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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(in))*

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WO 2017/033134 A1

(54) **Title:** ENZYMATIC PROCESS FOR THE FOR PREPARATION OF (R)-l-(l-NAPHTHYL) ETHYLAMINE, AN INTERMEDIATE OF CINACALCET HYDROCHLORIDE

(57) **Abstract:** The present invention provides a process for the preparation of enantiomerically pure (R)- l-(l-naphthyl)ethylamine of formula (Ha) by treating 1-acetylnaphthalene of formula (I) with R-selective transaminase enzyme in presence of amino donor. The (R)-l-(l-naphthyl)ethylamine of formula (Ila) thus obtained is further converted to cinacalcet hydrochloride of formula (III).

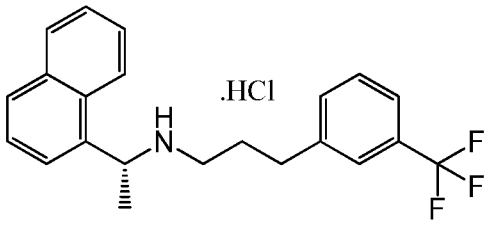
ENZYMATIC PROCESS FOR THE FOR PREPARATION OF (R)-l-(l-NAPHTHYL) ETHYLAMINE, AN INTERMEDIATE OF CINACALCET HYDROCHLORIDE

FIELD OF INVENTION

The present invention provides novel process for preparation of enantiomerically pure (R)-1-(1-Naphthyl)ethylamine of formula (Ila) by reacting 1-Acetylnaphthalene of formula (I) with transaminase enzyme and its conversion to Cinacalcet hydrochloride of formula (III).

BACKGROUND OF THE INVENTION

Cinacalcet hydrochloride (III) is chemically known as N-[l-(R)-(-)-(l-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-l-aminopropane hydrochloride known to be useful for the treatment of hyperparathyroidism and the preservation of bone density in patients with kidney failure or hypercalcemia due to cancer.



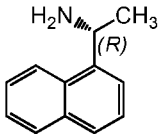
(III)

Cinacalcet hydrochloride is an oral calcimimetic drug. In the United States, it is marketed under the name Sensipar® and, in Europe, it is marketed under the name Mimpara® and Parareg®.

Enantiomerically pure chiral amine plays an important role in the pharmaceutical and chemical industry. Enantiomerically pure chiral amines in general are frequently used as a resolving agents or intermediates or synthons for the preparation of various physiologically, for instance pharmaceutically active substances. In a great number of the various applications of enantiomerically pure chiral amines, only one particular optically

active form, either the (R) or the (S) enantiomer has the desired physiological activity. Thus, there is a clear need to provide processes for the preparation of chiral amines in an optically active form.

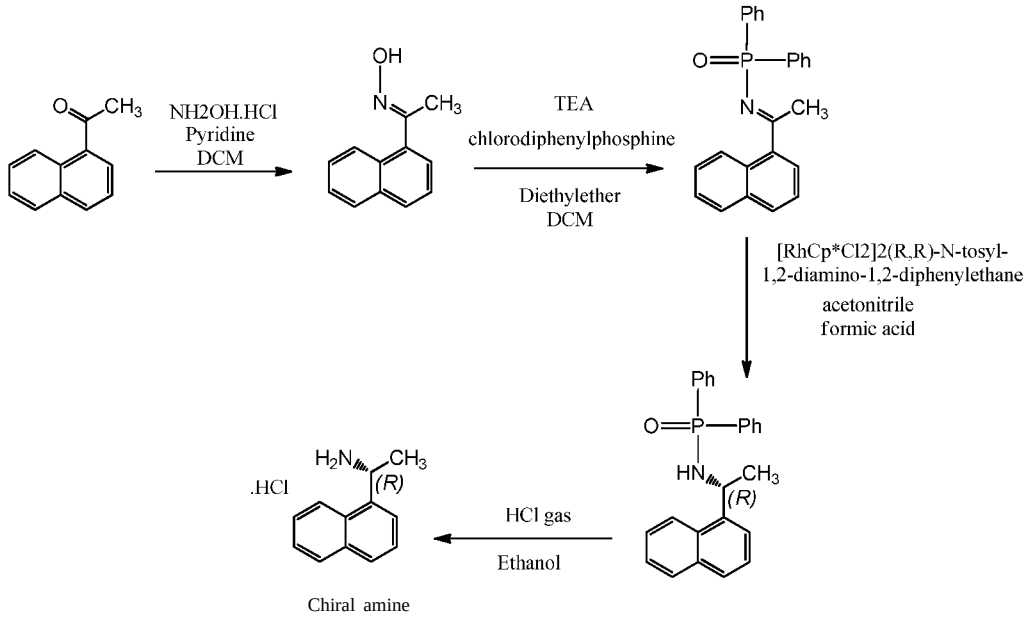
(R)-l-(l-naphthyl)ethylamine of formula (Ila) is used for the preparation of cinacalcet hydrochloride.



