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(54) Title: PROCESS FOR THE PREPARATION OF TELAPREVIR

(57) Abstract: Disclosed herein is a process for the preparation of telaprevir wherein (1S,3aR,6a S)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl] octahydrocyclopenta[c]pyrrole-1-carboximide and N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine are condensed to form hydroxy telaprevir, which is then converted into telaprevir.

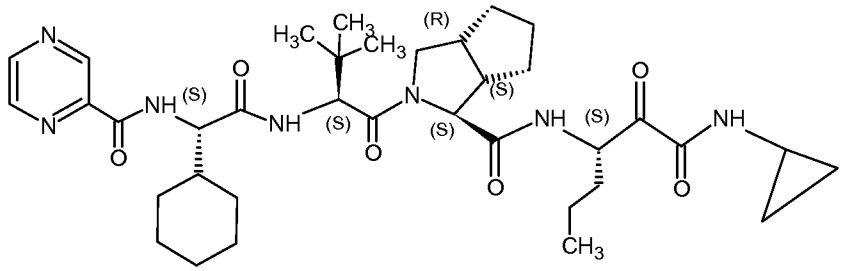
PROCESS FOR THE PREPARATION OF TELAPREVIR

Field of the Invention

The present invention provides a process for the preparation of telaprevir wherein (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide and N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine are condensed to form hydroxy telaprevir, which is then converted into telaprevir.

Background of the Invention

Telaprevir is chemically known as (1*S*,3a*R*,6a*S*)-2-[(2*S*)-2-({(2*S*)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl}amino)-3,3-dimethylbutanoyl]-*N*-[(3*S*)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[c]pyrrole-1-carboxamide, and has the structure depicted by Formula I:



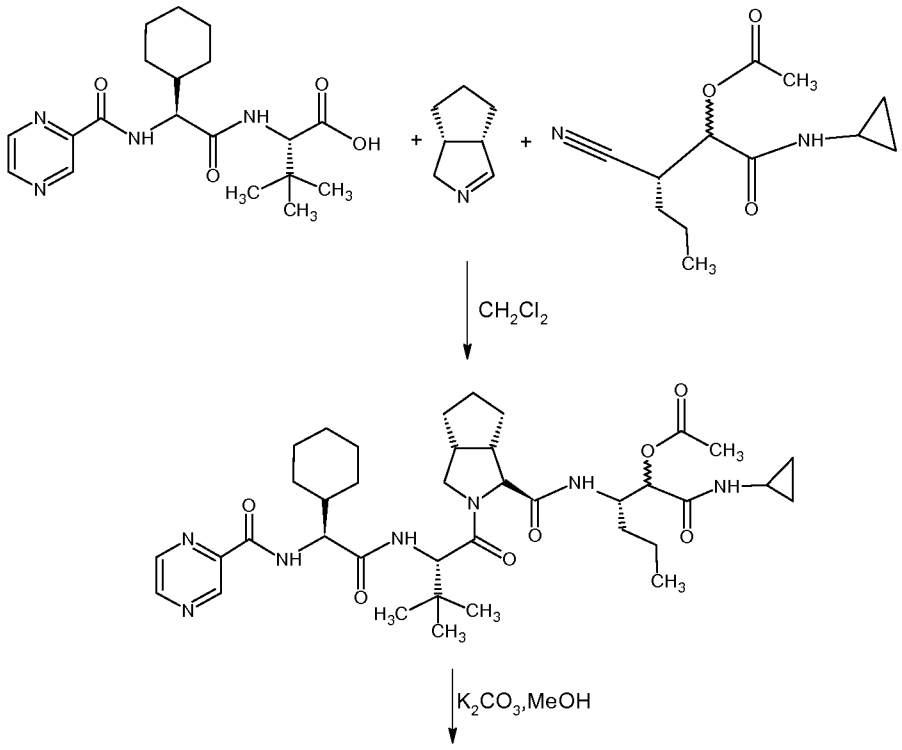
Formula I

Telaprevir is a serine protease inhibitor disclosed in PCT Publication No. WO 02/18369. Processes for the preparation of telaprevir are disclosed in U.S. Patent No. 7,776,887; U.S. Publication No. 2010/0298568; PCT Publication Nos. WO 02/18369, WO 2008/090819, and WO 2011/153423; and Chemical Communications 46(42):7918-7920 (2010).

