



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

05-53826

54. TITULO

PROCESO PARA PREPARAR 2,6DIAMINO-4,5,6,7-TETRAHIDRO-BENZOTIAZOL

51. CLASIFICACION INTERNACIONAL

A61K31/428 // A61P25/16

71. SOLICITANTE

CIPLA LIMITED

DOMICILIO

Mumbai, India.

74. APODERADO

EMILIO FERRERO

C.C. 438.019 de Usaquén

72. BOGOTA, D.C.,

02/06/2005.

SS


Industria y Comercio

SUPERINTENDENCIA

PETITORIO

DIRECCIÓN DE PATENTES Y MARCAS

Radicación: 025306 MARCAS

Folios: 45 n

Fecha (IMP): 2005-04-02 17:00:30

Fecha: 01/04/2005 17:00:30

Radicación: 025306 MARCAS

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 04-06-05
SOLICITUD DE:

1

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

**SOLICITANTE
(71)**

 Nombre: **CIPLA LIMITED**
 sociedad constituida y existente bajo las
 leyes de la India

 Dirección: 289 Bellasis Road,
 Mumbai Central,
 Mumbai 400 008,
 India

Domicilio: Mumbai, India

IDENTIFICACIÓN

 C.C. ☐

 NIT ☐

 C.E. ☐

 Otro ☐

Cual

Número

3

**REPRESENTANTE
APODERADO**

 Nombre: **EMILIO FERRERO**
 Dirección: Carrera 4ª. No. 72-35
 Teléfono: 347 38 11
 Fax: 211 88 50
 E-mail: cilentes@camyp.com.
 Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

 C.C. ☒

 NIT ☐

 C.E. ☐

 Otro ☐

Cual

 Número 438.019 T.P 31.929

4

**INVENTOR (ES)
(72)**

 1. **Dharmaraj Ramachandra RAO**
 4/403 Garden Enclave,
 Pokhran Road 2, Thane (Oeste),
 Mumbai 400 601, Maharashtra,
 India

 2. **Rajendra Narayanrao KANKAN**
 A-3/5, NBD Society,
 NSS Road, Gratkopar (Oeste),
 Mumbai 400 084, Maharashtra,
 India

5

PCT (86)

 Solicitud Internacional No. PCT/GB2003/004734

 Fecha: 3 de Noviembre de 2003

 Publicación Internacional No. WO 2004/041797 A1

 Fecha: 21 de Mayo de 2004

6

Título (54)
PROCESO PARA PREPARAR 2,6-DIAMINO-4,5,6,7-TETRAHIDRO-BENZOTIAZOL

7

Clasificación Internacional (51) C07D 277/02
A61K31/428.
A61P25/16.

8

Prioridad

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

 SI ☒ NO ☐
GB
4 de Noviembre de 2002
0225701.2

9

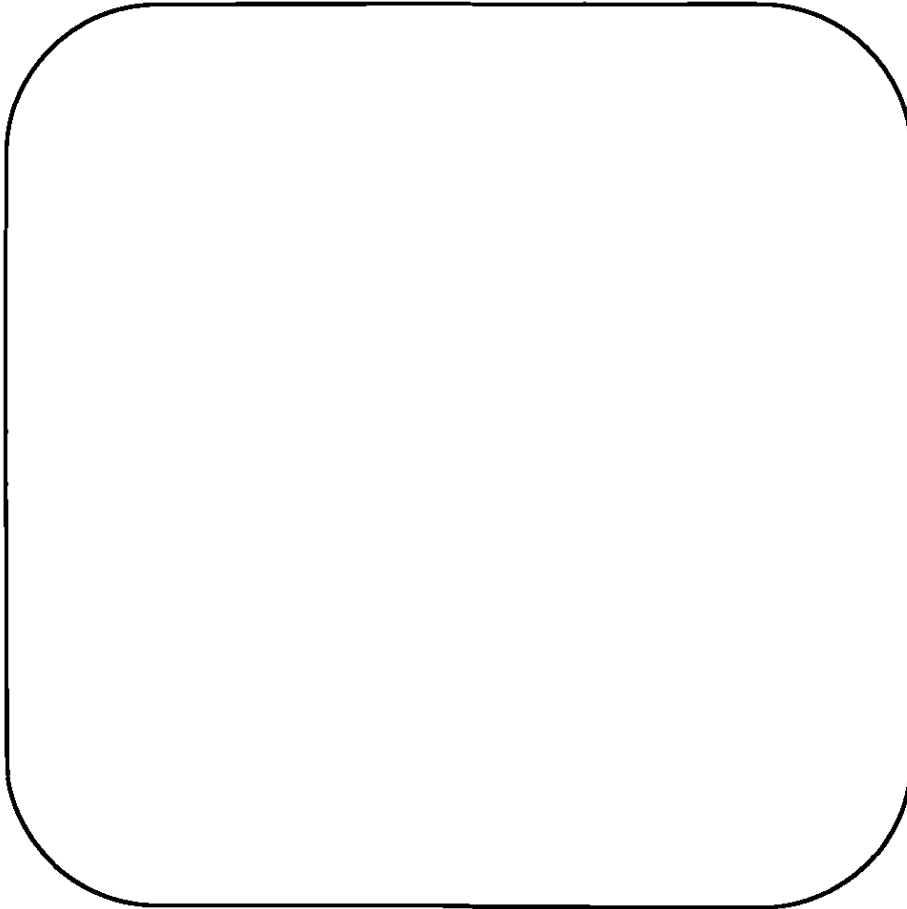
Comprobante de pago No.: 05 - 35.941
Fecha: 16 de Mayo de 2005

10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA

12

Solicito la concesión de la patente,

NOMBRE:

EMILIO FERRERO

FIRMA :

Emilio Ferrero
C.C. 438.019 de Usaquén T.P. 31.929

PRP

12092
6004
H
3

**CONSULADO DE COLOMBIA
NUEVA DELHI**

No17/2005

LA SUSCRITA CONSEJERA ENCARGADA DE LAS
FUNCIONES CONSULARES ANTE LA EMBAJADA DE COLOMBIA EN NUEVA
DELHI, INDIA,
VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

CERTIFICA:

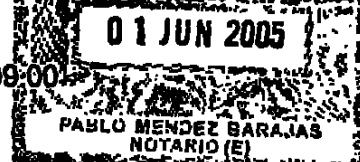
QUE EL SEÑOR SANKARA SUBBU, OFICIAL REGIONAL (OI) DEL MINISTERIO DE RELACIONES EXTERIORES DE INDIA, QUIEN AUTENTICO LA FIRMA DEL SEÑOR AMAR LULLA DE LA EMPRESA CIPLA LIMITED, FIRMANTE DEL PRESENTE DOCUMENTO, EJERCIÓ EN LA FECHA LAS FUNCIONES INDICADAS Y SU FIRMA CORRESPONDE A LA REGISTRADA EN ESTE CONSULADO; QUE LA EMPRESA "CIPLA LIMITED" ESTA CONSTITUIDA DE ACUERDO CON LAS LEYES DE INDIA Y CUMPLE SU OBJETO CONFORME A LAS MISMAS, SEGÚN DECLARACION NOTARIADA ADJUNTA, DOMICILIADA MUMBAI INDIA; QUE EL SEÑOR AMAR LULLA, EN SU CARÁCTER DE DIRECTOR GENERAL ADJUNTO DE LA EMPRESA ARRIBA MENCIONADA, ESTA FACULTADO PARA FIRMAR EL PRESENTE DOCUMENTO.

DADO EN NUEVA DELHI A LOS VEINTIDOS DIAS (22) DEL MES DE MARZO DE DOS MIL CINCO (2005).


OLGA BUITRAGO
CONSEJERA E. P. C.



PAGADO IMPUESTO DE TIMBRE Y
DERECHOS CONSULARES: US \$109.00
(Ciento nueve Dólares Americanos)



CUTAFIAMA ABRERE E. L. E.
DOCUMENTO DE SEPTIEMBRE
LAS FUNCIONES INDICADAS

MINISTERIO DE
RELACIONES EXTERIORES

JEFES DE LEGALIZACIONES
BOGOTÁ D.C.

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 ABR - 1 A 12: 54

3, Palam Marg, First Floor, Vasant Vihar, New Delhi-110057 INDIA
Tel.: 91-11-51-66-21-03, 51-66-21-05 Fax: 91-11-51-66-21-04, 51-66-21-08
e-mail: emcolin@bol.net.in

CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTÁ, 8 - COLOMBIA

Colombia (4 pgs)
Representación, Ratificación y Poder con autenticación notarial para patentes, modelos de utilidad y licencias.

Representation, Ratification and Power-of-Attorney with notarial authentication for patents, utility models and licenses.