(Ila)

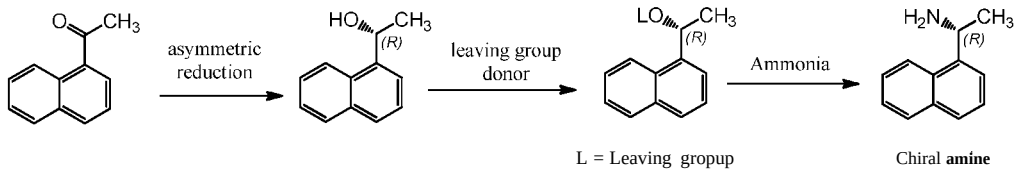
Prior art includes various synthetic methods for the preparation of (R)-l-(l-naphthyl)ethylamine of formula (Ila).

WO 2001012574 A1 discloses preparation of optically active amine by reacting 1-acetylnaphthylene with hydroxylamine hydrochloride to furnish oxime, which was further treated with chlorodiphenylphosphme to provide imine derivative, which was subjected to asymmetric transfer hydrogenation catalyzed by Rh complex, followed by treatment of the obtained protected amine with hydrogen chloride gas in ethanol as shown in the scheme 1:



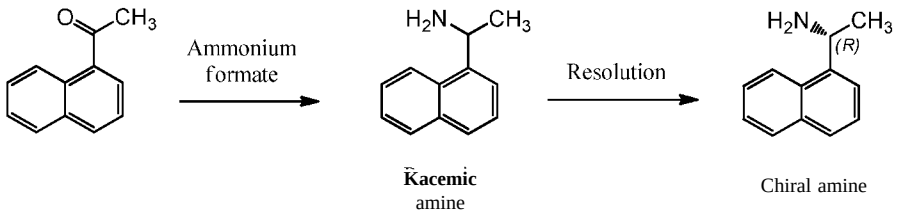
Scheme 1

WO 20041 10976 A2 discloses preparation of optically active amine from the corresponding aldehyde by asymmetric synthesis comprising asymmetrically reducing corresponding aldehyde compound using rhodium complex and chiral ligand and then reacting with ammonia as shown in scheme 2.



Scheme 2

WO 2008058235 A2 discloses preparation of optically active amine from the corresponding aldehyde from the corresponding aldehyde by treating the aldehyde compound with a base (ammonium formate) in solvent to form racemic amine which on resolution gives optically active amine as shown in scheme 3.



Scheme 3

CN 101407465 B discloses preparing optical pure amine by using chiral aspartic acid as chiral resolving agent with the formation of diastereomeric salts and separating desired optically pure amine difference in their solubility.

The drawbacks associated with the prior art synthetic methods are use of expensive ruthenium, iridium, or rhodium complexes and to show their content in final active pharmaceutical ingredient (API) is within the acceptable limits; high cost of asymmetric synthesis; difficulty to obtain a high optical purity of the product; poor yields (lack of diastereo- and enantioselectivity); cost, availability and difficulty of recovering these chiral resolving agents; cost and recyclability of hydrogenation catalyst.

In the view of the mentioned drawbacks in the prior art, there is an ongoing need to develop a process for the preparation of enantiomerically pure (R)-l-(l-naphthyl)ethylamine of formula (Ila) that bypasses the above limitations and is more efficient in terms of yield and resolution and at the same time is cost-effective for which an enzymatic approach would be the answer to the above mentioned problems.

