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(54) Title: ERTUGLIFLOZIN CO-CRYSTALS AND PROCESS FOR THEIR PREPARATION

(57) Abstract: The present invention relates to processes for the preparation of an ertugliflozin-L- pyroglutamic acid (1:1) and co-crystal ertugliflozin-L-proline (1:1) co-crystal. The present invention further relates to an ertugliflozin-L-proline (1:2) co-crystal, processes for its preparation, and its use for the treatment of type 2 diabetes mellitus.
ERTUGLIFLOZIN CO-CRYSTALS AND PROCESS FOR THEIR PREPARATION

Field of the Invention

The present invention relates to processes for the preparation of an ertugliflozin-L-pyroglutamic acid (1:1) co-crystal and ertugliflozin-L-proline (1:1) co-crystal. The present invention further relates to an ertugliflozin-L-proline (1:2) co-crystal, processes for its preparation, and its use for the treatment of type 2 diabetes mellitus.

Background of the Invention

Ertugliflozin chemically is \((1S,2S,3S,4R,5S)-5-\text{(4-chloro-3-(4-ethoxybenzyl)phenyl)}-\text{l-hydroxymethyl-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, represented by Formula I.}

![Formula I](image)

Ertugliflozin is a selective sodium glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus.

U.S. Patent No. 8,080,580 discloses processes for the preparation of ertugliflozin and its conversion to ertugliflozin-L-proline (1:1) co-crystal and ertugliflozin-L-pyroglutamic acid (1:1) co-crystal in solvents such as alcohol or aqueous alcohol. It also discloses the use of excess of L-proline and L-pyroglutamic acid.

PCT Publication No. WO 2014/15915 I discloses a process for the preparation of ertugliflozin and its conversion to an ertugliflozin-L-pyroglutamic acid (1:1) co-crystal using excess L-pyroglutamic acid.

There is a need in the art for providing a process for the preparation of ertugliflozin co-crystals which is commercially viable and economical. Further, there is a need in the art for providing an ertugliflozin co-crystal with desirable physico-chemical properties such as solubility, rate of dissolution of the drug, chemical stability, melting point, and hygroscopicity.
Summary of the Invention

The present invention relates to processes for the preparation of an ertugliflozin-L-pyroglutamic acid (1:1) co-crystal and ertugliflozin-L-proline (1:1) co-crystal. The present invention further relates to an ertugliflozin-L-proline (1:2) co-crystal, processes for its preparation, and its use for the treatment of type 2 diabetes mellitus.

Brief Description of the Drawings

Figure 1 depicts an X-Ray Powder Diffraction (XRPD) pattern of an ertugliflozin-L-proline (1:2) co-crystal.

Figure 2 depicts a Differential Scanning Calorimetry (DSC) thermogram of an ertugliflozin-L-proline (1:2) co-crystal.

Figure 3 depicts a Thermogravimetric Analysis (TGA) thermogram of an ertugliflozin-L-proline (1:2) co-crystal.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term "about," as used herein, refers to any value which lies within the range defined by a number up to ±10% of the value.

The term "ambient temperature," as used herein, refers to any value which lies within the range between 20°C and 30°C.

The term "contacting," as used herein, refers to bringing two or more components together by dissolving, mixing, suspending, blending, slurrying, or stirring.

The term "co-crystal," as used herein, refers to a stoichiometric multi component system comprising an active pharmaceutical ingredient (API) and a pharmaceutical co-crystal former, wherein the API and the pharmaceutical co-crystal former are connected by non-covalent interactions.

The term "co-crystal former," as used herein, refers to compounds which can form intermolecular interactions with an API and co-crystallize with it.

The term "solvent," as used herein, includes, for example, saturated or unsaturated hydrocarbons, alcohols, ethers, esters, halogenated hydrocarbons, carboxylic acids, ketones, amides, sulfoxides, water, or mixtures thereof.
The term "anhydrous solvent," as used herein, includes, for example, saturated or unsaturated hydrocarbons, alcohols, ethers, esters, halogenated hydrocarbons, carboxylic acids, ketones, amides, sulfoxides, or mixtures thereof.