REPRESENTACION, RATIFICACION Y PODER

REPRESENTATION, RATIFICATION AND POWER-OF-ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

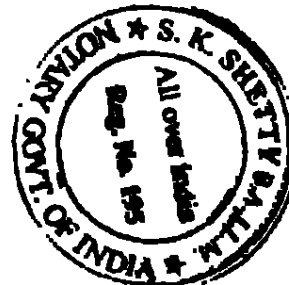
CIPLA LIMITED

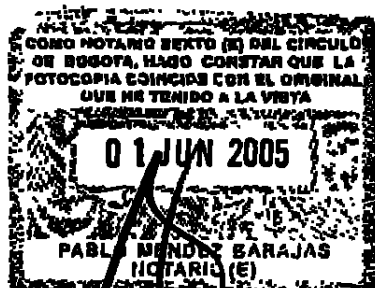
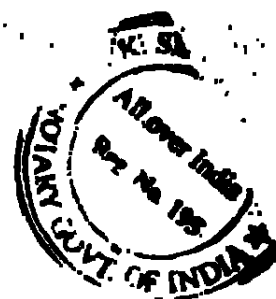
domiciliado (s) en/of 289 Bellasis Road,
Mumbai Central, Mumbai 400 008, India

por el presente ratificamos la Solicitud de Patente No. 05 - 000.895 presentada por EMILIO FERRERO como agente oficioso ante La Superintendencia de Industria y Comercio en Bogotá, Colombia el 6 de Enero de 2005 or el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4a N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de patentes con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

hereby ratify the Patent Application No. 05 - 000.895 filed without a Power of Attorney by EMILIO FERRERO before The Superintendence of Industry and Commerce in Bogota, Colombia on January 6, 2005 in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4a N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all patent matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

No 88591





Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) invención a cuyo efecto autorizo (autorizamos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a lo siguiente: a) la obtención de patentes de invención y modelos de utilidad, y traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, la tutela, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistír, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

CIPLA LIMITED se reserva el derecho de revocar el presente poder en cualquier momento y a su propia discreción.

Si existe algún conflicto entre los términos que se mencionan en inglés y los de cualquier otro idioma, entonces aquellos términos del inglés prevalecerán.

In addition, we grant a Power of Attorney in favor of the above-named attorneys at law so that they may obtain the protection of my (our) invention for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents and utility models, and assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) oppositions or observations, administrative or Court cancellation, nullity, infringement, the action for writ mandamus, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

CIPLA LIMITED retains the right to revoke this power at any time at their own discretion.

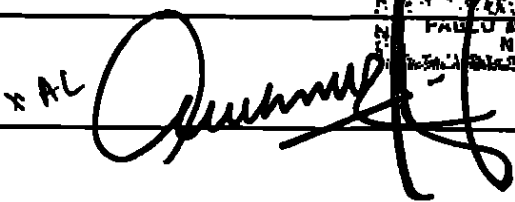
If there is any conflict in the terms as stated in English with those of any other language, then the terms of the English language will survive.

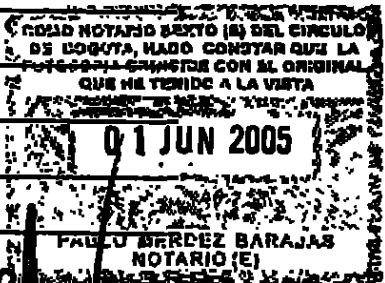
Dado y firmado hoy/Given and signed this 15.3.05

en/in MUMBAI

por/by MR. AMAR LULLA

Firma/Signature

AL 



88531

ATTESTED 

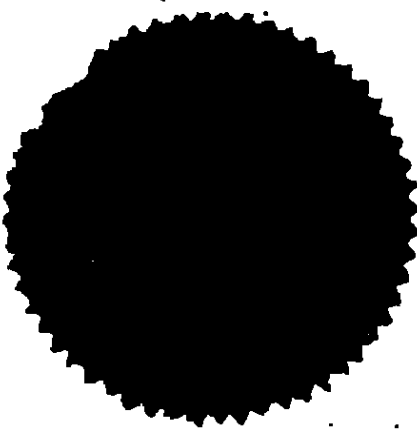
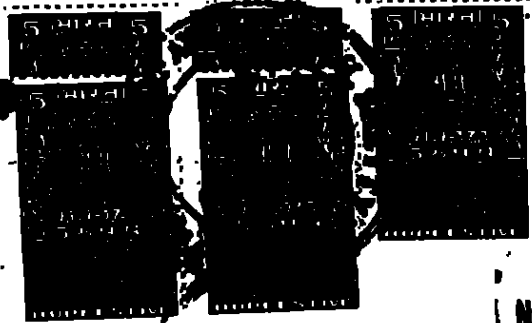
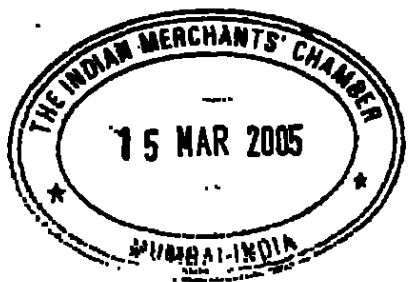
AUTHORISED SIGNATORY
INDIAN MERCHANTS' CHAMBER
MUMBAI-INDIA

No 885911

ATTESTED BY ME

 15/03/2005

S. K. SHETTY B.A., LL.M.
ADVOCATE
NOTARY GOVT. OF INDIA
8, "Prakash", Bestant Street,
Santacruz (W), Mumbai-400 054



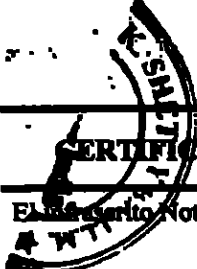


COMO NOTARIO SEXTO (B) DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA

01 JUN 2005

PABLO MENDOZA
NOTARIO

(संलग्न प्रमाण)
(BANKARA SECTION)
बपपाय बरिफाये (पी० वी०)
Section Officer (BI)
पी० वी० २०००
(C. P. V. Section)
विदेश मन्त्रालय, नई दिल्ली
Ministry of External Affairs
New Delhi.



CERTIFICACION NOTARIAL (SOCIEDAD)

El Notario Notario Certifica: Que la firma que antecede de

es auténtica; que el signatario desempeña actualmente el cargo de

de la compañía **CIPLA LIMITED**

sociedad que actualmente existe y está organizada de acuerdo a las leyes de

que la dirección de dicha compañía es

289 Bellasis Road,

Mumbai Central, Mumbai 400 008,

India

y que el signatario tiene facultad para otorgar este documento.

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo ello da fe.

Hecho y firmado en

Ciudad _____

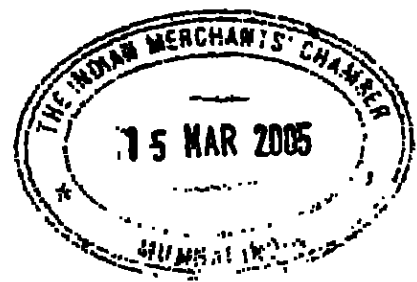
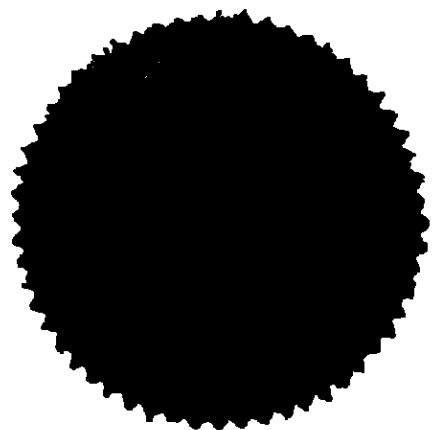
País _____

Hoy _____ del mes de _____ de 200 _____

— NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO — NOTARY PUBLIC OR ATTESTING OFFICIAL —

AUTENTICACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).



1 No 885 9 1

NOTARIAL CERTIFICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature of

MR. AMAR LULLA

is authentic, that the signatory currently acts in the position of

JOINT MANAGING DIRECTOR

of the company **CIPLA LIMITED**

a company currently existing and organized under the laws of

INDIA

that the address is

289 Bellasis Road,

Mumbai Central, Mumbai 400 008,

India

and that the signatory has the power to grant this document.

The Notary Public is satisfied with the facts upon examination of the corresponding documents.

Given and signed in

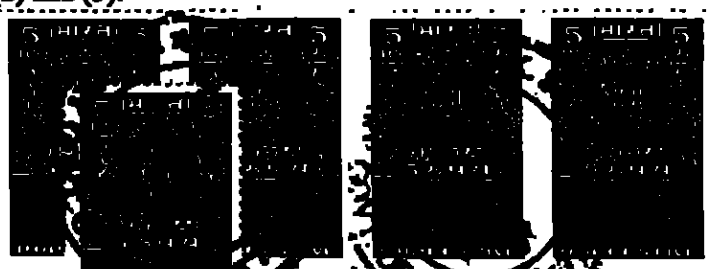
City **MUMBAI**

Country **INDIA**

This **15th** day of **JUN** 2005

AUTHENTICATION

The Colombia Consul must issue a *consular certificate*, on (1) the legal existence of the company which grants the Power-of-Attorney, (2) that it is in actual exercise of its company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

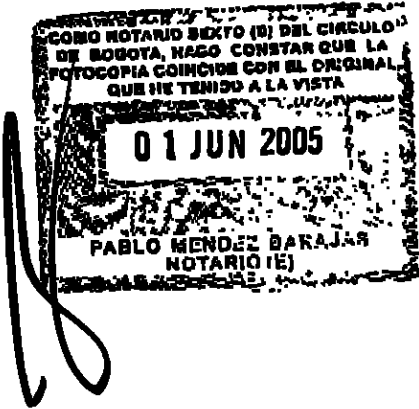


ATTESTED BY ME

S. K. Shetty
S. K. SHETTY B.A., LL.M.
ADVOCATE
NOTARY GOVT. OF INDIA
8, "Prakash", Bestant Street,
Santacruz (W), Mumbai-400 054

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.



