

03-55750

Industria y Comercio

SUPERINTENDENCIA

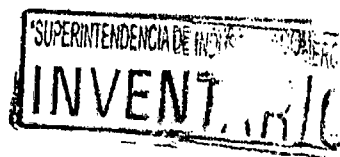
Organización CSA Ltda

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD



PATENTE DE INVENCION

03-55750

21. EXPEDIENTE No.

54. TÍTULO Proceso para preparar clopidogrel

51. CLASIFICACIÓN INTERNACIONAL ASIX31/4365

71. SOLICITANTE Cadila Healthcare limited

DOMICILIO (Gurat, India) Gujarat, India

74. APODERADO Dña María Rodríguez D'Aleman

22. BOGOTÁ, D. C., Junio 27, 2003 02/07/2003



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APODERADO

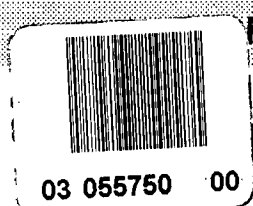
Delia Maria Rodriguez O' Aleman

BOGOTÁ, D. C.

Junio 27, 2003 / 02/07/2003

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PETITORIO

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☐ Capitulo I. ☒ Capitulo II.

2) SOLICITANTE (71)

Nombre: CADILA HEALTHCARE LIMITED Dirección: Zydus Towers, Satellite Cross Roads, Gandhinagar Sarkhej Highway, Ahmedabad - 380 015, Gujarat, India Nacionalidad o domicilio: Gujarat, India Lugar de constitución: Gujarat, India	IDENTIFICACIÓN
	C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____

Teléfono:	Fax:
E. Mail:	

3) REPRESENTANTE O APODERADO

Nombre: DILIA MARIA RODRÍGUEZ D'ALEMAN Dirección: Carrera 11 N°. 93-43 Of. 404 Santafé de Bogotá D.C. Teléfono: 6350835 Fax: 6350824 E. Mail: clarkemodet@clarkemodet.com.co	IDENTIFICACIÓN
	C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ

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Nombre: 1. PANDEY, Bipin; 2. LOHRAY, Vidya, Bhushan; 3. LOHRAY, Braj, Bhushan
Dirección: todos los anteriores: Zydus Towers, Satellite Cross Roads, Ahmedabad - 380 015, Gujarat, India.
Nacionalidad o Domicilio: Todos los anteriores, Hindúes

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8) PRIORIDAD	33) País de Origen	(32) Fecha	(31) Número de Solicitud
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9) Comprobante de pago N°. 03-42,988 Fecha: Junio 19, 2003

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 42,988
FECHA : JUNIO 19 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CD. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	9018436	18/06/2003	2,712,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL :	\$ 400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

10)

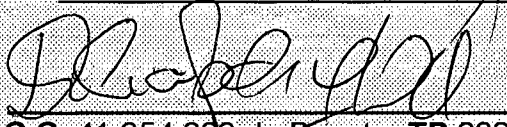
ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☒ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia 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 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros
 1. Búsqueda internacional
 2. Notificación de la recepción de la copia de la búsqueda
 3. Notificación del documento de prioridad
 4. Países designados
 5. Hoja de cálculo

11) FIGURA CARACTERISTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

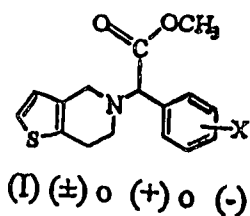
FIRMA: 

C.C. 41 654 882 de Bogotá TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

PROCESO PARA PREPARAR CLOPIDOGRELCAMPO DE LA INVENCION

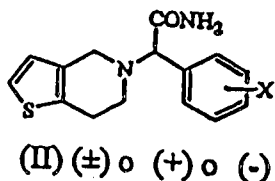
La presente invención se relaciona con un proceso para la preparación de derivados de tieno[3,2-c]piridina de la fórmula general (I), bien sea en sus formas racémicas u ópticamente activas (+) o (-) y sus sales, en donde X, el sustituyente sobre el anillo de benceno representa un átomo de hidrógeno o de halógeno tal como flúor, cloro, bromo o yodo.



Preferiblemente, X representa 2-cloro.

La presente invención también describe un proceso para la preparación de compuestos de fórmula general (II), en cualquiera de sus formas racémica u ópticamente activa (+) o (-) y sus sales, donde X, el sustituyente sobre el anillo de benceno representa un átomo de

hidrógeno o de halógeno tal como flúor, cloro, bromo, o yodo



Preferiblemente X representa 2-cloro. Estos compuestos son intermedios útiles para preparar compuestos de la fórmula general (I).

Los compuestos representados por la fórmula (I) y (II) tienen un carbono asimétrico y de esta forma, obtener compuestos ópticamente activos de la fórmula (I) o la fórmula (II), la opción disponible es resolver el producto intermedio/final racémico o utilizar un intermedio ópticamente activo.

ANTECEDENTES DE LA INVENCION

Los derivados de tieno[3,2-c]piridina descritos en los documentos FR 2,215,948, FR 2,530,247 y FR 2,612,929 son farmacológicamente activos y tienen propiedades

antitrombóticas y antiagregantes significativas. Uno de tales ejemplos es el "Clopidogrel", metiléster de ácido (S)-(+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acético y sus sales farmacéuticamente aceptables. Posteriormente, se encontró que la actividad biológica reside solo con el esteroisómero (S)-(+)-(US 4,847,265). Como la "base de Clopidogrel" es un líquido aceitoso, con el fin de preparar una formulación conveniente, la base se convierte en una sal farmacéuticamente aceptable. Las sales adecuadas de la "base de Clopidogrel" se puede formar con taurocolato, bromohidrato y ácido sulfúrico.

DESCRIPCIÓN DE LA TÉCNICA ANTERIOR

Los métodos reportados para sintetizar los compuestos de la fórmula general (I) (US 4529596, GB 0420706 y GB 0466569), utilizan derivados de α -halofenilacético, que son lacrimógenos e irritantes por naturaleza. Los procesos para sintetizar tales compuestos involucran múltiples etapas, y tienen otros inconvenientes debido a los químicos/reactivos utilizados, que usualmente son difíciles de manejar,

escalar y desfavorables para la salud humana así como también y del punto de vista ambiental. Más aún, los rendimientos totales de estos procesos varían desde pobre hasta promedio. Otras varias aproximaciones sintéticas encontradas en la literatura involucran químicos pocos costosos o riesgosos, los cuales no mejoran significativamente el rendimiento del producto deseado.

Recientemente, Clopidogrel racémico ($\pm$) radioetiquetado (benceno- $U-^{13}C$) se ha preparado como un estándar para estudios metabólicos en un rendimiento total del 7% utilizando ortometalación/clorinación de derivado de ácido benzoico (Chem. Abs., 133:281711, 2000). Otras varias estrategias se describen en: WO 98/51681, WO 98/51682, WO 98/51689, WO 99/18110, US 4,876,362, US 4,876,362, US 5,036,156, US 5,132,435, US 5,139,170 US 5,204,469 y US 6,080,875.

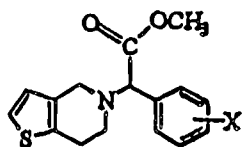
Recientemente, un nuevo polimorfo de bisulfato de Clopidogrel (denominado como forma II) se ha descrito en la solicitud de patente (WO 99/65915), que tiene un punto de fusión de $176 \pm 3^\circ$ C. Este también menciona que el compuesto descrito en la patente estadounidense anterior (US 4,847,265), tenía un punto de fusión diferente de

aproximadamente $184 \pm 3^\circ \text{C}$ (denominado ahora como, forma I). Se ha mostrado que ambos polimorfos tienen espectro XRD e IR distinto y característico.

Consecuentemente, la presente invención ayuda a proporcionar un proceso poco costoso y comercialmente viable para preparar compuestos de la fórmula (I) en buenos rendimientos.

OBJETOS DE LA INVENCION

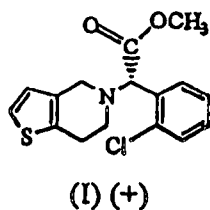
El principal objeto de la presente invención es proporcionar un proceso novedoso para prepara derivados de tieno[3,2-c]piridina, representado por la fórmula general (I), en su forma racémica u ópticamente activa (+) o (-) y sus sales, en donde X representa un átomo de hidrógeno o de halógeno tal como flúor, cloro, bromo o yodo.



(I) ($\pm$) o (+) o (-)

otro objeto de la presente invención es proporcionar un proceso novedoso para preparar derivados de tieno[3,2-c]piridina, representada por la fórmula general (I), en sus formas racémica u ópticamente activa (+) o (-) y sus sales, a través de una ruta comercialmente viable.

Un objeto particular de la presente invención es proporcionar un proceso novedoso para elaborar metiléster de ácido (S)-(+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acético como una sal de bisulfato, es decir, bisulfato de Clopidogrel, donde X es un sustituyente 2-cloro.

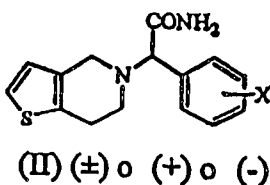


El objeto preferido de la presente invención es proporcionar un proceso novedoso para la elaboración de bisulfato de Clopidogrel, a través de un proceso comercialmente viable.

Otro objeto importante de la presente invención es proporcionar un proceso novedoso para elaborar una forma polimorfa (I) de Clopidogrel que tiene punto de fusión $184 \pm 3^\circ \text{C}$, a través de una ruta comercialmente viable.

Aún otro objeto de la presente invención es reciclar a través de un proceso novedoso el levoisómero de Clopidogrel o una mezcla variable de esteroisómeros (+) y (-) para hacer (+)- bisulfato de Clopidogrel.

Otro objeto de la presente invención es proporcionar un proceso para preparar un compuesto (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetamida de fórmula (II), en formas racémicas o como formas ópticamente activas (+) o (-) y sus sales.



Otro objeto de la presente invención es proporcionar un proceso para la preparación de un compuesto de fórmula

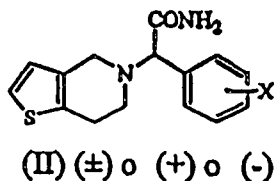
(II) donde X es 2-cloro, en formas racémicas así como también formas ópticamente activas (+) o (-) que tienen pureza química y quiral adecuada y junto con sus sales. El isómero texto dextro del compuesto con fórmula (II) con pureza adecuada o sus sales, son intermedios útiles para la síntesis de (+)-bisulfato de Clopidogrel.

Aún otro objeto de la presente invención es proporcionar un proceso novedoso para convertir (R)-(-)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]parid-5-il)acetamida o su mezcla con cantidades variables menores o su antípodo óptico, casi una mezcla 1:1 de isómero (+) y (-).

El proceso descrito aquí suministra un método simple y alternativo para separar compuestos de la fórmula general (I), particularmente la forma I polimorfa de (S)-(+)-bisulfato de Clopidogrel.

RESUMEN DE LA INVENCION

Los anteriores y otros objetos de la presente invención se logran mediante el proceso de la presente invención al emplear compuestos de la fórmula (II)



o sus sales, en formas racémicas u ópticamente activas (+) o (-), como se subraya en el esquema (I).

opcionalmente, la presente invención proporciona un método para resolver (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]parid-5-il) acetamida en formas ópticamente activas (+) o (-), que se pueden utilizar para preparar (+)-bisulfato de Clopidogrel.

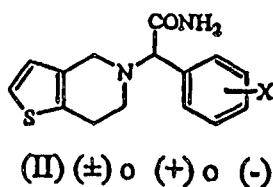
Opcionalmente, la presente invención proporciona un método para resolver ácido (±)-2-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]parid-5-il) acético en formas ópticamente activas (+) o (-).

Opcionalmente, la presente invención proporciona un método para resolver (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]parid-5-il) acetonitrilo en formas ópticamente activas (+) o (-).

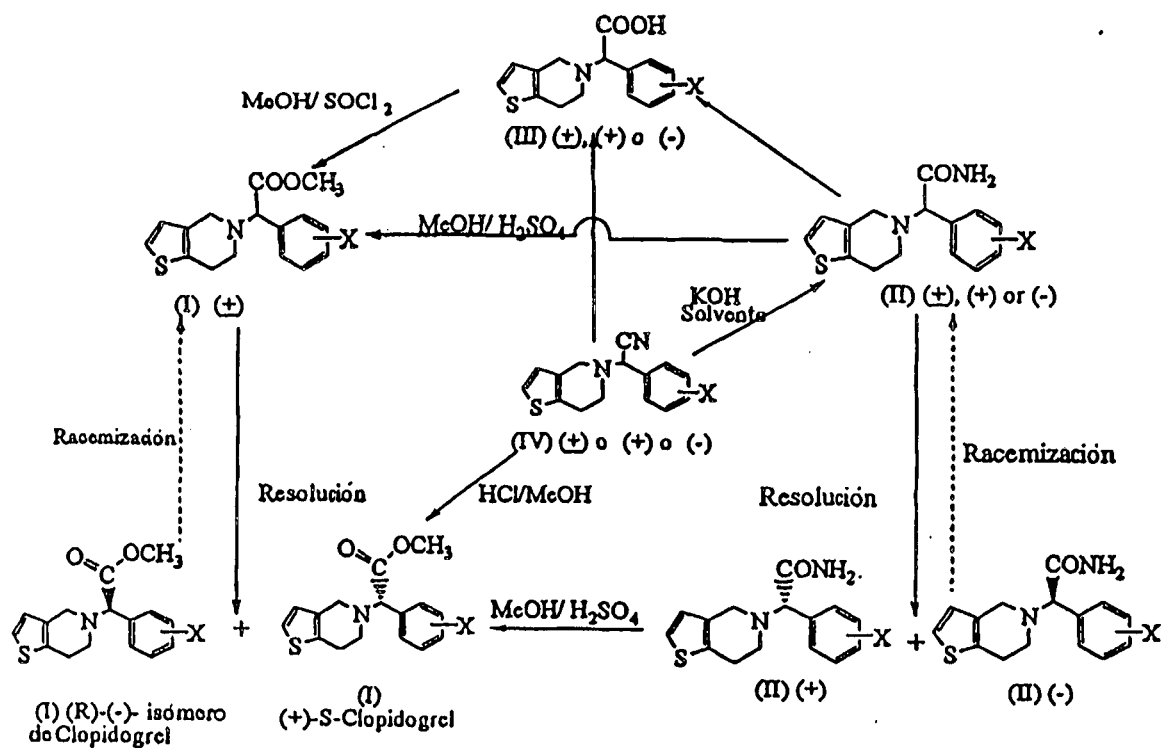
DESCRIPCIÓN DETALLADA DE LA INVENCION

De acuerdo con lo anterior, la presente invención proporciona un proceso para preparar compuestos de fórmula (I), en formas racémicas u ópticamente activas (+) o (-) y sus sales, donde X representa un átomo de hidrógeno o de halógeno tal como flúor, cloro, bromo o yodo. Más particularmente, la presente invención proporciona un proceso para preparar bisulfato de Clopidogrel.