The present invention uses transaminase enzyme to obtain optically active chiral amine. Depending on the enantio-preference of the selective transaminase used, an optically active chiral amine is obtained. For instance the R-selective transaminase enzyme herein is capable of catalyzing the transfer of an amino group from an amino donor to a keto substrate, thereby forming R-selective chiral amine. Eventually, the S-selective transaminase enzyme catalyses the transfer of an amino group from an amino donor to a keto substrate, thereby forming S-selective chiral amine.

SUMMARY OF THE INVENTION

The main object of the present invention is to provide, a process for the preparation of enantiomerically pure (R)-l-(l-naphthyl)ethylamine of formula (Ila) by treating 1-acetylnaphthalene of formula (I) with R-selective transaminase enzyme in presence of amino donor.

The (R)-l-(l-naphthyl)ethylamine of formula (Ila) thus obtained was further converted to cinacalcet hydrochloride of formula (III).

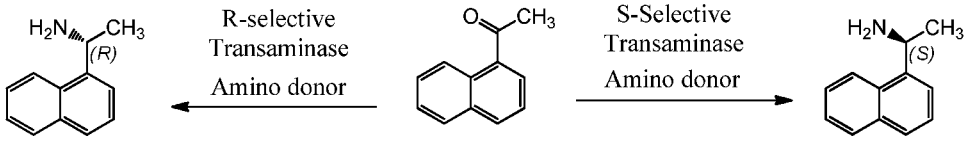
Another object of the present invention is to provide, a process for the preparation of enantiomerically pure (S)-l-(l-naphthyl)ethylamine of formula (lib) by treating 1-acetylnaphthalene of formula (I) with S-selective transaminase enzyme in presence of amino donor.

Yet another object of the present invention is to provide, pharmaceutical compositions comprising cinacalcet hydrochloride of formula (III) obtained from intermediate (R)-l-(l-naphthyl)ethylamine of formula (Ila), prepared by the process of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of enantiomerically pure (R)-l-(l-naphthyl)ethylamine of formula (Ila) from 1-acetylnaphthalene of formula (I) by treating it with R-selective transaminase enzyme in presence of amino donor as shown in scheme 4.

The present invention also provides a process for the preparation of enantiomerically pure (S)-l-(l-naphthyl)ethylamine of formula (lib) from 1-acetylnaphthalene of formula (I) by treating it with S-selective transaminase enzyme in presence of amino donor as shown in scheme 4.



(Ila) (l) (Tib)

(R)-1 -(1-Naphthyl)ethy lamine 1-acetylnaphthalene (S)- 1-(1-Naphthyl)ethy lamine

Scheme 4

The term "enantiomerically pure" refers to >97%, >98%, >99% and 100% enantiomeric excess (ee) of one of the enantiomers of l-(l-Naphthyl) ethylamine, as determined by HPLC.

The term "Transaminase" also referred as "Amine Transaminase (ATA)" is used to refer to a polypeptide having an enzymatic capability of transferring an amino group (NI¾) to a carbonyl group (C=0) of an acceptor molecule.

The term "Amino donor" is used to refer to any amino acid or amine that will react with a transaminase and a ketone, to produce desired amine product and a ketone by product.

The transamination reaction is carried out in presence of "Pyridoxal-phosphate (PLP)" that acts as a coenzyme. In transamination reactions using transaminase enzymes, the amine group of the amino donor is transferred to the coenzyme to produce a ketone as a by-product, while pyridoxal-5 '-phosphate is converted to pyridoxamine phosphate. The transfer of the amine group from pyridoxamine phosphate to the ketone substrate produces a chiral amine and regenerates the coenzyme.

R-selective transaminase enzyme include, but are not limited to ATA-P2-A07, ATA-025, ATA-013, ATA-033, Evo 1.2.131, Evo 1.2.133, Evo 1.2.134, Evo 1.2.137, ECS-ATA-07 and mixtures thereof; and S-selective transaminase enzyme include, but are not limited to ATA-1 13, ATA-237, ATA-251, ATA-256, ATA-260, and mixtures thereof.