TRADUCCIÓN OFICIAL No. 12.04/05 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia mediante Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

A continuación se traducen las legalizaciones de un documento de REPRESENTACIÓN, RATIFICACIÓN Y PODER escrito en inglés y español, por el cual CIPLA LIMITED, sociedad domiciliada en 289 Bellasis Road, Mumbai Central, Mumbai 400 008, India, ratifica la solicitud de patente No. 05-000.895 presentada por Emilio FERRERO el 6 de enero de 2005, y otorga poder a EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y GERMAN CAVELIER.

Dado y firmado el 15 de marzo de 2005

En Mumbai

Por Sr. AMAR LULLA, Firma ilegible

SELLOS:

CERTIFICADO POR MÍ

(Firma ilegible) el 15 de marzo de 2005

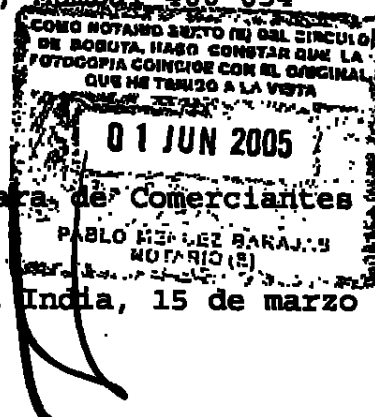
S.K. SHETTY BA., LL.M, ABOGADO, NOTARIO DEL GOBIERNO DE INDIA

8, "Prakash", Bestant Street, Santacruz (W), Mumbai-400 054

Estampillas de India por valor de 5 rupias.

(Firma ilegible), Firmante autorizado, Cámara de Comerciantes de India, Mumbai - India

Sello No. 88591, Cámara de Comerciantes de India, 15 de marzo de 2005, Mumbai, India.



CERTIFICACIÓN NOTARIAL - SOCIEDAD - expedida en inglés y español, referente a la firma y cargo del Sr. AMAR LULLA y a la existencia legal de CIPLA LIMITED.

Dado y firmado en Mumbai, India, el 15 de marzo de 2005.

SELLOS:

CERTIFICADO POR MÍ

(Firma ilegible) el 15 de marzo de 2005

S.K. SHETTY BA., LL.M, ABOGADO, NOTARIO DEL GOBIERNO DE INDIA

8, "Prakash", Bestant Street, Santacruz (W), Mumbai-400 054

9

Estampillas de India por valor de 5 rupias.

(Firma ilegible), Firmante autorizado, Cámara de Comerciantes de India, Mumbai - India

Sello No. 88591, Cámara de Comerciantes de India, 15 de marzo de 2005, Mumbai, India

Al dorso:

No. 38368 17 de marzo de 2005

La firma del Secretario Asistente / Subsecretario / Secretario de la Cámara de Comercio, certificada.

(Firma ilegible)

(SANKARA SUBBU)

Funcionario de Sección (OI)

Ministerio de Relaciones Exteriores, Nueva Delhi.

(En español) Certificación de la firma que antecede, del cargo del Sr. Amar Lulla y de la existencia legal del CIPLA LIMITED expedida por el Consulado de Colombia en Nueva Delhi bajo el No. 17/2005, con fecha 22 de marzo de 2005. Firmada por Olga Bula, Consejera EFC.

Legalización de la firma que antecede expedida por el MINISTERIO DE RELACIONES EXTERIORES bajo el No. 34 de Bogotá, del 17 de marzo de 2005, firmado por el Jefe de Legalizaciones.

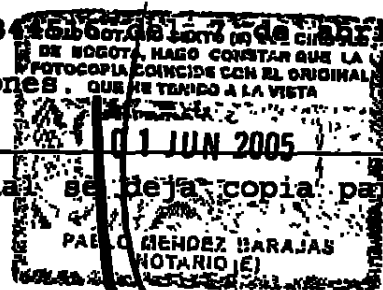
Es traducción fiel y completa de la cual se deja copia para su confrontación.

COLO 12092-841-001-4

WPC 12092 - ID 10

ABR 13/05

Maria E. Martel
TRADUCCION No. 120405
MARIA ELVIRA MARTEL
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia



COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
 BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE
Maria Elvira Martelo

 COINCIDE(N) CON LA FIRMA REGISTRADA POR
 EL (ELLOS) EN ESTA NOTARIA
 SANTAFE DE BOGOTA. **13 ABR 2005**



NO SE ASUME
 RESPONSABILIDAD DEL TEXTO
 1605 ABR 13 12:57
 JES
 JEFE DE LEGALIZACIONES
 BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO
 DE BOGOTA, HAGO CONSTAR QUE
 FOTOCopia COINCIDE CON EL ORIGINAL
 QUE HE TENIDO A LA VISTA
01 JUN 2005
 PABLO GARCIA SARAJAS
 NOTARIO

MINISTERIO DE
 RELACIONES EXTERIORES
 3488922
 Maria Elvira Martelo
 CUYA FIRMA APARECE EN EL
 DOCUMENTO DESEMPEÑA
 LAS FUNCIONES INDICADAS

DOCUMENTOS ANEXOS

1. ☒ **Publicación Internacional WO 2004/041797 A1**

Descripción:

Páginas 1-6 en el idioma original

Páginas 1-7 en español

Reivindicaciones: Número (s) 1-19

Figuras: Número (s) _____

2. ☒ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☒ **Forma PCT/ISA/210. Informe de Búsqueda Internacional.**
5. ☐ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
6. ☐ **Forma PCT/ISA/237. Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.**
7. ☐ **Forma PCT/IB/304. Notification Concerning Submission Or Transmittal Of Priority Document.**
8. ☐ **Forma PCT/IB/306. Notification Of The Recoding Of A Change.**
Descripción De Modificación:

9. ☐ **Forma PCT/IB/308. Notice Informing The Applicant Of The Communication Of The International Application To The Designated Offices.**
10. ☐ **Forma PCT/IB/332. Information Concerning Elected Offices Notified Of Their Election.**
11. ☐ **Forma PCT/IPEA/401. PCT Demand**
12. ☐ **Forma PCT/IPEA/402. Notification Of Receipt Of Demand By Competent International Preliminary Examining Authority.**
13. ☐ **Forma PCT/IPEA/408. Written Opinion.**
14. ☐ **Forma PCT/IPEA/416. Notification Of Transmittal Of The International Preliminary Examination Report.**
15. ☒ **Forma PCT/IPEA/409. Informe Del Examen Preliminar Internacional.**
16. ☐ **Traducción Al Español Del Informe Del Examen Preliminar Internacional.**
17. ☐ **Traducción Al Español De Los Anexos Presentados Junto Con El Informe Del Examen Preliminar Internacional.**

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041797 A1

(51) International Patent Classification⁷: C07D 277/82

Society, NSS Road, Gratkoper (West), Mumbai 400084,
Maharashtra (IN).

(21) International Application Number:
PCT/GB2003/004734

(74) Agents: WAIN, Christopher, Paul et al.; A.A. Thornton
& Co., 235 High Holborn, London WC1V 7LE (GB).

(22) International Filing Date:
3 November 2003 (03.11.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0225701.2 4 November 2002 (04.11.2002) GB

(84) Designated States (*regional*): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): CIPLA
LTD [IN/IN]; 289 Bellasis Road, Mumbai Central, Mum-
bai 400 008 (IN).

(71) Applicant (*for MW only*): WAIN, Christopher, Paul
[GB/GB]; A.A. Thornton & Co., 235 High Holborn,
London WC1V 7LE (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): RAO, Dharmaraj,
Ramachandra [IN/IN]; 4/403 Garden Enclave, Pokhran
Road 2, Thane (West), Mumbai 400 601, Maharashtra (IN).
KANKAN, Rajendra, Narayanrao [IN/IN]; A-3/5, NBD

Published:
— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING 2,6-DIAMINO-4,5,6,7-TETRAHYDRO-BENZOTHAZOLE

(57) Abstract: 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole, which is useful for making pramipexole, is made by: (i) reacting
bromine with a solution of 4-acetamido-cyclohexanone in water to produce 2-bromo-4-acetamido-cyclohexanone; (ii) after step (i),
adding thiourea to produce 6-acetyl amino- 2-amino-4,5,6,7-tetrahydro-benzthiazole; (iii) after step (ii), adding an aqueous solution
of hydrobromic acid to produce 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole dihydrobromide; and (iv) after step (iii), isolating 2,6-
diamino-4,5,6,7 -tetrahydro-benzthiazole.