PCT Publication No. WO 02/18369 discloses a process for the preparation of telaprevir which involves condensing (1S,3aR,6aS)-2-[(2S)-2-({(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino)acetyl}amino]-3,3-dimethylbutanoyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrole-1-carboxylic acid with (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide in the presence of dichloromethane, PyBOP ([benzotriazole-1-yl-oxy]-tripyrrolidinophosphonium hexafluorophosphate), and N,N-diisopropylethylamine

leading to the formation of hydroxy telaprevir, which is further oxidized using Dess Martin Periodinane to obtain telaprevir.

Chemical Communications 46(42):7918-7920 (2010) discloses the following process of preparation of telaprevir:



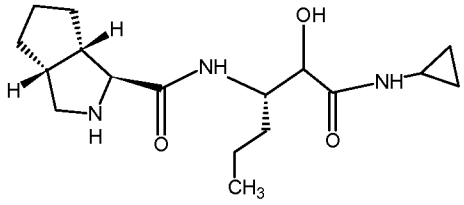
Telaprevir

There remains a need for development of an alternative process for the preparation of telaprevir, which is easier, more economical, and results in a final product with higher purity.

Summary of the Invention

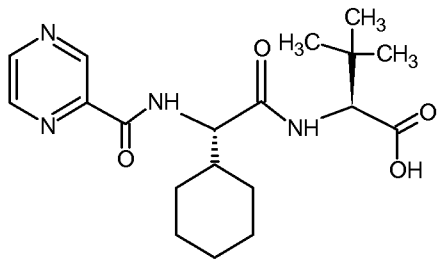
The present invention provides a process for the preparation of telaprevir of Formula I, comprising the steps of:

a) condensing (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]-octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III



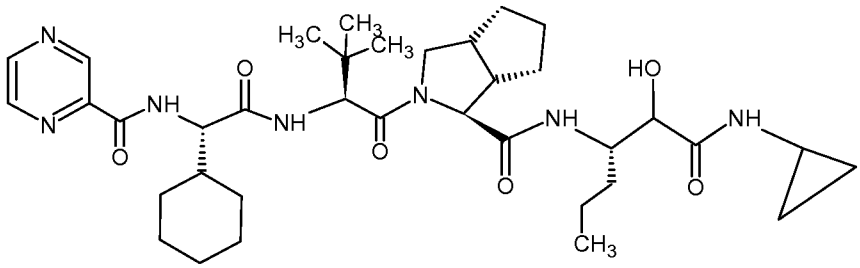
Formula III

with N-{(2S)-2-cyclohexyl-2-[(pyrazin-2ylcarbonyl)amino]acetyl}-3-methyl-L-valine of Formula IV



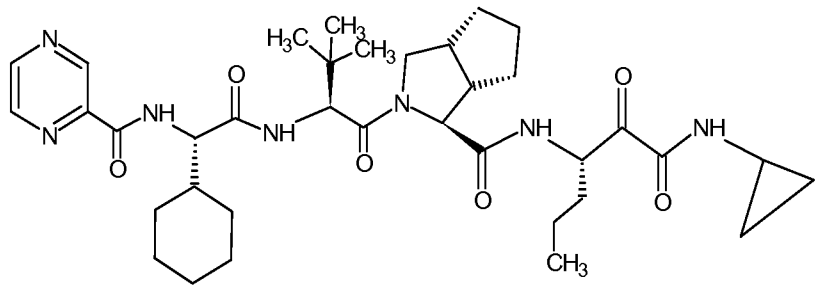
Formula IV

to obtain hydroxy telaprevir of Formula II; and



Formula II

b) oxidizing the hydroxy telaprevir of Formula II to obtain telaprevir of Formula I.



Formula I

Detailed Description of the Invention

(1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III may be prepared by the methods disclosed in U.S. Patent No. 8,188,137, and U.S. Publication No. 2010/0292219.

