The present invention relates to a process for preparing 1-[[2'-[2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl][1,l'-biphenyl]-4-yl]-methyl]-2-ethoxy-1H-benimidazole-7-carboxylic acid of formula (I) (azilsartan). The invention also relates to preparation of new solid forms of intermediates that make it possible to obtain azilsartan with a high purity over 99.7% (HPLC) and to their characterization.
A PROCESS FOR PREPARING HIGHLY PURE AZILSARTAN

Technical Field

This invention relates to a process for preparing 1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)l,r-biphenyl]-4-yl]methyl]-2-ethoxy-lH-benzimidazole-7-carboxylic acid (azilsartan) of formula (I)

The invention also relates to preparation of new solid forms of intermediates that make it possible to obtain azilsartan with a high purity over 99.7 % (HPLC) and to their characterization.

Background Art

Azilsartan (I), which is a highly selective blocker of angiotensin II AT1 receptors, was developed by Takeda and is used for the treatment of high blood pressure. Its synthesis is described in EP 0 520 423 (Scheme 1)

Scheme 1

wherein examples of azilsartan formulations are also given. The applications WO20 11063764, WO2012097697 and WO2013088384 describe salts of azilsartan with organic amines,
crystalline forms of azilsartan, J1 and J2, as well as an amorphous form of azilsartan. An isopropanol solvate of azilsartan is described in the new application US2014113942.

The application WO2012107814 discusses a process for preparing azilsartan using various cyclizing agents in the presence of a base. The application WO2012157980 describes cyclization with the use of carbonyl imidazole. A process for preparing azilsartan, comprising a cyclizing reaction without the presence of a solvent, is described in WO2014049512.

**Disclosure of Invention:**

The invention relates to preparation of very pure azilsartan. The process is based on the use and preparation of new solid forms of the key intermediates that have a principal influence on the purity of the final product - azilsartan. In particular, they are hemisolvates (2:1) of the ethyl ester (III) with 2-methyltetrahydrofuran (IIia) or with methyl isobutyl ketone.

Azilsartan (I), obtained according to the patent EP 2 119 715, exhibits a 95.0% HPLC purity at the most. Purity of the last intermediate, which is azilsartan ethyl ester (III), is of key importance for its preparation as the final compound is difficult to crystallize. In our process, where we obtain the ethyl ester (III), it is the impurity A, produced during the reaction of the intermediate (II) with diethyl carbonate under basic catalysis, that is the most problematic.

**Impurity A:**

![Impurity A](image)

It has surprisingly been found, during the investigation of purification of the ethyl ester (III), that the ethyl ester (III) is best purifies in the form of the newly discovered, highly crystalline solvates with 2-methyltetrahydrofuran (IIia), or methyl isobutyl ketone (IIlb). The table below illustrates advantages of purification of the ethyl ester during recrystallization in the form of the new crystalline solvates; the input raw material contained 3.6% of impurity A.
Both the solvates are in the form of hemisolvates (2:1); they contain one molecule of the solvent per a molecule of the ethyl ester.

Table 1

<table>
<thead>
<tr>
<th>Exp.</th>
<th>1 g /10 ml</th>
<th>Dimer A %</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>0.6</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>Tetrahydrofuran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ethyl acetate</td>
<td>0.7</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>Methyl ethyl ketone (MEK)</td>
<td>0.72</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>2-Methyl-THF</td>
<td>0.25</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Acetonitrile</td>
<td>0.88</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>Isopropanol</td>
<td>0.4</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>2-Butanol</td>
<td>0.37</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>Methylcyclohexane</td>
<td>not.cryst</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Toluene</td>
<td>not.cryst</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>n-Butanol</td>
<td>1.35</td>
<td>51</td>
</tr>
<tr>
<td>12</td>
<td>Methyl isobutyl ketone (MIBK)</td>
<td>0.32</td>
<td>86</td>
</tr>
<tr>
<td>13</td>
<td>Butyl acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Dimethyl acetamide</td>
<td>not.cryst</td>
<td></td>
</tr>
</tbody>
</table>

Solvates can also be produced in mixtures of solvents containing 2-methyltetrahydrofuran or methyl isobutyl ketone. Solvents in which the above mentioned crystalline solvates can develop include primary or secondary alcohols and ketones. The use of ethanol, methanol, isopropanol or acetone and methyl ethyl ketone is especially convenient.