WO 2004/041797 A1

PROCESS FOR PREPARING 2,6-DIAMINO-4,5,6,7-TETRAHYDRO-BENZOTHAZOLE

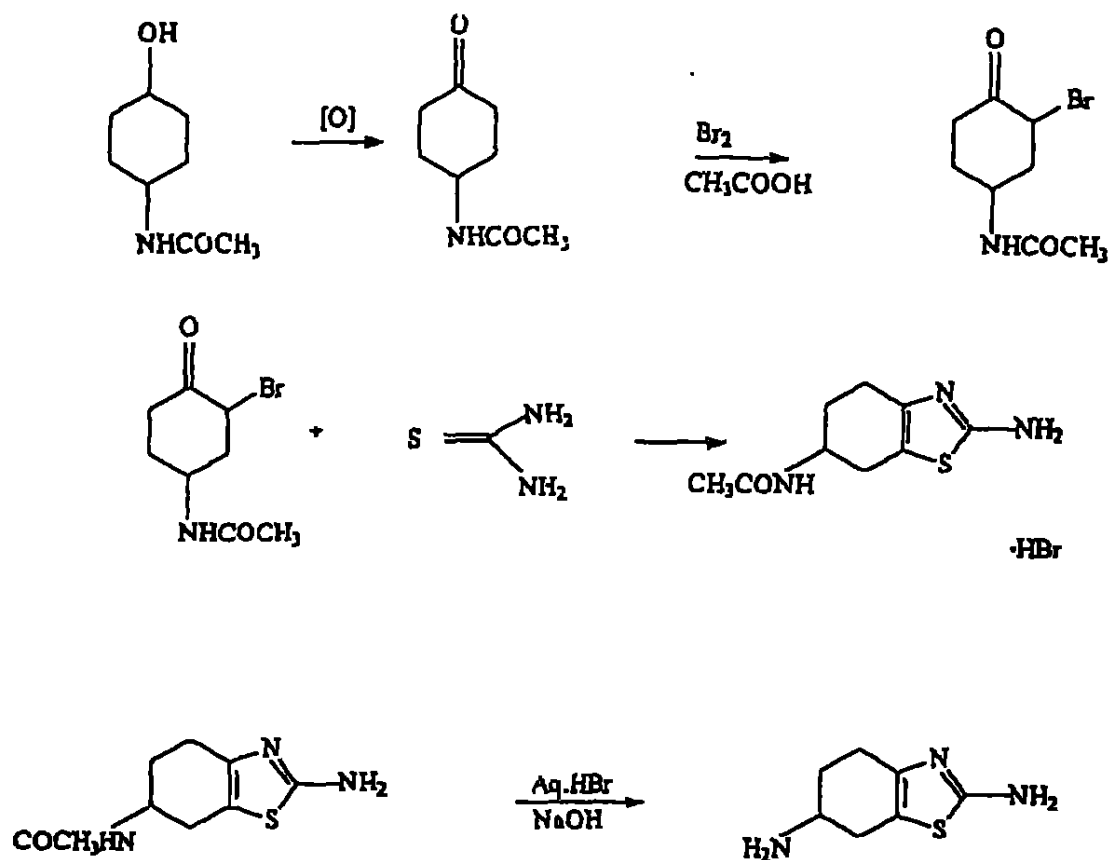
This invention relates to a process for making 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole, an intermediate useful in the production of pramipexole. The invention also relates to the synthesis of pramipexole.

(S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolediamine (or (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole), more commonly known as pramipexole, is used in both early and late Parkinson's disease as a dopamine agonist, to stimulate dopamine receptors in the brain. This has been described in EP 0 186 087.

EP 0 186 087 also describes the synthesis of various tetrahydro benzothiazoles, including pramipexole. In particular, the synthesis of pramipexole by the following reaction pathway is described. An initial reaction between bromine and 4-acetylamido-cyclohexanone is carried out in glacial acetic acid, with stirring for several hours, at room temperature. This is followed by the addition of thiourea under refluxing conditions. The reaction mixture is cooled, and crystals of 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-hydrobromide are precipitated. The precipitate is filtered, then washed with water and acetone. The crystals are then dissolved in hydrobromic acid and the solution is refluxed for several hours. The solution is then concentrated by evaporation and the residue dissolved in methanol, from which crystals of 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide are formed. Subsequently, the 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide may be converted to pramipexole.

This synthesis is illustrated by the following reaction scheme:

2



This synthetic pathway involves separate reaction steps, each requiring different conditions, solvents, temperatures, etc. This necessitates a discontinuous process and more than one isolation step, which entails longer processing time, lower yields (product is lost during each isolation step), increased effluent load and increased solvent usage, in comparison with a continuous process.

We have now found a way of synthesising 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole from 4-acetamido-cyclohexanone, which avoids the multiple isolation steps used in the previously described processes.

According to one aspect of the present invention there is provided a method of synthesising 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole, which method comprises comprising: (i) reacting bromine with a solution of 4-acetamido-cyclohexanone in water to produce 2-bromo-4-acetamido-cyclohexanone; (ii) after step (i), adding thiourea to produce 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide; (iii) after step (ii), adding an aqueous solution of hydrobromic acid to produce 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole; and (iv) after step (iii), isolating 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole free base.

It is an important feature of the present invention that step (iii) is carried out without any isolation of the 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole produced in step (ii). Thus the entire synthesis can be carried out in a single reaction vessel. Preferably at least three successive steps of steps (i) to (iv) are carried out in a single reaction vessel.

Prior to step (i), the method may comprise the step of oxidising 4-acetamido-cyclohexanol to produce 4-acetamido-cyclohexanone. This step may be carried out in the same reaction vessel as subsequent steps (i) to (iv), thereby avoiding an additional isolation step.

The oxidation reaction may be carried out using oxidising agents including, for example, Jones reagent, sodium hypochlorite, manganese dioxide, pyridinium dichromate or potassium permanganate.

In step (i), the 4-acetamido-cyclohexanone solution and the bromine are preferably combined in the reaction vessel at a temperature in the range 5°C to 75°C, more preferably in the range 15°C to 40°C, and most preferably about room temperature (approximately 25°C). The bromine is preferably added dropwise to the 4-acetamido-cyclohexanone solution. After the bromine and the 4-acetamido-cyclohexanone solution have been combined, the mixture is preferably heated to a temperature in the range 30°C to 80°C, more preferably 40°C to 50°C,

and most preferably about 45°C, and maintained at or near this temperature until the bromination is complete. The completion of bromination is indicated by the elimination of the characteristic brown colour of the bromine.

In step (ii), the temperature is preferably increased to 50°C to 95°C, more preferably to 70°C to 90°C, and most preferably to about 80°C.

In step (iii), the reaction mixture is preferably refluxed.

In step (iv), the reaction mixture is preferably cooled to 1°C to 35°C, more preferably to 5°C to 20°C, and most preferably to about 10°C, and the mixture is then neutralised. Typically the neutralisation is carried out with caustic lye solution (NaOH), although other alkalis may be used. Following neutralisation, the product, 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole, is isolated. The isolation may be carried out by filtration, centrifugation or any other suitable means. Following isolation, the product is preferably washed with chilled water.

The starting compound, 4-acetamido-cyclohexanone, may conveniently be formed by the oxidation of 4-acetamido-cyclohexanol.

The above described compound, 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole, is useful as an intermediate in the production of pramipexole and related compounds.

According to another aspect of the present invention there is provided a method of synthesising pramipexole, comprising the steps of: forming 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole by the method of the present invention, then converting it to pramipexole.

The conversion of 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole to pramipexole is well known in the prior art and is described, for example, in US 4,731,374. Any of the methods described in US 4,731,374, may be used in the present invention.

In one embodiment, the 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole is converted to pramipexole by reaction with a propionyl halide, such as propionyl bromide, under suitable reaction conditions.

Both 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole and pramipexole have an asymmetric carbon atom, and exist as two distinct enantiomers: the S(-) isomer and the R(+)

isomer. The pharmacological activity of the S(-) isomer of pramipexole is, however, twice as high as that of the R(+) isomer, and the name pramipexole is commonly used to refer to the optically pure S(-) form. In this specification, "2,6-diamino-4,5,6,7-tetrahydro-benzthiazole" encompasses the R(+) and S(-) enantiomers individually and also encompasses any mixture thereof including the racemic mixture, and the term "pramipexole" encompasses the R(+) and S(-) enantiomers individually and also the racemic mixture.

The resolution of a racemic mixture of 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole can be carried out after step (iv) above. Methods of resolution are known in the art. Alternatively, pramipexole racemate can be produced prior to resolution, then the mixture resolved, if desired.

The resolution of pramipexole racemate is described by Schneider and Mierau (J. Med. Chem. 30, 494 (1987)). This method uses the di-amino derivative of (±)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolodiamine as a substrate and L(+) tartaric acid as a resolution agent. Following resolution, optically active pramipexole has been prepared by two-step propylation of the single enantiomer of the di-amino precursor comprising the steps of reaction with propionanhydride followed by a reduction of the propionyl intermediate.

