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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF TENELIGLIPTIN HYDROBROMIDE HYDRATE

(57) Abstract: The present invention provides an improved process for the preparation of Teneligliptin HBr more particularly relates to a process for the preparation of Teneligliptin 2.5HBr hydrate salt.

AN IMPROVED PROCESS FOR THE PREPARATION OF TENELIGLIPTIN HYDROBROMIDE HYDRATE

FIELD OF THE INVENTION

The present invention provides an improved process for the preparation of Teneligliptin HBr more particularly relates to process for the preparation of Teneligliptin 2.5 HBr hydrate salt.

BACKGROUND OF THE INVENTION

Teneligliptin hydrobromide hydrate known chemically as {(2S,4S)-4-[4-(3- methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl} (1,3-thiazolidin3-yl) methanone hemipenta hydrobromide hydrate which belongs to dipeptidyl peptidase-4 (DPP-4) inhibitors. It is indicated for the treatment of type 2 diabetes. Tenelia® is available as tablet for oral use, containing 20 mg of free Teneligliptin, and the recommended dose is 20 mg (40 mg if insufficient) once daily for adults.

U.S. Patent No. 7,074,794 B2 (the US '794) discloses Teneligliptin as L-proline derivative and its pharmaceutically acceptable salts which exhibits a Dipeptidyl 5 peptidase IV (DPP-IV) inhibitory activity, which is useful for the treatment or prophylaxis of diabetes, obesity, HIV infection, cancer metastasis, dermopathy, prostatic hyperplasia, periodontitis, autoimmune diseases and the like. The example-222 of the US '794 discloses the process for the preparation of teneligliptin as trihydrochloride salt.

U.S. Patent No. 8,003,790 B2 (the US '790) discloses salts of proline derivative, solvate thereof and production method thereof. In particular, the US '790 discloses 2.0 hydrochloride or 2.5 hydrochloride; 2.0 hydrobromide or 2.5 hydrobromide, and hydrates thereof Teneligliptin.

U.S. Patent Nos. 7,807,676 B2 and 7,807,671 B2 discloses a process for the preparation of 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine and (2S,4R)-tert-butyl 4-hydroxy-2-(thiazolidine-3-carbonyl)pyrrolidine-1-carboxylate.

WO 2015/132679A1; WO2015173779A1; WO2016079699A1; IN 2688/MUM/2014; WO2015132679A1; WO2014041560A2 discloses various process for the preparation of Teneligliptin hydrobromide salt.

All the prior art reported examples for the preparation involves the use of aqueous 48% HBr for the preparation of Teneligliptin Hydrobromide salt. The use of aqueous 48% HBr has its own limitation with respect to concentration, getting desired purity in terms of chemical as well as well as polymorphic purity. Further all the reported processes the de-protection reaction is carried out at a temperature of about 75 to 90 °C. Preferably, at a temperature of about 80-85°C.

Teneligliptin has received much demand in the market, therefore, process chemists have focused considerable interest on designing of new or improved routes to produce this drug molecule on bulk scale which would be industrially feasible and facilitate simple and cost effective manufacture of Teneligliptin and salts thereof having better purity and yield.

OBJECTIVES OF THE INVENTION

An objective of the present invention is to provide an improved scalable process for the preparation of Teneligliptin Hydrobromide hydrate with good purity and overall yield.