Then, a solvate produced this way can be transformed to a free acid of azilsartan with a high yield without problems.

The resulting solvate of azilsartan ethyl ester (III) is transformed to azilsartan (I) by means of alkaline hydrolysis, which may be carried out with the use of sodium or potassium hydroxide in water or suitable solvents of the alcohol type at a temperature from 25°C to 80°C. As the hydrolysis does not virtually change the chemical purity of the intermediate, azilsartan can be, after acidification, obtained in an excellent purity of about 99.8%. Hydrochloric or acetic acid can be used for the acidification.
The solvate of azilsartan ethyl ester with 2-methyltetrahydrofuran exhibits the following main characteristic peaks in X-ray powder diffraction, measured with the use of CuKα radiation: 8.9; 10.5; 12.0; 16.8; 19.6 and 23.5 ± 0.2° 2-theta. The prepared solvate is further characterized with the use of DSC (Fig. 2).

Table 2: XRPD - diffraction peaks corresponding to the solvate of azilsartan ethyl ester with 2-methyltetrahydrofuran (IIia)

<table>
<thead>
<tr>
<th>Pos. [°2Th.]</th>
<th>d-interplanar spacing [Å]=0.1nm</th>
<th>Rel. Int. [%]</th>
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<tbody>
<tr>
<td>8.26</td>
<td>10.699</td>
<td>20.6</td>
</tr>
<tr>
<td>8.87</td>
<td>9.957</td>
<td>100.0</td>
</tr>
<tr>
<td>10.48</td>
<td>8.432</td>
<td>55.1</td>
</tr>
<tr>
<td>11.98</td>
<td>7.379</td>
<td>17.6</td>
</tr>
<tr>
<td>14.10</td>
<td>6.278</td>
<td>2.7</td>
</tr>
<tr>
<td>15.51</td>
<td>5.710</td>
<td>5.8</td>
</tr>
<tr>
<td>16.26</td>
<td>5.448</td>
<td>5.7</td>
</tr>
<tr>
<td>16.76</td>
<td>5.285</td>
<td>15.8</td>
</tr>
<tr>
<td>18.38</td>
<td>4.822</td>
<td>11.2</td>
</tr>
<tr>
<td>19.56</td>
<td>4.535</td>
<td>14.9</td>
</tr>
<tr>
<td>21.18</td>
<td>4.191</td>
<td>10.0</td>
</tr>
<tr>
<td>21.75</td>
<td>4.083</td>
<td>7.8</td>
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<td>22.77</td>
<td>3.903</td>
<td>7.0</td>
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<td>25.39</td>
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<td>25.87</td>
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<td>26.94</td>
<td>3.306</td>
<td>2.3</td>
</tr>
<tr>
<td>27.54</td>
<td>3.236</td>
<td>3.1</td>
</tr>
<tr>
<td>31.81</td>
<td>2.811</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Table 3: XRPD - characteristic diffraction peaks corresponding to the hemisolvate of azilsartan ethyl ester with methyl isobutyl ketone (IIIb)

<table>
<thead>
<tr>
<th>Pos. [°2Th.]</th>
<th>d-interplanar spacing [Å]=0.1nm</th>
<th>Rel. Int. [%]</th>
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<td>8.04</td>
<td>10.986</td>
<td>8.9</td>
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<td>8.61</td>
<td>10.256</td>
<td>100.0</td>
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<tr>
<td>10.75</td>
<td>8.221</td>
<td>2.4</td>
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<tr>
<td>11.72</td>
<td>7.546</td>
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<td>14.60</td>
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<td>19.17</td>
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<td>20.38</td>
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<tr>
<td>20.62</td>
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</tr>
<tr>
<td>20.86</td>
<td>4.255</td>
<td>3.9</td>
</tr>
<tr>
<td>21.36</td>
<td>4.156</td>
<td>3.6</td>
</tr>
<tr>
<td>22.02</td>
<td>4.033</td>
<td>2.3</td>
</tr>
<tr>
<td>22.45</td>
<td>3.957</td>
<td>4.1</td>
</tr>
<tr>
<td>23.66</td>
<td>3.757</td>
<td>2.3</td>
</tr>
<tr>
<td>24.21</td>
<td>3.673</td>
<td>1.6</td>
</tr>
<tr>
<td>25.16</td>
<td>3.537</td>
<td>2.8</td>
</tr>
<tr>
<td>25.52</td>
<td>3.487</td>
<td>4.1</td>
</tr>
<tr>
<td>27.22</td>
<td>3.274</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The solvate of azilsartan ethyl ester with methyl isobutyl ketone exhibits the following main characteristic peaks in X-ray powder diffraction, measured with the use of CuKα radiation: 8.6; 11.7; 16.6; 19.2; 21.4 and 25.5 ± 0.2° 2-theta.