El proceso para preparar compuestos de la fórmula (I) o sus sales, utiliza compuestos de fórmula (II)



o sus sales en formas racémicas u ópticamente activas (+) o (-), como se subraya en el esquema I.



ESQUEMA I

Cada intermedio en el esquema 1 tiene un centro quiral. Por lo tanto, preparar un producto ópticamente activo, tal como el compuesto representado por la fórmula (I), particularmente Clopidogrel y su sal, es posible utilizar un intermedio ópticamente activo desde la primer etapa en adelante.

La presente invención proporciona un proceso para la preparación del compuesto de fórmula (I) y sus sales como se muestra en el esquema 1, el cual comprende:

1. Preparar el compuesto de fórmula (IV),
(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetónitrilo
como se describió en el esquema 2, es decir vía la reacción de Strecker;
2. Resolver, si se desea, la mezcla racémica del compuesto del fórmula (IV) en sus estereoisómeros ópticamente activos (+) y (-); y reciclar el estereoisómero no deseado en el proceso mediante racemización;
3. transformar el compuesto de fórmula (IV) en su forma racémica u ópticamente activa (+) o (-) o su sal, en el compuesto de fórmula (II), (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetamida o la forma ópticamente activa correspondiente (+) o (-) basado en el material de partida utilizado;

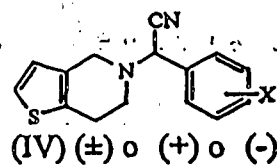
4. resolver, si se desea, el compuesto racémico de fórmula (II)- en sus esteroisómeros ópticamente activos (+) y (-); y reciclar el esteroisómero no deseado en el proceso mediante racemización;
5. transformar el compuesto de fórmula (II), en su forma racémica u ópticamente activa (+) y (-) o su sal, en el compuesto ópticamente activo o racémica de fórmula (I), metiléster de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato, en la forma racémica u ópticamente activa (+) y (-) y su sal, basados en el material de partida utilizado;
6. resolver adicionalmente y/o transformar el compuesto racémico/ópticamente activo de la fórmula (I) en sus sales farmacéuticamente aceptables y/o, liberar el compuesto racémico u ópticamente activo de fórmula (I) de sus sales.

Alternativamente, cualquiera de los compuestos de fórmula (IV) o (II), la fórmula racémica u ópticamente activa (+) o (-) se puede transformar en los compuestos correspondientes de fórmula (III); que se pueden entonces convertir en el compuesto correspondiente de fórmula (I).

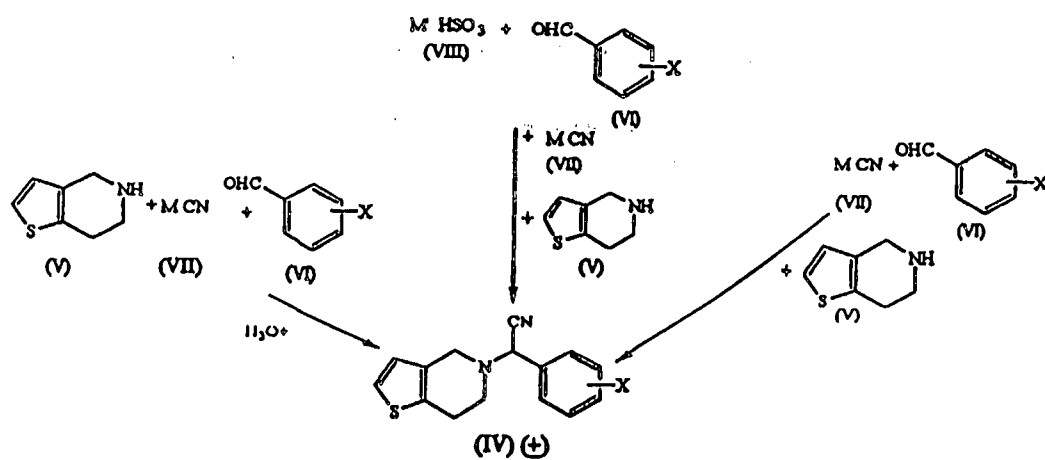
El compuesto de fórmula (IV) en formas ópticamente activas (+) o (-) puede ser directamente convertido en el compuesto correspondiente de fórmula (I).

Opcionalmente, las sales de adición ácida adecuadas de los intermedios de la fórmula II, III y IV se pueden utilizar en los procesos anteriormente mencionados. Los ácidos adecuados utilizados se pueden seleccionar de los ácidos acético, bnezoico, fumárico, maleico, cítrico, tartárico, gentísico, metanosulfónico, etanosulfónico, bencenosulfónico, t-toluenosulfónico, camforsulfónico, clorhídrico, sulfúrico, bromhídrico y similares.

Otro aspecto de la presente invención es proporcionar un proceso para la preparación de un intermedio novedoso de fórmula (IV) y sus sales.



Aún otro aspecto del proceso de la invención incluye la preparación del intermedio descrito mediante fórmula general (IV) y como se describió en el esquema 2, mediante la reacción de Strecker, utilizando una amina secundaria (Organic Synthesis Collective Volume III, página no. 275).



se definió anteriormente, y finalmente amina de la fórmula (V) o su sal en una reacción in situ. Sin importar las variaciones en la metodología de reacción, el rendimiento del intermedio resultante (IV) obtenido es comparable.

El método preferido involucra, la adición de 2-clorobenzaldehído de fórmula (VI) al derivado de sulfito de hidrógeno de fórmula (VIII). La sal formada se trata con cianuro de fórmula (VII), y finalmente con una amina de la fórmula (V) o su sal en presencia del reactivo y solventes adecuados.

Los reactivos adecuados incluyen catalizadores ácidos, tales como ácido acético glacial (Synthesis, 1989, 616, 618), ácido clorhídrico, ácido sulfúrico, ácido metanosulfónico, ácido trifluoroacético, ácido fosfórico y similar.

Los solventes adecuados pueden ser solventes hidrofílicos, próticos o apróticos, incluyendo agua, (C₁-C₄) alcohol, tetrahidrofurano, dimetilformamida, DMSO, dioxano, 1,2 dimetoxietano, ácido acético, ácido protónico y similar, o una mezcla de solventes de estos.

El solvente preferido es una mezcla de solventes y agua en una proporción variable. El medio de reacción más preferido incluye una mezcla que contiene agua y alcohol (C_1-C_4) en una proporción que varía entre 1:1 y 1:10.

Cuando la reacción se lleva a cabo en un solvente aprótico o hidrófobo, es necesario un catalizador de transferencia de fase y un sistema solvente bifásico. El catalizador de transferencia de fase adecuado utilizado en tal caso puede ser haluro de tetrabutilamonio, haluro de benziltrimetilamonio y similares.

Durante la reacción, ciertos aditivos se pueden agregar. Tales aditivos adecuados pueden ser ciclo [(S)histidina-(S)-fenil alanina] y similares.

La temperatura de reacción puede variar desde -30°C hasta temperatura de reflujo o los solventes utilizados. Los rangos preferidos de temperatura varían desde 0°C a 100°C y más preferiblemente, desde 40°C a 80°C . sin embargo, cuando HCN (g) (esquema 2, intermedio VII, $M = H$) se utiliza la temperatura requerida está en el rango de aproximadamente -30°C a -10°C .

Esta reacción se lleva a cabo en la ausencia de presencia de una atmósfera inerte tal como N_2 , He o Ar. La duración de la reacción puede variar desde una hora a tres días, más específicamente dos horas a dos días.

Es preferible hacer reaccionar un compuesto de fórmula (V), derivado de hidrogenosulfito (VIII), y derivado de cianuro (VII) con respecto al 2-clorobenzaldehído (VI) en la proporción preferiblemente entre 1 a 1,2 equivalentes. El compuesto racémico ciano (IV) así obtenido, puede ser resuelto en formas ópticamente activas (+) y (-).

El compuesto ciano (IV) así obtenido se puede convertir en el ácido correspondiente de fórmula (III), la amida de fórmula (II) o el ácido de fórmula (I) como se muestra en el esquema (I) (R.C. Larrock, en "Comprehensive Organic Transformations", John Wiley & Sons, Inc, 1.999, 2^{da} Ed., 815-818 y referenciado aquí.

Aún, otro aspecto de la presente invención es convertir estos intermedios II y III, en los compuestos de fórmula (I) como se muestra en el esquema 1. Cada uno de los isómeros ($\pm$), (+) o (-) del intermedio de fórmula

II y III se puede convertir en el isómero correspondiente de los compuestos de fórmula I.

La ruta preferida para obtener el compuesto de fórmula (I), involucra la conversión del compuesto de isómero ciano ($\pm$), (+) o (-) (IV) y sus sales, en el compuesto amida de fórmula (II), en la presencia de reactivos de ácidos/base adecuados en solventes adecuados. La resolución posterior de la amida en la forma ópticamente activa (+) o (-) o su sal y la amida ópticamente activa se convierte en un éster ópticamente activo de fórmula (I) en la presencia del catalizador adecuado y el reactivo.

La reacción para convertir el compuesto ciano de fórmula (IV) en el compuesto amida de la fórmula (II) se puede llevar a cabo en la presencia de reactivos, los cuales incluyen un ácido o una base. Los ácidos adecuados que se pueden utilizar son, ácido acético, ácido p-toluenosulfónico, ácido trifluoroacético, ácido cloroacético y similares o una solución alcohólica anhidra o acuosa y ácidos minerales tales como ácido sulfúrico, HCl, HBr y similares. Se prefiere una base siempre y cuando siempre y cuando el material de partida

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sea una mezcla racémica. Las bases adecuadas que se pueden utilizar son hidróxido de litio, hidróxido de sodio, hidróxido de potasio, terc-butóxido de potasio, o mezclas de estos, preferiblemente hidróxidos de metal alcalino. Junto con los hidróxidos de metal alcalino, el exceso de peróxidos de hidrógeno o peróxidos de metal también se pueden utilizar en la reacción anterior. El o los solventes adecuados para la reacción anterior pueden ser solventes acuosos, polares o próticos, tales como agua, alcohol (C₁-C₄), acetona, ácido acético, dimetilformamida, THF, DMSO, dioxano, DMI similares o mezclas de estos; preferiblemente el solvente consiste de agua, metanol, o terc-BuOH o mezclas de estos solventes, en una proporción que varía entre 1:1 a 1:10.

La temperatura varía de 20° C a 250° C, preferiblemente, de 50° C a 150° C. Los reactivos utilizados en el proceso anterior pueden estar en el rango de 0,1 a 1,2 equivalentes moles. La reacción se puede llevar a cabo en la ausencia de una atmósfera inerte tal como N₂, He o Ar. Las reacciones bajo las condiciones básicas son preferiblemente bajo atmósfera inerte. La duración de la reacción puede variar desde

adecuado. Opcionalmente el medio puede contener agua aproximadamente > 5%. El solvente adecuado se selecciona sobre la base de si la sal diastereomérica se precipita de manera diferente. La separación de la sal diastereomérica puede dar como resultado espontáneamente o mediante adición del cosolvente o adición de sales o evaporación del solvente o adición de un cosolvente. Alternativamente, la separación puede concebirse simplemente al agitar a una temperatura adecuada en un solvente(s) hasta que una de las sales preferencialmente se precipite. La purificación de la sal diastereomérica es posible al refluirla en un solvente adecuado. La base libre se libera de su sal utilizando un reactivo de base adecuada. La sal diastereomérica se suspende en una mezcla de agua y solvente orgánico y se neutraliza con una base bajo agitación. La base libre se obtiene después de la separación de la capa acuosa y la evaporación del solvente orgánico.

Los solventes utilizados durante la resolución pueden incluir solventes o mezclas de estos tales como alcohol (C_1-C_4), cetona (C_1-C_4), dimetilformamida, etilacetato, metilacetato, metiletilcetona, acetonitrilo,

media hora hasta 5 días, preferiblemente desde dos horas hasta dos días.

La amida de fórmula (II), en su forma racémica u ópticamente activa (+) o (-), o su sal, se puede convertir al metiléster correspondiente de fórmula (I), en la presencia de al menos un equivalente de metanol y ácido, en un solvente adecuado.

Los ácidos adecuados que se pueden utilizar incluyen ácido acético, ácido polifosfórico, ácido 3-toluenosulfónico, ácido trifluoroacético, ácido cloroacético, o ácidos minerales, que incluyen, ácido sulfúrico, HCl, HBr y similares, que pueden estar en diferentes formas como ácido disuelto en alcohol, ácidos anhidros disueltos o saturados en alcohol y el alcohol utilizado puede ser metanol. El ácido preferible es ácido sulfúrico concentrado en la proporción equivalente 1 a 50. los solventes adecuados para las transformaciones anteriores pueden ser solventes polares o próticos tales como solventes hidrofílicos que incluyen metanol, acetona, ácido acético, THF, DMSO, dioxano, DME y similares o mezclas de estos. El solvente preferible consiste de metanol al menos en un equivalente y puede

ser el mayor exceso de tal forma que este actúa como un solvente. Algunas veces el cosolvente inerte, tal como tolueno, xileno, etc. también se puede utilizar.

La temperatura varía desde 20° C a 250° C, preferiblemente de 50° C a 150° C. La reacción se puede llevar a cabo en la ausencia o presencia de una atmósfera inerte tal como N₂, H o Ar. La duración de la reacción puede variar de 3 horas a 5 días, preferiblemente de 4 horas a dos días.

Es posible convertir el compuesto de fórmula (IV) en la forma racémica u ópticamente activa (+) o (-) o su sal se convierte en derivado de ácido acético correspondiente de fórmula (III) en la presencia del solvente y reactivo adecuados. El o los solventes adecuados pueden ser acuosos pueden ser acuosos o de naturaleza alcohólica. Los reactivos adecuados para la reacción anterior incluyen ácidos así como también bases.

También es posible convertir el compuesto ciano de fórmula (IV) en la forma racémica u ópticamente activa (+) o (-) o sus sales, directamente del metiléster de fórmula (I), en la presencia de al menos un equivalente

de ácido y al menos un equivalente de metanol en los solventes adecuados de acuerdo con los métodos conocidos en la literatura.

El ácido de fórmula (III) en la fórmula racémica u ópticamente activa (+) o (-) o sus sales se puede convertir en el metiléster correspondiente de (fórmula (I), en la presencia de un reactivo adecuado en solventes adecuados y al menos un equivalente de metanol.

El reactivo adecuado que se puede utilizar incluye, cloruro de tienilo, cloruros ácidos tales como cloruro de pivaloilo, alquilocroformatos como etil o metil tioformatos y otros de tales reactivos que actúan en grupos COOH, en una proporción equivalente 1:1. Los solventes adecuados para las transformaciones anteriores pueden ser solventes polares o próticos tales como, metanol, acetona, trimetilformamida, THF, DMSO, diclorometano, dicloroetano, diioxano, DME y similares o mezclas de estos. El solvente preferible consiste de metanol en al menos un equivalente y puede ser en mayor exceso de tal forma que este actúa como un solvente. La temperatura varía desde 20° C a 250° C, preferiblemente de 50° C a 150° C.