SUMMARY OF THE INVENTION

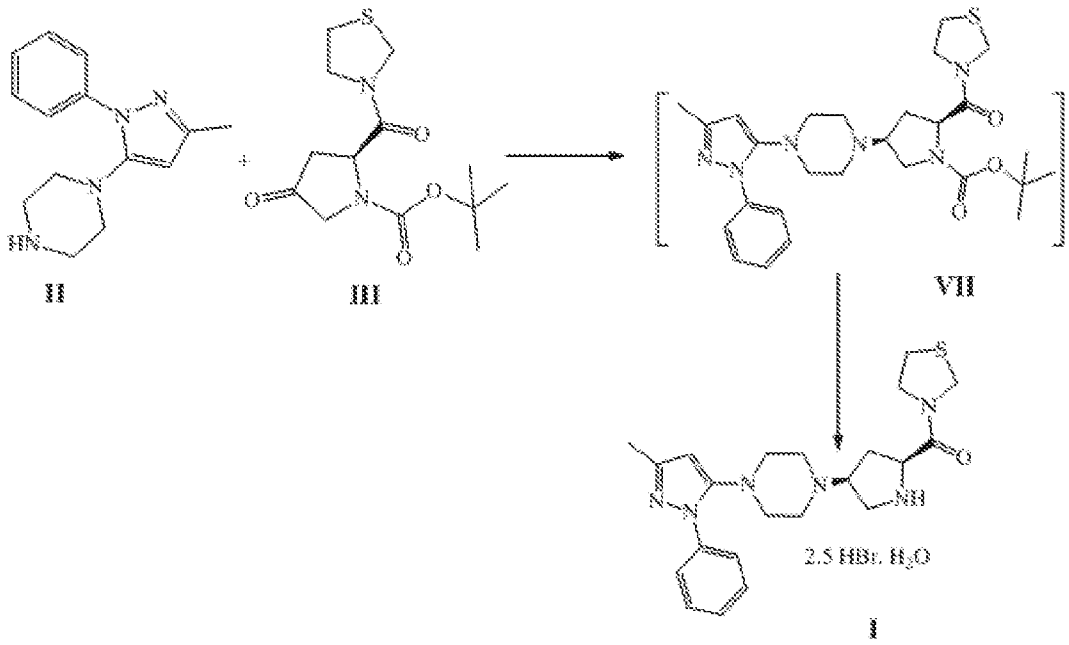
Accordingly, a first aspect of the present invention is directed to an improved process for Teneligliptin 2.5 Hydrobromide hydrate, comprising the steps of:

a) reacting 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazine of Formula (II) or its salt, with tert-butyl (2S)-4-oxo-2-(1, 3-thiazolidin-3-ylcarbonyl) pyrrolidine-1-carboxylate of Formula (III) or its salt in the presence of an reducing agent and in the presence or absence of solvent to yield compound of Formula (VII);

b) de-protecting the compound of Formula (VII) in *in situ* manner with Hydrobromic acid in acetic acid at a temperature of about 50 - 68°C to provide Teneligliptin 2.5 Hydrobromide hydrate of Formula (I); and

c) Optionally purifying the compound of Formula (I) with an suitable solvent system.

The above said process is shown as below:

