(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2008 (19.06.2008)

PCT

(10) International Publication Number
WO 2008/071400 A1

(51) International Patent Classification:
C07D 257/04 (2006.01) *C07D 413/04* (2006.01)
C07D 333/38 (2006.01) *C07D 413/14* (2006.01)
C07D 409/12 (2006.01)

(21) International Application Number:
PCT/EP2007/010834

(22) International Filing Date:
11 December 2007 (11.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
06025988.4 14 December 2006 (14.12.2006) EP

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

Published:
— *with international search report*

WO 2008/071400 A1

(54) Title: PROCESS FOR THE PREPARATION OF VALSARTAN AND INTERMEDIATE PRODUCTS

(57) Abstract: The present invention relates to a new method for the production of valsartan, a valine derivative having the chemical name is (S)-N-(1 -carboxy-2-methylprop-1 -yl)-N-pentanoyl-N- [2'-(1 H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine, and pharmacologically acceptable salts thereof. Furthermore the invention relates to new intermediate compounds which are suitable for the production of valsartan and new methods for the production of intermediate compounds which are suitable for the production of valsartan.

Process for the preparation of Valsartan and intermediate products

The present invention relates to a new method for the production of valsartan, a valine derivative having the chemical name (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]amine, and pharmacologically acceptable salts thereof. Furthermore the invention relates to new intermediate compounds which are suitable for the production of valsartan and new methods for the production of intermediate compounds which are suitable for the production of valsartan.

Valsartan and efficient and economic methods for its production are of considerable interest. It is a angiotensin II receptor antagonist and has proven to be a potent active agent for controlling high blood pressure in mammals including humans and secondary diseases arising there from.

Valsartan and its production have been described for the first time in EP-A-443983. The disclosed synthetic pathways comprises various steps among which oily intermediates are formed. Furthermore the synthesis comprises as an essential step an N-alkylation, the reaction of a primary amine with for instance a bromo methyl biphenyl derivative.

However, the above-mentioned synthetic processes still need to be improved in order to produce valsartan on an industrial scale. Intermediates as oily and/or high viscous liquids are very difficult to handle, to weight and to dry. Furthermore the total yield is still unsatisfactory.

Common to all synthesis routes is that a valine ester is prepared first and is then alkylated at the amine moiety. In this reaction, however, there is the possibility that an undesired double-alkylation occurs, forming not a secondary amine but a tertiary amine instead.

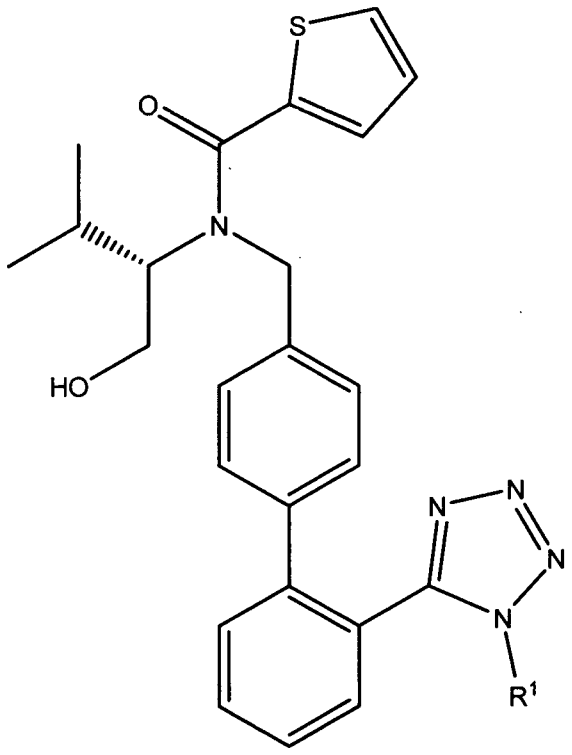
It is therefore an object of the invention to provide new synthetic processes and intermediate products for the production of valsartan and of its pharmacologically acceptable salts. In particular, it is an object of the invention to provide new synthetic

processes and intermediate products for the production of valsartan and of its pharmacologically acceptable salts by which valsartan is obtainable in a high overall yield.

It is furthermore an object of the invention to provide new synthetic processes and intermediate products for the production of valsartan and of its pharmacologically acceptable salts, which can be produced using industrially readily obtainable starting materials and to avoid the use of toxic substances or substances for which there is a labeling obligation.

Accordingly the subject matter described above has been found.

A key aspect of the invention is the production of a compound of general formula I

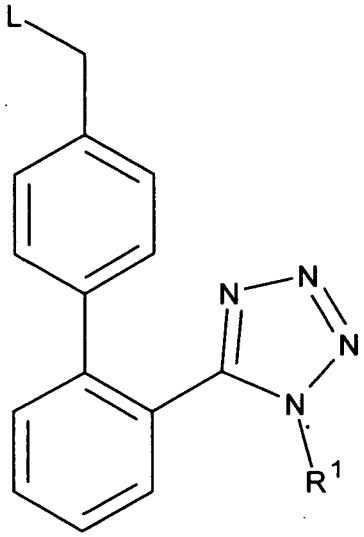


I

wherein R^1 represents hydrogen or a tetrazole protecting group.

Suitable tetrazole protecting groups in the residue of the above-given general formula I are known from EP-A-291969. Suitable tetrazole protecting groups are in particular triphenylmethyl, 1-methyl-1-phenylethyl or *tert*-butyl.

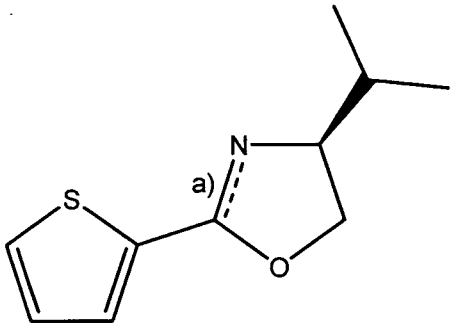
The compounds of general formula I are prepared by reacting a compound of general formula II



II

wherein R^1 represents hydrogen or a tetrazole protecting group and L represents a leaving group, such as halogen or an other suitable leaving group, preferably selected from the group consisting of Cl, Br, I, triflate, mesylate, tosylate, most preferably Br

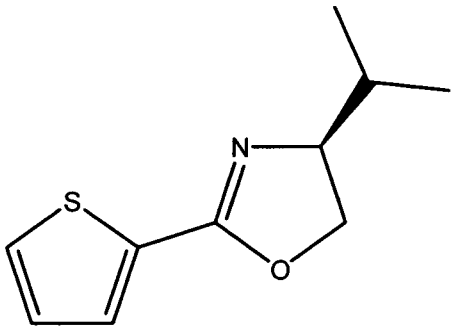
with a compound of general formula III or a pharmaceutically acceptable salt thereof



III

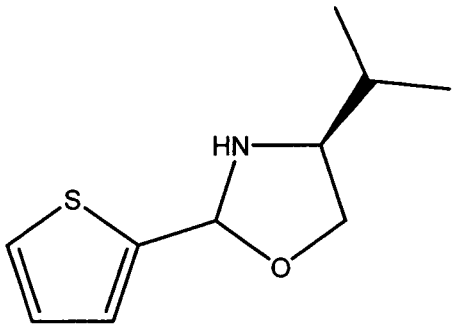
wherein a) denotes a double bond or a single bond and wherein when a) denotes a single bond the nitrogen atom is additionally substituted by a hydrogen atom.

Thus, the compound of general formula III is selected from the group consisting of a compound of general formula IIIa



IIIa,

a compound of general formula IIIb



IIIb

and pharmaceutically acceptable salts thereof.

The above described reaction is preferably carried out in the presence of a Bronsted base. Examples of suitable Bronsted bases are alkali metal carbonates or alkali metal bicarbonates, such as, for example, sodium carbonate, potassium carbonate or sodium bicarbonate. Potassium carbonate is preferred.

The above described reaction is advantageously carried out in the presence of an activator. The activator activates the reaction of a compound of general formula II with a compound of general formula III to give a compound of general formula I. Examples of suitable activators are alkali metal halides or earth alkali metal halides, such as, for example, alkali metal chlorides, alkali metal bromides, alkali metal iodides, earth alkali metal chlorides, earth

alkali metal bromides or earth alkali metal iodides, preferably alkali metal iodides, such as potassium iodide or sodium iodide. Potassium iodide is especially preferred.

The reaction is carried out in a suitable inert solvent. Examples of such suitable inert solvents are ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran), ketones (preferably acetone, methylisobutylketone or methylethylketone), chlorinated hydrocarbons (preferably dichloromethane) or nitrogen containing organic solvents (preferably N-methyl pyrrolidone). Methylethylketone is especially preferred.

