a base and phase transfer catalyst in aromatic solvent such as toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (IV)



Formula IV

c) followed by reacting organic layer obtained in step (b) containing compound of Formula (IV) with valeroyl chloride in presence of base to obtain compound of Formula (V)



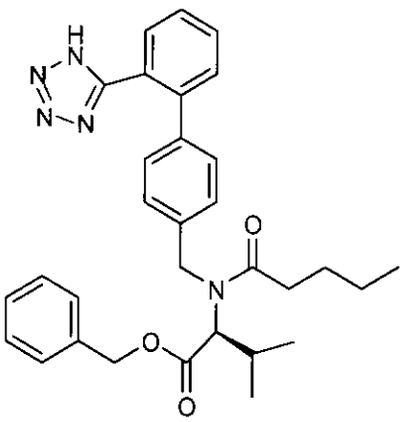
Formula V

d) followed by reacting the organic layer obtained in step (c) containing compound of Formula (V) with sodium azide in presence of tributyl tin chloride to obtain Valsartan intermediate of Formula (I).

Thus, the process of the present invention is carried out in-situ and without isolating intermediates at any steps. This makes the process economical by reducing the solvent volumes concerned with isolations and purifications of individual intermediates and overall cost. Also the process is simple and industrially feasible.

DETAILED DESCRIPTION OF THE INVENTION

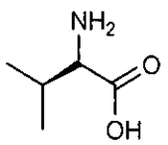
The present invention relates to an improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzyl ester of Formula (I).



Formula I

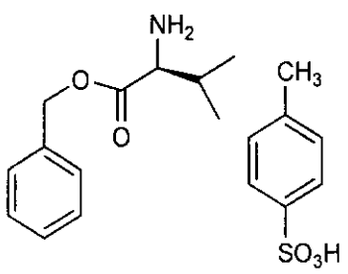
According to an aspect of the present invention there is provided an improved in-situ process for the preparation of Valsartan intermediate of Formula (I), comprising;

a) reacting L-valine of Formula (II)



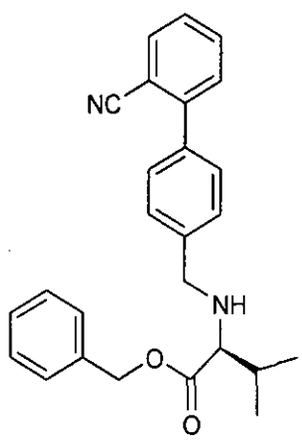
Formula II

with benzyl alcohol in presence of an organic acid such as para-toluene sulphonic acid and aromatic solvent such as toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (III), which is further brought into aqueous layer



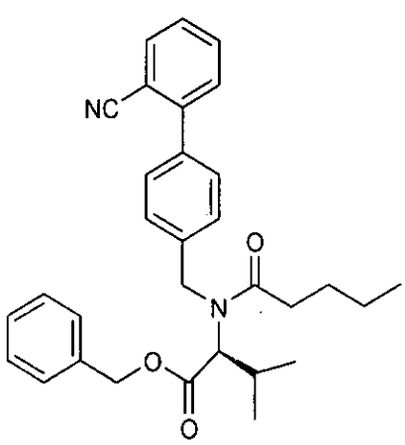
Formula III

b) followed by reacting aqueous layer obtained in step a) containing compound of Formula (III) with 2-cyano-4'-bromomethylbiphenyl (herein after referred as Br-OTBN) in presence of a base and phase transfer catalyst in aromatic solvent such as toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (IV)



Formula IV

c) followed by reacting organic layer obtain in step b) containing compound of Formula (IV) with valeroyl chloride in presence of base to obtain compound of Formula (V)