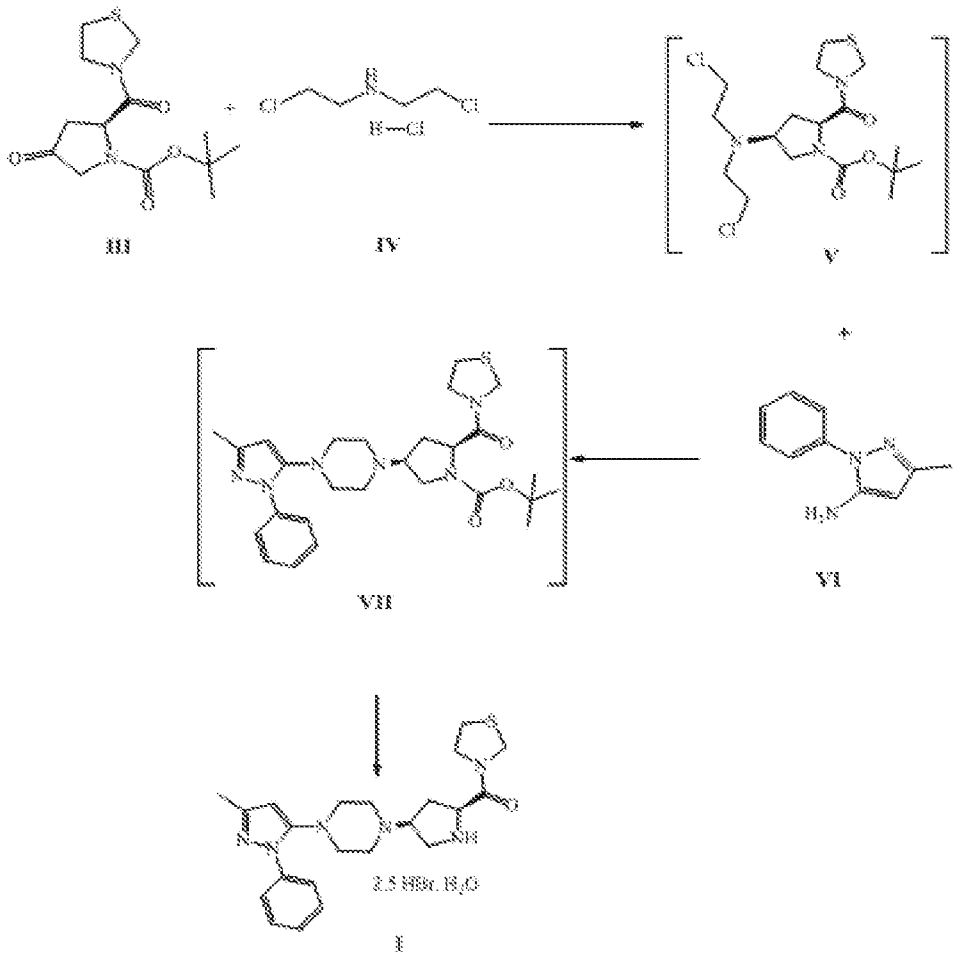


Another aspect of the invention is to provide a process for the preparation of Teneligliptin 2.5 Hydrobromide hydrate which comprises reacting Teneligliptin or its protected derivative like compound of Formula (VII) with Hydrobromic acid in acetic acid in presence of anhydrous solvent.

Yet another aspect of the invention is to provide a process for the preparation of Teneligliptin, the said process comprises step of :

i. reacting compound of Formula (III) or its activated derivative with bis(2-chloroethyl)amine hydrochloride (IV) under suitable reaction condition to provide compound of Formula (V);
ii. reacting the compound of Formula (V) with compound of Formula (VI) under suitable reaction condition followed by removing any protecting group using hydrobromic acid in acetic acid at a temperature of about 50 - 68°C to provide Teneligliptin 2.5 Hydrobromide hydrate; and
iii. optionally purifying the compound of Formula (I) with an suitable solvent system.

The above said process is shown as below:



DETAILED DESCRIPTION OF THE INVENTION

In an embodiment of the present invention the solvent used in step (a) is selected from toluene, xylene, dichloroethane, sulfolane, acetonitrile, acetic acid and the like.

In another embodiment of the present invention the reducing agent used in step (a) is selected from sodium borohydride, sodium triacetoxyborohydride, LAH, sodium cyanoborohydride dimethylamine borane, and the like, preferably include sodium triacetoxyborohydride.

In still another embodiment of the present invention the instead of tert-butoxycarbonyl in compound of Formula (VII) as a protecting group in tert-butyl (2S)-4-oxo-2-(1, 3-thiazolidin-3-ylcarbonyl) pyrrolidine-1-carboxylate other protecting group such as

acetyl, propionyl, methoxyacetyl, methoxypropionyl, benzoyl, thienylacetyl, thiazolylacetyl, tetrazolylacetyl, thiazolylglyoxyloyl, benzyl, p-nitrobenzyl, benzhydryl, trityl, trimethylsilyl, TBDMS, ethoxycarbonyl, methane sulfonyl, toluene sulfonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl can also be employed.

In another embodiment of the present invention after reaction is completed the compound of Formula (VII) is extracted in the organic layer, preferably in the reaction solvent, optionally washed with water and concentrated to obtain residue of compound of Formula (VII) which is subjected to next stage without further purification.