The reaction is preferably carried out at elevated temperatures, preferably at temperatures between 50 °C and the boiling point of the solvent.

The reaction of a compound of general formula II with a compound of general formula IIIb to give a compound of general formula I is carried out as a two step process. In a first step a compound of general formula II is reacted with a compound of general formula IIIb, following the procedure given above. Optionally the reaction product of the reaction of a compound of general formula II with a compound of general formula IIIb can be isolated. In a second step the reaction product of the reaction of a compound of general formula II with a compound of general formula IIIb is converted into a compound of general formula I by an oxidative ring opening reaction.

The oxidative ring opening reaction is preferably carried out using a suitable oxidant. Examples of such suitable oxidants are N-halosuccinimides like N-bromosuccinimide (NBS) or N-chlorosuccinimide, halides like chlorine, bromine or iodine, peroxides like ozone, H_2O_2, $KMnO_4$, $K_2Cr_2O_7$, $NaIO_4$ or trifluoroperoxyacetic acid, hypohalides like hypochloride, hypobromide or hypoiodide, or bromates, chlorates, perchlorates and perbromates. N-halosuccinimides and hypohalides are preferred. NBS and hypochlorides are especially preferred.

The oxidative ring opening reaction is advantageously carried out in the presence of a Bronsted base. Suitable Bronsted bases are alkali metal carbonates, alkali metal bicarbonates or alkali metal hydroxides, such as, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or sodium bicarbonate. Potassium carbonate is preferred.

If a compound of general formula II wherein R^1 represents a tetrazole protecting group is used in the reaction of a compound of general formula II with a compound of general formula IIIb, the tetrazole protecting group of the reaction product can, if desired, be removed prior to or after the oxidative ring opening reaction by the reaction with a suitable acid.

Examples of suitable acids are Lewis acids like metal halides, such as metal chlorides, metal bromides or metal iodides, or Bronsted acids like strong organic or inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, trichloroacetic acid, trifluoroacetic acid or methanesulfonic acid. Preferably zinc halides or strong organic acids are used. Most preferably the reaction is carried out with zinc chloride or methanesulfonic acid.

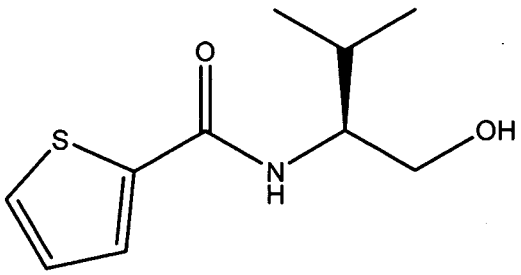
Compounds of the general formula I wherein R^1 denotes a tetrazole protecting group can be converted into compounds of general formula I wherein R^1 denotes hydrogen by the reaction of compound of general formula I wherein R^1 denotes a tetrazole protecting group with a suitable Lewis acid to give a compound of general formula I wherein R^1 denotes hydrogen.

Examples of suitable Lewis acids are metal halides, such as metal chlorides, metal bromides or metal iodides. Preferably zinc halides are used. Most preferably reaction is carried out with zinc chloride.

By the above described method compounds of general formula I can be obtained in high yield and high purity. Furthermore no racemisation occurs so that compounds of general formula I in high enantiomeric purity can be obtained. Compounds of general formula I in solid state are well crystalline materials which can be handled easily (e.g. separated, filtered, purified, dried, weighted, transported and/or stored).

The production of compounds of the general formula II is known from EP-A-291969.

In general, the production of compounds of the general formula III wherein a) denotes a double bond (i.e. compounds of the general formula IIIa) is effected by reacting a compound of general formula IV

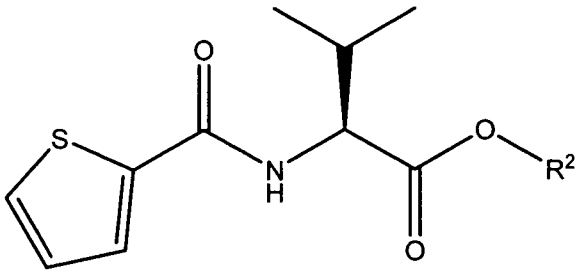


IV

with a suitable cyclisizing agent. Preferably such cyclisizing agents have dehydrating properties. Thionyl chloride is especially preferred. Optionally a dehydrating agent can be added, such as molecular sieves or a Dean-Stark apparatus can be used.

The reaction is usually carried out in a suitable inert solvent, e.g. aliphatic and aromatic hydrocarbons such as hexanes, benzene, toluene, xylenes or mixtures thereof at temperatures between room temperature and the boiling point of the suitable inert solvent. Most preferably reaction is carried out using the cyclisizing agent as solvent.

The production of compounds of the general formula IV is effected by reacting a compound of general formula V



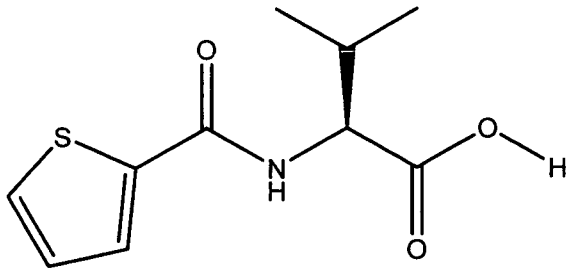
V

wherein R^2 represents alkyl or benzyl, especially C1 to C4 alkyl, preferably methyl, ethyl, propyl or butyl with methyl being especially preferred, with a suitable reducing agent. Preferably such reducing agents are hydrides. $NaBH_4$ is especially preferred.

The reaction is usually carried out in a suitable inert solvent, e.g. aliphatic alcohols such as methanol, ethanol, propanol, *iso*-propanol or in water or in mixtures of aliphatic alcohols and water. Most preferably reaction is carried out in water.

The above described reaction is advantageously carried out in the presence of an activator. The activator activates the reaction of a compound of general formula V with a suitable reducing agent to give a compound of general formula IV. Suitable activators are alkali metal halides or earth alkali metal halides, such as, for example, alkali metal chlorides, alkali metal bromides, alkali metal iodides, earth alkali metal chlorides, earth alkali metal bromides or earth alkali metal iodides, preferably earth alkali metal chlorides, such as calcium chloride or magnesium chloride. Calcium chloride is especially preferred.

The production of compounds of the general formula V is effected by reacting a compound of general formula VI



VI

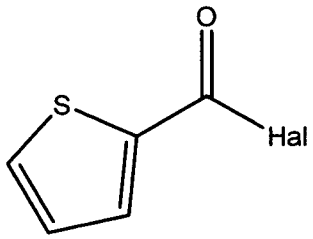
with a chlorinating agent and a compound of the general formula R^2-OH.

The chlorinating agents are suitable to convert carboxylic acids into carboxylic acid chlorides. Sulphuryl chloride is especially preferred as chlorinating agent.

The reaction is usually carried out in a suitable inert solvent, e.g. aliphatic alcohols such as methanol, ethanol, propanol, *iso*-propanol at temperatures between -20 °C and 50 °C. Preferably reaction is carried out in R^2-OH at room temperature.

Most preferably the reaction of compound of the general formula VI with a chlorinating agent and with compound of the general formula R^2-OH to give a compound of general formula V and the reaction of a compound of general formula V with a suitable reducing agent to produce a compound of the general formula IV is carried out as a one-pot reaction without the isolation of a compound of the general formula V.