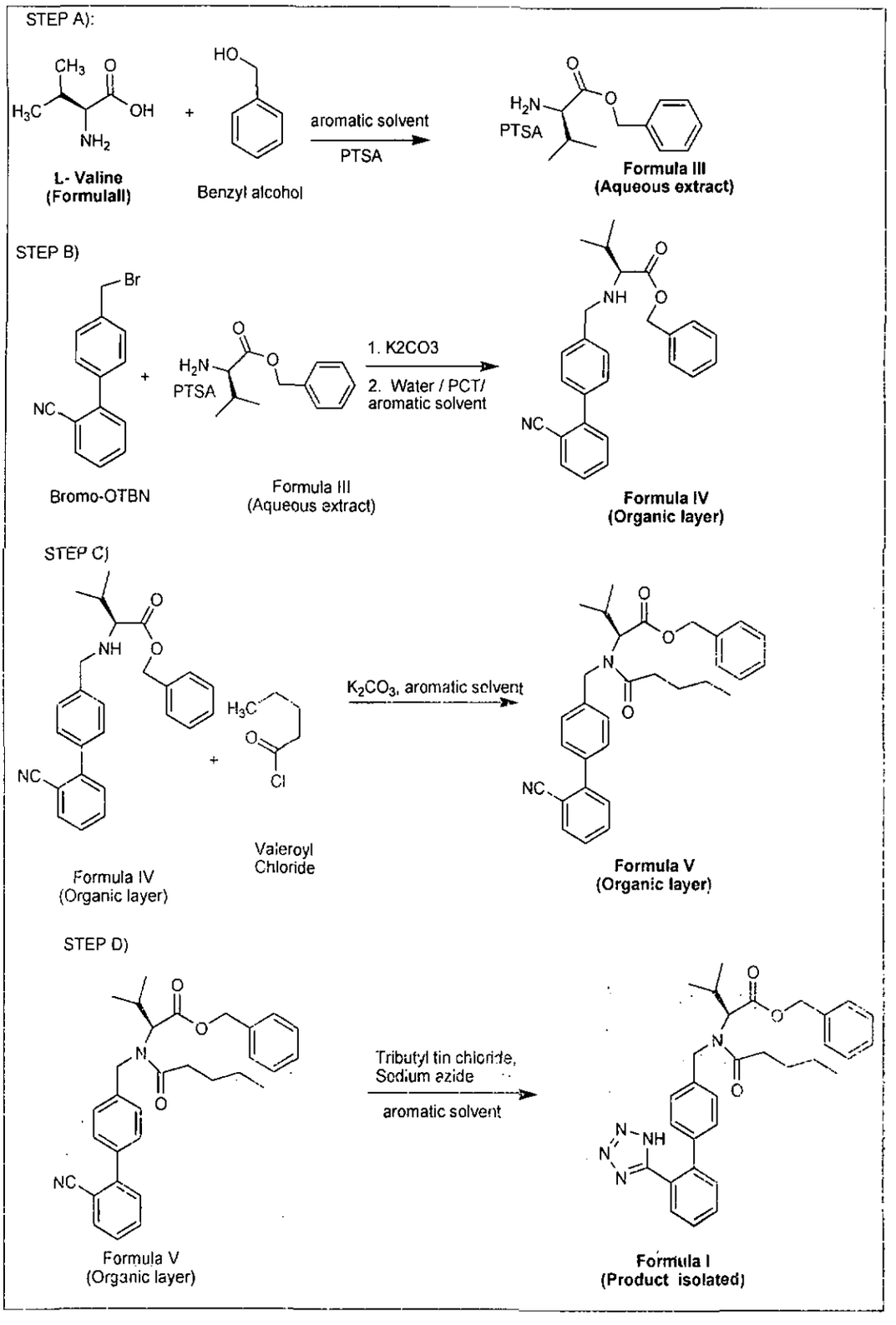
Formula V

d) followed by reacting the organic layer obtained in step c) containing compound of Formula (V) with sodium azide in presence of tributyl tin chloride to obtain Valsartan intermediate of Formula (I).

In another aspect, the in-situ process of the present invention avoids isolation of intermediates, compound of Formula (III), (IV), and (V). Thus, process of the present invention avoids the tedious work up process involving additional organic solvents, drying and concentrating organic phase etc. The process also avoids the crystallization of intermediates obtained at each step which further minimizes the overall use of solvent.

According to an embodiment of the present invention, the step a), step b), step c) and step d) are carried out in only one aromatic solvent selected from toluene, o-xylene or mono-chlorobenzene, more preferably in mono chlorobenzene.

The in-situ process of the present invention for the synthesis of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzyl ester of Formula (I) is as shown in the Scheme II herein below,



Scheme II

As shown in Scheme II, in-situ process of the present invention involves step a) reaction of L-valine of Formula (II) with benzyl alcohol in presence of para-toluene sulphonic acid and aromatic solvent such as toluene, o-xylene or mono-chlorobenzene at reflux temperature for 11-12 hrs. During the reaction water is removed azeotropically. After completion of reaction, organic layer is extracted with water and aqueous layer is separated. Aqueous layer containing compound of Formula (III) is taken as such for step b).