The prepared solvate is further characterized with the use of DSC (Fig. 5).
**Brief Description of Drawings**

Fig. 1: XRPD pattern for the solvate of azilsartan ethyl ester with 2-methyltetrahydrofuran (IIia)

Fig. 2: DSC curve for the solvate of azilsartan ethyl ester with 2-methyltetrahydrofuran (IIia)

Fig. 3: TGA curve for the solvate of azilsartan ethyl ester with 2-methyltetrahydrofuran (IIia)

Fig. 4: XRPD pattern for the solvate of azilsartan ethyl ester with methyl isobutyl ketone (IIlb)

Fig. 5: DSC curve for the solvate of azilsartan ethyl ester with methyl isobutyl ketone (Mb)

Fig. 6: TGA curve for the solvate of azilsartan ethyl ester with methyl isobutyl ketone (IIlb)

**Examples**

The samples in the examples below were characterized by the X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) methods. The amounts of solvents were determined with the use of GC.

**Measurement parameters of XRPD:** The diffraction patterns were measured using an X'PERT PRO MPD PANalytical diffractometer with a graphite monochromator, used radiation CuKa (λ= 1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2Θ increment: 0.01° 2Θ For the measurement a flat powder sample was used that was placed on a Si plate. For the setting of the primary optical equipment programmable divergence slits with the irradiated area of the sample of 10 mm, 0.02 rad Soller slits and a ¼ anti-diffusion slit were used. For the setting of the secondary optical equipment an X'Celerator detector with maximum opening of the detection slot, 0.02 rad Soller slits and a 5.0 mm anti-diffusion slit were used.

**Differential scanning calorimetry (DSC) records** were measured using a DSC Pyris 1 device from Perkin Elmer. The sample charge in a standard Al pot was between 3 and 4 mg and the heating rate was 10°C/min. The temperature program that was used consists of 1 min of stabilization at the temperature of 50°C and then of heating up to 250°C at the heating rate of 10°C/min. 4.0 N₂ at the flow rate of 20 ml/min was used as the carrier gas.
Thermogravimetric analysis (TGA) records were measured using a TGA 6 device from Perkin Elmer. The sample charge in a corundum pot was between 19 and 20 mg and the heating rate was 10°C/min. The temperature program that was used consists of 1 minute's stabilization at the temperature of 22°C and then of heating up to 250(300)°C at the heating rate of 10°C/min. 4.0 N₂ at the flow of 20 ml/min was used as the carrier gas.

The invention is clarified in a more detailed way using the working examples below. The examples, which illustrate the improvement of the procedure in accordance with the invention, only have an illustrative character and do not restrict the scope of the invention in any respect.

Example 1:
Preparation of 2-ethoxy-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1H-benzo[d]-imidazole-7-carboxylic acid ethyl ester (III).

The ethoxy oxime (II) (390 g; 851 mmol) is suspended in 3600 ml of diethyl carbonate. The suspension is heated up to 65°C. A solution of sodium ethoxide in ethanol (21 %, 400 ml, 1072 mmol) is added dropwise to the reaction mixture at 65°C during 30 minutes. After completion of the addition the reaction mixture is agitated at 65°C for 30 minutes. The reaction mixture is cooled down to 60°C and water (1350 ml) is added. The resulting emulsion is agitated for at least 15 minutes. After separation of the layers the organic phase is extracted with water (1350 ml). The combined aqueous extracts are diluted with ethanol (1350 ml) and the temperature is adjusted to 40°C. Acetic acid (111 ml, 1940 mmol) is added to the solution dropwise at 40°C during 30 minutes. The resulting suspension is agitated at 40°C for 30 minutes and then cooled down to 20°C. The separated substance is aspirated and washed with water (2 x 450 ml). The resulting product is then dried in a vacuum drier at 45°C. 397 g (86% of the theoretical quantity, HPLC 95.8%) of azilsartan ethyl ester (III) was obtained.
Example 2:
Preparation of 2-ethoxy-l-((2'-((5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-l H-benzo[£¾-imidazole-7-carboxylic acid ethyl ester hemisolvate with methyl isobutyl ketone (UJb).