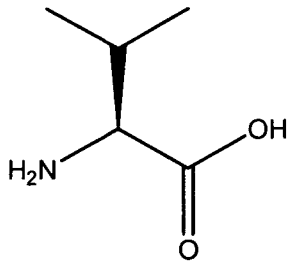
The production of compounds of the general formula VI is effected by reacting a compound of general formula VII



VII

wherein Hal represents halogen preferably selected from the group consisting of Cl, Br, I, preferably Cl

with a compound of general formula VIII



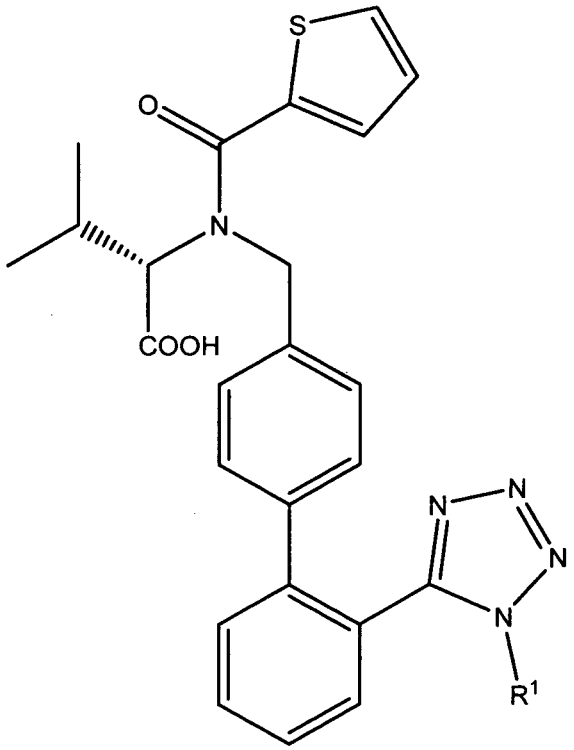
VIII

preferably in the presence of a Bronsted base. Suitable Bronsted bases are alkali metal carbonates, alkali metal bicarbonates or alkali metal hydroxides, such as, for example, sodium carbonate, potassium carbonate, sodium bicarbonate, sodium hydroxide or potassium hydroxide. Potassium hydroxide is preferred.

The preparation of compounds of the general formula III wherein a) denotes a single bond and wherein the nitrogen is additionally substituted by a hydrogen atom (i.e. of compounds of the general formula IIIb) is effected by reacting L-valinol with thiophene-2-carbaldehyde. The reaction is preferably carried out using water removal methods. The water removal methods can be for example azeothropic distillation, the use of a Dean-Stark apparatus or the addition of water absorbing agents like magnesium sulfate, sodium sulfate, phosphorous pentoxide, or molecular sieves like zeolites A, especially zeolite A3, A4 or A5. A zeolite molecular sieve of type A3 is preferred.

The preparation of valsartan is carried out by

- an oxidation of a compound of general formula I with a suitable oxidizing agent to give a compound of general formula X,



X

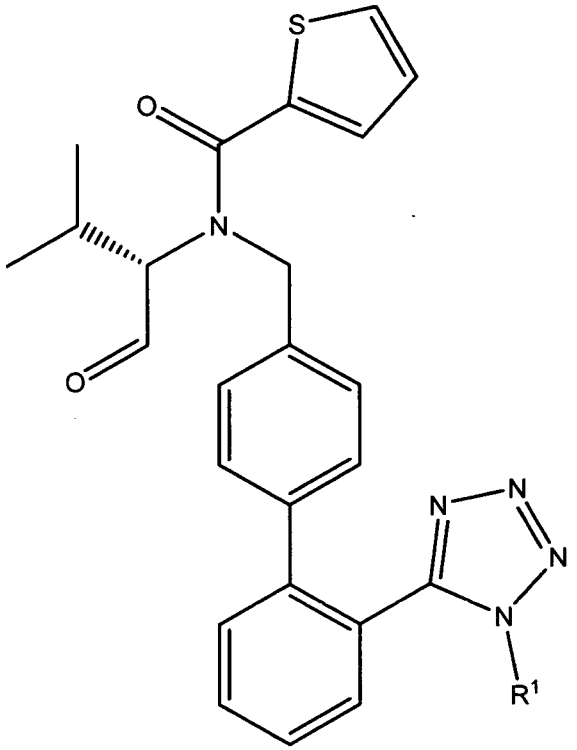
wherein R^1 represents hydrogen or a tetrazole protecting group and

- conversion of a compound of general formula X to valsartan by reaction with a suitable hydrogenating agent.

Suitable oxidizing agents oxidize primary alcohols to carboxylic acids and can be for example N-halosuccinimides like N-bromosuccinimide (NBS) or N-chlorosuccinimide, halides like chlorine, bromine or iodine, peroxides (e.g. trifluoroperoxyacetic acid, $NaIO_4$, potassium permanganate, hydrogen peroxide or benzoyl peroxide), ozone, chromium-(VI)-oxide, hypohalides like hypochloride, hypobromide or hypoiodide, or bromates, chlorates, perchlorates, perbromates and silver salts. Most preferably potassium permanganate is used.

Optionally the oxidation can be carried out as a two step oxidation with or without isolation of the reaction product of the first oxidation step. In the first step a compound of general

formula I is oxidized using a suitable oxidizing agent to give a compound of general formula IX,



IX

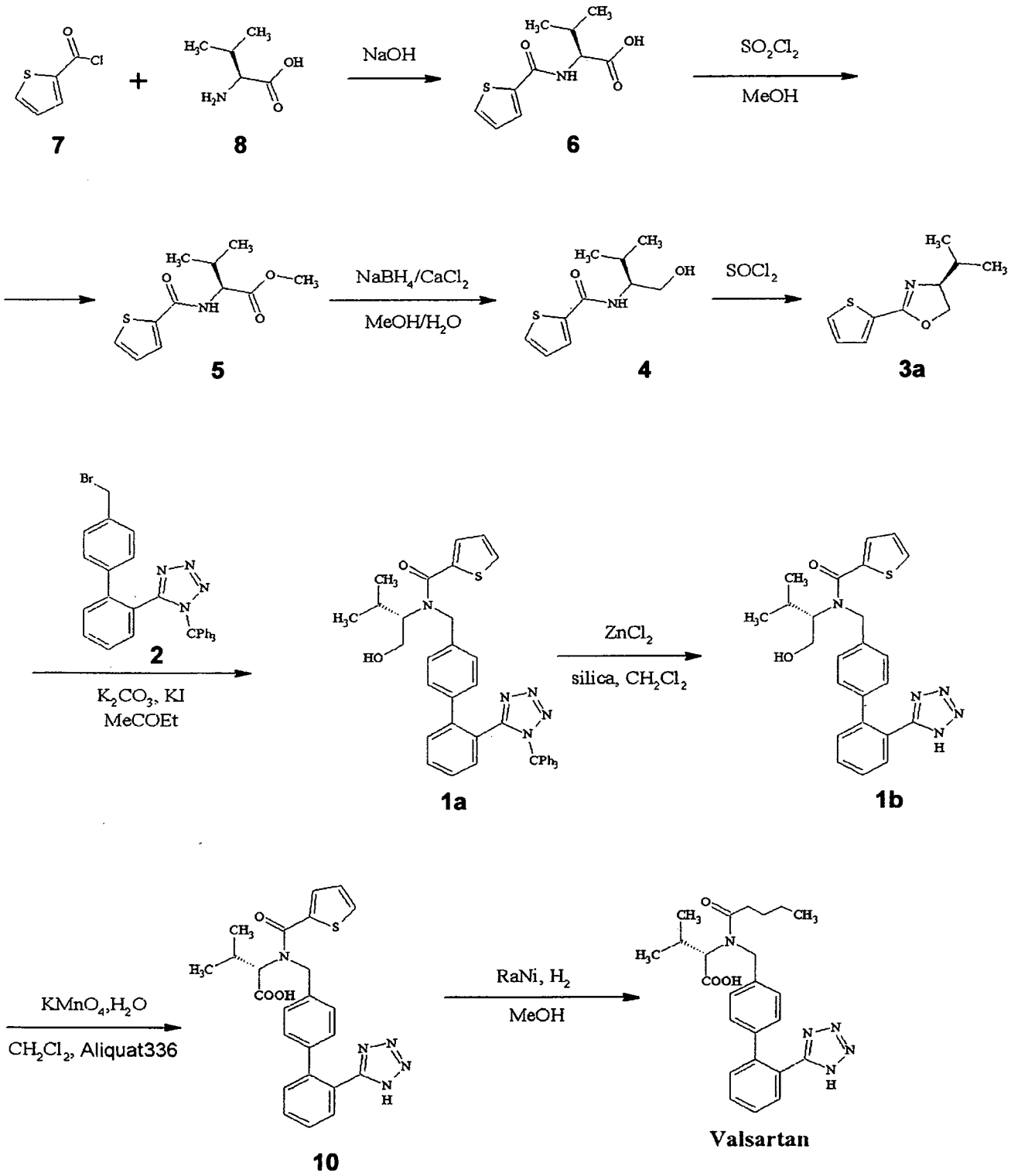
wherein R^1 represents hydrogen or a tetrazole protecting group.