In step b), first base is added to the aqueous layer obtained in step a) containing compound of Formula (III) followed by addition of the same aromatic solvent as used in step a). To this reaction mixture then added Br-OTBN and phase transfer catalyst. The reaction is carried out for 2-5 hrs. After completion of reaction organic layer containing compound of formula (IV) is separated from aqueous layer and used as such for step c).

In step c) , aqueous solution of base is added to the organic layer obtained in step b) containing compound of Formula (IV) followed by addition of valeroyl chloride at 0-5°C and then reaction is carried out at 20-35°C. After completion of reaction water is added and organic layer is separated. Separated organic layer is first treated with (2N) HCl and then with (10%) sodium bicarbonate followed by separating aqueous layers. Organic layer containing compound of Formula (V) is then washed with water and taken as such for step d).

In step d), organic layer obtained in step c) containing compound of Formula (V) is first dried by azeotropic distillation of which part of the solvent is distillated at 130-135°C to make it free from moisture and then treated with tributyl tin chloride and sodium azide to obtain compound of Formula (I). After completion of the reaction compound of Formula (I) is isolated by usual known procedures.

Overall, the step a), step b), step c) and step d) as depicted in Scheme II are carried out by in-situ process whereby isolation of intermediates of Formula (III), (IV) and (V) are avoided.

According to an embodiment of the present invention, the molar ratio of the Benzyl alcohol with respect to L-valine of Formula (II) is in the range of, 3.5:1 preferably it is 3:1

According to another embodiment of the present invention, the molar ratio of the para-toluene sulphonic acid with respect to L-valine of Formula (II) is in the range of 1.5:1; preferably it is 1.2: 1

According to another embodiment of the present invention, the volume of aromatic solvent used for the step a) is up to 15 equivalents, preferably it is 11 equivalents.

According to another embodiment of the present invention, step a) reaction is carried out at reflux temperature ranging from 110 to 140°C, preferably the reaction is carried out at temperature ranging from 116 to 140°C.

According to another embodiment of the present invention, the molar ratio of Br-OTBN to compound of Formula (III) is in the range of 1: 1, preferably it is 0.91:1.

The base used in step b) and step c) is selected from alkali metal hydroxides or alkali metal carbonates, wherein the alkali metal hydroxides such as sodium hydroxide, potassium hydroxides are used and the alkali metal carbonates such as potassium carbonate, sodium carbonate are used, preferably base used is potassium carbonate.

The phase transfer catalyst used in step b) is selected from quaternary ammonium salts selected from tetra butyl ammonium bromide (TBAB), triethyl benzyl ammonium chloride (TEBA) or PEG like PEG 400, preferably it is TBAB.

According to another embodiment of the present invention, the molar range of quaternary ammonium salt to L-valine benzyl ester of Formula (III) is in the range of 6 to 10% of L-valine benzyl ester of Formula (III); preferably it is 6.50% with respect to L-valine benzyl ester of Formula (III).

According to another embodiment of the present invention, the step b) reaction is carried out at temperature ranging from 40 to75°C, preferably the reaction is carried out at temperature ranging from 60 to 70°C.

According to another embodiment of the present invention, the molar ratio of valeroyl chloride to compound of Formula (IV) is in the range of 2: 1, preferably it is 1.6:1.

According to another embodiment of the present invention, step c) is carried out at temperature ranging from 20°C to 35°C, preferably from 20°C to 30°C for 3 to 5 hours, preferably for about 3 to 4 hours.

According to another embodiment of the present invention, the molar ratio of tributyl tin chloride to compound of Formula (V) is in the range of 2:1, preferably it is 1.74: 1.

According to another embodiment of the present invention, the molar ratio of sodium azide to compound of Formula (V) is in the range of 3:1 to 6:1; preferably it is 3:1

According to another embodiment of the present invention, step d) is carried out at temperature ranging from 115°C to 145°C, preferably from 120°C to 140°C for 6 to 25 hours, preferably for about 6 to 24 hours.

Thus, in-situ process of the present invention for preparation of Valsartan intermediate of Formula (I) avoids the tedious isolation and crystallization process at each step. It also minimizes the use of solvent volume. Hence, it is cost-effective, environmental friendly and industrially viable process.

Valsartan intermediate of Formula (I), obtained by in-situ process of the present invention is then converted to Valsartan or its salts by any process as known in the art.

The detail of the invention provided in the following examples is given by the way of illustration only and should not be construed to limit the scope of the present invention.