The ethoxy oxime (II) (150 g; 327 mmol) is suspended in 1370 ml of diethyl carbonate. The suspension is heated up to 65°C. A solution of sodium ethoxide in ethanol (21 %, 154 ml, 412 mmol) is added dropwise to the reaction mixture at 65°C during 30 minutes. After completion of the addition the reaction mixture is agitated at 65°C for 30 minutes. The reaction mixture is cooled down to 60 °C and water (520 ml) is added. The resulting emulsion is agitated for at least 15 minutes. After separation of the layers the organic phase is extracted with water (520 ml). The combined aqueous extracts are diluted with ethanol (600 ml) and methyl isobutyl ketone (100 ml). The temperature of the solution is adjusted to 40°C. Acetic acid (43 ml, 750 mmol) is added to the solution dropwise at 40°C during 30 minutes. The resulting suspension is agitated at 40°C for 30 minutes and then cooled down to 20°C. The separated substance is aspirated and washed with water (2 x 150 ml). The final product is dried in a vacuum drier at 45°C. 154 g (88% of the theoretical quantity, HPLC 99.5%) of azilsartan ethyl ester hemisolvate with methyl isobutyl ketone (Illb) was obtained.

Example 3:
Preparation of 2-ethoxy-l-((2'-((5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-l H-benzo[£¾-imidazole-7-carboxylic acid ethyl ester hemisolvate with 2-methyltetrahydrofuran (Illia).

The ethoxy oxime (II) (75 g; 164 mmol) is suspended in 690 ml of diethyl carbonate. The suspension is heated up to 65°C. A solution of sodium ethoxide in ethanol (21 %, 77 ml, 206 mmol) is added dropwise to the reaction mixture at 65°C during 30 minutes. After completion of the addition the reaction mixture is agitated at 65°C for 30 minutes. The reaction mixture is cooled down to 60 °C and water (260 ml) is added. The resulting emulsion is agitated for at least 15 minutes. After separation of the layers the organic phase is extracted with water (260 ml). The combined aqueous extracts are diluted with ethanol (260 ml) and 2-methyltetrahydrofuran (150 ml). The temperature of the solution is adjusted to 40°C. Acetic
Acid (21 ml, 370 mmol) is added to the solution dropwise at 40°C during 30 minutes. The resulting suspension is agitated at 40°C for 30 minutes and then cooled down to 20°C. The separated substance is aspirated and washed with water (2 x 75 ml). The final product is dried in a vacuum drier at 45°C. 72.5 g (84% of the theoretical quantity, HPLC 99.4%) of azilsartan ethyl ester hemisolvate 2-methyltetrahydrofuran (Ilia) was obtained.

Example 4:
Preparation of 2-ethoxy-1-((2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1H-benza[\textit{i}]-iraida2ole-7-carboxylic acid ethyl ester hemisolvate with 2-methyltetrahydrofuran (Ilia).

Azilsartan ethyl ester (III) (380 g; 784 mmol) is suspended in 2600 ml of 2-methyltetrahydrofuran. The suspension is heated up to reflux. 1200 ml of distillate is removed from the reaction mixture by distillation. The resulting suspension is cooled down to 45°C. The reaction mixture is agitated at 45°C for 30 minutes and then cooled down to 20°C. The separated substance is aspirated and washed with cooled 2-methyltetrahydrofuran (75 ml). The final product is dried in a vacuum drier at 45°C. 372 g (90% of the theoretical quantity, HPLC 99.7%) of azilsartan ethyl ester hemisolvate 2-methyltetrahydrofuran (Ilia) was obtained.

Example 5:
Preparation of 2-ethoxy-1-((2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1H-benza[\textit{f}]-imidazole-7-carboxylic acid ethyl ester hemisolvate with methyl isobutyl ketone (\textit{Ilb}).