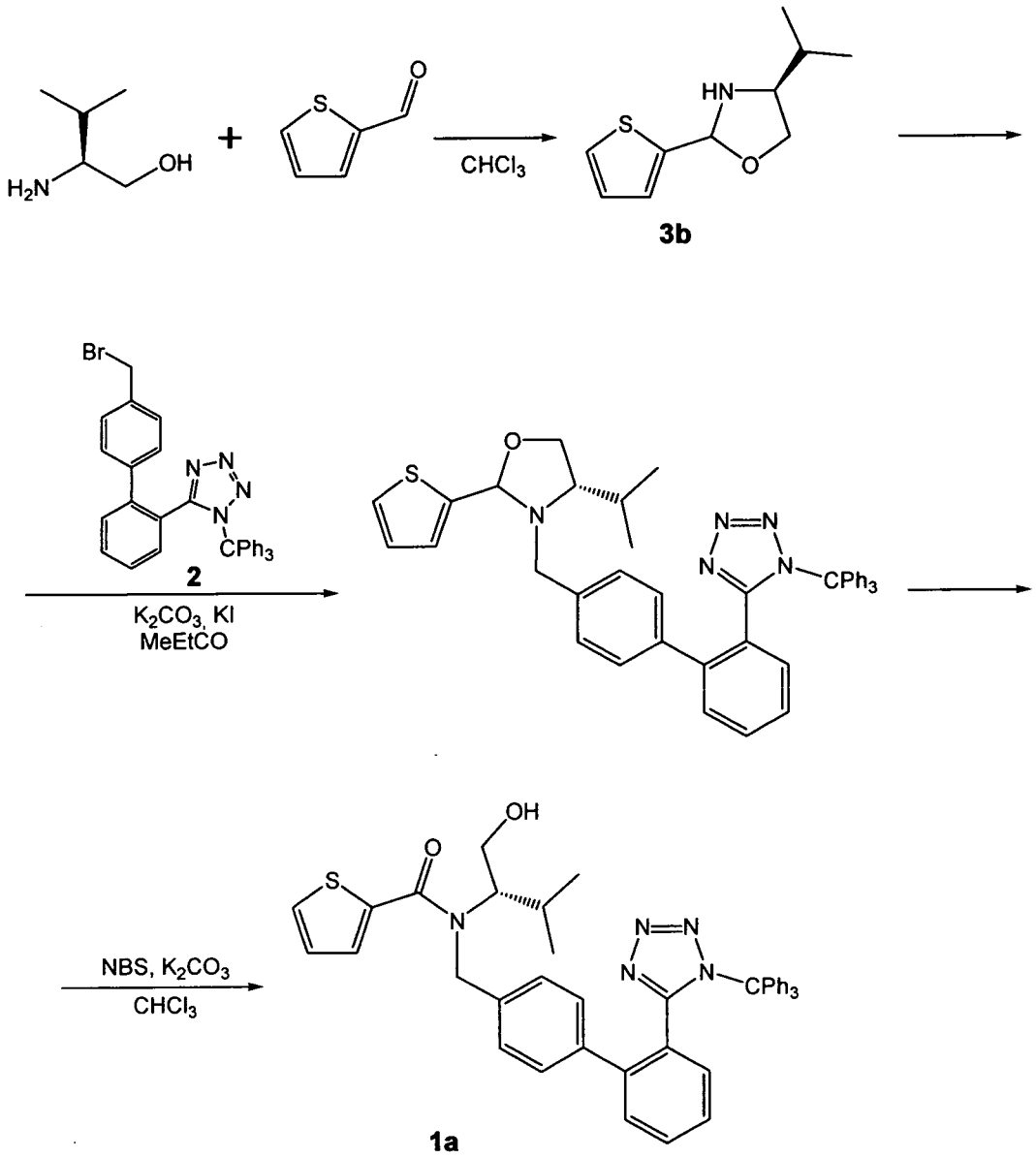
Examples of suitable oxidizing agents are hypohalides like hypochloride, hypobromide or hypoiodide, or bromates, chlorates, perchlorates, perbromates and the swern oxidant (oxalyl chloride and DMSO) with hypochloride and the swern oxidant being preferred. Optionally an oxidation catalyst such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) can be added.

In the second oxidation step a compound of general formula IX is oxidized using a suitable oxidizing agent to give a compound of general formula X. Preferably the suitable oxidizing agent is an oxidizing agent as defined above for the oxidation of primary alcohols to carboxylic acids.

An example of a suitable hydrogenating agent for the conversion of a compound of general formula X to valsartan is hydrogen, preferably in the presence of a metal catalyst such as nickel or palladium. Most preferably Raney nickel in the presence of methanol or water is used. The reaction can be carried out at normal pressure or preferably at elevated pressure.

Below the synthetic route is described and further explained showing one possible embodiment of the process of the present invention without intending to be limiting.




H2N
OH
S
O
CHCl3
HN
S
O
3b
Br
N
N
N
CPh3
2
K2CO3, KI
MeEtCO
S
O
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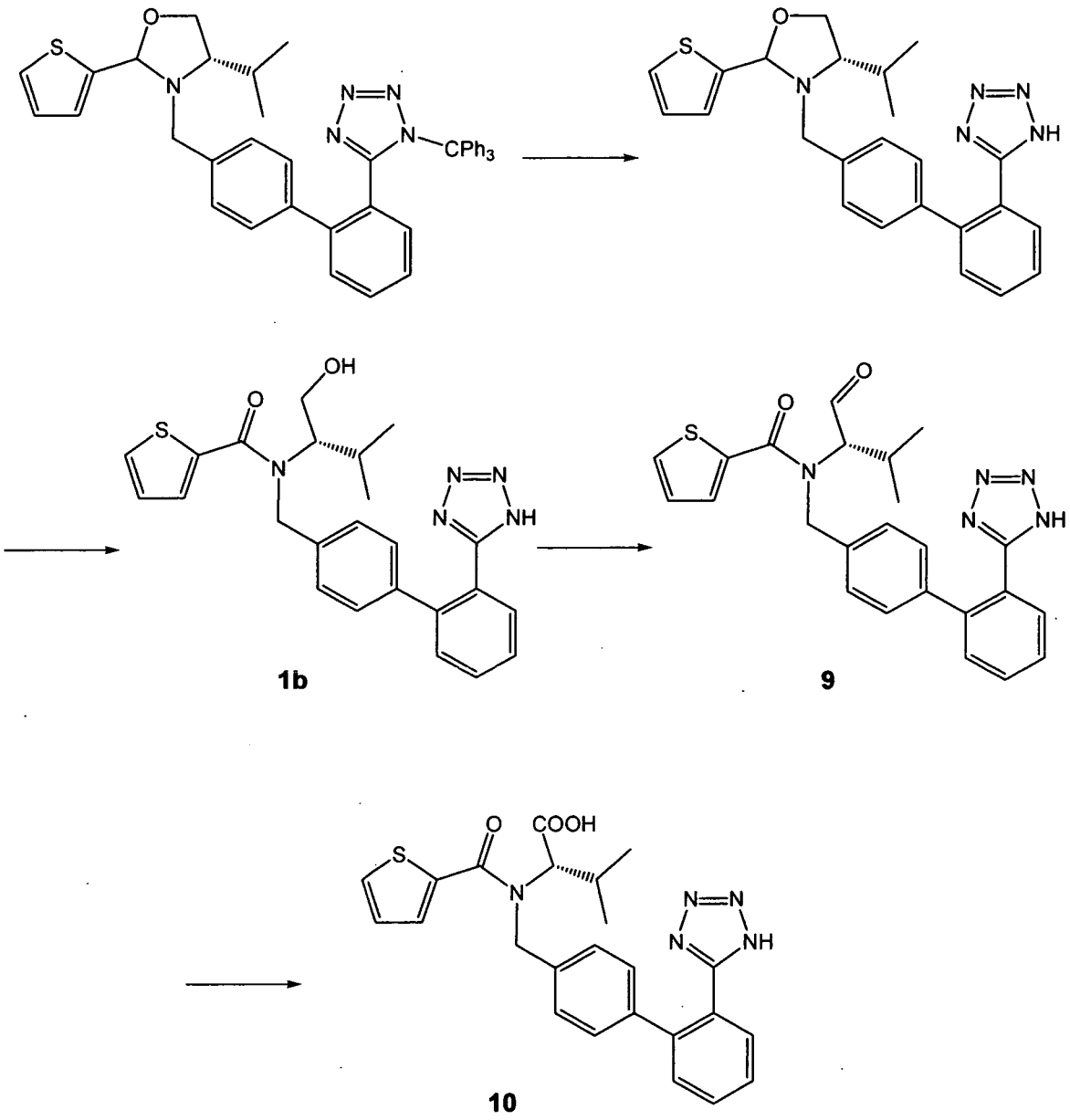


1b

9

10

The compounds used and/or being formed in the respective synthetic routes are referred to by Arabic numerals. With respect to the compounds described in the reaction scheme, the following applies:

- 1a corresponds to a compound of general formula I with residue R^1 is CPh_3 (triphenylmethyl),
- 1b corresponds to a compound of general formula I with residue R^1 is hydrogen

- 2 corresponds to a compound of general formula II with residue R^1 is CPh_3 (triphenylmethyl) and Hal is chloride,
- 3a corresponds to a compound of general formula IIIa,
- 3b corresponds to a compound of general formula IIIb,
- 4 corresponds to a compound of general formula IV,
- 5 corresponds to a compound of general formula V with R^2 is methyl,
- 6 corresponds to a compound of general formula VI,
- 7 corresponds to a compound of general formula VII with Hal is chloride,
- 8 corresponds to a compound of general formula VIII,
- 9 corresponds to a compound of general formula IX with R^1 is hydrogen and
- 10 corresponds to a compound of general formula X with R^1 is hydrogen.