EXAMPLES

Example: In-situ preparation of N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester (Formula I) comprising,

Step a) Preparation of L-valine Benzyl ester toluene sulphonate (Formula III) from L-valine (Formula II)

To 1000 mL of mono chlorobenzene (MCB) was added 100 gm of L-valine and the turbid solution was stirred at 25-30°C for 5 mins. To the turbid solution was added 276.93 gm of benzyl alcohol followed by 194.87 gm of para-toluene sulphonic acid (PTSA). The reaction mixture was stirred further heated to refluxing temperature simultaneously distilling out water by azeotropic distillation. The reaction mixture was heated for 11-12 hrs at 116-120 °C. On

completion of reaction (monitored by TLC-mobile phase: Acetonitrile: Acetic acid 9:1), the reaction mixture was cooled to 75-80°C. Organic matter was repeatedly extracted with hot water (5 x 100 mL). Aqueous layer containing tosylate salt of L-valine (about 280gm) was collected and taken up for step b).

Step b) In-situ preparation of N-[2'-cyano-(1,1-biphenyl)-4yl] methyl-L-valine benzyl ester (Formula IV) from L-valine Benzyl ester toluene sulphonate (Formula III)

To 280 mL of aqueous layer of step a) was added 283 gm of K_2CO_3 and was stirred for 15 mins at 25-30°C followed by addition of 855 mL of mono chlorobenzene (MCB). To the mixture was further added lot wise 186.10 gm of Br-OTBN under stirring at 25-35°C. 18 gm of TBAB was added to the reaction mixture and further stirred for 15 mins at 30-35°C. The reaction mixture was slowly heated to 65-70°C and maintained for 4-5 hrs. On completion of reaction (checked by HPLC), the reaction mixture was cooled to 25-35°C. The layers were subjected to separation. The upper aqueous layer was extracted with 100 mL MCB. Combined organic MCB layer (300gm) was further taken up directly for step c) . HPLC result of the organic layer showed Br-OTBN not more than 1%.

step c) In-situ preparation of N-[2'-cyano-(1,1-biphenyl)-4yl]methyl-N-valerol-L-valine benzyl ester (Formula V) from N-[2'-cyano-(1,1-biphenyl)-4yl] methyl-L-valine benzyl ester (Formula IV)

To the organic layer of step b) was added solution of K_2CO_3 (156 gm of K_2CO_3 dissolved in 740 mL of water) at 10-15°C and stirred for 30 mins. The reaction mixture was cooled to 0-5°C. To the cooled reaction mixture was added dropwise 145 gm of valeroyl chloride. The reaction mixture was further stirred at 20-35°C for 3-4 hrs. On completion of reaction (checked by HPLC, wherein step b) compound was not more than 1%), 285 mL of water was added to the reaction mixture and was stirred at 20-25°C for 30 mins. The organic layer and aqueous

layer were separated. To the organic layer was added 200 mL of 2N HCl and the reaction mixture was stirred for 30 mins at 20-25°C. The layers were separated. The organic layer was further washed with 150 mL of 10% sodium bicarbonate. The layers were subjected to separation. The organic layer was finally washed with 286 mL of water and taken up directly for next step d).

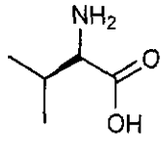
step d) In-situ preparation of N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester (Formula I) from N-[2'-cyano-(1,1-biphenyl)-4yl]methyl-N-valerol-L-valine benzyl ester (Formula V)

The organic layer of step c) was subjected to drying by heating at 132-136°C and distilling out 50-150 mL of mono chlorobenzene (MCB). The organic layer was cooled to 45-50°C. To the dried organic layer (free from moisture), were added 425 gm of tributyl tin chloride and 293 gm of sodium azide. The reaction mixture was heated at 120-140°C for 6 to 24 hrs. On completion of reaction (checked by HPLC, wherein Step c) compound was not more than 5%), the reaction mixture was cooled to 10-15°C. To the cooled reaction mixture was added 2140 mL of water followed by 311 gm of sodium nitrite. Reaction mixture was stirred at 10-15°C for 15 mins. Separation of layers was carried out. Aqueous layer was extracted with 425 mL of mono chlorobenzene (MCB). To the combined MCB layer was further added 143 mL of HCl adjusting pH of reaction mass up to 1-2 at 10-15°C. After 15 mins of stirring, layers were separated. Organic layer was washed with 100 mL of water and further subjected to distillation under vacuum at 60°C. To the residue obtained was added 230 mL of ethyl acetate. The mixture was heated at 60-65°C followed by cooling of reaction mass up to 20-25°C for 3hrs. Precipitation of solid is observed. The slurry was further cooled to 0 to 5°C for 5hrs. The solid obtained was further filtered and washed with 170 mL of toluene in order to remove traces of tin compound. The wet cake was dried under vacuum at 55-65°C for 6-12 hrs (600-700 mm of Hg) to obtain purified 250 gm of N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester (Formula I)Valsartan intermediate (Yield : 56.98 %) .