Azilsartan ethyl ester (III) (150 g; 310 mmol) is suspended in 600 ml of 2-methyl isobutyl ketone. The suspension is heated up to reflux. The solution is cooled down to 95°C and an inoculum of the product is added. The resulting suspension is gradually cooled down to 20°C. The separated substance is aspirated and washed with cooled methyl isobutyl ketone (250 ml). The final product is then dried in a vacuum drier at 45 °C. 140 g (85% of the theoretical quantity, HPLC 99.6%) of azilsartan ethyl ester hemisolvate with methyl isobutyl ketone (\textit{Ilb}) was obtained.
Example 6:
Preparation of 1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)[^\^] 1'-biphenyl]-4-yl]methyl]-2-ethoxy-1H-benzimidazole-7-carboxylic acid (I).

Ethoxy azilsartan hemisolvate with 2-methyltetrafuran (IIa) (160 g) was weighed into a 5 liter pot and suspended in a NaOH/water solution (38 g/500 ml). The reaction mixture is heated up to 50°C and agitated for 4 hours. The reaction mixture is diluted with acetone (250 ml), acetic acid (101 g) is added and the mixture is left to crystallize at 50°C for 1 hour. After cooling to 20°C and agitation for half an hour the product is aspirated and washed with water (2 x 110 ml). The final product is then dried in a vacuum drier at 45°C. 129 g (93% of the theoretical quantity, HPLC 99.7%) of azilsartan (I) was obtained.

Example 7:
Preparation of 1-[[2-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)[l,1'-biphenyl]-4-yl]methyl]-2-ethoxy-1H-benzimidazole-7-carboxylic acid (I).

Ethoxy azilsartan hemisolvate with methyl isobutyl ketone (IIb) (100 g) was weighed into a 5 liter pot and suspended in a NaOH/water solution (23 g/315 ml). It was heated up to 50°C and agitated for 4 hours. The reaction mixture is diluted with acetone (160 ml), acetic acid (63 g) is added and the mixture is left to crystallize at 50°C for 1 hour. Then, the suspension is cooled down to 20°C and, after half an hour, aspirated and washed with water (2 x 70 ml). The resulting product is dried in a vacuum drier at 45°C. 82 g (95% of the theoretical quantity, HPLC 99.7%) of azilsartan (I) was obtained.
Claims:

1. A process for preparing azilsartan of formula (I),

   ![Chemical Structure](image1)

   characterized in that azilsartan ethyl ester of formula (III)

   ![Chemical Structure](image2)

   is transformed to a solvate with a solvent selected from 2-methyltetrahydrofuran and methyl isobutyl ketone, which solvate is transformed to azilsartan by subsequent basic hydrolysis, the preparation of the solvate being optionally conducted in the presence of another solvent.

2. The process for preparing azilsartan according to claim 1, characterized in that the preparation of the solvate is conducted in the presence of ethanol at 40°C.

3. The process for preparing azilsartan according to claim 1, characterized in that the hydrolysis is conducted in the presence of a base selected from NaOH and KOH at 50°C.

4. The solvate of azilsartan ethyl ester with 2-methyltetrahydrofuran, which exhibits the following main characteristic peaks in X-ray powder diffraction, measured with the use of CuKα radiation: 8.9; 10.5; 12.0; 16.8; 19.6 and 23.5 ± 0.2° 2-theta.
5. The solvate of azilsartan ethyl ester with methyl isobutyl ketone, which exhibits the following main characteristic peaks in X-ray powder diffraction, measured with the use of CuKa radiation: 8.6; 11.7; 16.6; 19.2; 21.4 and 25.5 ± 0.2° 2-theta.
Onset = 175.49°C
Delta H = 100.4 J/g

Onset = 95.09°C
Delta H = 5.6 J/g
Fig. 3

Delta Y = 3.46%
Onset = 176.5°C  
Delta H = 89.8 J/g

Onset = 110.6°C  
Delta H = 21.5 J/g
A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/10 A61K31/4245 A61P9/12

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)

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  * "A" document defining the general state of the art which is not considered to be of particular relevance
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* S document member of the same patent family

Date of the actual completion of the international search: 1 December 2015

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Authorized officer: Sahagun Krause, H
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<th>Category</th>
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