Los reactivos utilizados en el proceso anterior pueden variar desde 0,01 moles a proporciones equimolares. La reacción se puede llevar a cabo en la ausencia o presencia de una atmósfera inerte, tal como N_2 , He o Ar. La duración de la reacción puede variar desde 3 horas a 5 días, preferiblemente desde 3 horas a dos días.

Este proceso de elaboración para preparar los compuestos de la fórmula general (I) como se muestra en el esquema 1, tiene las siguientes ventajas:

- 1) requiere un menor número de etapa para preparar los compuestos de fórmula (I).
- 2) se utilizan reactivos/químicos simples fácilmente disponibles.
- 3) Se emplean condiciones de reacción más ligeras en varias etapas.
- 4) Es posible conseguir intermedios quirales/ópticamente activos en cada etapa (I, II, III, IV, o V).

- 5) Es posible racemizar los isómeros no deseados mejorando de esta manera la eficiencia y reduciendo la carga ambiental.
- 6) Los factores anteriores contribuyen a mejorar la efectividad de costo de los procesos descritos aquí.

Los compuestos de fórmula (I); (II), (III) y (IV) se pueden resolver mediante varios métodos para conseguir los compuestos ópticamente activos de las fórmulas (I), (II), (III), y (IV), que pueden dar Clopidogrel de la estereoquímica deseada (R.A. Sheldon, en "Chirotechnology", Marcel Dekker, Inc. NY, Basel, 1993, 173-204 y referenciado aquí; A. N. Collins, G.N. Sheldrack y J. Crosby, en "Chirality in Industry II", John Wiley & Sons, Inc. 1997, 81-98 y referenciado aquí; E. L. Eliel y S. H. Wilen, en "Stereochemistry of Organic Compound", John Wiley & Sons, Inc., 1.999, 297-464 y referenciado aquí).

El proceso de resolución comprende la disolución de la mezcla racémica (de las fórmulas I, II, III, o IV) en el solvente adecuado y la adición de un reactivo quiral

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adecuado. Opcionalmente el medio puede contener agua aproximadamente > 5%. El solvente adecuado se selecciona sobre la base de si la sal diastereomérica se precipita de manera diferente. La separación de la sal diastereomérica puede dar como resultado espontáneamente o mediante adición del cosolvente o adición de sales o evaporación del solvente o adición de un cosolvente. Alternativamente, la separación puede concebirse simplemente al agitar a una temperatura adecuada en un solvente(s) hasta que una de las sales preferencialmente se precipite. La purificación de la sal diastereomérica es posible al refluirla en un solvente adecuado. La base libre se libera de su sal utilizando un reactivo de base adecuada. La sal diastereomérica se suspende en una mezcla de agua y solvente orgánico y se neutraliza con una base bajo agitación. La base libre se obtiene después de la separación de la capa acuosa y la evaporación del solvente orgánico.

Los solventes utilizados durante la resolución pueden incluir solventes o mezclas de estos tales como alcohol (C₁-C₄), cetona (C₁-C₄), dimetilformamida, etilacetato, metilacetato, metiletilcetona, acetonitrilo,

propionitrilo, THF, dioxano y similares; el solvente utilizado opcionalmente puede contener agua hasta un 5% pero la presencia de agua o su cantidad no es crítica. El rango de temperatura adecuado para la resolución incluye temperaturas de 0° C a temperatura de reflujo del solvente utilizado, preferiblemente 0° C a 80° C. los reactivos quirales ácidos, que se pueden utilizar para formar una sal diastereomérica, incluyen ácido tartárico, ácido mandélico, ácido láctico, ácido camforsulfónico, ácido láctico, ácido maléico, aminoácidos y similares.

Mediante cristalización repetida de un solvente adecuado, la sal precipitada se enriquece en la sal del isómero dextrorrotatorio del diastereómero deseado para producir un producto de rotación óptica constante.

El reactivo de base adecuada para la hidrólisis de la sal diastereomérica incluye carbonato de sodio, carbonato de potasio, carbonato ácido de sodio y carbonato ácido de potasio en medio acuoso a temperaturas que varían entre 5° C a 25° C.

Finalmente, la sal deseada del compuesto de fórmula (II), (III), o (IV); o la sal farmacéuticamente aceptable

del compuesto de fórmula (I) se puede formar del esteroisómero correspondiente y un ácido adecuado. El compuesto ópticamente puro (S)-(+ de fórmula (I), se convierte en su sal de bisulfato utilizando ácido sulfúrico al 70% a 98%, en un solvente apropiado a temperatura adecuada para lograr el polimorfo I (+)-bisulfato de Clopidogrel como se desee.

Alternativamente, los distereómeros formados se pueden separar mediante métodos convencionales de purificación tal como cristalización fraccional, cromatografía de columna y similares seguido por la división de sal para dar el producto de estereoquímica deseado. Es preferible utilizar, tal como un agente quiral, que se puede seleccionar del diastereoisómero con cualquiera de los isómeros R o S de los intermedios I, II, III, o IV. El reactivo quiral utilizado puede estar en una proporción molar de 0,5 a 1,1.

La determinación de la pureza enantiomérica de los enantiómeros (+) dextrorrotatorio y (-)- levorotatorio pueden ser llevados a cabo a través de espectroscopia RMN de protón con la adición de unos reactivos de tierras raras quirales (reactivos de cambio) o mediante HPLC

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utilizando una fase estacionaria quirál así como también a través de la medición de la rotación óptica.

La estereoquímica absoluta de la sal diastereomérica de los compuestos II, III, o IV se puede determinar utilizando métodos convencionales, tales como cristalografía de rayos X. La estereoquímica absoluta de los compuestos quirales también se puede determinar al compararla con los estándares de referencia conocidos en la literatura.

Las sales ácidas minerales y orgánicas farmacéuticamente aceptables de los enantiómeros ópticamente activos de Clopidogrel se prepararan utilizando varias sales ácidas, que forman una parte de esta invención pero no están limitadas a sulfatos de hidrógeno, hidrohaluros, taurocolatos y similares. Más específicamente el presente proceso de invención da como resultado bisulfato de Clopidogrel de punto de fusión $184 \pm 3^\circ \text{C}$ que es característico de la forma I de bisulfato de Clopidogrel. Alternativamente, la forma II de bisulfato de Clopidogrel también se puede preparar mediante un método conocido (WO 99/65915, Fr 07464).

El proceso de esta invención también incluye el proceso para reciclar el esteroisómero no deseado a través de racemización. Las condiciones para la racemización de todos los intermedios de fórmula general II, III o IV así como también el producto final I, involucra el solvente similar y el catalizador en cantidades equimolares. El catalizador adecuado es generalmente una base tal como LDA (diisopropilamida de litio), KOH, NaOH, $K^+t\text{-BuO}^-$, NaOMe, NaH, KH y similares. Los solventes adecuados utilizados durante la resolución pueden incluir solventes o mezclas de estos tales como alcohol ($C_1\text{-}C_4$), cetona ($C_1\text{-}C_4$), etilacetato, metilacetato, metiletilcetona, THF, dioxano y similares; el solvente utilizado opcionalmente puede contener agua hasta el 5%. El rango de temperatura adecuado para la resolución incluye temperaturas de 0°C a temperatura de reflujo de solvente utilizado, preferiblemente 0° a 80°C .

El proceso descrito en la presente invención se demuestra en los ejemplos ilustrados adelante. Estos ejemplos se suministran como ilustración solamente y por lo tanto no deben entenderse como limitación del alcance de la invención.

EJEMPLO 1

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo (IV)

A una solución de 8,98 g (76,33 mmoles) de bisulfito de sodio en agua (27 ml), se agregó O-clorobenzaldehído 12,4 g (86,33 mmoles) dando como resultado un precipitado blanco. El precipitado, se agregó 15 g (0,107 moles) de 6,7-dihidro-4H-tieno[3,2-c]piridina, seguida por la adición de 4,4 g (89,7 mmoles) NaCl (disuelto en 15 ml de agua). La mezcla de reacción se calentó a 40 - 50° C durante 6 h y fue apagada al verterla en agua (50 ml). La mezcla se extrajo con 2 x 100 ml de acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y el solvente se removió bajo presión reducida. El rendimiento del producto de título es de 24 g (97%).

El producto obtenido se caracterizó utilizando espectro IR, masa ^{13}C - RMN y ^1H -RMN, que son como se da a continuación:

Espectro IR (cm^{-1}) : 2227(w, grupo CN)

Espectro de masa (m/z) : 289.1 (M+H)⁺

¹³C-RMN(CDCl₃) : δ 136,46, 132,78, 132,38, 130,69, 130,46, 130,38, 129,90, 126,73, 124,96, 123,01, 115,09, 59,12, 49,30, 47,66, 25,47.

¹H-RMN (CDCl₃) : δ 7,2-7,3, (4H, m), 7,0 (1H, d), 6,69 (1H, d), 5,32 (1H, s), 3,78 (1H, d) 3,65 (1H, d), 2,8- δ 3,0 (4H, m).

EJEMPLO 2

($\pm$)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo (IV)

140,5 g (1 mol) de o-clorobenzaldehido en 65 g de (1,01 mol) de KCN se agregaron a 3,5 L de metanol. 139,05 g (1 mol) de 6,7-dihidro-4H-tieno[3,2-c]piridina y 190 ml de ácido acético glacial se agregaron a la mezcla de reacción, la cual se calentó a 60° C durante 20 horas con agitación. Después de 8 horas, el precipitado comenzó a aparecer y entonces la mezcla de reacción se vertió en

agua y se extrajo con (2 x 25 ml) de etilacetato. El solvente se removió bajo presión reducida y el residuo se purificó como se describió en el ejemplo 1. el rendimiento del producto fue de 178 g (65%), que tiene un punto de fusión igual a 123-124° C.

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C -RMN y ^1H RMN y se encontró que era idéntico al producto obtenido en el ejemplo 1.

EJEMPLO 3

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo (IV)

27,6 g (266 mmoles) de bisulfito de sodio se disolvieron en 100 ml de agua, y 38,2 g (271 mmol) o-clorobenzaldehído se agregaron después de disolver en 100 ml de metanol. Se obtuvo como resultado una lechada blanca gruesa, la cual se calentó a 60° C durante una hora, seguida por la adición de, 36,97 g (266 mmol) de 6,7-dihidro-4H-tieno[3,2-c]piridina a 40° C y se agitó durante 2 horas. A esta reacción, 17,29 g (266 mmol) de KCN disueltas en 50 ml de agua se agregaron

cuidadosamente y el calentamiento se continuo a 40° C durante 5-6 horas, dando un precipitado blanco. La mezcla de reacción se trabajó como se describió en el ejemplo 1 y el rendimiento que se obtuvo fue de 54,6 g (72%).

El producto obtenido se caracterizó utilizando espectro IR, masa, ¹³C RMN y ¹H-RMN y se observó que era idéntico al producto obtenido en el ejemplo 1.

EJEMPLO 4

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetonitrilo (IV)

4,5 g (25,64 mmoles) clorhidrato de 6,7-dihidro-4H-tieno[3,2-c]piridinio se agregaron (a 10° C) a una solución de cianuro de potasio 1,95 g (30 mmol) en 2 ml de hielo - agua fría, y se disolvieron mediante adición gota a gota de 5 ml de ácido clorhídrico concentrado a 0° C. Después de la adición de HCl 3,3 g, 23,47 mmol) de o-clorobenzaldehído se disolvieron en 50 ml de metanol, fueron agregados gota a gota. Posteriormente la mezcla de reacción se mantuvo a temperatura ambiente durante 3 días y luego a 50° C durante tres horas. El pH se ajustó a

7,5-8,0 mediante adición gota a gota de NH_4OH y el producto se extrajo con etilacetato (2 x 50 ml). El solvente se secó sobre sulfato de sodio y se evaporó bajo presión reducida. La cantidad de producto obtenida fue de 1,67 g (18%) con un punto de fusión = $122 - 124^\circ \text{C}$.

El producto obtenido se caracterizó utilizando espectro IR masa, ^{13}C - RMN y ^1H RMN y se encontró que era idéntico al producto obtenido en el ejemplo 1.

EJEMPLO 5

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo (IV)

6,25 g (44,46 mmoles) de o-clorobenzaldehído se disolvieron en 60 ml de tolueno. Al mismo frasco, se agregaron 10 ml de ácido acético glacial y 1,24 g (24,343 mmol) de ciclo[(S)-histidina-(S)-fenil alanina] y la temperatura se disminuyó a -25°C . Esto fue seguido por la adición de 7 g (50,35 mmol) 6,7-dihidro-4H-tieno[3,2-c]piridina y el frasco de reacción se purgó con gas de HCN (a la proporción de 30 burbujas/minuto) a -25°C durante 6 horas y posteriormente se agitó a 31°C durante

dos días. El solvente se removi6 bajo vacio, el residuo se purific6 como se mencion6 en el ejemplo 1. La cantidad de producto obtenido fue de 5,5 g (43%) con punto de fusión = 124-125° C.

El producto obtenido se caracteriz6 utilizando espectro IR, masa, ^{13}C -RMN y ^1H -RMN y se encontr6 que era id6ntico al producto obtenido en el ejemplo 1.

EJEMPLO 6

($\pm$)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetonitrilo (IV)

Como se describi6 en el ejemplo 5, el aducto se form6 entre 104,3 g (1 mol) de bisulfito de sodio y 144,39 g (1,02 mol) de O-clorobenzaldehido, al cual se agregaron 150 g (1,078 mol) de 6,7-dihidro-4H-tieno[3,2-c]piridina a 31° C y se agitaron durante 1 h. 102 g de TMS-CN se agregaron gota a gota y la temperatura se mantuvo a 31° C durante 6 h, dando como resultado un producto blanco, el cual se aisl6 y se purific6 de acuerdo con el procedimiento en el ejemplo 1. El

rendimiento obtenido fue de 30 g (10%) que tenía un punto de fusión de aproximadamente 123-124° C.

El producto obtenido fue caracterizado utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 1.

EJEMPLO 7

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetonitrilo (IV)

A 19,5 g (250 mmol) de KCN disuelto en agua (20 ml) y 43 g (250 mmol) se agregó 6,7-dihidro-4-tieno[3,2-c]piridina, seguida por la adición gota a gota de 50 ml de ácido clorhídrico concentrado. Después de que se completó la adición, una solución de 33 g (230 mmol) 2-clorobenzaldehído en 10 ml de metanol se agregaron gota a gota y se agitaron durante 8 h a 31° C. El pH de la mezcla de reacción se ajustó a 7,5-8,0 utilizando NH_4OH y el producto se extrajo con etilacetato (2 x 500 ml) y se lavó con agua (2 x 500 ml), agua salobre (500 ml) y se secó sobre sulfato de sodio. El solvente se evaporó bajo

presión reducida para dar 50 g (74%) el producto con punto de fusión de aproximadamente 123-125° C.

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 1.