At the same time the compounds are preferred working examples of the compound groups defined by the respective general formulae.

Experimental Part

All reactions were monitored by HPLC-PDA method and structures of all products, by-products and impurities were elucidated and confirmed by LC-MS-MS. Where the identification was not definite ^1H and ^{13}C-NMR was used. The measured melting points are uncorrected.

(2S)-3-methyl-2-((2thenoyl)-amino)butanoic acid (N-thenoyl-L-valine, 6)

L-valine (35,8 g, 0.306 mol) was dissolved in 2M NaOH (153 ml) and cooled down to 0°C. Thiopen-2-carbonyl chloride (44,9 g, 0.306 mol) and 4M NaOH (76.5 ml) was added drop wise alternately under stirring while maintaining the temperature between 0 and 5 °C. Reaction mixture was let to warm up to room temperature within 20 minutes after the last addition. Reaction mixture was acidified with 32-% HCl to pH 2 and then extracted with ethylacetate (4-times 170 ml), dried over Na_2SO_4 and evaporated on RVE to yield 62.0 g (89%) of product. HR-MS:228.0694 (MH^+, calc. for $C_{10}H_{14}NO_3S^+$:228.0702).

N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]thiophene-2-carboxamide(N-thenoyl-L-valinol, 4):

N-thenoyl-L-valine (78.2 g, 0.344 mol) was dissolved in methanol (550 ml) and sulphuryl chloride (1.4 ml, 0.017 mol) was slowly added drop-wise. Reaction mixture was allowed to stand for 48 hours at laboratory temperature. Then methanol (1010 ml) and $CaCl_2.2H_2O$ (152 g, 1.03 mol) dissolved in water (970 ml) were added. $NaBH_4$ (75.8 g, 2.003 mol) was added in small portions under cooling in the ice bath and stirring, and then left stand at laboratory temperature for 24 hours. White suspension was filtered off, washed with mixture of methanol - water 1:1 (twice 200 ml) and filtrate was concentrated *in vacuo* and extracted with chloroform (5-times 400 ml). Combined organic layers were re-extracted with brine, dried over Na_2SO_4 and evaporated on RVE to yield 62.5 g (85.2%) of white solid. HR-MS:214.0902 (MH^+, calc. for $C_{10}H_{16}NO_2S^+$:214.0900).

(4S)-4-isopropyl-2-(2-thienyl)-4,5-dihydro-1,3-oxazole (3a):

N-thenoyl-L-valinol (20.0 g, 93.77 mmol) was added to thionyl chloride (20.0 ml, 275.7 mmol) and reaction mixture was stirred for 1 hour at laboratory temperature and evaporated on RVE to yield 20.0 g of the hydrochloride of title substance. The product was suspended in dichloromethane (200 ml) and 2M NaOH was added to adjust pH of aqueous layer to 9-10 (approx. 200 ml). Aqueous layer was separated and extracted with dichloromethane (twice 200 ml). Combined organic layer was dried over K_2CO_3 and evaporated on RVE to yield 16.7 g (91%) of free base. HR-MS: 196.0796 (MH^+, calc. for $C_{10}H_{14}NOS^+$:196.0791).

(1S)-N-(1-Hydroxymethyl-2-methyl-propyl)-N'-[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-thiophene-2-carboxamide(1a):

(4S)-4-isopropyl-2-(2-thienyl)-4,5-dihydro-1,3-oxazole (18.3 g, 93.71 mmol) was dissolved in 2-butanone (360 ml) and then 5-(4'-bromomethyl-biphenyl-2-yl)-1-trityl-1H-tetrazole (15.6 g, 93.98 mmol), KI (15.6 g, 93.98 mmol), K_2CO_3 (64.8 g, 486.9 mmol) and triphenylmethyl chloride (26.1 g, 91.61 mmol) were added. Reaction mixture was refluxed for 24 hours and then evaporated on RVE. Orange solid was dissolved in dichloromethane (300 ml) and extracted with saturated aqueous solution of $Na_2S_2O_3$ (300 ml) and water (twice 300 ml). Organic layer was dried over Na_2SO_4 and evaporated on RVE to yield 58.1 g (90%) of the product. It can be used without purification in the next step. HR-MS: 690.2903 (MH^+, calc. for $C_{43}H_{40}N_5O_2S^+$:690.2902).

(4S)-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine (3b):

L-valinol (92.7 g, 0.9 mol) was dissolved in $CHCl_3$ (750 ml), and thiophene-2-carbaldehyde (100.8 g, 0.9 mol) and molecular sieve A3 (90 g) was added. The reaction mixture was refluxed for 2 hours. The molecular sieve was filtered off and the filtrate was evaporated on RVE yielding 158 g of the product. It can be used without purification in the next step. HR-MS: 198.0946 (MH^+, calc. for $C_{10}H_{16}NOS$ 198.0953)

(1S)-N-(1-Hydroxymethyl-2-methyl-propyl)-N'-[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-thiophene-2-carboxamide (1a):

(4S)-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine (98.6 g, 0.5 mol) was dissolved in 2-butanone (750 ml), and 5-(4'-bromomethyl-biphenyl-2-yl)-1-trityl-1H-tetrazole (278.8 g, 0.5 mol), KI (83.0 g, 0.5 mol) and K_2CO_3 (69.0 g, 0.5 mol) were added. The reaction mixture was refluxed for 72 hours and the resulting yellow suspension was evaporated on RVE. The solid product was transferred to $CHCl_3$ (1.5 l) and extracted with water (1.5 l). The organic layer was washed thrice with 1.2 l of water and evaporated on RVE yielding 286.5 g (85 %) of (4S)-3-[2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine (HR-MS: 674.2931 (MH^+, calc. for $C_{43}H_{40}N_5OS$: 674.2954)). 29.6 g (44.0 mmol) of (4S)-3-[2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine were dissolved in $CHCl_3$ (100 ml). The solution was cooled to about 0 °C, and K_2CO_3 (12.2 g, 88.0 mmol) and NBS (7.8 g, 44.0 mmol) were added. The reaction mixture was stirred for 1 hour at 0 °C and then extracted 6 times with 100 ml of water. The organic layer was dried over K_2CO_3 and evaporated on RVE to yield 20.6 g (68 %) of the product. It can be used without purification in the next step.

(1S)-N-(1-Hydroxymethyl-2-methyl-propyl)-N'-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-thiophene-2-carboxamide (1b):

(1S)-N-(1-hydroxymethyl-2-methyl-propyl)-N'-[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-thiophene-2-carboxamide (64.6 g, 93.7 mmol) was dissolved in dichloromethane (650 ml) and silica gel (325 g) and $ZnCl_2$ (12.8 g, 93.9 mmol) was added. Reaction mixture was stirred for 1 hour at laboratory temperature and then filtered off. The silica gel was washed with dichloromethane (thrice 300 ml) and methanol (thrice 300 ml). Methanol fraction was evaporated on RVE to yield yellow amorphous product (41.9 g, 100%).

If desired the amorphous product can be further purified. It was dissolved in dichloromethane (1800 ml) and extracted with 0.4M NaOH solution (6-times 300 ml) and water (4-times 2000 ml). Combined alkaline and water layer were acidified with 35-% HCl to

pH 3 and extracted with dichloromethane (thrice 400 ml). Organic layer was washed with water (twice 300 ml), dried over Na_2SO_4 and evaporated on RVE to yield 28.0 g (66.8%) of product. HR-MS: 448.1807 (MH^+, calc. for $C_{24}H_{26}N_5O_2S^+$:448.1800).