N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine of Formula IV may be prepared by following the process disclosed in PCT Publication No. WO 02/18369.

The condensation in step a) is carried out in the presence of a coupling agent, a base, and a solvent. Examples of coupling agents include HATU (2-(1H-7-azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium); HBTU (O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate); HDBTU (2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; HOTU (*O*-[(Ethoxycarbonyl) cyanomethylenamino]-N,N,N′,N′-tetramethyluronium hexafluorophosphate); HOBT (N-hydroxybenzotriazole); EDC (N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide); EDC. HCl (N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride); BOP ((benzotriazole-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate); PyBOP (benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate); DEPBT (3-(diethoxy-phosphoryloxy)-3H-benzo[d][1,2,3]triazin-4-one); Oxyma (ethyl (hydroxyimino)cyanoacetate); COMU ((1-cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate); TNTU (2-(endo-5-norborene-2,3-dicarboxyamido)-1,1,3,3-tetramethyluronium tetrafluoroborate; TPTDP (S-

(1-oxo-2-pyridyl)-thio-1,3-dimethylpropyleneuronium tetrafluoroborate); TPTU (O-[1,2-dihydro-2-oxo-1-pyridyl]-N,N, N',N'-tetramethyluronium tetrafluoroborate); TBTU (O-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate); DIC (N,N'-diisopropylcarbodiimide); DCC (*N,N'*-dicyclohexylcarbodiimide); or mixtures thereof. Preferably, the coupling reagent is selected from HOBT, HATU, HBTU, TBTU, EDC, EDC· HCl, or mixtures thereof.

The base may be selected from weak organic or inorganic bases which facilitate the coupling reagent in carrying out the peptide synthesis. Examples of organic bases include N,N-diisopropylethylamine, triethylamine, triisopropylamine, N,N-2-trimethyl-2-propanamine, N-methylmorpholine, 4-dimethylaminopyridine, 2,6-di-tert-butyl-4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or mixtures thereof. Examples of inorganic bases include sodium bicarbonate and potassium bicarbonate. Preferably, the reaction is carried out in the presence of an organic base. Preferably, the organic base is selected from N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, or N,N-2-trimethyl-2-propanamine.

The solvent is selected from the group comprising of nitriles, chlorinated solvents, amides, dialkylsulfoxides, or mixtures thereof. Examples of nitriles include acetonitrile, propionitrile, butyronitrile, or valeronitrile. Examples of chlorinated solvents include dichloromethane, dichloroethane, chlorobenzene, or chloroform. Examples of amides include dimethylformamide, dimethylacetamide, or N-methyl formamide. Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, or dibutylsulfoxide. Preferably, the solvent is selected from dichloromethane, acetonitrile, or dimethylformamide.

The condensation is carried out at about 0°C to about 20°C. Preferably, the condensation is carried out at about 0°C to about 15°C. The temperature of the reaction mixture may be maintained at about 20°C to about 40°C for about 2 hours to about 20 hours. Preferably, the temperature of the reaction mixture is maintained at about 20°C to about 25°C for about 5 hours to about 10 hours.

Isolation of the hydroxy telaprevir of Formula II may be carried out by filtration, concentration, decantation, or combinations thereof. Preferably, the isolation of the hydroxy telaprevir of Formula II is carried out by concentration.

The oxidation in step b) is carried out in the presence of an oxidizing agent and a solvent. Examples of oxidizing agents include Dess-Martin Periodinane, oxalyl chloride, chromium trioxide, or potassium permanganate. Additionally, for rapid oxidation, the oxidizing agents may be used in combination with a catalyst such as TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxy), or TPAP (tetrapropylammonium perruthenate). Preferably, the oxidation is carried out in the presence of Dess-Martin Periodinane.