EJEMPLO 8

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetonitrilo (IV)

A la solución de 35,5 g (342 mmol) de bisulfito de sodio en 35 ml de agua, 49,1 g (349 mmol) de o-clorobenzaldehído se agregó gota a gota, luego de lo cual se formó un aducto sólido instantáneamente. A este se agregaron 50 g (284,9 mmol) de clorhidrato de 6,7-dihidro-4H-tieno[3,2-c]piridina y se refluyeron durante 5 horas. El trabajo usual de la purificación dieron 40 g (40%) del producto.

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN. El producto

obtenido se encontró que era idéntico al producto obtenido en el ejemplo 1.

EJEMPLO 9

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetonitrilo (IV)

123,83 g (880 mmol) de o-clorobenzaldehído y 44 g (897 mmol) de cianuro de sodio se agregaron a una mezcla de 100 ml de metanol y agua (1:1). A este se agregaron 150 g (1070 mmol) de 6,7-dihidro-4H-tieno[3,2-c]piridina, seguido por la adición de 10 ml de ácido clorhídrico concentrado y se agitaron durante dos días a una temperatura de 31° C. El pH de la mezcla de reacción se ajustó a 7,5-8,0 utilizando NH₄OH. El producto se extrajo con etilacetato (2 x 50 ml) y se lavó con agua (2 x 50 ml), agua salobre (50 ml) y se secó sobre sulfato de sodio y se aisló como se da en el ejemplo 1. La cantidad de producto sólido blanco obtenida fue de 33 g (13%), el cual se caracterizó como es usual.

EJEMPLO 10

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

48 g (0,166 mol) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo se suspendieron en 240 ml de t-BuOH, y se agregó 18,26 g (0,332 mol) de KOH fueron agregados en un lote con agitación. La mezcla de reacción se reflujo a 80-81° C durante 3H, luego se enfrió a 30° C, 240 ml de agua se agregaron y se agitaron durante 20 minutos. La capa acuosa inferior se separó y se agregó 720 ml de agua congelada fresca (5 - 10° C) lentamente en 15 min. El producto se extrajo con acetato de etilo (2 x 50 ml) y se lavó con agua (2 x 50 ml), agua salobre (50 ml) y se secó sobre sulfato de sodio, seguido por aislamiento mediante evaporación del solvente bajo presión reducida. Se obtuvo bajo tratamiento con sólido de hexano. El rendimiento del producto fue de 48 g (94%).

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H RMN, los cuales son como se da a continuación.

Espectro IR (cm^{-1}) : 1656 (s, grupo C=O),
2333.7 (N-H)

Espectro de masa (m/z) : 307.2 (M+Z)⁺

¹³C-RMN (CDCl₃) : δ 173,82, 135,32, 133,42,
133, 130,27, 129,99, 129,4, 126,98, 125,18, 122,98,
69,12, 50,77, 49,10, 25,82.

¹H - RMN (CDCl₃) : 7,4-7,5 (4H, m), 7,24
(1H, d), 7,0 (1H, d), 6,0 (1H, s), 4,88 (1H, d), 3,61
(2H, q), 2,88 (4H, m).

punto de fusión : 125 - 127° C.

EJEMPLO 11

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

100 mg (0,3466 mmoles) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo de fórmula (IV) preparado de acuerdo con el ejemplo 1-9, se disolvió en HCl 5 ml y 1 ml de ácido trifluoroacético y 5 ml de t-butanol se agregaron y refluyeron durante 4 h. después se completó la reacción, el producto se aisló como se

mencionó en el ejemplo 11. El rendimiento del producto fue de 40 mg (38%).

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 12

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

En 100 mg (0,346 mmoles) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo de fórmula (IV) (preparado de acuerdo al ejemplo 1 a 9), se agregaron 5 ml de ácido fórmico y 5 ml de ácido clorhídrico concentrado y la mezcla de reacción se agitó durante 48 horas a 25-30° C, y más tarde se refluyen a aproximadamente 100° C a aproximadamente 100° C durante 6 horas y se agitaron durante 8 días a 25-30° C. Después de completar la reacción, la mezcla de reacción se trabajó como se mencionó en el ejemplo 10. El rendimiento del producto fue de 50 mg (47%).

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN. El producto obtenido fue idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 13

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-cl]pirid-5-il)acetamida (II)

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-cl]pirid-5-il)acetonitrilo de fórmula (IV) preparado de acuerdo al ejemplo 1 a 9, fue agregado a 5 ml HBr y 5 ml de H_2O y se agitó durante 72 horas a temperatura ambiente. La mezcla de reacción se reflujo durante 11 horas a 100°C y el producto se aisló como se mencionó en el ejemplo 10. El rendimiento del producto fue de 50 mg (47%).

El producto se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 14

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

1 g (3,47 mmoles) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo, se disolvió en 65 ml de H₂SO₄ (50%). A la mezcla de reacción se agregó 0,405 g de NaCl anhidro y se reflujo la reacción durante 2 - 3 horas. Al final de la reacción, el producto se aisló como se describió en el ejemplo 10. El rendimiento del producto fue de 600 mg (57%).

El producto se caracterizó utilizando espectro IR, masa, ¹³C - RMN y ¹H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 15

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

1 g (3,47 mol) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo se disolvió en los 5 g (5 mmol) de HClO₄ y 10 ml de H₂O se agregaron a la

mezcla de reacción. La mezcla de reacción se refluyó a 105° C durante 7 horas y posteriormente se agitó a temperatura ambiente durante 12 horas. El pH se elevó hasta 10-12, utilizando 10% p/v de solución de Hanoi posteriormente se extrajo con 50 ml de diclorometano. La capa orgánica se aisló, se lavó con agua y se evaporó bajo presión reducida. El residuo se trató con hexano para dar 50 mg de sólido (47% de rendimiento), que tiene punto de fusión 125 - 127° C.

El producto se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 16

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

1 g (3,47 mmol) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo fue suspendido en 10 ml de t-BuOH y 277 mg (6,925 mmol) NaOH molido fue vertido bajo agitación. La mezcla de reacción se refluyó a 80 - 82° C durante 4 h, seguida por enfriamiento a

50

mencionó en el ejemplo 11. El rendimiento del producto fue de 40 mg (38%).

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 12

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-clpirid-5-il)acetamida (II)

En 100 mg (0,346 mmoles) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-clpirid-5-il)acetonitrilo de fórmula (IV) (preparado de acuerdo al ejemplo 1 a 9), se agregaron 5 ml de ácido fórmico y 5 ml de ácido clorhídrico concentrado y la mezcla de reacción se agitó durante 48 horas a 25-30° C, y más tarde se refluyen a aproximadamente 100° C a aproximadamente 100° C durante 6 horas y se agitaron durante 8 días a 25-30° C. Después de completar la reacción, la mezcla de reacción se trabajó como se mencionó en el ejemplo 10. El rendimiento del producto fue de 50 mg (47%).

temperatura ambiente. El producto se aisló mediante extracción con acetato de etilo. El extracto orgánico se evaporó, y se dejó un material aceitoso detrás luego que el tratamiento con hexano produce 400 mg de sólido (38%).

El producto se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 17

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

3 g (0,01 mol) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo se suspendió en 50 ml de acetona. Esta solución 1 g (0,023 mmol) de NaOH disuelto en 10 ml de agua se agregó, seguido por 5 ml de H_2O_2 (0,05 mol, 30% p/v) en un lote y se reflujo durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente y se agregaron 5 ml de H_2O_2 (0,05 mol, 30% p/v) de nuevo se agitó durante 12 horas. El producto se aisló mediante adición de exceso de agua y se extrajo con 1 l de acetato de etilo. El extracto orgánico se evaporó para

dar 2,8 g de un material aceitoso crudo, el cual después de tratamiento con hexano, produjo 1 g de sólido (31%).

El producto se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 18

(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

A 10 g (0,0346 mol) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo suspendido en 30 ml de alcohol isopropilo, 3,9 g (0,0589 mol) se agregó KOH molido (85%) lentamente y la mezcla se calentó, y se agregaron 120 ml de agua. El pH de la capa acuosa se llevó a 7 utilizando ácido clorhídrico diluido. El precipitado sólido blanco se filtró y se lavó con 100 ml de agua. El rendimiento del producto fue 9 g (85%) con punto de fusión: 122° C.

El producto se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN y se encontró que era idéntico al producto obtenido en el ejemplo 10.

EJEMPLO 19

Sal de sulfato ácido de $(\pm)$ -(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

2 g (6,48 mol) de $(\pm)$ -(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida de la fórmula (IV), se disolvió en 10 ml de acetona. A la mezcla de reacción se agregó 1 ml de ácido sulfúrico y se agitó durante 0,5 h. Posteriormente se agregaron 5 ml de dietiléter y se agitaron durante toda la noche a temperatura ambiente para obtener una sal. La sal de 2 g (76%) se aisló mediante filtración y se lavó con acetona.

Punto de fusión: $199,1^\circ \text{C}$

Espectro IR: 1682,8, 3116 (cm^{-1}).

EJEMPLO 20

Ácido (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acético (III)

A 100 mg de (0,3466 mmoles) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo se disolvió en 2 ml de t-butanol y se agregó 1,5 ml de HCl. La mezcla de reacción se reflujo durante 9 h a 100° C. al final, después de completar la reacción, se agregó agua y el pH se llevó a 34 con una solución al 10% de KOH. El producto se extrajo con 5 ml de diclorometano y se procedió como se dio en el ejemplo anterior. El rendimiento fue de 40, mg (38%).

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN los cuales son como se da a continuación;

Espectro IR: (cm^{-1}): 1637,5 (s, grupo C=O), 3399,3 (O-H)

Picos de masa (m/z): 308,1 (M+H) $^{+}$

^1H - RMN (δ 7,22-7,89 (4H, m), δ 7,11-7,12 (1H, d), δ 6,61-6,63 (1H, d), δ 3,57-3,67, (2H, d), δ 4,13 (2H, s), δ 3,32-3,42 (2H, s).

EJEMPLO 21

Ácido ($\pm$)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acético (III)

5 g (17,33 mmoles) ($\pm$)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo se agregó a 100 ml de HCl y la mezcla se agitó durante dos días y más tarde se reflujo durante 15 horas al final la mezcla de reacción se vertió en agua, y el pH se elevó a 4 utilizando KOH al 10%. El producto se extrajo con 2 l de diclorometano, se lavó con agua y la capa orgánica se evaporó para obtener el residuo. La purificación usual del residuo dio 2 g de sólido (38%).

El producto obtenido se caracterizó utilizando espectro IR, masa, ^{13}C - RMN y ^1H - RMN. El producto obtenido se encontró que era idéntico al producto obtenido en el ejemplo 20.

EJEMPLO 22

(±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

Se mezcla 10 g (32,62 mmol) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (preparada de acuerdo con el ejemplo 15), con 19,8 g (161,7 mmol) DMFDMA (dimetil formamida dimetilacetal) en 100 ml de metanol. La mezcla se reflujo a 70° C durante 14 h. posteriormente la mezcla de reacción se apagó en agua y se extrajo con acetato de etilo. El extracto orgánico se evaporó bajo presión reducida para dar 5 g de producto aceitoso (48%). Este aceite fue utilizado sin ningún tratamiento adicional para preparar sales de éster (I).

EJEMPLO 23

(±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

15 g (0,0490 mol) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida, se disolvió

en 105 ml de metanol, con agitación. A la solución anterior, 45 ml (0,823 mol) de ácido sulfúrico concentrado (98%) se agregó gota a gota a temperatura ambiente y durante un periodo de 1,5 horas. Posteriormente la mezcla de reacción se refluyó a 80° C durante 26 horas, seguida por destilación de metanol. Al residuo dejado atrás, se le agregaron 200 ml de acetato de etilo a una temperatura entre 0° C a 5° C junto con agitación. Después de la adición de 99 g (1,764 mol) de KOH disueltos en 700 ml de agua se agregaron a la reacción y se agitaron durante 0,5 horas. Finalmente, la mezcla de reacción se filtró y se le permitió asentarse. La capa orgánica se aisló y se secó sobre Na₂SO₄ anhidro. El solvente se evaporó para obtener un producto aceitoso. El rendimiento fue de 10 g (64%).

EJEMPLO 24

Sal de sulfato ácido de (±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

10 g de (±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato preparado de acuerdo con el ejemplo 22, se disolvieron en 100 ml de hielo-acetona

fía y 2 ml de ácido sulfúrico concentrado se agregaron entre 0° C a 5° C. El producto cristalino de blanco a blanco mate formado se aisló por filtración y se lavó con 20 ml de acetona. El producto obtenido se secó al vacío en un horno a 50° C. El rendimiento del producto titulado fue de 7,2 g (56%).

EJEMPLO 25

(±)-metil (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

2 g (0,00652 mol) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida y 2 ml (0,0308 mol) de ácido metanosulfónico y 20 ml de metanol se mezclaron y la solución se reflujo a 85° C durante 12 horas. El exceso de solvente se removió bajo presión reducida. El pH se ajustó a aproximadamente 9 con una solución acuosa de bicarbonato de sodio a 0° C, el producto se extrajo con 70 ml de acetato de etilo. Los extractos orgánicos combinados se secaron sobre Na₂SO₄ anhidro y se concentraron. El residuo obtenido se purificó mediante cromatografía de columna utilizando hexano : acetato de etilo como eluyente. El producto así obtenido se

concentró, se almacenó bajo atmósfera de nitrógeno, y permaneció en el refrigerador antes de convertirlo en sal. El rendimiento del producto titulado fue de 0,419 g (20%).

EJEMPLO 26

(±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

1 g (0,00326 ml) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se disolvió en 20 ml de etanol y se reflujo a 85° C. Durante el reflujo se agregaron 10 ml de ácido polifosfórico gota a gota durante un periodo de una hora y el reflujo se continuó durante 6 horas. El exceso de solvente se removió bajo presión reducida. Al residuo, 50 ml de acetato de etilo se agregó a 0° C y la mezcla de reacción se hizo básica con NaHCO₃ acuoso hasta un pH 9. Además de las dos fases separadas, la capa orgánica se aisló, se secó sobre Na₂SO₄ anhidro y se concentró. El residuo obtenido se purificó mediante cromatografía de columna utilizando hexano : acetato de etilo (9:1) como eluyente. El producto obtenido se almacenó bajo atmósfera de nitrógeno y se mantuvo en

refrigerador antes de convertirlo en sal. El rendimiento del producto titulado fue 310 mg (30%).

EJEMPLO 27

(±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

1 g (0,00326 ml) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se agregó a 2 ml de tolueno a 0° C junto con agitación, seguida por adición gota a gota de 1 ml de tetracloruro de titanio, y la reacción se agitó a 0° C durante una hora. Más tarde 18 ml de metanol se agregaron, y luego la mezcla de reacción se agitó durante 36 horas a 29° C y posteriormente se reflujo durante 3 horas. El solvente se destiló bajo presión reducida y el residuo se agregó a carbonato de sodio acuoso a 0° C. El producto se extrajo con 20 ml de acetato de etilo, y la capa orgánica se aisló, se secó sobre Na₂SO₄ anhidro, se concentró y se purificó mediante cromatografía de columna utilizando hexano : acetato de etilo como eluyente. El producto obtenido se almacenó bajo atmósfera de nitrógeno y se mantuvo en refrigerador antes

de convertirlo en sal. El rendimiento del producto titulado fue de 0,157 g (12 - 15%).