In yet another embodiment of the present invention acetic acid and the reaction is carried out at a temperature in the range of 50 - 68°C. The de-protection is optionally carried out in anhydrous solvent like iso-propanol (IPA), acetone, ethanol. The inventor found that the use of HBr in acetic acid allows to carry out reaction at a temperature in the range of 50 - 68°C; preferably 58 - 65°C.

The use of HBr in acetic acid provides several advantages in industrial scale like 1) there is an significant improvement of overall yield to an extent more than 20% to 30% over the use of aqueous HBr 2) simple and eco-friendly in terms of operation point of view and 3) provides Teneligliptin hydrobromide hydrate in polymorphically pure. The present inventor finds that so far none of the reported process provides exemplified process for the use of HBr in acetic acid in the synthesis Teneligliptin 2.5 hydrobromide hydrate. The hydrate may be mono or dehydrate or non- stoichiometric. The use of anhydrous solvent in anhydrous condition and 33% HBr in acetic acid significantly increases the yield over 48% HBr in water as shown below :

S.No.	Input	Reagent	Yield (w/w)
1.	1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine	48% HBr in water	1.85
2.	1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine	33% HBr in Acetic acid	2.35

In one more embodiment of the present invention the Teneligliptin 2.5 hydrobromide hydrate obtained according to the present invention is optionally purified using a method known in the art, for example by re-crystallization.

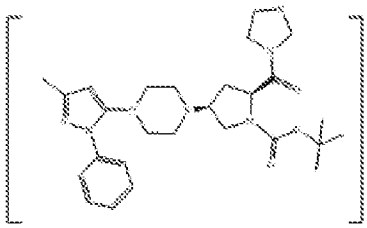
In still another embodiment of the present invention the solvent used in step (iii) for purification includes lower alcohol selected from methanol, ethanol, propanol, isopropanol, butanol; acetone, water THF, me-THF or mixtures thereof like methanol/water; n-butanol/water; IPA/water; acetone/water etc. The use of mixed solvent provides advantages to get pure product.

In one more embodiment of the invention the reaction of compound of Formula (III) with bis(2-chloroethyl)amine hydrochloride is preferably effected under the reducing condition described above for the step (a) or converting the compound of fomula (III) to its reactive derivative like halo. mesylate, or tosylate and then reacting the ensuinng compound with bis(2-chloroethyl)amine hydrochloride.

In yet another embodiment of the invention, the compound of Formula (V) is preferably taken into next stage without isolation.

In yet another embodiment the reaction of compound of Formula (V) with amine of Formula (VI) is carried out using a solvent that does not affect the course of cyclization condition preferably having high boiling point and selected from toluene, xylene, monoglyme, diglyme, methyldiglycol and the like and the reaction is effected at a temperature of 25 to 200°C.

In another aspect the present invention relates to a process for the preparation of Teneligliptin 2.5 hydrobromide hydrate comprises reacting the compound of Formula (VII) or Teneliglptin free base with HBr in acetic acid optionally in presence of anhydrous solvent.



VII

In another embodiment of the present invention, the compound of Formula (VII) can be prepared by following the invention of present application or by following the conventional methods.

In another embodiment of the present invention, the anhydrous solvent used is selected from ethanol, acetone, n-propanol or isopropanol.

In yet another embodiment of the present invention, wherever possible the clear solution is subjected to carbon treatment and or silica treatement.

Further Teneligliptin hydrobromide hydrate obtained as per the present invention can be further micronized, milled or sieved to get the desired particle size (d90 less than 100 micron, preferably less than 50 micron or below 10 micron) required for pharmaceutical composition to achieve the desired dissolution profile. Teneligliptin hydrobromide hydrate prepared according to the present invention is a free flow solid and suitable for pharmaceutical composition.

Teneligliptin hydrobromide hydrate prepared according to the invention is polymorphically pure and stable.