Typical amino donors that can be used with the invention include chiral and achiral amino acids, and chiral and achiral amines. Amino donors that can be used with the invention include, by way of example and not limitation, isopropylamine, 1-phenylethanamine, and

its enantiomers (S)-l-phenylethanamine and (R)-l-phenylethanamine, 2-aminobutane, 2-amino-l-butanol, l-phenyl-2-aminobutane, including both (R) and (S) single isomers where possible and including all possible salts of the amines. More preferably, the amino donor is isopropylamine thereby obtaining acetone as a by-product.

Transamination of the substrates is carried out in a bioreactor using an aliquot of the enzyme with the substrate typically at a defined concentration. The reaction parameters such as pH = 6-9, temperature = 20 - 40°C, and reaction time = 12-48 hrs are maintained at levels that favor optimal biocatalytic activity and stability.

We have screened several transaminase enzymes for conversion of 1-acetylnaphtahalene of formula (I) to obtain (R)-l-(l-naphthyl)ethylamine of formula (Ila) and (S)-l-(l-naphthyl)ethylamine of formula (lib). These are summarised in Table 1.

Screening protocol: 10 mg Transaminase enzyme was dissolved in 0.9 mL buffer solution (1 M isopropyl amine, 0.1 M triethanolamine and 1 mM PLP) at 30°C. The reaction is initiated by adding O.lmL substrate-DMSO Sol (5 mg 1-acetylnaphthalene in 0.1 mL DMSO). Reaction mixture having a pH from approximately 6-9 is maintained at 25-35°C for 12-48 hrs and samples were analyzed by HPLC.

Table 1: Performance of Transaminase enzymes after screening.

Sr. No.	Transaminase Enzyme Code	(%)-Conversion	Desired (R)-Amine	Undesired (S)-Amine
1.	ATA-P2-A07	64.75	100 %	0
2.	ATA-025	54.99	100 %	0
3.	ATA-013	64.81	100 %	0
4.	ATA-033	78.81	100 %	0
5.	ATA-113	58.44	0	100 %
6.	ATA-237	62.30	0	100 %
7.	ATA-251	78.72	0	100 %
8.	ATA-256	52.07	0	100 %
9.	ATA-260	53.48	0	100 %
10.	Evo 1.2.131	9.10	98.85%	1.15%

11.	Evo 1.2.133	19.13	99.2%	00.8%
12.	Evo 1.2.134	7.36	98.53%	1.47%
13.	Evo 1.2.137	3.99	97.33%	2.67%
14.	ECS-ATA-07	17.49	99.52%	0.48%

In another aspect, the present invention also provides process for the preparation of Cinacalcet hydrochloride of formula (III) comprising:

i) reacting 1-acetylnaphthalene of formula (I) with R-selective transaminase enzyme in presence of amino donor to obtain (R)-l-(l-naphthyl)ethylamine of formula (Ila) and

ii) converting the (R)-l-(l-naphthyl)ethylamine of formula (Ila) to cinacalcet hydrochloride of formula (III).

Intermediate (R)-l-(l-naphthyl)ethylamine of formula (Ila) made by the process of the present invention can be converted to cinacalcet hydrochloride of formula (III) by the methods known in the literature.

In another aspect, the present invention also provides pharmaceutical compositions comprising cinacalcet hydrochloride of formula (III) obtained from intermediate (R)-l-(l-naphthyl)ethylamine of formula (Ila), prepared by the process of the present invention. The pharmaceutical composition may be formulated in conventional manner using one or more physiologically acceptable carriers, excipients, or diluents.

To understand the present invention following preparative and testing examples are set forth, which are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLES:

Source of enzyme:

1. **Supplier:** Codexis; **Kit Name:** Codex® ATA Screening Kit; **Supplier code:** ATASK-200250P; **Kit content:** 24 transaminases and co- factor PLP.

2. **Supplier:** Evocatal GmbH; **Kit Name:** ATA Screening Kit; **Supplier code:** ECS-ATA-kit; **Kit content:** 7- transaminases enzyme.

3. **Supplier:** Enzymicals AG; **Kit Name:** Transaminase Kit; **Supplier code:** EVO-1.2.800; **Kit content:** 19 transaminases enzyme.

Buffer solution preparation: To a 10 mL of DM water added 1.25 mL isopropylamine, 0.25 gm of triethanolamine and 4mg PLP. Dissolved to get clear solution and made up 15 mL with water with pH ≈ 7.5.