The solvent is selected from the group comprising of nitriles, aromatic hydrocarbons, chlorinated solvents, dialkylsulfoxides, water, or mixtures thereof. Examples of nitriles include acetonitrile, propionitrile, butyronitrile, and valeronitrile. Examples of aromatic hydrocarbons include toluene and xylene. Examples of chlorinated solvents include dichloromethane, dichloroethane, chlorobenzene, and chloroform. Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, and dibutylsulfoxide. Preferably, the solvent is selected from dichloromethane or toluene.

The oxidation is carried out at about 0°C to about 20°C, preferably at about 0°C to about 10°C. The reaction mixture is stirred at the same temperature for about 30 minutes to about 20 hours. Preferably, the reaction mixture is maintained at about 0°C to about 5°C for about 1 hour to about 5 hours.

Isolation of telaprevir of Formula I may be carried out by filtration, concentration, decantation, or a combination thereof. Preferably, the isolation of telaprevir of Formula I is carried out by concentration.

The processes disclosed above are further illustrated in the examples below. These examples are provided as illustrations only, and therefore should not be construed as limiting of the scope of the invention. Thus, specific embodiments, certain modifications, and equivalents will be apparent to those skilled in the art, and are intended to be included within the scope of the present invention.

EXAMPLES

Example Ia: Preparation of Hydroxy Telaprevir (Formula II)

N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl}-3-methyl-L-valine (Formula IV; 1.16 g) was dissolved in dichloromethane (30 mL). To this solution, TBTU (1.2 g) was added at 12°C. (1S,3aR,6aS)-N-(3S)-1-(cyclopropylamino)-2-hydroxy-1-

oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula III; 1.0 g) and N,N-diisopropylethylamine (0.56 mL) were added at 0°C to 5°C. After the addition, the temperature of the reaction mixture was raised from about 23°C to about 25°C, and the reaction mixture was stirred at the same temperature for about 7 hours. The reaction mixture was washed with 1N HCl and 5% sodium bicarbonate solution. The dichloromethane layer was concentrated to obtain hydroxy telaprevir as a solid residue.

Yield: 1.7 g

Example Ib: Preparation of Hydroxy Telaprevir (Formula II)

N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl}-3-methyl-L-valine (Formula IV; 1.45 g) was dissolved in dichloromethane (25 mL). To this solution, HOBT (0.5 g) and EDC. HCl (0.9 g) were added at 12°C. (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula III; 1.25 g) and N,N-diisopropylethylamine (1.5 mL) were added at 0°C to 5°C. After the addition, the temperature of the reaction mixture was raised from about 23°C to about 25°C, and the reaction mixture was stirred at the same temperature for about 8 hours. The reaction mixture was washed with 1N HCl and 5% sodium bicarbonate solution. The dichloromethane layer was concentrated to obtain hydroxy telaprevir as a solid residue.

Yield: 1.8 g

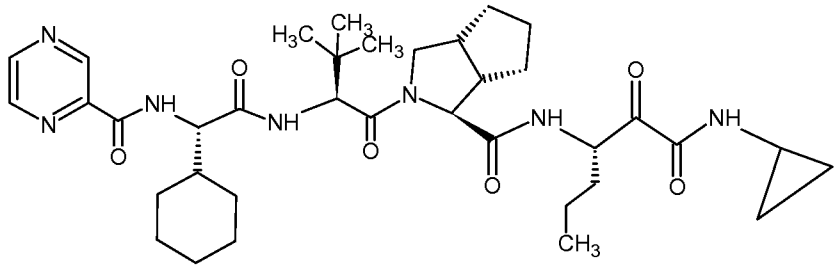
Example II: Preparation of Telaprevir (Formula I)

Hydroxy telaprevir (Formula II; 1.05 g) was dissolved in dichloromethane (25 mL). To the resulting solution, Dess-Martin Periodinane was added at about 5°C. The reaction mixture was stirred at about 0°C to about 5°C for about 2 hours. The progress of the reaction was monitored by thin layer chromatography. After the reaction was complete, the reaction mixture was quenched with sodium thiosulphate solution and washed with sodium bicarbonate solution (20 mL). The dichloromethane layer was concentrated under reduced pressure to obtain telaprevir as a solid residue.