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure. The present invention is provided by the examples below, which are provided by way of illustration only and should not be considered to limit the scope of the invention.

Example 1

To toluene (1 lt), 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazine (100.0 g), tert-butyl (2S)-4-oxo-2-(1, 3-thiazolidin-3-ylcarbonyl) pyrrolidine-1-carboxylate (124.0 g) were added at 25°C. To this reaction sodium triacetoxyborohydride (120 g) were added and stirred till completion of reaction. The organic layer washed optionally with 5% aqueous sodium bicarbonate solution followed by water. The toluene layer concentrated in vacuo, to dryness, the obtained residue in 2-propanol (1 L) was added drop wise 33% hydrobromic acid in acetic acid (300.0 g) and heated to 59 ~ 67 ° C for about 2.5 hours (during said period the product precipitates). The reaction mass cooled and stirred for 2 hr. The precipitated crystals

were collected by filtration, crystals were washed with IPA. The resulting crystal was dried to offer title compound (235gm). HPLC NLT 99.5%

Example 2 (by alternative route)

To a reaction mass of bis (2-chloroethyl)amine hydrochloride (7.14gm) in MDC (250 ml) acetic acid and tert-butyl (2S)-4-oxo-2-(1, 3-thiazolidin-3-ylcarbonyl) pyrrolidine-1-carboxylate (10.0 gm) were added under nitrogen atmosphere. Sodium triacetoxy borohydride were added to reaction mass and stirred till completion of reaction under nitrogen atmosphere and reaction progress controlled by TLC After disappearance of starting material by TLC, the reaction mass quenched with water and then the product is extracted with organic solvent (like MDC, EtOAc) and then concentrated. The residue was dissolved in diglyme, 3-methyl-1 phenyl -1H Pyrazole-5 amine (6 gm), potassium carbonate were charged and heated to reflux temperature and reaction progress controlled by TLC After disappearance of starting material by TLC, reaction mass quenched with water and then the product is extracted with organic solvent (like MDC, EtOAc) and then concentrated. The residue was dissolved in IPA and treated with HBr in acetic acid as described in example-1 to yield Teneligliptin 2.5 hydrobromide hydrate.

Example 3

To the solution of compound of Foumula (VII) in 2-propanol was added drop wise 33% hydrobromic acid in acetic acid and heated to 59 ~ 67 ° C for about 2.5 hours (during said period the product precipitates). The reaction mass cooled and stirred for 2 hr. The precipitated crystals were collected by filtration, crystals were washed with IPA. The resulting crystal was dried to offer title compound. The Teneligliptin 2.5HBr monohydrate optionally purified by recrystallisation using solvent selected from methanol, methanol/water/acetone mixture, acetone/water, IPA, ethanol to provide pure Teneligliptin 2.5HBr monohydrate.

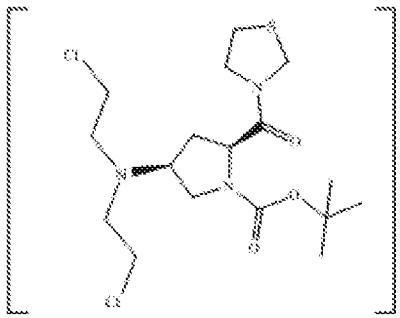
HBr content-32.90%, Purity: 99.91%, M.C-6.0%, SOR: -34.70.