The enantiomeric purity was determined by HPLC method using the following parameters: Column: Chiralpak IB (4.6x250 mm) 5 µ; Flow rate: 1.0 ml/min (isocratic); Wavelength: UV at 223 nm; Injection volume: 5 µĩ; Column oven temperature: 25° C; Auto sampler temperature: 10° C; Run time: 25 min and Mobile phase: n-heptane: ethanol: trifluoroacetic acid: diethyl amine (90:10:0.02:0.02).

Example 1: Preparation of (R)-l-(l-naphthyl)ethylamine (Ila).

10 mg Transaminase enzyme ATA-P2-A07 was dissolved in 0.9 mL buffer solution (1 M isopropyl amine, 0.1 M triethanolamine and 1 mM PLP) at 30°C. The reaction is initiated by adding O.lmL substrate-DMSO Sol (5 mg 1-acetylnaphthalene in 0.1 mL DMSO). Reaction mixture was maintained at 30°C for 24 hrs and samples were analyzed by HPLC. 64.75% conversion was obtained with 100% R-isomer.

Example 2: Preparation of (S)-l-naphthylethylamine (lib).

10 mg Transaminase enzyme ATA-113 was dissolved in 0.9 mL buffer solution (1 M isopropyl amine, 0.1 M triethanolamine and 1 mM PLP) at 30°C. The reaction is initiated by adding O.lmL substrate-DMSO Sol (5 mg 1-acetylnaphthalene in 0.1 mL DMSO). Reaction mixture was maintained at 30°C for 24 hrs and samples were analyzed by HPLC. 58.44% conversion was obtained with 100% S-isomer.

Example 3: Preparation of cinacalcet hydrochloride (III):

Reaction mixture from example 1 was treated with 4.20 mg of l-(3-chloroprop-l-en-l-yl)-3-(trifluoromethyl)benzene in presence of $K2CO_3$ in water, heated the mixture to 70-100°C for 2 hours and then extracted with dichloromethane. The residue obtained by

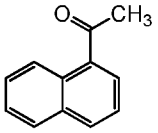
removing the dichloromethane is reduced with Pd/C in methanol to give reaction mixture containing cinacalcet hydrochloride (III).

Example 4: Preparation of cinacalcet hydrochloride (III):

Reaction mixture from example 1 was treated with 4.23 mg of l-(3-chloropropyl)-3-(trifluoromethyl)benzene in presence of $K2CO_3$ in water, heated the mixture to 70-100°C for 2-4 hours and then extracted with dichloromethane. Dichloromethane is distilled out to give reaction mixture containing cinacalcet hydrochloride (III).

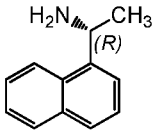
CLAIMS

1. A process for preparation of enantiomerically pure (R)-1-(1-Naphthyl)ethyl amine of formula (Ila) comprising:



(I)

1-acetylnaphthalene

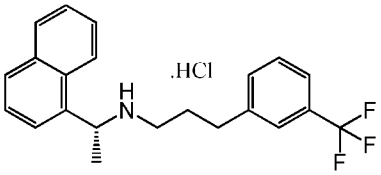


(Ila)

(R)- 1-(1 -Naphthyl)ethylamine

treating 1-acetylnaphthalene of formula (I) with R-selective transaminase enzyme in presence of amino donor.

2. A process for preparation of cinacalcet hydrochloride of formula (III) comprising:



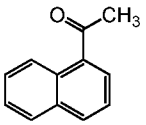
(III)

i) reacting 1-acetylnaphthalene of formula (I) with R-selective transaminase enzyme in presence of amino donor to obtain (R)-l-(l-Naphthyl)ethylamine of formula (Ila) and

ii) converting the (R)-1-(1-Naphthyl)ethylamine of formula (Ila) to Cinacalcet hydrochloride of formula (III).

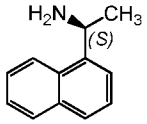
3. The process according to claim 1 or 2, wherein the R-selective transaminase enzyme is selected from ATA-P2-A07, ATA-025, ATA-013, ATA-033, Evo 1.2.131, Evo 1.2.133, Evo 1.2.134, Evo 1.2.137, ECS-ATA-07 and mixture thereof.