EJEMPLO 28

(±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

A 5 g (16,31 mmoles) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida, se agregaron 25 ml de POCl₃ bajo agitación. Los contenidos se refluieron hasta que la amida se consumió completamente (aproximadamente 4 horas). Posteriormente se agregaron 20 ml de etanol y 5 ml de H₂SO₄ concentrado y se agitaron a temperatura ambiente durante una hora. Más tarde la mezcla de reacción se refluyó durante una hora. La mezcla de reacción se apagó con Na₂CO₃ acuoso a 0° C, y se extrajo con 200 ml de acetato de etilo. La capa orgánica se aisló, se secó sobre Na₂SO₄ anhidro, se concentró y se purificó mediante cromatografía de columna utilizando hexano : acetato de etilo como eluyente. El producto obtenido se almacenó bajo atmósfera de nitrógeno y se mantuvo en refrigerador antes de convertirlo en sal. El rendimiento del producto titulado fue de 0,943 g (18%).

(±)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

A 1 g (0,00326 ml) (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida, se agregaron 3 g (24,2 mol) de DMFDMA (dimetilformamida dimetil acetal) y 10 ml de metanol. La mezcla de reacción se refluyó a 70° C durante 14 horas. Y luego se vertió en agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre Na₂SO₄ anhidro, se evaporaron bajo presión reducida. El residuo se purificó adicionalmente mediante cromatografía de columna utilizando hexano : acetato de etilo (9:1) como eluyente. El rendimiento del producto titulado fue 500 mg (48%).

EJEMPLO 31

(S)-(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

a) Una solución de 5 g (16,31 mmoles) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (se prepararon como se da en el ejemplo 10-15) y 4,15 g (16,2 mmoles) de monohidrato de ácido

(1S) (+)-camfor-10-sulfónico en 100 ml de acetona se agitaron a temperatura ambiente durante 20 h. Subsecuentemente este se mantuvo durante una semana en un congelador. Aparecieron pocos cristales la concentración de volumen al evaporar el solvente bajo presión reducida y recrystalización repetida en el congelador durante pocos días dio 3,3 g. (75% de rendimiento) de sal de ácido (S)-2-(2-cloro-fenil)-(4,5,6,7-tetrahidrotieno[3,2-c]parid-5-il)acetamida (+)-camforsulfónico. La sal se purificó adicionalmente mediante recrystalización en acetona, hasta que se obtuvo una rotación óptica específica constante. El producto obtenido se secó adecuadamente. Las características fisicoquímico típicas del producto obtenido fueron como sigue,

Rango de fusión: 223-225° C

SOR: + 51° C (C = 1, MeOH)

b) 3,3 g de sal de ácido de (S)-(+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]parid-5-il)acetamida 10-D-camforsulfónico se agregó a 20 ml de solución de Na₂SO₃ acuosa saturada y el producto se extrajo con 20 ml de acetato de etilo. La capa

orgánica se aisló, se secó sobre Na_2SO_4 y se concentró bajo presión reducida. Se obtuvo un producto de aceite crudo, el cual luego de purificación dio, 1,6 g de cristales blancos (64%).

El producto obtenido se caracterizó por diferentes características físico químicas incluyendo espectro IR, masa, ^{13}C - RMN y ^1H - RMN, los cuales son como se dan a continuación;

Punto de fusión : 153 - 154° C

SOR : +41° C (C=1, MeOH)

Pureza óptica : 99,5% mediante columna HPLC
quiral

Espectro IR (cm^{-1}) : 1656 (s, grupo C=O), 2333,7 (m, C-N), 3357,9 (s, N-H str).

Picos de masa (m/z) : 307,2 (M+H)⁺

^{13}C -RMN (CDCl_3) : δ 173,25, 134,84, 132,87,
132,65, 129,98, 129,56, 129,0, 126,72, 124,87,
122,64, 68,65, 50,43, 48,73, 25,28.

^1H -RMN (CDCl_3) : δ 7,4-7,5, (4H, m), 7,07 (1H, d), 7,06 (1H, d), 6,66 (1H, d), 6,5 (1H, s), 4,9 (1H, s), 3,6 (2H, q), 2,88 (4H, m).

pureza HPLC : 99,85%

EJEMPLO 32

(S)-(±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

a) 2 g (6,5 mmol) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se agregó a 30 ml de acetona. 0,82 g (3,28 mmol) de monohidrato de ácido (1S)-(+)-camfor-10-sulfónico en 10 ml de acetona se agregaron a la anterior solución a 15 - 20° C en 4 horas. La mezcla de reacción se agitó durante otros cinco minutos, donde se formaron unos pocos cristales. El solvente se destiló bajo presión reducida y luego la mezcla de reacción se mantuvo en condición fría a temperatura inferior a 8° C. El precipitado formado se filtró y se lavó con solvente. El rendimiento del producto titulado fue 1,2 g (60%)

con rango de fusión = 223-225° C y $[\alpha]_D = + 51^\circ$ (C = 1, CH₃OH).

b) A la suspensión de 1,1 g de sal de ácido (+)-(S)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]parid-5-il)acetamida ((1s)-(+)-camfor-10 sulfónico en 50 ml de agua, se agregaron 50 ml de solución de Na₂CO₃ saturado en agua. La mezcla de reacción se agitó durante algún tiempo, y se extinguió mediante la adición de 100 ml de acetato de etilo. La capa orgánica se aisló, y se destiló para conseguir el producto del título. La cantidad del producto obtenido fue de 600 mg (60%, basados en dextroisómero presente de la mezcla racémica).

El producto obtenido se caracterizó mediante diferentes características fisicoquímicas, las cuales se dan a continuación;

Punto de fusión : 149-153° C

$[\alpha]_D$: +38° C (C = 1, CH₃OH) con % ee
= 97,24%.

EJEMPLO 33

(S)-(+)-(2-cloro-fenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

a) 5 g (16,3 mmol) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se agregaron a 60 ml de acetato de etilo. 2 g (8,6 mmol) de monohidrato de ácido (1S)-(+) -camfor-10-sulfónico se disolvieron en una cantidad mínima de agua y se agregaron a la solución anterior en un lote, y se agitaron a 35-40° C durante una hora. Al poco tiempo se formó sal y se aisló, se lavó con 50 ml de acetona y se secó. La cantidad del producto obtenida fue de 1,81 g (36%).

El producto obtenido se caracterizó por diferentes características fisicoquímicas, las cuales son dadas adelante;

Rango de fusión : 223-225° C

$[\alpha]_D$: + 52.12° (C = 1, CH₃OH).

b) a la suspensión de 1,8 g de sal de ácido (S)-(+)-(2-cloro-fenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il acetamida(1S)-(+)-camfor-10-sulfónico en 100 ml de agua, 50 ml de bicarbonato de sodio en agua fueron agregados. Después de agitar la mezcla, se agregó 150 ml de agua. Las capas orgánicas combinadas de destilaron para obtener el producto del título. La cantidad de producto obtenido fue de 1 g (65%).

El producto obtenido se caracterizó por diferentes características fisicoquímicas, las cuales se dan adelante, similares al ejemplo 31;

Rango de fusión : 153-154° C

$[\alpha]_D$: + 42° (C = 1, CH₃OH) y con % ee = 100% (mediante cromatografía de columna HPLC quiral).

EJEMPLO 34

(R)-(-)-(2-cloro-fenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il) acetamida (I) (0,016 mol) se agregó a 60 ml de acetato de etilo y a la solución 2 g de

monohidrato de ácido (0,0086 mol) (1R)-(-)-camfor-10-sulfónico en 5 ml de agua fue agregado a este en un lote. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Después la mezcla de reacción se almacenó en un congelador durante una semana, unos pocos cristales fueron vistos. Después, la evaporación del solvente a presión reducida y almacenamiento en condiciones de frío la sal se precipitó afuera, la cual fue luego filtrada y lavada con 50 ml de acetona. La cantidad de producto obtenida fue de 1,7 g (39%).

El producto obtenido fue caracterizado por diferentes características fisicoquímicas de (R)-(-)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida y de esta sal (-)CSA, ambas de las cuales se dan adelante;

Rango de fusión (-)-CSA-(-)acetamida: 219-220° C

$[\alpha]_D$ (-)-CSA-(-)acetamida: -52,12° (C = 1,
CH₃OH)

b) a la suspensión de 1,6 g de sal de ácido (R)-(-)-(2-cloro-fenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il) acetamida (1R)-(-)-camfor-10-sulfónico en 100 ml de agua, se agregó 50 ml de solución de bicarbonato de sodio en agua. Después de agitar la mezcla, 150 ml de acetato de etilo se agregó. La capa orgánica se extrajo y se combinó y se destiló para obtener el producto del título. La cantidad de producto obtenido se de 900 mg (36%).

El producto obtenido se caracterizó por diferentes características fisicoquímicas, las cuales se dan adelante;

Rango de fusión : 145 - 149° C

$[\alpha]_D$ acetamida : -36,49° (C = 1, CH₃OH)

Ejemplo 35

Bisulfato (S)-(+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

15 g de (+) (S)-(2-cloro-fenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (0,0489 mol), se convirtieron en el éster correspondiente como se da en el ejemplo 23. el éster se puede convertir en su sal de sulfato ácida, de acuerdo con el procedimiento dado en el ejemplo 24. La cantidad de producto obtenida fue de 7 g (44,5%), con un punto de fusión = 184-185° C.

El punto de fusión, espectro IR y el XRD del producto obtenido reflejan aquello del producto obtenido en la EP 281459 y la US 4847265 es decir ahora denominadas como polimorfo forma I de bisulfato de Clopidogrel (WO 99/65915).

El producto obtenido se caracterizó mediante diferentes características fisicoquímicas como se dan a continuación;

$[\alpha]_D$: + 55° C (C 0.1, CH₃OH)
punto de fusión : 185° C ± 2° C
Espectro IR : 2980, 1755, 1224, 1175 y 840
respectivamente con el respectivo % de porcentaje
Transmitancia de aproximadamente: 45; 16; 19; 15; 45.

El XRD se encontró que coincidía con el XRD forma I reportado en el WO 99/65915.

EJEMPLO 36.

Bisulfato de (R)-(-)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

Utilizando 5 g de (R)-(-)-(2-cloro-fenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida obtenida en el ejemplo anterior 34, se puede convertir en éster como se da en el ejemplo 23. Posteriormente el éster se puede convertir en una sal de sulfato ácida como se da en el ejemplo 24. La cantidad de producto obtenida fue de 3,01 g (44%).

El producto obtenido se caracterizó por diferentes características fisicoquímicas/pureza como se dan a continuación;

$[\alpha]_D -52^\circ \text{ C (C=1, CH}_3\text{OH)}$

EJEMPLO 37

Bisulfato de (S)-(+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

a) 10 g de (0,0185 mol) de sal de ácido (1S)-(+)-camfor-10-sulfónico de (+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se disolvieron en 40 ml de metanol a 0° C. A la solución se agregó 15 ml (0,28 mol) de H₂SO₄ concentrado gota a gota durante 1,5 horas. Se incrementó gradualmente la temperatura de la reacción, y este reflujo durante 26 horas. Al final, el solvente se destiló bajo presión reducida. El residuo dejado atrás se mezcló con 120 ml de acetato de etilo y el pH se ajustó entre 9 y 10 utilizando carbonato de sodio acuoso para extracción. La capa orgánica se aisló, se secó sobre Na₂SO₄ anhidra, y se evaporó bajo vacío. El producto obtenido se purificó mediante cromatografía de columna utilizando hexano: etilacetato (9:1) como eluyente. El eluyente combinado se evaporó a presión reducida para producir 5,76 g (25%) del producto.

b) 2 g de (S)-(+)-metil (2-clorofenil)- metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato se convirtieron en una sal de bisulfato de acuerdo con el procedimiento dado en el ejemplo 24. El producto obtenido fue de 2,2 g (84%) del producto y se encontró idéntico a aquel obtenido en el ejemplo 35.

EJEMPLO 38

Polimorfo I de la sal de Bisulfato de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

52,5 ml de hielo-acetona fría se agregaron a 17,5 g de ($\pm$)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato mientras se agita a 0° C. 3,6 ml de H₂SO₄ concentrado se agregaron gota a gota y la temperatura se mantuvo por debajo de 5° C. 20 ml de acetona se agregaron adicionalmente y la mezcla de reacción se agitó adicionalmente durante 4 horas a temperatura ambiente. El precipitado fue aislado (17 g, 74%), secada bajo vacío a temperatura que no excedió 50° C.

El producto obtenido se caracterizó por diferentes características fisicoquímicas y se encontró idéntico a aquel obtenido del ejemplo 35, como se da a continuación;

Rotación óptica específica : $+54^{\circ}$ ($C=1$, CH_3OH)

Punto de fusión : $185^{\circ} \text{C} \pm 2^{\circ} \text{C}$

El IR y el XRD se encontraron similares a aquellos reportados en la literatura.

EJEMPLO 39

Polimorfo I de la sal de Bisulfato de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

2,1 g ($\pm$)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato se agregaron 7,6 ml de acetona para obtener una solución clara. A esta solución, se agregaron 0,887 g de H_2SO_4 (80%) lentamente y la temperatura se mantuvo alrededor de los 20°C bajo atmósfera de nitrógeno. Posteriormente la mezcla de

reacción se enfrió hasta -20°C durante 2 horas y luego la temperatura se llevó hasta temperatura ambiente (20°C). La mezcla de reacción se agitó a $20-25^{\circ}\text{C}$. el precipitado se aisló (600 mg), se secó bajo vacío a temperatura que no excedía 50°C .

El producto obtenido se caracterizó por diferentes características fisicoquímicas y se encontró idéntico a aquel obtenido en el ejemplo 35, como se da a continuación;

SOR (α^D) : $+54,03^{\circ}$ ($C = 1,89$, MeOH)

Punto de fusión : $185^{\circ}\text{C} \pm 1^{\circ}\text{C}$

Pureza quiral : 99,80% (ee)

El IR y el XRD se encontraron similares a aquellos reportados en la literatura.

EJEMPLO 40

Polimorfo I de la sal de Bisulfato de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

A 2 g (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato se agregaron 5 ml de acetona y se agitó a 25 - 30° C. La temperatura de la mezcla de reacción se elevó de 25 a 65° C y luego se mantuvo a 65° C durante 5 minutos. A una temperatura de 50-52° C se agregaron 0,676 g de H₂SO₄ concentrado. La mezcla de reacción se enfrió de 52° C a 5° C, y se agregó acetona adicional y se agitó durante 5 minutos. Posteriormente la mezcla de reacción se agitó a 25-30° C durante 12 horas, el precipitado grueso obtenido se filtró, se lavó con 5 ml de acetona y el residuo se secó en un horno al vacío. El rendimiento del producto titulado obtenido fue de 1,27 g (47%).