(4S)-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine

(4S)-3-[2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine (20.0 g, 29.68 mmol) obtainable according to the previous example was suspended in methanol (130 mL) and 1.5 mL of methansulfonic acid were added drop wise during 30 minutes. The end of the reaction was indicated by dissolution of the suspension. The reaction mixture was stirred for additional 15 minutes and it was then checked for conversion. K_2CO_3 (5.6 g, 40.52 mmol) was added and it was stirred for 30 minutes. The reaction mixture was filtered and filtrate was evaporated on RVE to yield crystalline material. For further purification the crystals can be washed twice with diisopropyl ether (50 mL). The potassium salt of compound (4S)-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine was obtained in nearly quantitative yield (10.2 g) and can be used directly in the next reaction step. HR-MS: 432.1859 (MH^+, calc. for $C_{24}H_{26}N_5OS$:432.1858).

(2S)-3-Methyl-2-{N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N'-(thiophene-2-carbonyl)-amino}-butanoic acid (10):

Method A: (4S)-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine (0.64 g, 1.48 mmol) was dissolved in chloroform (10 mL) and cooled down to 0 °C. To the solution were consequently added KBr (0.18 g, 1.48 mmol), K_2CO_3 (0.41 g, 2.97 mmol) and KBF_4 (0.19 g, 1.48 mmol). A solution of 6-% NaOCl (1.52 mL, 1.48 mmol) in 8 mL of water was added drop wise at 0 °C. The temperature of reaction mixture was let to increase to RT and then stirred for 1 hour. 2,2,6,6-tetramethylpiperidene-N-oxyl (2 mg, 0.015 mmol) and 6-% NaOCl (3.05 mL, 2.96 mmol) were added. The mixture was stirred until completion of the reaction. The water layer was neutralized with tartaric acid and separated and the organic layer was washed with 10 mL of 0.01M HCl and 10 mL of saturated solution of NaCl. Then the organic layer was extracted 6-times with 10 mL of 0.1M NaOH and then discarded. Water phases were carefully acidified with 0.1M HCl to pH 2 and extracted thrice with 20 mL of chloroform. Organic layer was dried over Na_2SO_4 and evaporated on RVE yielding 0.44 g (64 %) of product. HR-MS: 462.1586 (MH^+).

Method B: The reaction was done according to the method A with the addition of tetrabutylammonium bromide (0.05 g, 0.15 mmol).

Method C: (4S)-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine (0.64 g, 1.48 mmol) was dissolved in acetonitrile (10 mL) and cooled down to 0 °C. To the solution were consequently added KBr (0.18 g, 1.48 mmol) and K_2CO_3 (0.41 g, 2.97 mmol). A solution of 6-% NaOCl (1.52 mL, 1.48 mmol) was added drop wise during 15 minutes at 0 °C. The temperature of reaction mixture was let to increase to RT and then stirred for 1 hour. 2,2,6,6-tetramethylpiperidene-N-oxyl (2 mg, 0.015 mmol) and 6-% NaOCl (3.05 mL, 2.96 mmol) were added. The mixture was stirred until completion of the reaction. The isolation of product was done according to the method A, giving 0.49 g (72 %) (2S)-3-Methyl-2-{N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N'-(thiophene-2-carbonyl)-amino}-butanoic acid

Method D: The reaction was done according to the method C. N,N-dimethylformamide or N-methyl-pyrrolidone were used instead of acetonitrile.

(2S)-3-Methyl-2-{N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N'-(thiophene-2-carbonyl)-amino}-butanoic acid (10):

(1S)-N-(1-Hydroxymethyl-2-methyl-propyl)-N'-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-thiophene-2-carboxamide (9) (5 g, 11.2 mmol) was dissolved in dichloromethane (60 ml) and 18crown6 (0.6 g, 2.3 mmol) was added. $KMnO_4$ (1.8 g, 11.4 mmol) dissolved in 0.5M NaOH (6 ml) was added drop-wise within 2 hours, and then mixture was stirred for 10 hours at laboratory temperature. Then Na_2SO_3 (20.0 g) and 35-% HCl (16 ml) were added and reaction mixture was stirred until black suspension of MnO_2 dissolve. Organic and aqueous phase were separated and organic layer was washed with 2M NaOH (100 ml) and water (100 ml). Combined alkaline and aqueous phase were extracted with dichloromethane (twice 100 ml), acidified with 35-% HCl to pH 2 and extracted with dichloromethane (twice 10 ml). Organic layer was dried over Na_2SO_4 and evaporated on RVE to yield 4.0 g (80.0%) of product. HR-MS: 462.1600 (MH^+, calc. for $C_{24}H_{24}N_5O_3S^+$:462.1617).

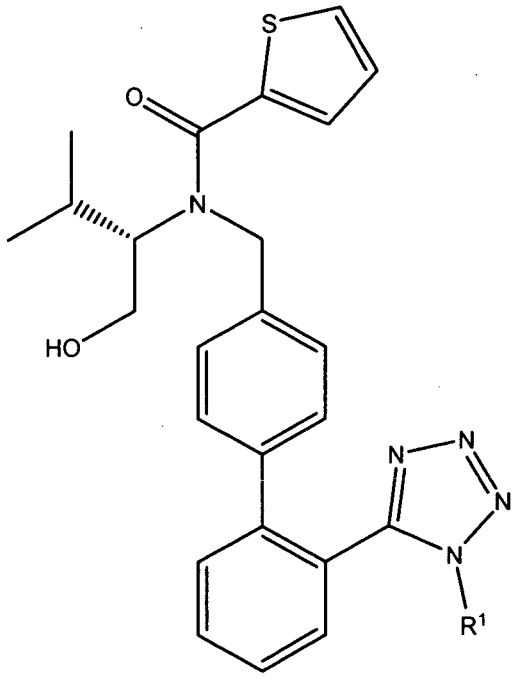
(2S)-3-Methyl-2-{N-pentanoyl-N'-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-butanoic acid (Valsartan):

(2S)-3-Methyl-2-{N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-N'-(thiophene-2-carbonyl)-amino}-butanoic acid (VS.INT7) (0.4 g, 0.87 mmol) dissolved in methanol (5 ml) and Raney Nickel was added. Reaction mixture was stirred in hydrogen atmosphere at normal pressure at room temperature for 24 hours. Reaction mixture was filtered through celite and

evaporated on RVE to yield 0.35 g (90%) of Valsartan. HR-MS: 436.2349 (MH^+, calc. for $C_{24}H_{30}N_5O_3^+$: 436.2353).

Claims

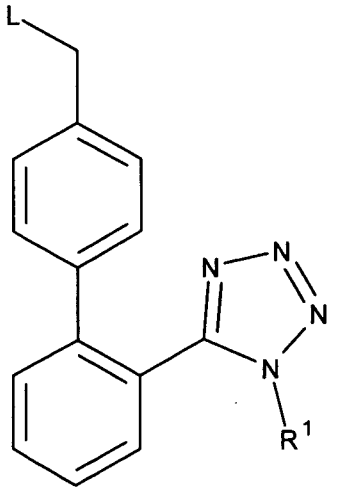
1. Method for the production of a compound of general formula I



I

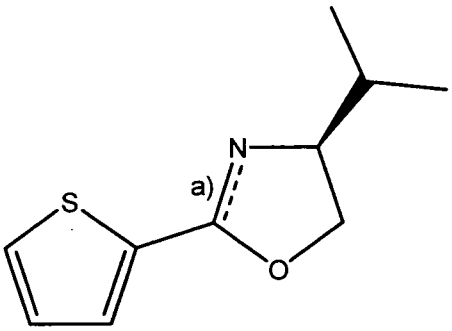
wherein R^1 represents hydrogen or a tetrazole protecting group

by reacting a compound of general formula II



II

wherein R^1 represents hydrogen or a tetrazole protecting group and L represents a leaving group with a compound of the formula III or a pharmaceutically acceptable salt thereof



III

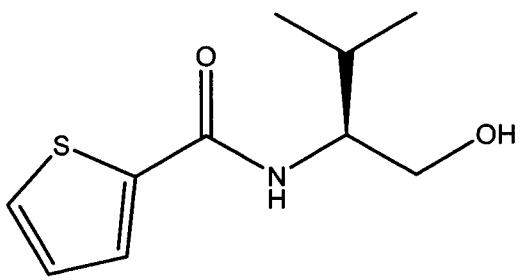
wherein a) denotes a double bond or a single bond and wherein when a) denotes a single bond the nitrogen atom is additionally substituted by a hydrogen atom.