4. A process for preparation of enantiomerically pure (S)-1-(1-Naphthyl)ethyl amine of formula (lib) comprising:



(I)

1-acetylnaphthalene



(IIb)

(S)-1-(1-Naphthyl)ethylamine

treating 1-acetylnaphthalene of formula **(I)** with S-selective transaminase enzyme in presence of amino donor.

5. The process according to claim 4, wherein the S-selective transaminase enzyme is selected from ATA-237, ATA-25 1, ATA-256, ATA-260 and mixture thereof.

6. The process according to claim 1, 2 or 3, wherein the amino donor is selected from isopropylamine, 1-phenylethanamine, (S)-l-phenylethanamine, (R)-l-phenylethanamine, 2-aminobutane, 2-amino-l-butanol, l-phenyl-2-aminobutane.

7. The process according to claim 6, wherein the amino donor is isopropylamine.

8. The process according to claim 1 or 4, wherein pH is in the range 6-9.

9. The process according to claim 1 or 4, wherein the process is carried out at a temperature of 20-40 °C.

10. A pharmaceutical composition comprising cinacalcet hydrochloride of formula **(III)** obtained according to claim 2 and pharmaceutically acceptable carrier, excipient, or diluent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/055047

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12P41/00 C12P13/00
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)
C12P C12N C07C

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SANG-WOO HAN ET AL: "Mechanism-Guided Engineering of [omega]-Transaminase to Accelerate Reductive Amination of Ketones" **ADVANCED SYNTHESIS & CATALYSIS,** vol. 357, no. 8, 26 May 2015 (2015-05-26), pages 1732-1740, XP055310046, DE ISSN: 1615-4150, DOI: 10.1002/adsc.201500211 the whole document	1-3,6-9
Y	EP 0 857 790 A1 (KANEKA CORP [JP]) 12 August 1998 (1998-08-12) claims	1,3,6-9

-/-

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

X 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
13 October 2016	12/12/2016

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	Boeker, Ruth

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MATTHEW D. TRUPPO ET AL: "Efficient kinetic resolution of racemic amines using a transamination combination with an amino acid oxidase" , CHEMICAL COMMUNICATIONS - CHEMCOM. , no. 16, 16 March 2009 (2009-03-16) , pages 2127-2129 , XP055310337 , ISSN: 1359-7345 , DOI: 10.1039/b902995h the whole document	1,3,6-9
Y	WO 2010/103531 A2 (MEGAFINE PHARMA P LTD [IN] ; MATHAD VIJAYVITTHAL THIPPANNACHAR [IN] ; NI) 16 September 2010 (2010-09-16) claims	1,2
X	PABLO UREÑA TORRES: "Cinacalcet HCl: A Novel Treatment for Secondary Hyperparathyroidism Caused by Chronic Kidney Disease" , JOURNAL OF RENAL NUTRITION , vol . 16, no. 3, July 2006 (2006-07) , pages 253-258, XP055310099 , US ISSN: 1051-2276, DOI: 10.1053/j.jrn.2006.04.010 the whole document	10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/055047

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3, 10(completely); 6-9 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, lO(completely) ; 6-9 (partially)

   A process for preparation of enantiomerically pure (R)-l-(l-naphthyl)ethyl amine and cinacalcet hydrochloride, and a pharmaceutical composition comprising cinacalcet hydrochloride

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2. claims: 4, 5(completely) ; 6-9 (partially)

   A process for preparation of enantiomerically pure (S)-1-(1-Naphthyl)ethyl amine

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/055047

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0857790 A1	12-08-1998	DE 69635082 D1	22-09-2005
		DE 69635082 T2	01-06-2006
		EP 0857790 A1	12-08-1998
		US 6221638 B1	24-04-2001
		US 2001031487 A1	18-10-2001
		WO 9715682 A1	01-05-1997
WO 2010103531 A2	16-09-2010	EP 2406211 A2	18-01-2012
		US 2011319663 A1	29-12-2011
		US 2014081048 A1	20-03-2014
		US 2015152040 A1	04-06-2015
		WO 2010103531 A2	16-09-2010