El producto obtenido se caracterizó por diferentes características fisicoquímicas y se encontró idéntico a aquel obtenido en el ejemplo 35, como se da a continuación;

SOR (α^D)	: +54,03° (C = 1,89, MeOH)
Punto de fusión	: 185° C $\pm$ 1° C
Pureza quiral	: 99,80% (ee)

El IR y el XRD se encontraron similares a aquellos reportados en la literatura.

EJEMPLO 41

Polimorfo I de la sal de Bisulfato de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

A 1,98 g ($\pm$)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato se agregaron 5 ml de acetona y agitó a 25-30° C. La temperatura de la mezcla de reacción se delegó de 25-52° C y dentro de un lote de 0,7 g de H₂SO₄ concentrado (95%) se agregó con agitación constante y la mezcla de reacción se enfrió súbitamente a 0° C a -5° C durante 10 minutos. posteriormente la mezcla de reacción se agitó a 25-30° C durante 12 horas, el precipitado grueso obtenido se filtró, se lavó con 5 ml de acetona y el residuo (0,6 g, 62%) se secó en un horno al vacío.

El producto obtenido se caracterizó por diferentes características fisicoquímicas y se encontró idéntico a

aquel obtenido en el ejemplo 35, como se da a continuación;

SOR (α^D) : +55,96° (C = 1,89, MeOH)

Punto de fusión : 185° C $\pm$ 1° C

Pureza quiral : 99,85% (ee)

El IR y el XRD se encontraron similares a aquellos reportados en la literatura.

EJEMPLO 42

Racemización de (R)-(-)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

Una mezcla de 20 g de Bisulfato de (R)-(-)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida levorotatorio de fórmula (II) y 11 g de t-butóxido de potasio en 100 ml de t-butanol se agitaron desde 25° C a 30° C durante 30 min. Después de completar la reacción, la mezcla de reacción se vertió en 750 ml de agua fría para obtener un precipitado amarillo. El sólido obtenido se filtró y se disolvió en dicloruro de metileno. La capa orgánica se lavó con 2 x 100 ml de agua

DM (2 x 10 ml) y se concentró para dar 18 g de la amida racémica correspondiente. Es decir $(\pm)$ -2-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II).

La rotación óptica específica de la amida racémica (II) fue de $\pm 1^\circ$ (C=1, CH₃, CH₃OH).

EJEMPLO 43

Racemización de (R)-(-)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

Una mezcla de 1 g de (R)-(-)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida levorotatorio de fórmula (II) y 1 g de t-butóxido de potasio en 20 ml de DMSO se agitaron desde 50° C a 60° C durante 3 horas. Después de completar la reacción, la mezcla de reacción se vertió en 150 ml de agua fría para obtener un precipitado amarillo. Este sólido obtenido se filtró y se disolvió en dicloruro de metileno. La capa orgánica se lavó con 2 x 250 ml de agua DM (2 x 25 ml) y se concentró para dar 0,8 g de la amida racémica correspondiente es decir $(\pm)$ -2-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida.

La rotación óptica específica de la amida racémica (II) fue de $\pm 0,5^\circ$ ($C=1$, CH_3OH).

EJEMPLO 44

Racemización de (R)-(-)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

Una mezcla de 1 g de (R)-(-)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida levorotatorio de fórmula (II) y 250 mg de hidruro de sodio en tetrahidrofurano seco se agitó a desde 25°C a 30°C durante 3 horas. Después de completar la reacción, la mezcla de reacción se vertió en 150 ml de agua fría lentamente para obtener un precipitado amarillo. Este sólido obtenido se filtró y se disolvió en dicloruro de metileno. La capa orgánica se lavó con 2 x 25 ml de agua DM (2 x 25 ml) y se concentró para dar 0,95 g de la amida racémica correspondiente. Es decir ($\pm$)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II).

EJEMPLO 45

Racemización de (R)-(-)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

Una mezcla de 1 g de (R)-(-)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida levorotatorio de fórmula (II) y 21 g de t-butóxido de potasio en 100 ml de DMSO se agitaron a desde 50° C a 60° C durante 3 horas. Después de completar la reacción, la mezcla de reacción se vertió en 750 ml de agua fría para obtener un precipitado amarillo. Este sólido obtenido se filtró y se disolvió en dicloruro de metileno. La capa orgánica se lavó con 2 x 100 ml de agua DM (2 x 100 ml) y se concentró para dar 0,8 g de la amida racémica correspondiente. Es decir (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida.

EJEMPLO 46

(S)-(+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

5 g de (+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se disolvieron en 35 ml de metanol y la solución se congeló a desde 0 a -5° C. 15 ml (0,28

mol) de H_2SO_4 concentrado (98%) se agregaron lentamente en una hora manteniendo la temperatura hasta -5°C . Después de completar la adición de la mezcla de reacción se agitó a temperatura ambiente durante 30 min. La solución se reflujo a 60°C durante 6 horas. La mezcla de reacción se enfrió a temperatura ambiente y el solvente se destiló bajo presión reducida. El residuo se agregó a 200 ml de agua helada y se enfrió a -5°C . el pH de la mezcla de reacción se ajustó entre 9 y 10 utilizando carbonato de sodio acuoso. El residuo se extrajo con 100 ml de acetato de etilo. La capa orgánica se secó sobre Na_2SO_4 anhidro, y se evaporó bajo presión reducida. Eluente combinado se evaporó a presión reducida para rendir 3,2 g del producto purificado mediante cromatografía de columna, utilizando hexano : acetato de etilo (9 : 1) como eluente.

EJEMPLO 47

(S)-(+) -metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

5 g de (+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se disolvieron en 45 ml de metanol seguidos por 15 ml de tolueno. 5 ml (0,28 mol) de H_2SO_4

concentrado fueron agregados instantáneamente y otros 10 ml de H_2SO_4 concentrado fueron lentamente agregados más tarde, mientras que se mantenía la temperatura a 90°C . Después de aquello, la mezcla de reacción se refluyó a 90°C durante 13 horas. El solvente se destiló bajo presión reducida, se agregaron 50 ml de agua y el pH de la mezcla de reacción se ajustó entre 9 a 10 utilizando carbonato de sodio acuoso. El residuo se extrajo con 100 ml de acetato de etilo. La capa orgánica se secó sobre Na_2SO_4 anhidro, y se evaporó bajo vacío. El eluente combinado se evaporó a presión reducida para rendir 2,8 g del producto crudo purificado mediante cromatografía de columna, utilizando hexano : acetato de etilo (9 : 1) como eluente.

EJEMPLO 48

(S)-(+) -metil (2-clorofenil) - (6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

5 g de (S)-(+) - (2-clorofenil) - (6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se disolvieron en 50 ml de metanol y la solución se enfrió hasta -15°C . 15 ml (0,28 mol) de H_2SO_4 concentrado (98%) se agregaron gota a

gota en una hora manteniendo la temperatura hasta -15° C. Después de completar la adición de la mezcla de reacción fue gradualmente incrementada, y agitada a 310° C durante 30 min y luego refluída a 70° C durante 21 horas. El solvente se destiló bajo presión reducida y al residuo se agregó a 50 ml de agua y se agitó durante 30 min seguido por enfriamiento a -5° C. El pH de la mezcla de reacción se ajustó entre 9 y 10 utilizando carbonato de sodio acuoso. El residuo se extrajo con 100 ml de acetato de etilo. La capa orgánica se secó sobre Na_2SO_4 anhidro, y se evaporó bajo vacío. El rendimiento fue de 3,8 g del producto purificado mediante columna, utilizando hexano : acetato de etilo (9 : 1) como eluyente.

EJEMPLO 49

(S) - (+) - metil (2-clorofenil) - (6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

5 g de (+) - (2-clorofenil) - (6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida se disolvieron en 20 ml de metanol y la solución se calentó a 65 a 70° C. 15 ml (0,28 mol) de H_2SO_4 concentrado helado (98%) se agregaron lentamente en una hora manteniendo la temperatura hasta -15° C.

Después de completar la adición de la mezcla de reacción se calentó a 70° C durante 16 horas. El solvente se destiló bajo presión reducida y al residuo se agregaron 50 ml de agua y se agitaron durante 30 minutos seguido por enfriamiento a -5° C. El pH de la mezcla de reacción se ajustó entre 9 y 10 utilizando carbonato de sodio acuoso. El residuo se extrajo con 100 ml de acetato de etilo. La capa orgánica se secó sobre Na₂SO₄ anhidro, y se evaporó bajo vacío. El eluyente combinado se evaporó a presión reducida para rendir 2,8 g del producto crudo purificado mediante cromatografía de columna, utilizando hexano : acetato de etilo (9 : 1) como eluyente para dar 2 g del compuesto titulado (I) y 1 g del material de partida (S)-(+)-(II).

EJEMPLO 50

(S)-(+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (II)

- a) Una solución de 5 g de (16,31 mmol) de (±)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida (preparada como se da en los ejemplos 10-15) y 4,15 g (16,2 mmol) de monohidrato de ácido

(1S) (+)-camfor-10-sulfónico en 100 ml de acetona se mantuvieron calientes durante 20 horas seguido por almacenamiento a temperatura inferior a 10° C. aparecieron pocos cristales, el licor madre se concentró adicionalmente y la recrystalización se repitió, seguido por almacenamiento en condición fría durante pocos días dando 3,1 g (70% de rendimiento) de sal de ácido (S)-2-(2-cloro-fenil)-(4,5,6,7-tetrahidrotienol[3,2-c]pirid-5-il)acetamida (+)-camforsulfónico. La sal se purificó adicionalmente mediante recrystalización en acetona, hasta que se obtuvo una rotación óptica específica constante.

El producto obtenido se secó adecuadamente. Las características típicas fisicoquímicas del producto obtenido son como siguen:

Rango de fusión : 223-225° C

SOR : +52° (C = 1, MeOH)

b) 3,1 g de sal de ácido (S)-(+)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]parid-5-il) acetamida (10-D-camfor sulfónico se agregaron a 20 ml de una solución de Na₂CO₃ saturada y el producto se extrajo

con 20 ml de acetato de etilo. La capa orgánica se aisló, se secó sobre NaSO_4 y se concentró bajo presión reducida. Se obtuvo un producto de aceite crudo, el cual luego de purificación dio 1,5 g de cristales blancos (60%).

EJEMPLO 51

Remoción quiral del (-)-esteroisómeros de una mezcla que contiene exceso de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

2 g (0,0173 moles) metil (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (donde el ee fue de 80%) se disolvieron en 10 ml de acetona y la mezcla de reacción se agitó durante 10 min, seguido por reflujo. A la mezcla de reacción, se agregaron 1,49 g de hidrato de ácido (1S)-(+)-camfor-10-sulfónico en 0,8 ml de agua seguido por 1 ml de acetona. Luego la mezcla de reacción completa se refluyó durante una hora y se enfrió gradualmente. Esta posteriormente se agitó durante toda la noche a temperatura ambiente. La solución clara se enfrió adicionalmente desde 0 a -5°C , en donde se obtuvo un precipitado. A la sal formada se agregó acetato de

etilo y agua, la cual fue posteriormente basificada con NaHCO_3 , la capa orgánica se lavó con agua, se concentró bajo presión reducida, para dar una base libre de 0,386 g con pureza quiral = 99,85% de (+)-isómero (ee = 99,7%).

EJEMPLO 52

Remoción quiral del (-)-esteroisómeros de una mezcla que contiene exceso de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

2 g (0,0173 moles) metil (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (donde el ee fue de 90%) se disolvieron en 10 ml de acetona y la mezcla de reacción se agitó durante 10 min, seguido por reflujo. A la mezcla de reacción, se agregaron 1,49 g de hidrato de ácido (1S)-(+)-camfor-10-sulfónico en 0,8 ml de agua seguido por 1 ml de acetona. Luego la mezcla de reacción completa se reflujo durante una hora y se enfrió gradualmente. Esta posteriormente se agitó durante toda la noche a temperatura ambiente. La solución clara se enfrió adicionalmente desde 0 a -5°C , en donde se obtuvo un precipitado. A la sal formada se agregó acetato de etilo y agua, la cual fue posteriormente basificada con

NaHCO₃, la capa orgánica se lavó con agua, se concentró bajo presión reducida, para dar una base libre de 0,386 g con pureza quiral = 99,85% de (+)-isómero (ee = 99,7%).

EJEMPLO 53

Remoción quiral del (-)-esteroisómeros de una mezcla que contiene exceso de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

2 g (0,0173 moles) metil (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (donde el ee fue de 95%) se disolvieron en 10 ml de acetona y la mezcla de reacción se agitó durante 10 min, seguido por reflujo. A la mezcla de reacción, se agregaron 1,49 g de hidrato de ácido (1S)-(+)-camfor-10-sulfónico en 0,8 ml de agua seguido por 1 ml de acetona. Luego la mezcla de reacción completa se reflujo durante una hora y se enfrió gradualmente. Esta posteriormente se agitó durante toda la noche a temperatura ambiente. La solución clara se enfrió adicionalmente desde 0 a -5° C, en donde se obtuvo un precipitado. A la sal formada se agregó acetato de etilo y agua, la cual fue posteriormente basificada con NaHCO₃, la capa orgánica se lavó con agua, se concentró

bajo presión reducida, para dar una base libre de 0,386 g con pureza quiral = 99,85% de (+)-isómero (ee = 99,7%).

EJEMPLO 54

Resolución de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato (I)

33 g (0,1 mol) de (+)-metil(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetato se disolvieron en 200 ml de acetona y la mezcla de reacción se calentó a desde 60 a 70° C, refluendo durante 15 minutos. La mezcla de reacción, se agregaron 25,6 g de hidrato de ácido (1S)-(+)-camfor-10-sulfónico en agua, en donde la formación de sal inició a desde 60 a 70° C. Después de que se completó la formación de la sal, la mezcla de formación se enfrió gradualmente a temperatura ambiente y luego a desde 0° C a 5° C. El aislamiento de sal diastereomérica mediante filtración y lavado utilizando acetona, y secado. El rendimiento del producto diastereomérico fue de 20,5 g (70%).

La generación de (-) isómero del compuesto del título se llevó a cabo utilizando solución de bicarbonato

de sodio diluida y extracción en acetato de etilo, remoción de solvente y dando el compuesto del título 10,9 g (66%).

EJEMPLO 55

Resolución de $(\pm)$ - (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo (IV)

a) A 5 g (0,0173 mol) $(\pm)$ -(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo disuelto en 100 ml de acetona, se agregaron 4,35 g (0,174 moles) de hidrato de ácido (1S)-(+)-camfor-10-sulfónico en 5 ml de agua en un lote a 60 - 62° C durante adición. La mezcla se agita a 60° C durante 60 horas, la agitación continúa entonces durante toda la noche y más tarde se mantiene en refrigerador durante un día. La sal diastereomérica precipitada fue entonces filtrada para producir 730 mg del producto.