Examples of saturated or unsaturated hydrocarbons include benzene, toluene, cyclohexane, and xylenes. Examples of alcohols include methanol, ethanol, 1-propanol, 1-butanol, 2-butanol, and tertiary alcohols having from one to six carbon atoms. Examples of ethers include diethyl ether, ethyl methyl ether, methyl tertiary butyl ether, diisopropyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, and 1,4-dioxane. Examples of esters include ethyl acetate, methyl acetate, isopropyl acetate, and tertiary butyl acetate. Examples of halogenated hydrocarbons include dichloromethane and chloroform. Examples of carboxylic acids include formic acid, acetic acid, and propionic acid. Examples of ketones include acetone, 2-butanone, diethyl ketone, ethyl methyl ketone, and methyl isobutyl ketone. Examples of amides include N,N-dimethylformamide and N,N-dimethylacetamide. Examples of sulfoxides include dimethyl sulfoxide and diethyl sulfoxide.

A first aspect of the present invention provides a process for the preparation of an ertugliflozin-L-pyroglutamic acid (1:1) co-crystal of Formula Ic,

![Formula Ic](image)

wherein the process comprises contacting ertugliflozin with L-pyroglutamic acid in the presence of a solvent, wherein the amount of L-pyroglutamic acid is about 1 mole equivalent to about 1.5 mole equivalents with respect to ertugliflozin.

Ertugliflozin used as the starting material can be prepared by methods known in the art, for example, as in U.S. Patent No. 8,080,580.

The solvent is selected from the group comprising water, ethyl acetate, isopropyl acetate, 2-butanone, methyl isobutyl ketone, and methyl tertiary butyl ether.

In one embodiment of this aspect, the contacting of the ertugliflozin with the L-pyroglutamic acid is carried out at ambient temperature.
Preferably, the amount of L-pyroglutamic acid is about 1 mole equivalent to about 1.1 mole equivalents with respect to ertugliflozin.

The ertugliflozin-L-pyroglutamic acid (1:1) co-crystal may be isolated by employing one or more techniques selected from the group consisting of filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, and recrystallization. The ertugliflozin-L-pyroglutamic acid (1:1) co-crystal may further be dried using conventional techniques, for example, drying, drying under vacuum, spray drying, freeze drying, air drying, or agitated thin film drying.

A second aspect of the present invention provides a process for the preparation of an ertugliflozin-L-proline (1:1) co-crystal of Formula lb.

![Formula lb](image)

wherein the process comprises contacting ertugliflozin with L-proline in the presence of a solvent, wherein the amount of L-proline is about 1 mole equivalent to about 1.5 mole equivalents with respect to ertugliflozin.

Ertugliflozin used as the starting material can be prepared by methods known in the art, for example, as in U.S. Patent No. 8,080,580.

Preferably, the solvent is ethyl acetate.

In one embodiment of this aspect, the contacting of the ertugliflozin with the L-proline is carried out at ambient temperature.

Preferably, the amount of L-proline is about 1 mole equivalent to about 1.1 mole equivalents with respect to ertugliflozin.

The ertugliflozin-L-proline (1:1) co-crystal may be isolated by employing one or more techniques selected from the group consisting of filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, and recrystallization. The ertugliflozin-L-proline (1:1) co-crystal may
further be dried using conventional techniques, for example, drying, drying under vacuum, spray drying, freeze drying, air drying, or agitated thin film drying.

A third aspect of the present invention provides an ertugliflozin-L-proline (1:2) co-crystal of Formula 1a.

![Formula 1a](image)

In one embodiment of this aspect, the ertugliflozin-L-proline (1:2) co-crystal is characterized by an X-ray powder diffraction (XRPD) pattern substantially as depicted in Figure 1.

In another embodiment of this aspect, the ertugliflozin-L-proline (1:2) co-crystal is characterized by an XRPD having interplanar spacing (d) values at about 27.3, 5.5, 4.8, 4.7, and 4.2 Å. The ertugliflozin-L-proline (1:2) co-crystal is further characterized by an XRPD having additional interplanar spacing (d) values at about 13.7, 5.1, 4.4, 3.8, 3.5, and 2.8 Å.