The compound has following PXRD characterization peaks 4.89, 5.09, 5.29, 7.07, 13.22, 14.26, 16.87, 17.50, 17.87, 19.23, 19.54, 19.84, 21.08, 21.39, 21.86, 22.34, 22.55, 22.89, 23.30, 24.69, 25.07, 26.38, 26.73° (±2Θ) (Peaks having at least 10% intensity only provided)

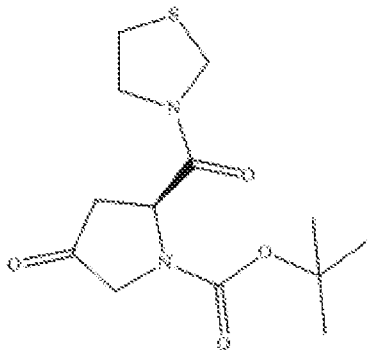
We Claim:

1) A process for the preparation of Teneligliptin 2.5 hydrobromide hydrate comprises step of :

i. reacting compound of Formula (III) or its activated derivative with bis(2-chloroethyl)amine hydrochloride (IV) under suitable reaction condition to provide compound of Formula (V);

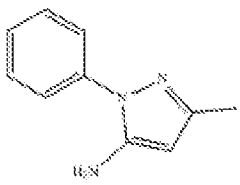


V



III

ii. reacting the compound of Formula (V) with compound of Formula (VI) in presence of high boiling point solvent under suitable reaction condition followed by removing any protecting group in compound of Formula (VII) using hydrobromic acid in acetic acid and in presence of anhydrous solvent at a temperature of about 50 - 68°C to provide Teneligliptin 2.5 hydrobromide hydrate (I); and



VI

iii. optionally purifying the compound of Formula (I) with an suitable solvent system.

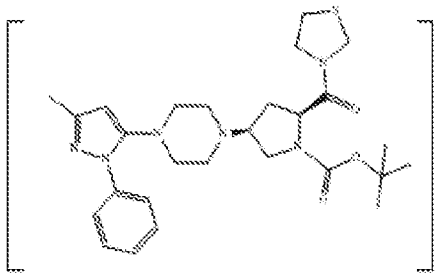
2) The process as claimed in claim 1, wherein the step (i) reaction is carried out in presence of the reducing agent such as sodium borohydride, sodium triacetoxyborohydride, LAH, sodium cyanoborohydride dimethylamine borane, and the like, preferably include sodium triacetoxyborohydride.

3) The process as claimed in claim 1, wherein the step (i) reaction is carried out in presence from toluene, xylene, dichloroethane, sulfolane, acetonitrile, acetic acid.

4) The process as claimed in claim 1, wherein the purification in step (iii) is carried out by using a solvent selected from methanol, methanol/water/acetone mixture, acetone/water, IPA, ethanol

5) The process as claimed in claim 1, wherein the high boiling solvent as described in step (ii) is selected from toluene, xylene, monoglyme, diglyme.

6) A process for the preparation of Teneligliptin 2.5 hydrobromide hydrate comprises reacting the compound of Formula (VII) or Teneliglptin free base with HBr in acetic acid optionally in presence of anhydrous solvent.



VII

7) The process as claimed in claim 6, wherein the reaction is carried out at a temperature in the range of 50 - 68°C.

8) The process as claimed in claim 6, wherein the anhydrous solvent is ethanol, acetone or isopropanol.

9) The process as claimed in claim 6, wherein the compound of Formula (VII) is prepared by following the claim 1 or by conventional manner.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/052585

A. CLASSIFICATION OF SUBJECT MATTER
C07D417/14 Version=2020.01

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)

STNext, TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IN2010MUM2013 A (CADILA HEALTHCARE LIMITED [IN]) 12 June 2015 (12.06.2015) (Family None) Page 5 line 28-page 7 line 7, examples 1-10 and claims 1-8;	1-9
X	WO 2014041560 A2 (GLENMARK PHARMACEUTICALS LIMITED [IN]) 20 March 2014 (20.03.2014) Pages 5-6, page 16 second paragraph, examples 1-6 and claim 1;	1-9

☐ 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
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21-08-2020	21-08-2020
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Veera R Kattula Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2020/052585

Citation	Pub.Date	Family	Pub.Date
WO 2014041560 A2	20-03-2014	US 20150203484 A1	23-07-2015
		BR 112015004029 A8	23-01-2018
		RU 2015105294 A	20-10-2016
		MX 2015002487 A	10-09-2015