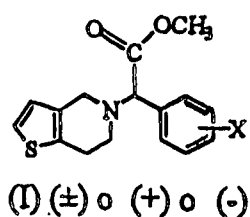
b) a 730 mg de la sal de ácido $(\pm)$ -(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo (1S)-(+)-camfor-10-sulfónico en 20 ml de agua, 10 ml

(5%) de solución de Na_2CO_3 se agregó ($\text{pH} = 10$). Después de agitar la mezcla, se agregaron 100 ml de acetato de etilo a esta. La capa orgánica fue entonces agregada a esta. La capa orgánica se separó entonces y se destiló entonces hasta conseguir el producto. El rendimiento del producto fue de 400 mg (16%).

Rotación óptica específica (α^D): $+7,5787^\circ$ ($C = 1$, DMF).

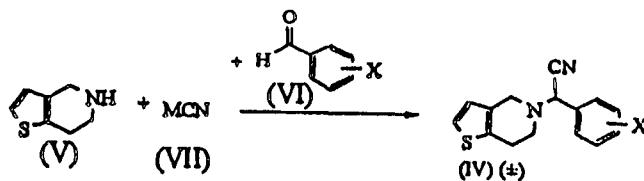
REIVINDICACIONES

1. Un proceso para la preparación del compuesto de fórmula (I),



En donde X representa un átomo de hidrógeno, flúor, cloro, bromo, o yodo, preferiblemente 2-cloro, el cual comprende:

- i) hacer reaccionar un compuesto de fórmula (V) o su sal,



con un cianuro de fórmula general (VII) donde N representa metal alcalino, trimetilsilil, Cu, o hidrógeno, y seguido por la adición de un compuesto de fórmula general (VI), donde X es como se definió anteriormente, para obtener un compuesto racémico de fórmula general (IV), donde X es como se definió anteriormente,

- ii) hacer reaccionar un compuesto de fórmula general IV) en forma ($\pm$) o en cualquiera de sus formas ópticamente activas (+), o (-),



con reactivos ácidos o básicos para obtener un compuesto de fórmula (II) o su sal con retención de configuración,

sus sales, seguido por la liberación de la sal del compuesto.

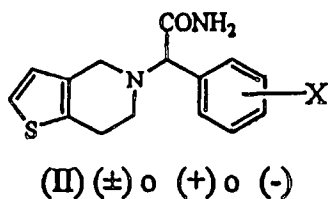
3. Un proceso de acuerdo a la reivindicación 1, en donde opcionalmente, resolver un compuesto racémico de fórmula (II) en sus isómeros ópticos, o también, transformar el compuesto racémico o sus isómeros ópticos en un sales, seguido por la liberación de la sal del compuesto.

4. Un proceso para la preparación del compuesto de fórmula (III) o su sal, en donde X representa un átomo de hidrógeno, cloro, bromo o yodo, preferiblemente 2-cloro, el cual comprende,



- 49
- i) hacer reaccionar un compuesto de fórmula general (IV) o su sal, en cualquiera de sus formas ópticas, en presencia de un catalizador ácido/básico en un solvente adecuado, dando el ácido correspondiente de la fórmula (III) o su sal, con la misma configuración como aquella del material de partida,
 - ii) si se desea, finalmente el compuesto racémico de fórmula (III) o su sal, se resuelven en sus correspondientes formas ópticamente puras (+) y (-).

5. Un proceso de acuerdo a la reivindicación 1, en donde un compuesto de fórmula (II) (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida, o sus isómeros ópticos activos, donde X representa un átomo de halógeno tal como cloro, bromo, yodo, sustituyente, más preferiblemente 2-cloro, se prepara mediante un proceso que comprende,

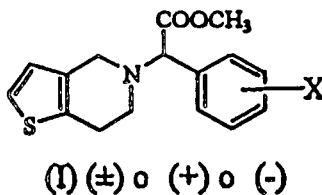


- i) tratar el compuesto de fórmula (IV) o su sal o en cualquiera de sus formas ópticas, con reactivos básicos donde el material de partida es racémico o también con un catalizador ácido cuando el material de partida es ópticamente activo, en la presencia de solvente adecuado;
 - ii) formar finalmente una sal del compuesto racémico de fórmula (II), el cual se resuelve en sus correspondientes formas ópticamente puras (+) y (-).
6. Un proceso de acuerdo a la reivindicación 5, el cual comprende la preparación del compuesto de fórmula (II) caracterizado porque, el reactivo básico utilizado es hidróxido de litio, hidróxido de potasio, hidróxido de sodio y t-butoxido de potasio.

7. Un proceso de acuerdo a la reivindicación 5, el cual comprende la preparación de un compuesto de fórmula (II), en donde dicho reactivo ácido utilizado se selecciona del grupo que consiste de ácido acético, ácido p-toluenosulfónico, ácido trifluoroacético, ácido cloroacético, ácido perclórico, ácido fórmico o ácidos minerales tales como haluros de hidrógeno alcohólicos anhidros, o ácido clorhídrico acuoso, ácido sulfúrico, Hbro una mezcla de estos.
8. Un proceso de acuerdo a la reivindicación 5, el cual comprende la preparación del compuesto de fórmula (II) en donde, el solvente utilizado es agua, alcohol (C₁-C₄), acetona, ácido acético, dimetilformamida, THF, DMSO, dioxano, DME y similares o mezclas de estos, preferiblemente, mezclas de agua, metanol o terc-BuOH.
9. Un proceso de acuerdo a la reivindicación 5 en donde un compuesto de fórmula (II) (±)-

- (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida, se resuelve en sus formas (-), y (+) utilizando 10-ácido 1-(R) o 1-(S)-camforsulfónico, ácido tartárico, más particularmente 10-ácido 1-(R) o 1-(S)-camforsulfónico, en la presencia de solvente tal como agua, acetona, acetato de etilo o una mezcla de estos, y la sal utilizada puede estar en una proporción molar de 0,5 a 1,1 equivalentes.
10. Un proceso de acuerdo a la reivindicación 5, en donde un compuesto de fórmula (II) ($\pm$)-(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetamida, se convierte la sal correspondiente, en donde la sal reivindicada es D-camforsulfonato, L-camforsulfonato, ácido D-tartárico, ácido L-tartárico, o hidrogenosulfato.
11. Un proceso de acuerdo con la reivindicación 1, donde dicho compuesto de fórmula (I) es metil (2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)acetato, o sus

isómeros ópticos activos o sus sales, donde X representa un átomo de halógeno tal como cloro, bromo, yodo sustituyente, más preferiblemente 2-cloro, dicho proceso comprende,



- i) tratar el compuesto de fórmula (II) o su sal en cualquiera de sus formas ópticas, con reactivos ácidos, en la presencia del solvente adecuado;
 - ii) formar finalmente una sal del compuesto racémico de fórmula (I), el cual se resuelve en sus correspondientes formas ópticamente puras (+) y (-).
12. Un proceso de acuerdo con las reivindicación 11, donde dicho reactivo ácido utilizado se selecciona de ácido sulfúrico concentrado en

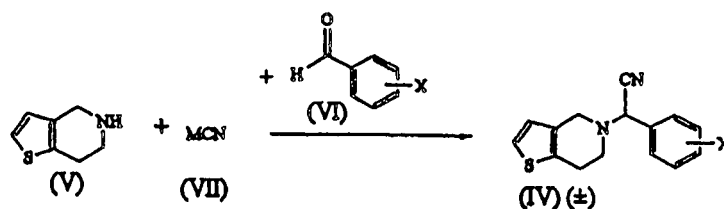
el rango de 1 equivalente a 50 equivalentes, preferiblemente la adición es favorecida a desde 0° C a 5° C o a temperatura de reflujo de absorbente utilizado.

13. Un proceso de acuerdo a la reivindicación 11, en donde el solvente utilizado es metanol en el rango de 3 a 30 volúmenes, junto con otros cosolventes tales como tolueno, DMSO, xileno y similares o mezclas de estos.
14. Un proceso de acuerdo a la reivindicación 11, donde la duración de los rangos de reacción van de 4 horas a 4 días.
15. Un proceso de acuerdo a la reivindicación 11, en donde la reacción se lleva a cabo a una temperatura en el rango de 40° C a 140° C.
16. Un proceso de acuerdo a la reivindicación 11, en donde un compuesto de fórmula (I), se resuelve utilizando 10-ácido 1-(R) o 1-(S)-

camforsulfónico, ácido (R) o (S)-tartárico, más particularmente 10-ácido 1-(R) o 1-(S)-camforsulfónico, en la presencia de solvente tal como agua, acetona, acetato de etilo o una mezcla de estos.

17. Un proceso de acuerdo a la reivindicación 16, en donde una mezcla que contiene las prporciones variantes de los dos enantiómeros, (-)-I y (+)-I es quiralmemente enriquecida a (+)-(I) esteroisómero, o remoción quiral de (-)-I enantiómero en una mezcla variable de (-)-I y (+)-I esteroisómeros.

18. Un proceso para la preparación de un compuesto de fórmula (IV) y sus sales,



donde X representa un átomo de halógeno tal como cloro, bromo, yodo sustituyente, más particularmente X representa 2-cloro, junto con sus sales, que comprende,

- i) hacer reaccionar un compuesto de fórmula (V) o su sal de adición ácida con un cianuro de fórmula general (VII) donde el significado de M representa metal alcalino, TMS, Cu, e hidrógeno, seguido por reacción con halogenobenzaldehído de fórmula (VI), donde X es un átomo de halógeno, los cuales se resuelven en sus isómeros ópticos, y si se desea, liberándose de sus sales o transformándose en sus sales; o

hacer reaccionar un halobenzaldehído de fórmula general (VI) en donde el significado de X es átomo de halógeno con cianuro de fórmula general (VII) en donde, es como se definió anteriormente, y seguido por in situ con el compuesto de fórmula general (V) o su sal de adición ácida; o,

iii) hacer reaccionar el halobenzaldehído de fórmula general (VI), en donde el significado de X es átomo de halógeno, con hidrogenosulfito de fórmula general (VIII) donde M es como se definió anteriormente, y finalmente, con cianuro de fórmula general (VII), donde M es como se definió anteriormente, y subsecuentemente reaccionar in situ con el compuesto de fórmula general (V) o sua sal de adición ácida; y

resolver finalmente el compuesto de fórmula (IV) o su sal, así obtenida a su forma ópticamente pura (+) y (-) del compuesto de fórmula (IV) o su sal.

19. El proceso de acuerdo a la reivindicación 18, en donde la reacción se lleva a cabo a temperatura entre 0° C y 100° C, en donde con gas HCN, la temperatura de reacción iría adicionalmente hacia abajo hasta -30° C.

20. El proceso de acuerdo a la reivindicación 18, en donde la reacción se lleva a cabo en un medio acuoso o no acuoso que contiene

ácidos tales como ácido acético, ácido propiónico, metanol y HCl/MeOH.

21. El proceso de acuerdo a la reivindicación 18, en donde un ácido catalizador tal como ácido clorhídrico seco, ácido sulfúrico, ácido p-toluenosulfónico o ácido acético se utiliza.
22. Un proceso de acuerdo a la reivindicación 18, en donde dicho compuesto de fórmula (IV) $(\pm)$ -(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo, se resuelve en las formas (-), y (+) utilizando 10-ácido 1-(S)-camforsulfónico, ácido tartárico, más particularmente 10-ácido 1-(R) o 1-(S)-camforsulfónico, presencia de acetona, acetato de etilo o una mezcla de estos, y agua.
23. Un proceso de acuerdo a la reiv 18, un compuesto de fórmula (IV) $(\pm)$ -(2-clorofenil)-(6,7-dihidro-4H-tieno[3,2-c]pirid-5-il)acetonitrilo, en $(\pm)$ o las

formas (-) o (+) se convierten en su sal, en donde la sal reivindicada es D-camfosulfonato, L-camforsulfonato, ácido D-tartárico, ácido L-tartárico o hidrógeno sulfato.

24. El proceso de acuerdo a la reivindicación 18, en donde, la racemización del isómero (-) del compuesto de fórmula (II) se efectúa en una mezcla que contiene el estereoisómero (+) para conseguir el compuesto ($\pm$) utilizando una base tal como LDA, KOH, NaOH, K-t-BuOH, NaOMe, NaH, KH en un solvente adecuado.

25. El proceso de acuerdo a la reivindicación 5, en donde, la racemización del isómero (-) del compuesto de fórmula (I) se efectúa en una mezcla que puede contener el estereoisómero (+) para conseguir el compuesto ($\pm$) utilizando una base tal como LDA, NaOMe, NaH, KH en un solvente adecuado.

26. El proceso de acuerdo a la reivindicación olución se lleva a cabo en la presencia de acetona, un solvente en el rango de 5 a 10 volúmenes, que puede contener agua hasta 5%.
27. El proceso de acuerdo a la reivindicación 17, en donde dicho agente quiral adecuado utilizado está en una proporción molar 1 : 1.
28. El proceso de acuerdo a la reiv 27, en donde, la temperatura adecuada va de 0° C a la temperatura de reflujo del solvente.

RESUMEN

La presente invención describe un proceso para la preparación de derivados de tieno[3,2-c]piridina de la fórmula (I), formas racémicas u ópticamente activas (+) o (-) y sus sales en donde X, el sustituyente sobre el anillo de benceno representa un átomo de hidrógeno o de halógeno tal como flúor, cloro, bromo o yodo. La presente invención también describe un proceso para la preparación de compuestos de la fórmula general (II), en cualquiera de las formas racémicas u ópticamente activas (+) o (-) y sus sales, donde X, el sustituyente sobre el anillo de benceno representa cualquiera de un átomo de hidrógeno o halógeno tal como flúor, cloro, bromo o yodo. Los compuestos representados por la fórmula (I) y (II) tienen un carbono asimétrico y de esta forma, los compuestos ópticamente activos de la fórmula (I) o la fórmula (II) se pueden obtener bien sea al resolver el producto intermedio/racémico o utilizando un intermedio ópticamente activo. Los compuestos de la invención son farmacológicamente activos y tienen propiedades antiagregantes y antitrombóticas.

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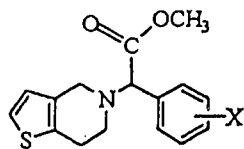
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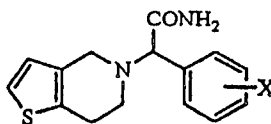
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(54) Title: PROCESS FOR PREPARING CLOPIDOGREL



(I)



(II)

(57) Abstract: The present invention discloses a process for the preparation of thieno[3,2-c]pyridine derivatives of general formula (I), in either racemic or optically active (+) or (-) forms and their salts, wherein X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine. The

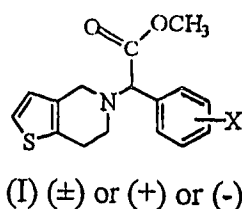
present invention also describes a process for preparing the compounds of general formula (II), in either racemic or optically active (+) or (-) forms and their salts, where X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine. The compounds represented by formulae (I) and (II) have one asymmetric carbon and hence, the optically active compounds of formula (I) or of formula (ii), may be obtained either by resolving the racemic intermediate/final product or using an optically active intermediate. The compounds of the invention are pharmacologically active and have significant anti-aggregating and anti-thrombotic properties.