2. Method according to claim 1 which is carried out in the presence of a Bronsted base.

3. Method according to claim 1 or 2, wherein the compound of formula III wherein a) denotes a single bond and the nitrogen atom is additionally substituted by a hydrogen atom is used and wherein the reaction intermediate (4S)-3-[2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine is optionally isolated, optionally converted to (4S)-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine, and further converted to I.

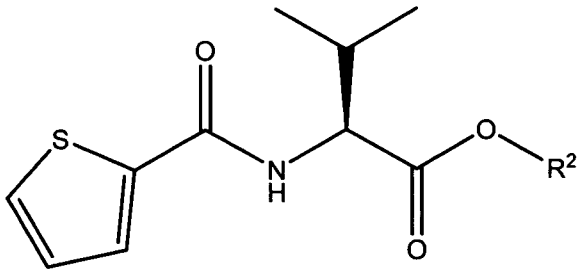
4. Method according to claim 1 or 2, wherein the compound of formula III wherein a) denotes a single bond and the nitrogen atom is additionally substituted by a hydrogen atom is obtained by the reaction of L-valinol with thipophene-2-carbaldehyde.

5. Method according to claim 1 or 2, wherein the compound of formula III wherein a) denotes a double bond is obtained by cyclizising a compound of formula IV



IV.

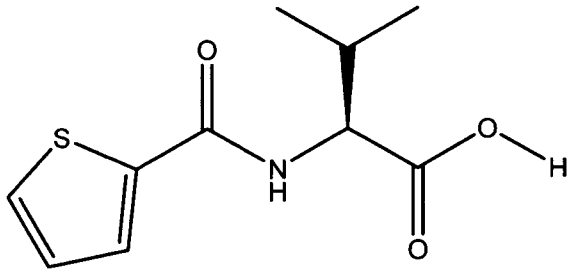
6. Method according to claim 5, wherein the compound of formula IV is obtained by reducing a compound of general formula V



V

wherein R^2 represents alkyl or benzyl.

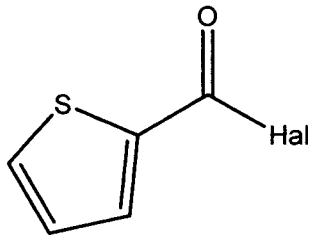
7. Method according to claim 6, wherein the compound of general formula V is obtained by reacting a compound of formula VI



VI

with a chlorinating agent and R^2-OH wherein R^2 is defined as in claim 4.

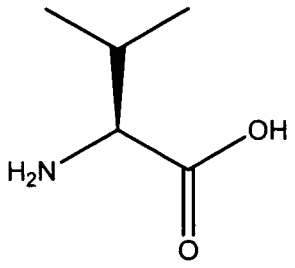
8. Method according to claim 7, wherein the compound of formula VI is obtained by reacting a compound of general formula VII



VII

wherein Hal represents halogen

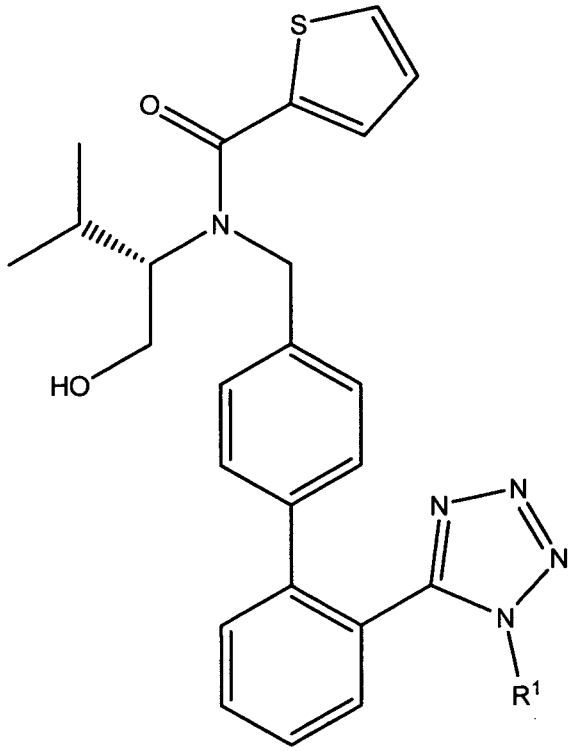
with a compound of formula VIII



VIII.

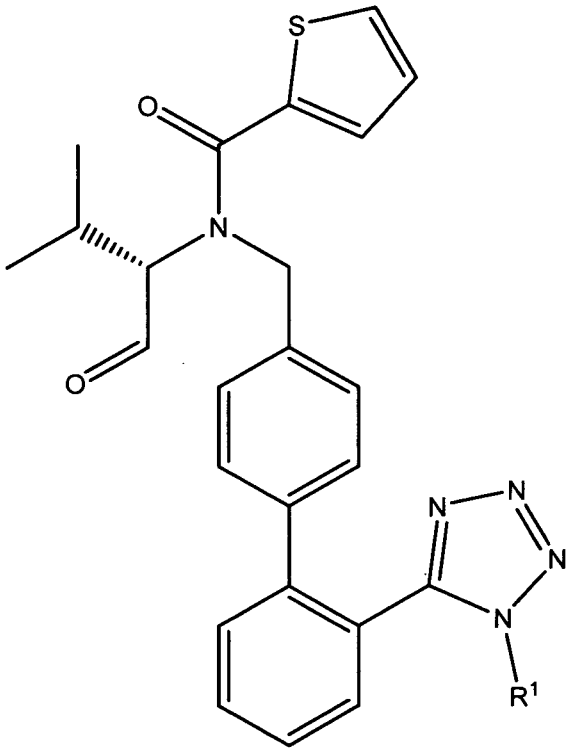
9. Method for the production of valsartan comprising the steps of any one of the preceding claims.

10. Method of claim 9, further comprising the step of oxidizing a compound of general formula I



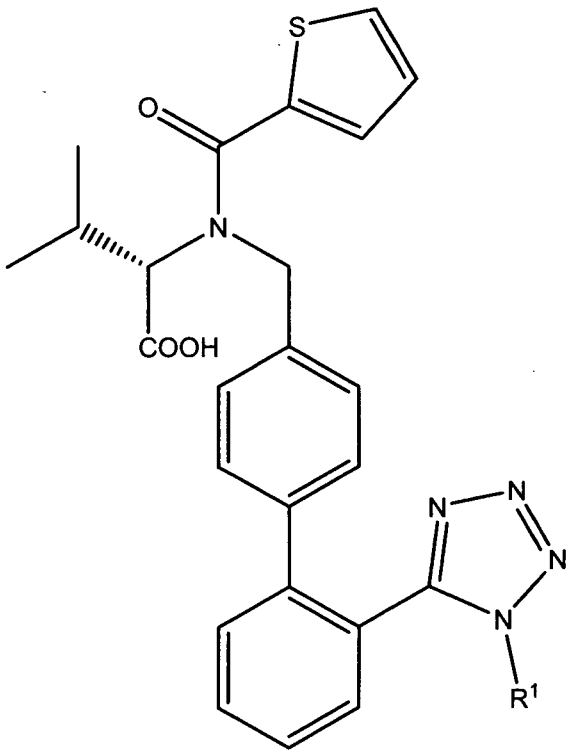
I

wherein R^1 represents hydrogen or a tetrazole protecting group, to a compound of general formula IX



IX

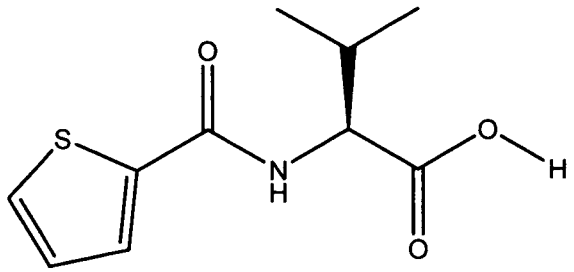
wherein R^1 represents hydrogen or a tetrazole protecting group, or to a compound of general formula X



X

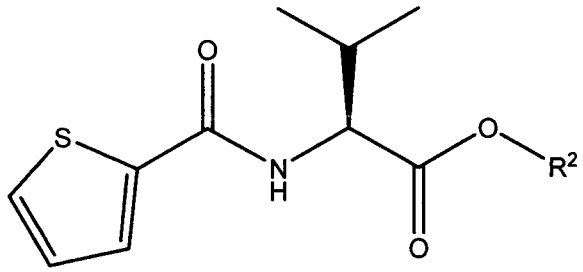
wherein R^1 represents hydrogen or a tetrazole protecting group.

11. Compound of the formula VI



VI.