We claim,

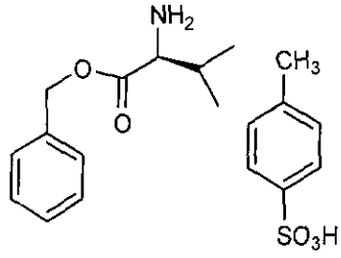
1. An improved in-situ process for the preparation of Valsartan intermediate, N-[2'-(1H-tetrazol-5yl)biphenyl-4-yl)methyl]N-valeryl-(L)-valine benzylester of Formula (I) ,comprising;

   a) reacting L-valine of Formula (II)



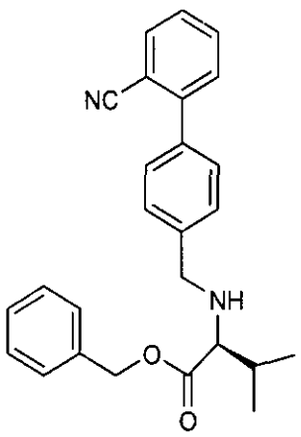
Formula II

with benzyl alcohol in presence of an organic acid such as para-toluene sulphonic acid and aromatic solvent selected from toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (III), which is further brought into aqueous layer



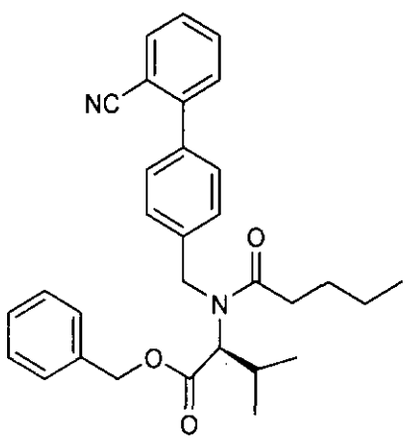
Formula III

   b) followed by reacting aqueous layer obtained in step a) containing compound of Formula (III) with 2-cyano-4'-bromomethylbiphenyl (herewith referring as Br-OTBN) in presence of a base and phase transfer catalyst in aromatic solvent selected from toluene, o-xylene or mono-chlorobenzene to obtain compound of Formula (IV)



Formula IV

c) followed by reacting organic layer obtain in step b) containing compound of Formula (IV) with valeroyl chloride in presence of base to obtain compound of Formula (V)



Formula V

d) followed by reacting the organic layer obtained in step c) containing compound of Formula (V) with sodium azide in presence of tributyl tin chloride to obtain Valsartan intermediate of Formula (I)

2. The process as claimed in claim 1, wherein intermediate compounds of Formula (III), (IV) and (V), obtained in step a), step b) and step c) respectively are not isolated

3. The process as claimed in claim 1, wherein step a), step b), step c) and step d) reactions are carried out in only one aromatic solvent such as toluene, o-xylene or mono-chlorobenzene, more preferably mono chlorobenzene is used

4. The process as claimed in claim 1, wherein the base used in step b) and step c) is selected from alkali metal hydroxides or alkali metal carbonates, wherein the alkali metal hydroxides such as sodium hydroxide, potassium hydroxide are used and the alkali metal carbonates such as potassium carbonate, sodium carbonate are used, preferably base used is potassium carbonate

5. The process as claimed in claim 1, wherein the phase transfer catalyst used in step b) is selected from quaternary ammonium salts selected from tetra butyl ammonium bromide (TBAB), triethyl benzyl ammonium chloride (TEBA) or PEG like PEG 400 , preferably it is TBAB

6. The process as claimed in claim 1, wherein in-situ process of the present invention is carried out at temperature ranging from 20 to 150°C

7. The process as claimed in claim 1, wherein molar ratio of Br-OTBN to compound of Formula (III) in step b) is in the range of 1: 1, preferably it is 0.91:1

8. The process as claimed in claim 1, wherein the molar ratio of valeroyl chloride to compound of Formula (IV) in step c) is in the range of 2: 1, preferably it is 1.6:1.

Dated this 8th day of July, 2013

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(Applicant)