In yet another embodiment of this aspect, the ertugliflozin-L-proline (1:2) co-crystal is characterized by an XRPD having characteristic peak values at about 3.2, 16.2, 18.4, 18.9, and 21.4 ±0.2° 2Θ. The ertugliflozin-L-proline (1:2) co-crystal is further characterized by an XRPD having additional characteristic peak values at about 6.5, 17.4, 20.4, 23.5, 25.5, and 31.6 ±0.2° 2Θ.

Table 1 provides the 2Θ values, the corresponding d-spacing values (Å), and the relative intensity of the ertugliflozin-L-proline (1:2) co-crystal.
In another embodiment of this aspect, the ertugliflozin-L-proline (1:2) co-crystal is characterized by a differential scanning calorimetric (DSC) thermogram having endothermic peaks at about 148°C and 236°C, as depicted in Figure 2.
In another embodiment of this aspect, the ertugliflozin-L-proline (1:2) co-crystal is characterized by a thermogravimetric analysis (TGA) thermogram as depicted in Figure 3.

A fourth aspect of the present invention provides a process for the preparation of an ertugliflozin-L-proline (1:2) co-crystal of Formula 1a,

![Chemical Structure](image)

**Formula 1a**

wherein the process comprises contacting ertugliflozin with L-proline in the presence of an anhydrous solvent.

Ertugliflozin used as the starting material can be prepared by methods known in the art, for example, as in U.S. Patent No. 8,080,580.

Preferably, the anhydrous solvent is selected from the group comprising 2-butanone, ethyl acetate, and a mixture of ethanol and methyl tertiary butyl ether.

In one embodiment of this aspect, the contacting of ertugliflozin with L-proline is carried out at ambient temperature.

In another embodiment of this aspect, the amount of L-proline is about 0.5 mole equivalent to about 5 mole equivalents with respect to ertugliflozin. Preferably, the amount of L-proline is about 0.8 mole equivalent to about 2 mole equivalents with respect to ertugliflozin.

In yet another embodiment of this aspect, the water content of the anhydrous solvent is not more than 0.15%. Preferably, the water content of the anhydrous solvent is not more than 0.1%.

The ertugliflozin-L-proline (1:2) co-crystal may be isolated by employing one or more techniques selected from the group consisting of filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, and recrystallization. The ertugliflozin-L-proline (1:2) co-crystal may further be dried using conventional techniques, for example, drying, drying under vacuum, spray drying, freeze drying, air drying, or agitated thin film drying.
A fifth aspect of the present invention provides a pharmaceutical composition comprising an ertugliflozin-L-proline (1:2) co-crystal and one or more pharmaceutically acceptable carriers, diluents, or excipients.

A sixth aspect of the present invention provides the use of an ertugliflozin-L-proline (1:2) co-crystal for the treatment of type 2 diabetes mellitus.

While the present invention has been described in terms of its specific aspects, 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.

**Methods:**

The XRPD of the samples were determined by using Instrument: PANalytical®; Model: X’pert PRO; Detector: X’celerator ®; Step size: 0.02; Range: 3-40 degree 2 theta; CuKa radiation at 45kV and 40 mA.

The DSC of the samples were determined using a Mettler-Toledo® 821e. Data collection parameters: Scanning rate: 10°C/min; Temperature: 30°C to 300°C.

The TGA of the samples were determined by using a TA® Q500 between 30°C and 300°C at 10°C/min scan rate.

The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

**EXAMPLES**

**Example 1:** Preparation of ertugliflozin-L-proline (1:1) co-crystal

Ertugliflozin (0.5 g) and L-proline (0.131 g) were added to ethyl acetate (3 mL, water content ~ 0.18%), and then the mixture was stirred for 1 hour at 25°C to 30°C. Ethyl acetate (2 mL) was added to the reaction mixture, and the mixture was stirred for 16 hours. The obtained solid was filtered, and then dried under vacuum at 25°C to 30°C.