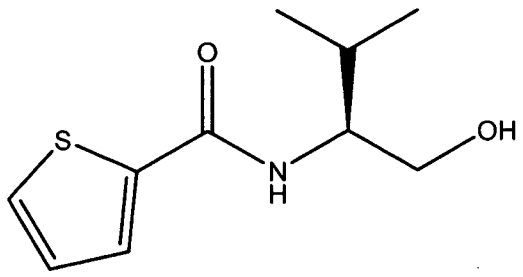
12. Compound of the general formula V



V

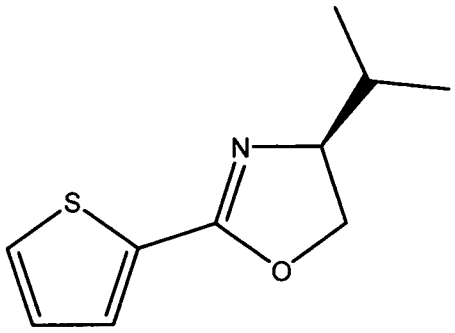
wherein R^2 represents alkyl or benzyl.

13. Compound of the formula IV



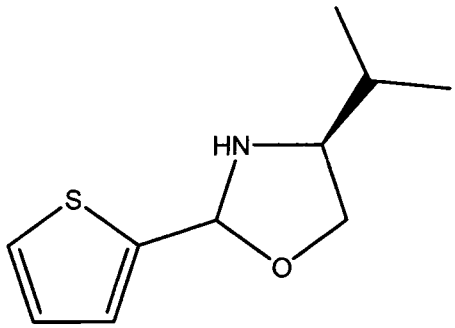
IV.

14. Compound of the formula IIIa



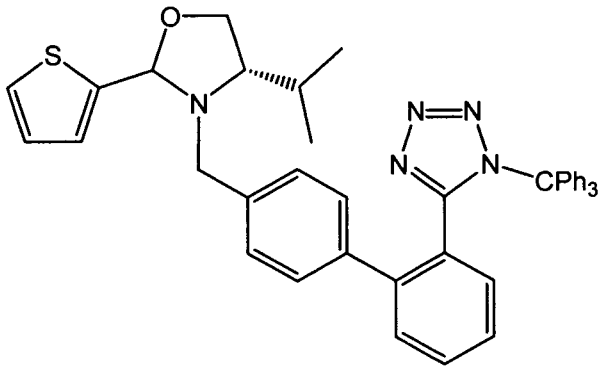
IIIa.

15. Compound of the formula IIIb

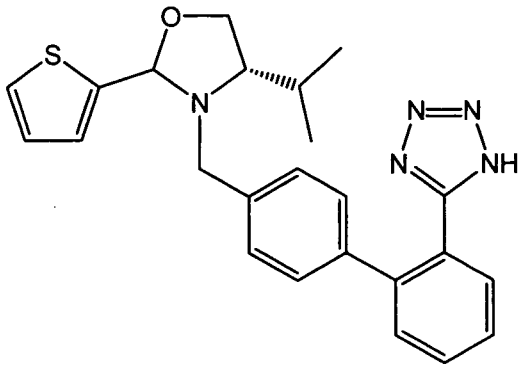


IIIb.

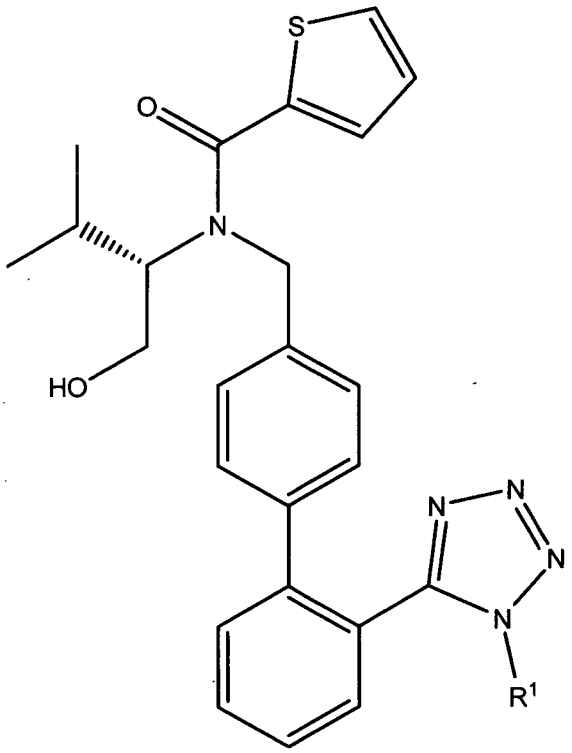
16. (4S)-3-[2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine of the formula



17. (4S)-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl-methyl]-4-isopropyl-2-(2-thienyl)-1,3-oxazolidine of the formula



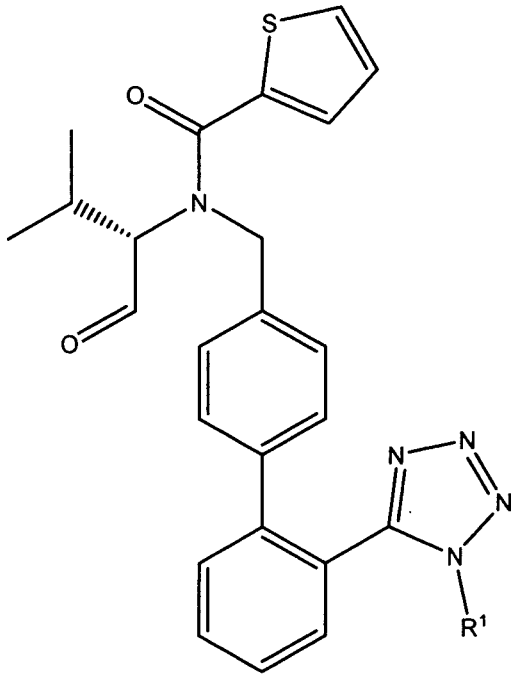
18. Compound of general formula I



I

wherein R^1 represents hydrogen or a tetrazole protecting group.

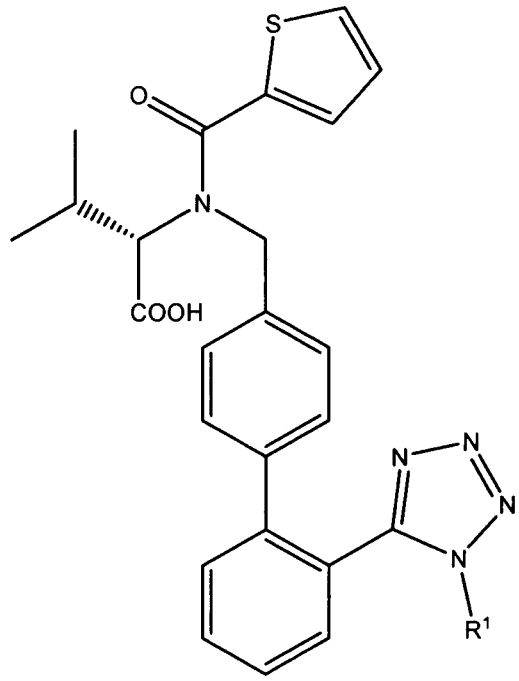
19. Compound of general formula IX



IX

wherein R^1 represents hydrogen or a tetrazole protecting group.

20. Compound of general formula X



X

wherein R^1 represents hydrogen or a tetrazole protecting group.

21. Use of any of the compounds of claims 11-20 for the production of valsartan.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/010834

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D257/04 C07D333/38 C07D409/12 C07D413/04 C07D413/14

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, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EL-NAGGAR A M ET AL: "SYNTHESIS OF SOME 2-THENOYL-, 5-BROMO-2-THENOYL- AND 5-NITRO-2-THENOYLAMINO ACID DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY" JOURNAL OF THE INDIAN CHEMICAL SOCIETY, THE INDIAN CHEMICAL SOCIETY, CALCUTTA, IN, vol. 59, no. 6, June 1982 (1982-06), pages 783-786, XP008045968 ISSN: 0019-4522 compound VII	12

-/--

[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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"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	Date of mailing of the international search report
17 March 2008	26/03/2008

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	Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/010834

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALLEN J V ET AL: "Preparation of sulfur and phosphorus containing oxazolines as ligands for asymmetric catalysis" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 50, no. 3, 17 January 1994 (1994-01-17), pages 799-808, XP002152148 ISSN: 0040-4020 compound 7C ----	14
A	EP 0 443 983 A (CIBA GEIGY AG [CH]) 28 August 1991 (1991-08-28) cited in the application the whole document ----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/010834

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 644844 B2	23-12-1993
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