The synthesis of the present invention avoids the need to isolate intermediate compounds, and thus the yield is higher and the processing time is lower. Furthermore, owing to the absence of an organic solvent (such as acetic acid) the costs are lower, and the reaction conditions are milder – the milder reaction conditions also have a positive impact on product purity.

The invention will now be further described with reference to the following Examples.

Example 1

Bromine (112g) was added dropwise to a solution of 4-acetamidocyclohexanone (100g) in 500ml water at room temperature. The mixture was warmed to approximately 45°C and maintained at this temperature until the bromine colour had been lost. To this,

thiourea (125g) was added, and the mixture was heated to approximately 80°C. To this, aqueous hydrobromic acid (100ml) was added, and the contents of the reaction vessel were refluxed. The contents were then cooled to approximately 10°C, and neutralized with caustic lye solution. The product, 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole, was isolated by filtration, and washed with chilled water and dried. The product was off-white in colour, and the yield was approximately 60g in weight.

Example 2

To a solution of 4-acetamido-cyclohexanol (100 g) in acetone (1L) was added Jones reagent (prepared from 68.5 g chromic oxide, 105 g sulphuric acid and 400 ml water) at 10-15°C. The excess of the reagent was quenched by addition of isopropanol (400 ml) and the solvent was removed under reduced pressure. Ethyl acetate (600 ml) was added, the contents stirred for 10 minutes and the lower aqueous portion drained off. Ethyl acetate was concentrated under reduced pressure and the residue dissolved in water (500 ml). Bromine (112 g) was added dropwise and the further reactions were carried out as described in Example 1.

Example 3

To a suspension of 4-acetamido-cyclohexanol (100 g) in water (300 ml) was added a solution of 10% sodium hypochlorite (500ml) and the contents stirred at room temperature for 12 hours. To this was added liquid bromine (112 g) and further reactions carried out as described in Example 1.

It will be appreciated that the invention described above may be modified.

CLAIMS:

- 1 A method of making 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole, which method comprises the steps in sequence of: (i) reacting bromine with a solution of 4-acetamido-cyclohexanone in water to produce 2-bromo-4-acetamido-cyclohexanone; (ii) adding thiourea to produce 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole; (iii) adding an aqueous solution of hydrobromic acid to produce 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole; and (iv) isolating 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole.
- 2 A method according to claim 1 wherein step (iii) is carried out without isolating the 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole produced in step (ii).
- 3 A method according to claim 1 or 2, wherein any three successive steps of steps (i) to (iv) are carried out in a single reaction vessel.
- 4 A method according to claim 1, 2 or 3, wherein steps (i) to (iv) are carried out in a single reaction vessel.
- 5 A method according to claim 1, 2, 3 or 4, further comprising, prior to step (i), the step of oxidising 4-acetamido-cyclohexanol to produce 4-acetamido-cyclohexanone.
- 6 A method according to claim 5, wherein the step of oxidising 4-acetamido-cyclohexanol to produce 4-acetamido-cyclohexanone and at least three successive steps of steps (i) to (iv) are carried out in a single reaction vessel.
- 7 A method according to any preceding claim wherein in step (i) the solution of 4-acetamido-cyclohexanone in water and bromine are combined at a temperature of from 15°C to 40°C.

8 A method according to any preceding claim wherein, after the bromine and the 4-acetamido-cyclohexanone solution have been combined, the mixture is heated to a temperature of from 40°C to 50°C, and maintained at or near this temperature until the bromination is complete.

9 A method according to any preceding claim wherein, in step (ii), the temperature is increased to 70°C to 90°C.

10 A method according to any preceding claim, wherein step (iii) is carried out under refluxing conditions.

11 A method according to any preceding claim wherein, after step (iii) but before step (iv), the reaction mixture is cooled to 5°C to 20°C, then neutralised.

12 A method according to any preceding claim, further comprising the step of resolving the 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole isolated in step (iv) into its R(+) and S(-) enantiomers and recovering the R(+) and/or S(-) enantiomer.

13 A method of synthesising pramipexole, comprising the steps of : forming 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole by a method according to any preceding claim, and converting it to pramipexole.

14 A method according to claim 13, wherein 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole is converted to pramipexole by reaction with a propionyl halide.

15 A method according to claim 13 or 14, wherein the 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole comprises the R(+) enantiomer.

16 A method according to claim 13 or 14, wherein the 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole comprises the S(-) enantiomer.

17 A method according to claim 13 or 14, wherein the 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole comprises a racemic mixture.

18 A method according to claim 14, further comprising the step of resolving the pramipexole into its R(+) and S(-) enantiomers and recovering the R(+) and/or S(-) enantiomer.

19 A method of synthesising 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole substantially as herein described with reference to the Examples.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum) CPW/20725

Box No. I TITLE OF INVENTION PROCESS	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Cipla Ltd 289 Bellasis Road Mumbai Central Mumbai 400 008 India	Telephone No. Facsimile No. Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) RAO Dharmaraj Ramachandra 4/403 Garden Enclave Pokhran Road 2 Thane (West), Mumbai-400 601 Maharashtra, INDIA	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) WAIN Christopher Paul A A Thornton & Co 235 High Holborn London WC1V 7LE	Telephone No. +44 1604 638242 Facsimile No. +44 1604 638164 Teleprinter No. Agent's registration No. with the Office
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) KANKAN Rajendra Narayanrao A-3/5, NBD Society NSS Road Ghatkopar (West), Mumbai-400 084 Maharashtra, INDIA	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office	
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) WAIN Christopher Paul A A Thornton & Co 235 High Holborn London WC1V 7LE	This person is: ☒ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office	
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office	
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☐ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☐ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|---|---|
| ☐ AE United Arab Emirates | ☐ GM Gambia | ☐ NZ New Zealand |
| ☐ AG Antigua and Barbuda | ☐ HR Croatia | ☐ OM Oman |
| ☐ AL Albania | ☐ HU Hungary | ☐ PH Philippines |
| ☐ AM Armenia | ☐ ID Indonesia | ☐ PL Poland |
| ☐ AT Austria | ☐ IL Israel | ☐ PT Portugal |
| ☐ AU Australia | ☐ IN India | ☐ RO Romania |
| ☐ AZ Azerbaijan | ☐ IS Iceland | ☐ RU Russian Federation |
| ☐ BA Bosnia and Herzegovina | ☐ JP Japan | |
| ☐ BB Barbados | ☐ KE Kenya | ☐ SD Sudan |
| ☐ BG Bulgaria | ☐ KG Kyrgyzstan | ☐ SE Sweden |
| ☐ BR Brazil | ☐ KP Democratic People's Republic of Korea | ☐ SG Singapore |
| ☐ BY Belarus | ☐ KR Republic of Korea | ☐ SI Slovenia |
| ☐ BZ Belize | ☐ KZ Kazakhstan | ☐ SK Slovakia |
| ☐ CA Canada | ☐ LC Saint Lucia | ☐ SL Sierra Leone |
| ☐ CH & LI Switzerland and Liechtenstein | ☐ LK Sri Lanka | ☐ TJ Tajikistan |
| ☐ CN China | ☐ LR Liberia | ☐ TM Turkmenistan |
| ☐ CO Colombia | ☐ LS Lesotho | ☐ TN Tunisia |
| ☐ CR Costa Rica | ☐ LT Lithuania | ☐ TR Turkey |
| ☐ CU Cuba | ☐ LU Luxembourg | ☐ TT Trinidad and Tobago |
| ☐ CZ Czech Republic | ☐ LV Latvia | |
| ☐ DE Germany | ☐ MA Morocco | ☐ TZ United Republic of Tanzania |
| ☐ DK Denmark | ☐ MD Republic of Moldova | ☐ UA Ukraine |
| ☐ DM Dominica | | ☐ UG Uganda |
| ☐ DZ Algeria | ☐ MG Madagascar | ☐ US United States of America |
| ☐ EC Ecuador | ☐ MK The former Yugoslav Republic of Macedonia | |
| ☐ EE Estonia | ☐ MN Mongolia | ☐ UZ Uzbekistan |
| ☐ ES Spain | ☐ MW Malawi | ☐ VN Viet Nam |
| ☐ FI Finland | ☐ MX Mexico | ☐ YU Yugoslavia |
| ☐ GB United Kingdom | ☐ MZ Mozambique | ☐ ZA South Africa |
| ☐ GD Grenada | ☐ NO Norway | ☐ ZM Zambia |
| ☐ GE Georgia | | ☐ ZW Zimbabwe |
| ☐ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Supplemental Box If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(f) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

CONTINUATION OF BOX III

Mr C P Wain is applicant for Malawi (MW) only.

(i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

CONTINUATION OF BOX NO IV

Further agents of A A Thornton & Co., 235 High Holborn, London, WC1V 7LE, United Kingdom, who have been appointed to act on behalf of the applicants before the competent International Authorities are:

(ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

CRAWFORD, Andrew Birkby,
LERWILL, John,
GOODENOUGH, Nigel,
CURTIS, Philip Anthony,
BUTCHER, Ian James,
GILL, Ian Stephen,
HEDGES, Martin Nicholas.

(iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

25

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 4/11/2002	0225701.2	GB		
item (2)				
item (3)				
item (4)				
item (5)				
☐ Further priority claims are indicated in the Supplemental Box.				
The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:				
☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box				
* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):				
ISA / EP				
Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):				
Date (day/month/year)	Number	Country (or regional Office)		
18/08/2003	RS 110105GB	EPO(GB)		
Box No. VIII DECLARATIONS				
The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):				Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor			:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent			:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application			:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)			:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty			:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

- (a) the following number of sheets in paper form:
- request (including declaration sheets) : 6
- description (excluding sequence listing part) : 6
- claims : 3
- abstract : 1
- drawings : -
- Sub-total number of sheets : 16
- sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) : -
- Total number of sheets : 16
- (b) sequence listing part of description filed in computer readable form
- (i) ☐ only (under Section 801(a)(i))
- (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))
- Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(b), in right column):

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

- | | Number of items |
|---|-----------------|
| 1. ☒ fee calculation sheet | 1 |
| 2. ☒ original separate power of attorney | 1 |
| 3. ☐ original general power of attorney | |
| 4. ☒ copy of general power of attorney; reference number, if any: | 1 |
| 5. ☐ statement explaining lack of signature | |
| 6. ☐ priority document(s) identified in Box No. VI as item(s): | |
| 7. ☐ translation of international application into (language): | |
| 8. ☐ separate indications concerning deposited microorganism or other biological material | |
| 9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) | |
| (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) | |
| (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter | |
| (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column | |
| 10. ☐ other (specify): | |

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



WAIN, Christopher Paul

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	
6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

INTERNATIONAL SEARCH REPORT

Intern: Application No

PCT/GB 03/04734

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D277/82

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)
IPC 7 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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 186 087 A (DR. KARL THOMAE GMBH) 2 July 1986 (1986-07-02) cited in the application the whole document, particularly page 5478, right-hand column, first paragraph	1-19
Y	ALLINGER J ET AL: "The conformers of 2-bromocyclohexanone" TETRAHEDRON. ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 2, 1958, pages 64-74, XP002253277 ISSN: 0040-4020 the whole document, particularly paragraph bridging pages 71 and 72	1-19
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document 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
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

20 January 2004

Date of mailing of the international search report

28/01/2004

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Allard, M

28

INTERNATIONAL SEARCH REPORT

Internat	Application No
PCT/GB 03/04734	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALLINGER N L ET AL: "Conformational analysis. II. The 2-bromo-4-t-butylcyclohexanones" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 80, no. 20, 20 October 1958 (1958-10-20), pages 5476-5480, XP002253278 ISSN: 0002-7863 the whole document, particularly page 5478, right-hand column, first paragraph	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 03/04734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 186087	A	02-07-1986	
		DE 3447075 A1	03-07-1986
		DE 3508947 A1	18-09-1986
		AT 45735 T	15-09-1989
		AU 583874 B2	11-05-1989
		AU 5154485 A	17-07-1986
		BG 62023 B2	30-12-1998
		BR 1100678 A3	13-10-1999
		CA 1263653 A1	05-12-1989
		CS 9104099 A3	16-09-1992
		DD 242230 A5	21-01-1987
		DE 3572485 D1	28-09-1989
		DK 590285 A	23-06-1986
		EP 0186087 A1	02-07-1986
		ES 8702787 A1	01-04-1987
		ES 8707513 A1	16-10-1987
		ES 8707514 A1	16-10-1987
		ES 8707515 A1	16-10-1987
		FI 855102 A ,B,	23-06-1986
		GR 853126 A1	22-04-1986
		HK 78692 A	23-10-1992
		HU 39736 A2	29-10-1986
		IE 58863 B1	17-11-1993
		IL 77415 A	19-03-1990
		JP 1854941 C	07-07-1994
		JP 5072907 B	13-10-1993
		JP 61155377 A	15-07-1986
		KR 9309791 B1	11-10-1993
		LU 90208 A9	06-04-1998
		MX 9202792 A1	30-06-1992
		NO 855195 A ,B,	23-06-1986
		NZ 214661 A	26-04-1990
		PH 24533 A	03-08-1990
		PT 81735 A ,B	01-01-1986
		SG 82492 G	04-12-1992
		US 4843086 A	27-06-1989
		US 4886812 A	12-12-1989
		US 4731374 A	15-03-1988
		ZA 8509731 A	26-08-1987

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CPW20725		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA416)	
International application No. PCT/GB 03/04734	International filing date (day/month/year) 03.11.2003	Priority date (day/month/year) 04.11.2002	
International Patent Classification (IPC) or both national classification and IPC C07D277/B2			
Applicant CIPLA LTD. et al			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application			
Date of submission of the demand 12.05.2004		Date of completion of this report 22.10.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3018		Authorized Officer Allard, M Telephone No. +31 70 340-2002 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 03/04734**

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-6 as originally filed

Claims, Numbers

1-19 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 03/04734**

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-19
	No: Claims	-
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-19
Industrial applicability (IA)	Yes: Claims	1-19
	No: Claims	-

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB 03/04734

Reference is made to the following documents:

- D1: EP-A-0 186 087 (DR. KARL THOMAE GMBH) 2 July 1986 (1986-07-02)
D2: ALLINGER J ET AL: "The conformers of 2-bromocyclohexanone"
TETRAHEDRON, vol. 2, 1958, pages 64-74, XP002253277
D3: ALLINGER N L ET AL: "Conformational analysis. II. The 2-bromo-4-t-
butylcyclohexanones" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol.
80, no. 20, 20 October 1958 (1958-10-20), pages 5476-5480, XP002253278

Re Item V**Reasoned statement with regard to novelty, inventive step or industrial
applicability; citations and explanations supporting such statement****Novelty (Article 33(2) PCT)**

None of the available prior art documents discloses the preparation of 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole by a series of reactions comprising bromination of 4-acetamido-cyclohexanone *in water*; the subject-matter of claims 1-19 is therefore novel.

Inventive step (Article 33(3) PCT)

D1, which is considered to represent the closest prior art, describes the preparation of 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole by bromination of 4-acetylaminocyclohexanone in acetic acid, reaction of the obtained compound with thiourea, and deacetylation with HBr, see examples 3 and 4.

In the light of the teachings of D1 the problem underlying the present application can be seen in the provision of a further process to prepare 2,6-diamino-4,5,6,7-tetrahydro-benzothiazole.

To solve this problem the present application proposes to perform the bromination step in aqueous solution.

It is however already known from D2 and D3 that bromination of cyclohexanones can be performed in aqueous solution, see D2, paragraph bridging pages 71 and 72, and D3, page 5478, right-hand column, first paragraph.

The proposed solution appears therefore to be an obvious measure in the design of an alternative process. As all further measures recited in the claims are known from D1 or obvious, the subject-matter of claims 1-19 lacks an inventive step.

It has been submitted that the above-mentioned bromination in aqueous solution *without isolation of the brominated compound* leads to an unexpected improvement in the overall process: as however this specific feature of not isolating the intermediate compound is not recited, explicitly or implicitly, in the claims, it cannot be taken into account for assessing the inventive step.

In this context it should be noted from the wording of claim 2, that the term "adding" used in claim 1 does not necessarily imply that the compound produced in the preceding step is not isolated. Moreover, even the use of a single reaction vessel, as recited in claims 3 or 4, does not preclude isolation of the different intermediates.

Industrial applicability (Article 33(4) PCT)

The processes of claims 1-19 can be used in the chemical, particularly pharmaceutical, industry.