Yield: 0.61 g

**Example 2:** Preparation of ertugliflozin-L-pyroglutamic acid (1:1) co-crystal

Ertugliflozin (0.5 g) was added to a solution of L-pyroglutamic acid (2.2 mL; L-pyroglutamic acid (0.563 g) dissolved in water (2.73 mL)), and then the solution was stirred for 1.5 hours at 25°C to 30°C. Water (1.5 mL) was added to the reaction mixture,
and then the mixture was stirred for 1 hour. The obtained solid was filtered, and then
dried under vacuum at 40°C for 6 hours.

Yield: 0.472 g

Example 3: Preparation of erugliflozin-L-pyroglutamic acid (1:1) co-crystal

Ertugliflozin (0.225 g) and L-pyroglutamic acid (0.067 g) were added to ethyl acetate (3 mL), and then the mixture was stirred for 3 hours at 25°C to 30°C. Ethyl acetate (2 mL) was added to the reaction mixture, and the mixture was stirred for 4 hours. The obtained solid was filtered, and then washed with ethyl acetate (3 mL). The solid was dried under vacuum at 25°C to 30°C for 1 hour, and then at 40°C for 5 hours.

Yield: 0.2 g

Example 4: Preparation of erugliflozin-L-pyroglutamic acid (1:1) co-crystal

Ertugliflozin (0.225 g) and L-pyroglutamic acid (0.067 g) were added to isopropyl acetate (3 mL), and then the mixture was stirred for 3 hours at 25°C to 30°C. Isopropyl acetate (2 mL) was added to the reaction mixture, and the mixture was stirred for 4 hours. The obtained solid was filtered, and then washed with isopropyl acetate (4 mL). The solid was dried under vacuum at 25°C to 30°C for 1 hour, and then at 40°C for 5 hours.

Yield: 0.22 g

Example 5: Preparation of erugliflozin-L-pyroglutamic acid (1:1) co-crystal

Ertugliflozin (0.225 g) and L-pyroglutamic acid (0.067 g) were added to 2-butanone (3 mL), and then the mixture was stirred for 3 hours at 25°C to 30°C. 2-Butanone (2 mL) was added to the reaction mixture, and the mixture was stirred for 4 hours. The obtained solid was filtered, and then washed with 2-butanone (3 mL). The solid was dried under vacuum at 25°C to 30°C for 1 hour, and then at 40°C for 5 hours.

Yield: 0.14 g

Example 6: Preparation of erugliflozin-L-pyroglutamic acid (1:1) co-crystal

Ertugliflozin (0.225 g) and L-pyroglutamic acid (0.067 g) were added to methyl isobutyl ketone (3 mL), and then the mixture was stirred for 3 hours at 25°C to 30°C. Methyl isobutyl ketone (2 mL) was added to the reaction mixture, and the mixture was stirred for 4 hours. The obtained solid was filtered, and then washed with methyl isobutyl
ketone (4 mL). The solid was dried under vacuum at 25°C to 30°C for 1 hour, and then at 40°C for 5 hours.

Yield: 0.23 g

Example 7: Preparation of ertugliflozin-L-proline (1:2) co-crystal

Ertugliflozin (0.756 g) and L-proline monohydrate (0.4 g) were added to ethanol (4 mL), and then the mixture was heated in a water bath to 70°C. The solution was cooled to 25°C to 30°C. Methyl tertiary butyl ether (30 mL) was added in three lots (10 mL each), and the mixture was stirred for 6 hours at 25°C to 30°C to obtain a solid. The solid so obtained was filtered under nitrogen atmosphere. The solid was washed with methyl tertiary butyl ether (20 mL), and then dried under vacuum at 25°C to 30°C for 4 hours, and then at 40°C for 6 hours.

Yield: 0.862 g

$^1$H NMR (400 MHz, MeOD): δ ppm 1.35-1.39 (t, 3H), 1.96-2.02 (m, 4H), 2.12-2.15 (m, 2H), 2.28-2.30 (m, 2H), 3.22-3.23 (m, 2H), 3.25-3.33 (m, 2H), 3.54-3.61 (m, 4H), 3.64-3.67 (m, 2H), 3.68-3.86 (m, 4H), 3.95-4.03 (m, 2H), 4.04-4.16 (d, 1H), 6.80-6.82 (d, 2H), 7.09-7.11 (d, 2H), 7.37-7.46 (m, 2H), 7.47 (s, 1H).