Yield: 0.7 g

We claim:

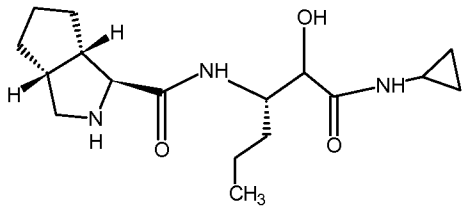
1. A process for the preparation of telaprevir of Formula I



Formula I

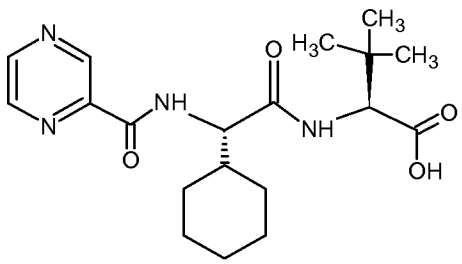
comprising the steps of:

a) condensing (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-



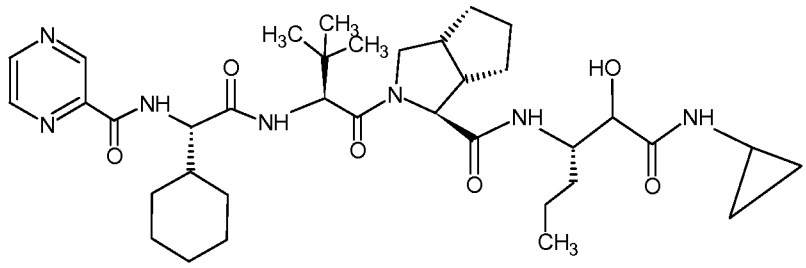
Formula III

oxohexan-3-yl]-octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl}-3-methyl-L-valine of Formula IV



Formula IV

to obtain hydroxy telaprevir of Formula II; and



Formula II

b) oxidizing the hydroxy telaprevir of Formula II to obtain telaprevir of Formula I.

2. The process according to claim 1, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]-octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl) amino]acetyl}-3-methyl-L-valine of Formula IV is carried out in the presence of a coupling agent.

3. The process according to claim 2 wherein the coupling agent is selected from the group consisting of HOBT, HATU, HBTU, TBTU, EDC, EDC· HCl, or mixtures thereof.

4. The process according to claim 1, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]-octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl) amino]acetyl}-3-methyl-L-valine of Formula IV is carried out in the presence of a base selected from N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, or N,N-2-trimethyl-2-propanamine.

5. The process according to claim 1, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]-octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl) amino]acetyl}-3-methyl-L-valine of Formula IV is carried out in the presence of a solvent selected from nitriles, chlorinated solvents, amides, dialkylsulfoxides, or mixtures thereof.

6. The process according to claim 4, wherein the solvent is dichloromethane.

7. The process according to claim 1, wherein the oxidation of the hydroxy telaprevir of Formula II is carried out in the presence of an oxidizing agent selected from Dess-Martin Periodinane, oxalyl chloride, chromium trioxide, or potassium permanganate.

8. The process according to claim 1, wherein the oxidation is carried out in the presence of a solvent selected from the group comprising of nitriles, aromatic hydrocarbons, chlorinated solvents, dialkylsulfoxides, water, or mixtures thereof.

9. The process according to claim 7, wherein the solvent is dichloromethane.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/058130

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K5/117
ADD.

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)
C07K

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7 776 887 B2 (TANOURY GERALD J [US] ET AL) 17 August 2010 (2010-08-17) cited in the application claim 1	1-9
A	US 2006/276404 A1 (GHOSAL ANIMA [US] ET AL) 7 December 2006 (2006-12-07) paragraph [0644] - paragraph [0650]	1-9
X,P	WO 2013/120871 A1 (DIPHARMA FRANCIS SRL [IT]) 22 August 2013 (2013-08-22) claim 15	1-9
E	WO 2013/131978 A1 (DIPHARMA FRANCIS SRL [IT]) 12 September 2013 (2013-09-12) claim 15	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2014	11/02/2014

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, Fax: (+31-70) 340-3016	Schleifenbaum, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/058130

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