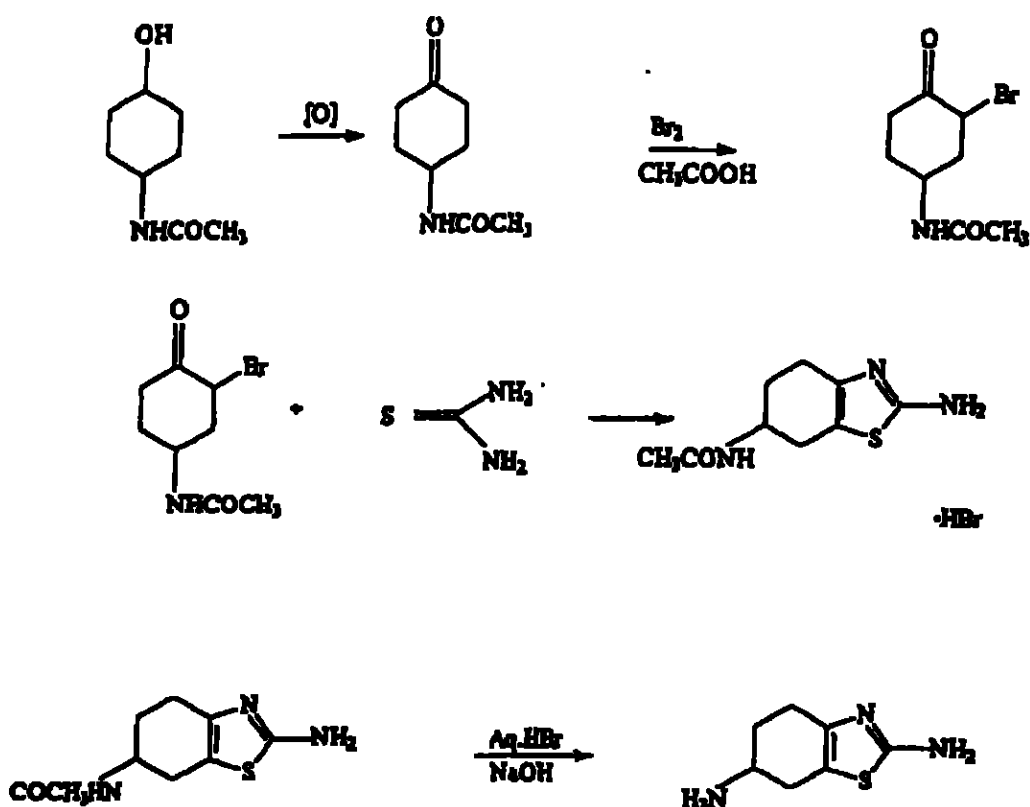
PROCESO PARA PREPARAR 2,6-DIAMINO-4,5,6,7-TETRAHIDRO-BENZOTIAZOL

Es invento se relaciona con un proceso para hace 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol, un intermedio útil en la producción de pramipexol. La invención tambien se relaciona con la síntesis de pramipexol.

(S)-4,5,6,7-tetrahidro-N&-propil-2,6-benzotiazolodiamina (o (S)-2-amino-4,5,6,7-tetrahidro-6-(propilamino)benzotiazol), mas comúnmente conocido como pramipexol, es usado en ambas, Parkinson temprano y tardío como una agonista de dopamina, para estimular los receptores de dopamina en el cerebro. Esto ha sido descrito en EP 0 186 087.

EP 0 186 087 también describe la síntesis de varias tetrahidro benzotiazoles, incluyendo el pramipexol. En particular, la síntesis de pramipexol por la siguiente trayectoria de reacción es descrita. Una reacción inicial entre bromo y 4-acetilamido-ciclohexanona es llevada a cabo en ácido acético congelado, con agitación por varias horas, a temperatura ambiente. Esto es seguido por la adición de tiourea bajo condiciones de reflujo. La mezcla de la reacción es enfriada, y los cristales de 6-acetilamino-2-amino-4,5,6,7-tetrahidro-benzotiazol-hidrobromuro son precipitados. El precipitado es filtrado , luego lavado con agua y acetona. Los cristales son luego disueltos en ácido bromhídrico y la solución es refluja por varias horas. La solución es luego concentrada por evaporación y el residuo disuelto en metanol, desde el cual los cristales de 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol-dihidromuro son formados. Subsecuentemente, el 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol-dihidromuro puede ser convertido en pramipexol.

Esta síntesis es ilustrada por el siguiente esquema de reacciones:



Esta trayectoria de síntesis involucra pasos de reacción separados, cada uno requiriendo condiciones diferentes, solventes, temperaturas, etc. Esto necesita de un proceso discontinuo y mas de un paso de aislamiento, lo cual conlleva un tiempo de procesamiento mas largo, rendimientos mas bajos (el producto se pierde durante cada paso de aislamiento), carga de efluentes incrementada y uso incrementado de solvente en comparación con un proceso continuo.

Nosotros hemos ahora encontrado un camino para sintetizar 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol a partir de 4-acetamida-ciclohexanona, que evita los multiples pasos de aislamiento usado en los procesos descritos anteriormente.

/

De acuerdo con un aspecto de la presente invención, se provee un método de sintetizar 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol, el cual comprende: (i) Reaccionar bromo con una solución de 4-acetamida-ciclohexanona en agua para producir 2-bromo-4-acetamido-ciclohexanona; (ii) después del paso (i), adicionar tiourea para producir 6-acetilamina-2-amino-4,5,6,7-tetrahidro-benzotiazol-dihidrobromuro; (iii) después del

paso (ii), adicionar una solución acuosa de ácido bromhídrico para producir 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol, y (iv) después del paso (iii), aislar la base de libre de 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol.

Es un rasgo importante de la presente invención el que el paso (iii) es realizado sin ningún aislamiento del 6-acetilamina-2-amino-4,5,6,7-tetrahidro-benzotiazol-dihidrobromuro producido en el paso (ii). Así la síntesis completa puede ser realizada en un solo tanque de reacción. Preferiblemente al menos tres pasos sucesivos de los pasos (i) a (iv) son realizados en un único tanque de reacción.

Antes del paso (i), el método puede incluir el paso de oxidar el 4-acetamidaciclohexanol para producir 4-acetamido-ciclohexanona. Este paso puede ser realizado en el mismo tanque de reacción que los pasos subsecuentes (i) a (iv), en consecuencia evitando un paso de aislamiento adicional.

La reacción de oxidación puede ser realizada usando agentes oxidantes, que incluyen, por ejemplo, el reagente Jones, hipoclorito de sodio, dióxido de manganeso, dicromato de piridium o permanganato de potasio.

En el paso (i), la solución de 4-acetamidociclohexanona y el bromo son preferiblemente combinados en el tanque de reacción a una temperatura en el rango de 5 °C a 75 °C, mas preferiblemente en el rango de 15 °C a 40 °C, y mas preferiblemente cerca a la temperatura ambiente (aproximadamente 25 °C). El bromo es preferiblemente adicionado en gotas a la solución de 4-acetamidociclohexanona. Después de que el bromo y la solución de 4-acetamidociclohexanona han sido combinadas, la mezcla es preferiblemente calentada a una temperatura en el rango de 30 °C a 80 °C, mas preferiblemente de 40 °C a 50 °C, y la mas preferida a cerca de 45 °C, y mantenida en esta o cerca de esta temperatura hasta que la brominación esta completa. La

brominación completa es indicada por la eliminación del color marrón característico del bromo.

En el paso (ii), la temperatura es preferiblemente incrementada a 50 °C a 95 °C, mas preferiblemente a 70 °C a 90 °C y la mas preferida a cerca de 80 °C.

En el paso (iii), la mezcla de reacción es preferiblemente refluja.

En el paso (iv), la mezcla de reacción es preferiblemente enfriada a 1 °C a 35 °C, mas preferiblemente a 5 °C a 20 °C, y la mas preferida a cerca de 10 °C y la mezcal es luego neutralizada. Típicamente la neutralización se realiza con lejía cáustica (NaOH) aunque otros álcalis pueden ser usados. Luego de la neutralización, el producto, 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol, es aislado. El aislamiento puede ser realizado por filtración, centrifugación o cualquier otro medio adecuado. Luego de la separación, el producto es preferiblemente lavado con agua helada.

El compuesto de inicio, 4-acetamido-ciclohexanona, puede ser convenientemente preparado por la oxidación de 4-ecetamido-ciclohexanol.

El compuesto descrito arriba, 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol, es intermedio útil en la producción de pramipexol y compuestos relacionados.

De acuerdo con otro aspecto de la presente invención se provee un método para sintetizar pramipexol, que comprende los pasos de: preparar 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol por el método de la presente invención, y luego convertirla a pramipexol.

La conversión de 2,6-diamino-4,5,6,7-tetrahydro-benzotiazol a pramipexol es bien conocida en el arte existente y es descrita, por ejemplo, en US 4,731,374. Cualquiera de los métodos descritos en US 4,731,374 puede ser usado en la presente invención.

En una incorporación, el 2,6-diamino-4,5,6,7-tetrahydro-benzotiazol es convertido a pramipexol por reacción con un haluro de propionyl, tale como bromuro de propionil, bajo condiciones adecuadas de reacción.

Ambos 2,6-diamino-4,5,6,7-tetrahydro-benzotiazol y pramipexol tienen un átomo de carbono asimétrico, y existen como dos enantiomeros distintos: el isomero S(-) y el isomero R (+). La actividad farmacológica del isomero S (-) de pramipexol es, sin embargo, dos veces mas alto que el isomero R (+), y el nombre de pramipexol es comúnmente usado para referir la forma óptimamente pura S (-). En esta especificación "2,6-diamino-4,5,6,7-tetrahydro-benzotiazol" encompasa individualmente los enantiomeros R(+) y S(-) y también encompasa cualquier mezcla de ellos incluyendo la mezcla racémica, y el término " pramipexol " encompasa los enantiomeros R(+) y S(-) individualmente y también la mezcla racémica.

La resolución de la mezcla racémica de 2,6-diamino-4,5,6,7-tetrahydro-benzotiazol puede ser realizada después del paso (iv) de arriba. Los métodos de resolucion son conocidos en el arte. Alternativamente, pramipexol racemico puede ser producido antes de la resolución, luego la mezcla es resolucionada, si se desea.

La resolución de pramipexol racemico es descrito por Schneider and Mierau (J. Med. Chem. 30, 494 (1987)). Este método usa el derivado di-amino de (+)-4,5,6,7-tetrahydro-N6-propil-2,6-benzotiazoldiamina como un sustrato y ácido tartárico L (+) como un agente de resolución. Luego de la resolución, el pramipexol óptimamente activo ha sido preparado por propilación de dos pasos del enantiomero único del precursor di-amino,

que comprende los pasos de reacción con propion anhidrido seguido de una reducción del intermedio propionil.