Example 8: Preparation of ertugliflozin-L-proline (1:2) co-crystal

Ertugliflozin (0.75 g) and L-proline (0.393 g) were added to 2-butanone (9 mL) at 25°C to 30°C, and then the mixture was stirred for 30 minutes to occur precipitation. The mixture was stirred for 5 hours at 25°C to 30°C to obtain a solid. The solid so obtained was filtered under nitrogen atmosphere. The solid was washed with 2-butanone (5 mL), and then dried under vacuum at 25°C to 30°C for 4 hours, and then at 40°C for 6 hours.

Yield: 0.918 g

Example 9: Preparation of ertugliflozin-L-proline (1:2) co-crystal

Ertugliflozin (0.25 g) and L-proline monohydrate (0.152 g) were added to ethyl acetate (3.5 mL, water content < 0.06%), and then the mixture was stirred for 6 hours at 25°C to 30°C. The mixture was filtered, and then dried under vacuum at 25°C to 30°C.

Yield: 0.295 g

Example 10: Preparation of ertugliflozin-L-proline (1:2) co-crystal
Ertugliflozin (0.25 g) and L-proline monohydrate (0.067 g) were added to ethanol (1 mL), and then the mixture was heated in a water bath to 70°C. The solution was cooled to 25°C to 30°C. Methyl tertiary butyl ether (10 mL) was added, and the mixture was stirred for 5 hours at 25°C to 30°C to obtain a solid. The solid so obtained was filtered under nitrogen atmosphere. The solid was dried under vacuum at 25°C to 30°C for 6 hours, and then at 40°C for 4 hours.

Yield: 0.19 g

**Example 11: Preparation of ertugliflozin-L-proline (1:2) co-crystal**

Ertugliflozin (0.25 g) and L-proline monohydrate (0.201 g) were added to ethanol (1.5 mL), and then the mixture was heated in a water bath to 70°C. The solution was cooled to 25°C to 30°C. Methyl tertiary butyl ether (10 mL) was added, and the mixture was stirred for 5 hours at 25°C to 30°C to obtain a solid. The solid so obtained was filtered under nitrogen atmosphere. The solid was dried under vacuum at 25°C to 30°C for 6 hours, and then at 40°C for 4 hours.

Yield: 0.33 g
We claim:

1. A process for the preparation of an ertugliflozin-L-pyroglutamic acid (1:1) co-crystal of Formula Ic,

   \[ \text{Formula Ic} \]

   wherein the process comprises contacting ertugliflozin with L-pyroglutamic acid in the presence of a solvent, wherein the amount of L-pyroglutamic acid is about 1 mole equivalent to about 1.5 mole equivalents with respect to ertugliflozin.

2. The process according to claim 1, wherein the solvent is selected from the group comprising water, ethyl acetate, isopropyl acetate, 2-butanone, and methyl isobutyl ketone.

3. The process according to claim 1, wherein the contacting of ertugliflozin with L-pyroglutamic acid in the presence of a solvent is carried out at ambient temperature.

4. The process according to claim 1, wherein the amount of L-pyroglutamic acid is about 1 mole equivalent to about 1.1 mole equivalents with respect to ertugliflozin.

5. A process for the preparation of an ertugliflozin-L-proline (1:1) co-crystal of Formula Ib,

   \[ \text{Formula Ib} \]

   wherein the process comprises contacting ertugliflozin with L-proline in the presence of a solvent, wherein the amount of L-proline is about 1 mole equivalent to about 1.5 mole equivalents with respect to ertugliflozin.

6. The process according to claim 5, wherein the solvent is ethyl acetate.
7. The process according to claim 5, wherein the contacting of ertugliflozin with L-proline in the presence of a solvent is carried out at ambient temperature.

8. The process according to claim 5, wherein the amount of L-proline is about 1 mole equivalent to about 1.1 mole equivalent with respect to ertugliflozin.

9. Ertugliflozin-L-proline (1:2) co-crystal of Formula 1a.

![Formula 1a](image)

10. The ertugliflozin-L-proline (1:2) co-crystal according to claim 9, characterized by an X-ray powder diffraction (XRPD) pattern as depicted in Figure 1.

11. The ertugliflozin-L-proline (1:2) co-crystal according to claim 9, characterized by an XRPD having interplanar spacing (d) values at about 27.3, 5.8, 4.8, 4.7, and 4.2 Å.

12. The ertugliflozin-L-proline (1:2) co-crystal according to claim 11, characterized by an XRPD having additional interplanar spacing (d) values at about 13.7, 5.1, 4.4, 3.8, 3.5, and 2.8 Å.

13. The ertugliflozin-L-proline (1:2) co-crystal according to claim 9, characterized by an XRPD having characteristic peak values at about 3.2, 16.2, 18.4, 18.9, and 21.4 ±0.2° 2Θ.

14. The ertugliflozin-L-proline (1:2) co-crystal according to claim 13, further characterized by an XRPD having additional characteristic peak values at about 6.5, 17.4, 20.4, 23.5, 25.5, and 31.6 ±0.2° 2Θ.

15. The ertugliflozin-L-proline (1:2) co-crystal according to claim 9, characterized by a differential scanning calorimetric (DSC) thermogram having endothermic peaks at about 148°C and 236°C as depicted in Figure 2.

16. The ertugliflozin-L-proline (1:2) co-crystal according to claim 9, characterized by a thermogravimetric analysis (TGA) thermogram as depicted in Figure 3.
17. A process for the preparation of an ertugliflozin-L-proline (1:2) co-crystal of Formula 1a, wherein the process comprises contacting ertugliflozin with L-proline in the presence of an anhydrous solvent.

18. The process according to claim 17, wherein the anhydrous solvent is selected from the group comprising 2-butanone, ethyl acetate, and a mixture of ethanol and methyl tertiary butyl ether.

19. The process according to claim 17, wherein the amount of L-proline for contacting with ertugliflozin is about 0.5 mole equivalent to about 5 mole equivalents with respect to ertugliflozin.

20. The process according to claim 19, wherein the amount of L-proline is about 0.8 mole equivalent to about 2 mole equivalents with respect to ertugliflozin.

21. The process according to claim 17, wherein the water content of the anhydrous solvent is not more than 0.15%.

22. The process according to claim 21, wherein the water content of the anhydrous solvent is not more than 0.1%.

23. A pharmaceutical composition comprising an ertugliflozin-L-proline (1:2) co-crystal and one or more pharmaceutically acceptable carriers, diluents, or excipients.

24. The use of an ertugliflozin-L-proline (1:2) co-crystal for the treatment of type 2 diabetes mellitus.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053042

A. CLASSIFICATION OF SUBJECT MATTER

IPC(S) - C07D 493/08; A61K 31/357; A61K 31/401; A61K 31/70; A61K 31/7048 (2016.01)
CPC - C07D 493/08; A61K 31/357; A61K 31/401; A61K 31/70; A61K 31/7048 (2016.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum data searched (classification system followed by classification symbols)
IPC - A61K 31/357; A61K 31/401; A61K 31/4015; A61K 31/70; A61K 31/7048; C07D 493/08; C07H 15/207 (2016.01)
CPC - A61K 31/357; A61K 31/401; A61K 31/70; A61K 31/7048; C07D 493/08; C07H 15/207 (2016.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/456; 514/5; 514/5.200; 514/5.300; 549/397; IPC: A61K 31/357; A61K 31/401; A61K 31/4015; A61K 31/70; A61K 31/7048; C07D 493/08; C07H 15/207; CPC: A61K 31/357; A61K 31/401; A61K 31/70; A61K 31/7048; C07D 493/08 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google, PubChem, STN
Search terms used: erthropilozin, pyroglutamic, proline, co-crystal, ethyl acetate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

| "A" | Special categories of cited documents: |
| "B" | document defining the general state of the art which is not considered to be of particular relevance |
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Date of the actual completion of the international search
19 July 2016

Date of mailing of the international search report
30 AUG 2016

Name and mailing address of the ISA/Authorized officer
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PCT HelpDesk: 517-272-4300
PCT OSP: 517-272-1774

Form PCT/ISA/210 (second sheet) (January 2015)