La síntesis de la presente invención evita la necesidad de aislar compuestos intermedios, y así el rendimiento es mayor y el tiempo de procesamiento menor. Mas aún debido a la ausencia de un solvente orgánico (tal como el ácido acético) los costos son mas bajos, y las condiciones de reacción son moderadas –las condiciones de reacción moderadas también tienen un impacto positivo en la pureza del producto.

La invención será ahora descrita aún mas con referencia a los siguientes ejemplos.

Ejemplo 1

Bromo (112 g) fue adicionado por goteo a una solución de 4-acetamido-ciclohexanona 8 (100g) en 500 ml de agua a temperatura ambiente. La mezcla fue calentada a aproximadamente 45 °C y mantenida a esta temperatura hasta que el color del bromo se había desaparecido. A esta, tiourea (125 g) fue adicionada, ya la mezcla fue calentada a aproximadamente 80 °C. A esta, una solución acuosa de ácido bromhídrico (100 ml) fue adicionada, y los contenidos del tanque de reacción fueron refluados. Los contenidos fueron luego enfriados a aproximadamente 10 °C, y neutralizados con lejía cáustica. El producto 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol, fue aislado por filtración, y lavado con agua helada y secado. El producto fue de color blancuzco, y el rendimiento fue aproximadamente 60 g en peso.

Ejemplo 2

A una solución de 4-acetamido-ciclohexanol (100g) en acetona (1L) le fue adicionada reagente Jones (preparado de 68.5 g de oxido crómico, 105 g de ácido sulfúrico y 400 ml de agua) a 15 °C. El exceso del reagente fue apagado por la adición de isopropanol (400ml) y el solvente fue removido bajo presión reducida. Acetato de etil (600ml) fue

adicionado, los contenidos revueltos por 10 minutos y la porción acuosa inferior drenada. El acetato de etilo fue concentrado bajo presión reducida y el residuo disuelto en agua (500ml). El bromo (112 g) fue adicionado por goteo y las demás reacciones llevadas a cabo como se describió en el ejemplo 1.

Ejemplo 3

A una suspensión de 4-acetamido-ciclohexanol (100g) en agua (300ml) fue adicionada una solución de hipoclorito de sodio al 10% (500ml) y los contenidos revueltos a temperatura ambiente por 12 horas. A esta fue adicionada bromo líquido (112 g) y las demás reacciones realizadas como se describió en el ejemplo 1.

Será apreciado que la invención descrita anteriormente puede ser modificada.

REIVINDICACIONES

1. Un método para hacer 2,6-diamino-4,5,6,7-tetrahydro-benzotiazol, el cual comprende: (i) Reaccionar bromo con una solución de 4-acetamida-ciclohexanona en agua para producir 2-bromo-4-acetamido-ciclohexanona; (ii) adicionar tiourea para producir 6-acetilamino-2-amino-4,5,6,7-tetrahydro-benzotiazol; (iii) adicionar una solución acuosa de ácido bromhídrico para producir 2,6-diamino-4,5,6,7-tetrahydro-benzotiazol, y (iv) aislar la base de libre de 2,6-diamino-4,5,6,7-tetrahydro-benzotiazol.
2. Un método de acuerdo a la reivindicación 1 donde el paso (iii) es realizado sin aislar el 6-acetilamino-2-amino-4,5,6,7-tetrahydro-benzotiazol producido en el paso (ii).
3. Un método de acuerdo a las reivindicaciones 1 o 2, donde cualquiera tres pasos sucesivos de los pasos (i) a (iv) son realizados en un solo tanque de reacción.
4. Un método de acuerdo a las reivindicaciones 1, 2 o 3, donde los pasos (i) a (iv) son realizados en un solo tanque de reacción.
5. Un método de acuerdo a las reivindicaciones 1, 2, 3 o 4, que comprende además, antes del paso (i), el paso de oxidar 4-acetamido-ciclohexanol para producir 4-acetamido-ciclohexanona.
6. Un método de acuerdo a la reivindicación 5, donde el paso de oxidar 4-acetamido-ciclohexanol para producir 4-acetamido-ciclohexanona y al menos tres pasos sucesivos de los pasos (i) a (iv) son realizados en un solo tanque de reacción.

7. Un método de acuerdo a cualquiera de las reivindicaciones precedentes donde el paso (i) la solución 4-acetamido-ciclohexanona en agua y el bromo son combinados a una temperatura de 15 °C a 40 °C.
8. Un método de acuerdo a cualquiera de las reivindicaciones precedentes donde, después de que el bromo y la solución de 4-acetamido.ciclohexanona han sido combinadas, la mezcla es calentada a una temperatura de 40 °C a 50 °C, y mantenida a esta o cerca de esta temperatura hasta que la bromonización es completa.
9. Un método de acuerdo a cualquiera de las reivindicaciones precedentes donde en el paso (ii), la temperatura es incrementada a 70 °C a 90 °C.
10. Un método de acuerdo a cualquiera de las reivindicaciones precedentes donde en el paso (iii) es realizado bajo condiciones de reflujo.
11. Un método de acuerdo a cualquiera de las reivindicaciones precedentes donde después del paso (iii), pero antes del paso (iv), la mezcla de la reacción es enfriada a 5 °C a 20 °C, y luego neutralizada.
12. Un método de acuerdo a cualquiera de las reivindicaciones precedentes, que comprende además el paso de resolver la 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol aislada en el paso (iv) en sus enantiomeros R (+) y S(-) y recuperar el enantiomero R (+) y/o S (-).

13. Un método de sintetizar pramipexol, que comprende los pasos de : preparar 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol por un método de acuerdo a cualquiera de las reivindicaciones precedentes y convertirlo a pramipexol.
14. Un método de acuerdo a la reivindicación 13, donde el 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol es convertido en pramipexol por reacción con un haluro de propionil.
15. Un método de acuerdo a la reivindicación 13 o 14, donde el 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol incluye el enantiomero R (+).
16. Un método de acuerdo a la reivindicación 13 o 14, donde el 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol incluye el enantiomero S (-).
17. Un método de acuerdo a la reivindicación 13 o 14, donde el 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol incluye una mezcla racémica.
18. Un método de acuerdo a la reivindicación 14, que incluye además el paso de resolver el pramipexol en sus enantiomeros R (+) y S (-) y recuperar el enantiomero R (+) y/o S(-).
19. Un método de sintetizar 2,6-diamino-4,5,6,7-tetrahidro-benzotiazol sustancialmente como se describió aquí con referencia a los ejemplos.

1145

COORDINACIÓN Y CONTROL
Dirección : 4552426 00000000
Código (BIB): 0005-01-01 17:00:30
Tercero : 011 000 0000000 720 0000 0000 00000000
Dependencia: 0000 00000000 DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800174089-2

RECIBO OFICIAL DE CAJA : 05 - 35,941
FECHA : MAYO 16 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	40116714	16/05/2005	39,471,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	7 TRAMITES DE SOL. DE DISENOS INDUS	443,000.00
		TOTAL :	\$ 443,000.00

SOM: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

060 12092-841-002-2

REGISTRO DE PATENTES Y MARCAS
Radicación: 85653496 00000000 Folio: 45
E-obj: (ADM): 0005-02-02 17:00:10
T-obj: 011 INT-001001 179 CROC MAR 111 00000000
Recepción: 2020 INSTITUTO DE MARCAS Y PATENTES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	() ✓
- Indicación de que se solicita la concesión de una patente.	()	() ✓
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	() ✓
- Descripción de la invención.	()	() ✓
- Dibujos de ser estos pertinentes.	()	() ✓
- Comprobante de Pago de las tasas establecidas.	()	() ✓

COMPLETA ✓	INCOMPLETA ()
-------------------	-----------------------

DISEÑO INDUSTRIAL ()	
- Indicación de que se solicita el registro de Diseño Industrial	() ()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	() ()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	() ()
- Comprobante de pago de las tasas establecidas	() ()
COMPLETA ()	INCOMPLETA ()

ESQUEMA DE TRAZADO ()	
- Indicación de que solicita el registro de un Esquema de trazado.	() ()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	() ()
- Representación gráfica del esquema de trazado	() ()
- Comprobante de pago de las tasas establecidas.	() ()
COMPLETA ()	INCOMPLETA ()

Firma Responsable: 

Fecha:

47

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
CIPLA LIMITED

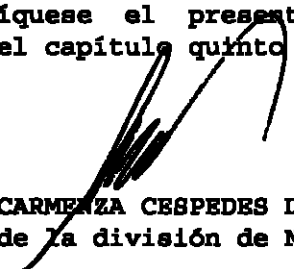
REFERENCIA	Radicación No.	05 53826
	Solicitud internacional	GB2003/004734
	Fecha inicio fase nacional	04/06/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	8032

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMONA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 09 SET. 2005
adpal

9/25/05

..