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PROCESS FOR PREPARING CLOPIDOGREL

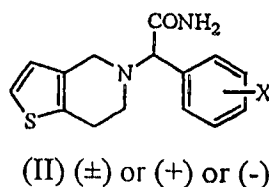
FIELD OF THE INVENTION

The present invention relates to a process for the preparation of thieno[3,2-c]pyridine derivatives of general formula (I), in either racemic or optically active (+) or (-) forms and their salts, wherein X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine.



Preferably, X represents 2-chloro.

The present invention also describes a process for preparing the compounds of general formula (II), in either racemic or optically active (+) or (-) forms and their salts, where X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine.



Preferably X represents 2-chloro. These compounds are useful intermediates to prepare compounds of general formula (I).

The compounds represented by formulae (I) and (II) have one asymmetric carbon and hence, to obtain optically active compounds of formula (I) or of formula (II), option available is either to resolve the racemic intermediate/final product or use an optically active intermediate.

BACKGROUND OF THE INVENTION

Thieno[3,2-c]pyridine derivatives disclosed in FR 2,215,948, FR 2,530,247 and FR 2,612,929, are pharmacologically active and have significant anti-aggregating and anti-thrombotic properties. One such example is 'Clopidogrel', (S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl) acetic acid methyl ester and its pharmaceutically acceptable salts. Later, it was found that the biological activity resides only with (S)-(+)-stereoisomer (US 4,847,265). As 'Clopidogrel base' is an oily liquid, in order to prepare a convenient formulation, the base is converted into a pharmaceutically acceptable salt.

Suitable salts of 'Clopidogrel base' can be formed with taurocholate, hydrobromide and sulfuric acid.

DESCRIPTION OF THE PRIOR ART

The reported methods to synthesize the compounds of general formula (I) (US 4529596, GB 0420706 and GB 0466569), use α -halophenylacetic acid derivatives, which are lachrimatory and irritant in nature. The processes to synthesize such compounds involve multiple steps, and have other drawbacks due to the chemicals/reagents used, which usually are difficult to handle, scale-up and unfavorable from human health as well as environmental point of view. Moreover, overall yields of these processes range from poor to average. Various other synthetic approaches found in literature, involve expensive or hazardous chemicals, which do not significantly improve the yield of the desired product.

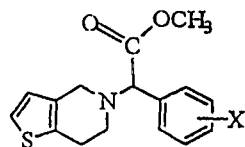
Recently, radiolabelled (benzene- U - ^{13}C) racemic($\pm$)-Clopidogrel has been prepared as a standard for metabolic studies in an overall yield of 7 % using orthometalation/chlorination of benzoic acid derivative (*Chem. Abst.*, 133:281711, 2000). Various other strategies are disclosed in: WO 98/51681, WO 98/51682, WO 98/51689, WO 99/18110, US 4,876,362, US 5,036,156, US 5,132,435, US 5,139,170, US 5,204,469 and US 6,080,875.

Recently, a new polymorph of Clopidogrel bisulfate (named as form II) has been disclosed in patent application (WO 99/65915), which has a melting point of 176 ± 3 °C. It also mentions that the compound disclosed in the earlier US patent (US 4,847,265), had a different melting point of about 184 ± 3 °C (now referred as, form I). It has been shown that both the polymorphs have distinct and characteristic XRD and IR spectrum.

Consequently, the present invention aims to provide an inexpensive and commercially viable process to prepare compounds of formula (I) in good yields.

OBJECTS OF THE INVENTION

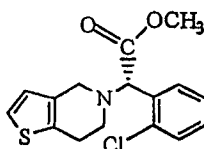
The main object of the present invention is to provide a novel process to prepare thieno[3,2-c]pyridine derivatives, represented by the general formula (I), in either racemic or optically active (+) or (-) forms and their salts, wherein X represents either hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine.



(I) ($\pm$) or (+) or (-)

Another the object of the present invention is to provide a novel process to prepare thieno[3,2-c]pyridine derivatives, represented by the general formula (I), in either racemic or optically active (+) or (-) forms and their salts, through a commercially viable route.

A particular object of the present invention is to provide a novel process to manufacture (S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetic acid methyl ester as bisulfate salt, i.e. Clopidogrel bisulfate, where X is 2-chloro substituent.



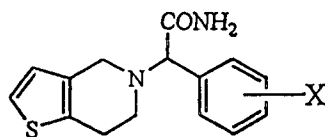
(I) (+)

The preferred object of the present invention is to provide a novel process to manufacture Clopidogrel bisulfate, through a commercially viable process.

Another important object of the present invention is to provide a novel process to manufacture polymorph form I of Clopidogrel having melting point 184 ± 3 °C, through a commercially viable route.

Yet another object of the present invention is to recycle through a novel process the laevoisomer of Clopidogrel or a variable mixture of (+) and (-) stereoisomers to make (+)-Clopidogrel bisulfate.

Another object of the present invention is to provide a process to prepare a compound (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide of formula (II), either in racemic or as optically active (+) or (-) forms and their salts.



(II) (±) or (+) or (-)

Another object of the present invention is to provide a process for the preparation of a compound of formula (II) where X is 2-chloro, in racemic as well as optically active (+) or (-) forms having suitable chemical and chiral purity and along with their salts. The dextro isomer of compound with formula (II) with suitable purity or its salts, are useful intermediates for the synthesis of (+)-Clopidogrel bisulfate.

Still another object of the present invention is to provide a novel process to convert (R)-(-)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide or its mixture with variable minor amounts of its optical antipode, into almost a 1:1 mixture of (+) and (-) isomer.

It is also an object of the present invention is to provide a process to prepare compound of formula (III), (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetic acid, in racemic ($\pm$) or in either of the optically active (+) or (-) form, and their salts.

Still another object of the present invention is to provide a novel process to convert (*R*)-(-)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl) acetic acid in a mixture to (*S*)-(+)-stereoisomer.

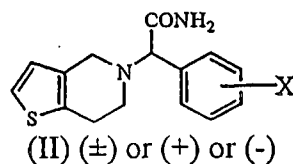
Another object of the present invention is to provide a process for the preparation of a compound of formula (IV), ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetonitrile, and their salts.

Still another object of the present invention is to provide a novel process to convert (*R*)-(-)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetonitrile or its mixture with variable minor amounts of its optical antipode, into almost a 1:1 mixture of (+) and (-) isomer.

The process described herein provides a simple and alternative method to prepare compounds of the general formula (I), particularly (*S*)-(+)-Clopidogrel bisulfate, polymorph form I.

SUMMARY OF THE INVENTION

The above and other objects of the present invention are achieved by the process of the present invention by employing compounds of formula (II)



or its salts, in either racemic or optically active (+) or (-) forms, as outlined in Scheme 1.

Optionally, the present invention provides a method to resolve ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide into optically active (+) or (-) forms, which can be used to prepare (+)-Clopidogrel bisulfate.

Optionally, the present invention provides a method to resolve ($\pm$)-2-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetic acid into optically active (+) or (-) forms.

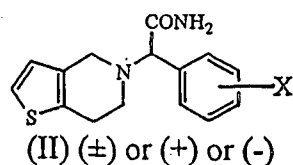
Optionally, the present invention provides a method to resolve ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetonitrile into optically active (+) or (-) forms

DETAILED DESCRIPTION OF THE INVENTION

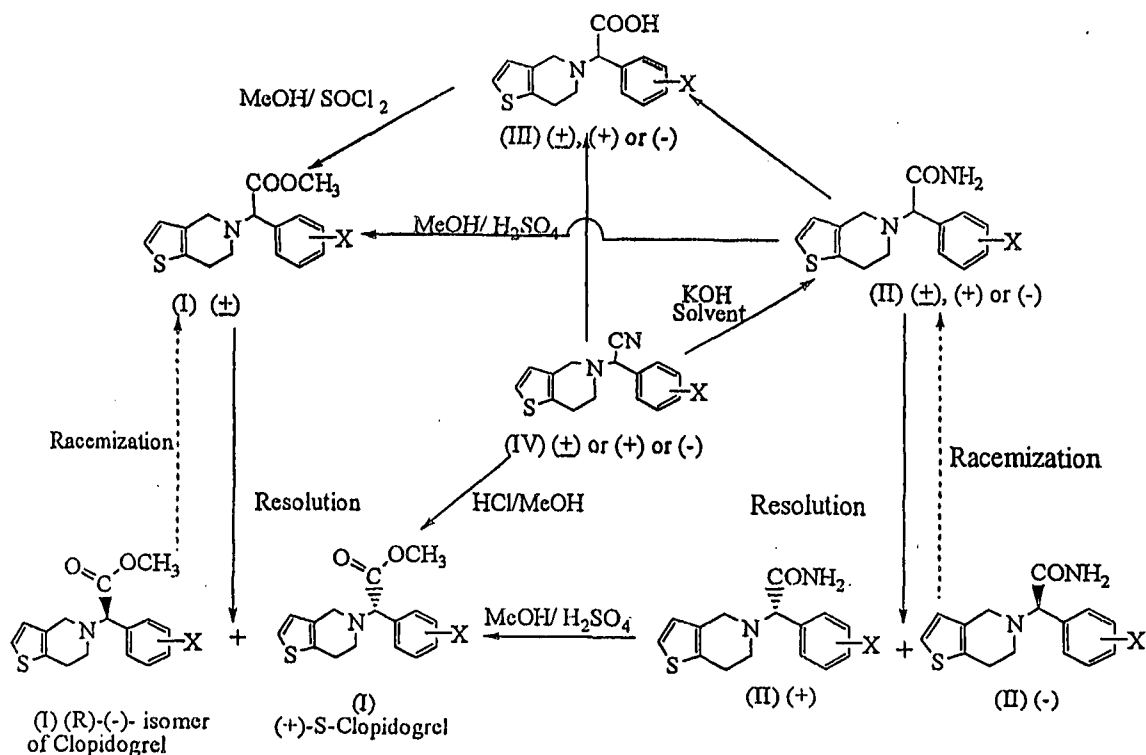
Accordingly, the present invention provides a process to prepare compounds of formula (I), in either racemic or optically active (+) or (-) forms and their salts, where X represents either hydrogen or a halogen atom such as fluorine, chlorine, bromine or iodine. More

particularly, the present invention provides a process to prepare Clopidogrel bisulfate.

The process to prepare compounds of formula (I) or its salts, uses compounds of formula (II)



or its salts, in either racemic or optically active (+) or (-) forms, as outlined in Scheme 1.



SCHEME 1

Each intermediate in Scheme 1 has one chiral center. Hence, to prepare an optically active product, such as compound represented by formula (I), particularly Clopidogrel and its salt, it is possible to use an optically active intermediate from the first step onwards.

The present invention provides a process for the preparation of compounds of formula (I) and their salts as shown in scheme 1, which comprises:

1. preparing compound of formula (IV), (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile as described in Scheme 2, i.e. via Strecker reaction;
2. resolving, if desired, the racemic mixture of compound of formula (IV) into its optically active (+) and (-) stereoisomers; and recycling the unwanted stereoisomer into the process by racemization;

3. transforming the compound of formula (IV) in either racemic or optically active (+) or (-) form or its salt, into the compound of formula (II), ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide or optically active corresponding (+) or (-) form, based upon starting material used;

4. resolving, if desired, the racemic compound of formula (II) - into its optically active (+) and (-) stereoisomers; and recycling the unwanted stereoisomer into the process by racemization;

5. transforming the compound of formula (II), either in racemic or optically active (+) and (-) form or its salt, into either optically active or racemic compound of formula (I), ($\pm$)-(2-chloro phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate methyl ester, in racemic or optically active (+) and (-) form and its salt, based upon starting material used;

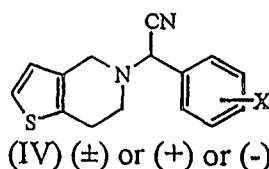
6. further resolving and/or transforming the racemic/optically active compound of formula (I) into their pharmaceutically acceptable salts and/or, liberating the racemic or optically active compound of formula (I) from its salts.

Alternatively, either of the compounds of formulae (IV) or (II), either racemic or optically active (+) or (-) form can be transformed into corresponding compounds of formula (III); which can then be converted into corresponding compound of formula (I).

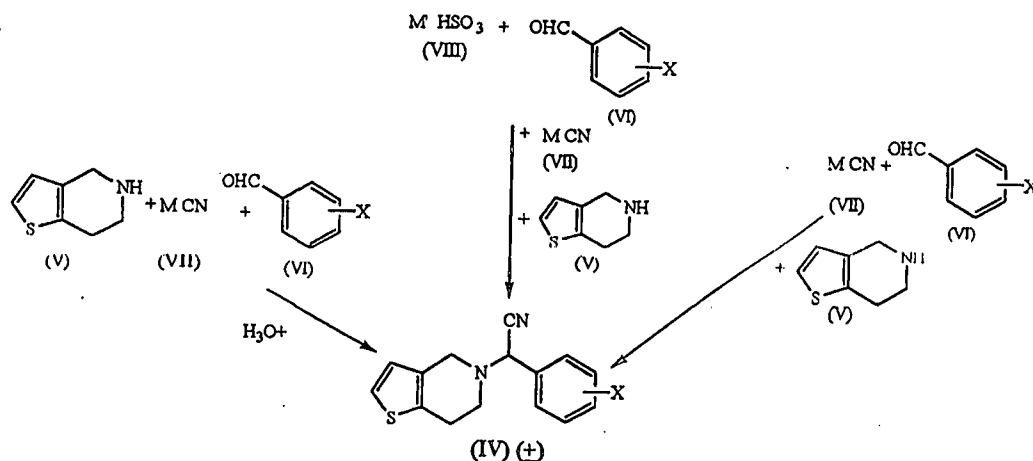
The compound of formula (IV) in racemic or optically active (+) or (-) forms can be directly converted into corresponding compound of formula (I).

Optionally, suitable acid addition salts of the intermediates of formula II, III and IV may be used in the above mentioned processes. Suitable acids used may be selected from acetic, benzoic, fumaric, maleic, citric, tartaric, gentisic, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, camphor sulfonic, hydrochloric, sulfuric, hydrobromic acids and the like.

Another aspect of the present invention is to provide a process for the preparation of a novel intermediate of formula (IV) and its salts.



Yet another aspect of the process of invention includes preparation of intermediate described by general formula (IV) and as depicted in the Scheme 2, by Strecker reaction, using a secondary amine (Organic Synthesis Collective Volume III, page no. 275).



SCHEME 2

The process to prepare compounds of formula (IV) includes, reacting amine of formula (V) or its salt, with a cyanide derivative of the general formula (VII), wherein M represents either alkali metals such as Na, K, Li, or H, trimethylsilyl (TMS) and the like; with 2-chlorobenzaldehyde of formula (VI). The synthesis of amine or its salt having formula (V) is described in FR 2608607.

The above reaction can be carried out in various ways. A few such methods are outlined in Scheme 2 shown above. Initially, amine of formula (V), or its salt, is reacted with cyanide (VII), wherein M is as defined earlier, followed by addition of 2-chlorobenzaldehyde (VI). Alternatively, 2-chlorobenzaldehyde (VI) is treated with cyanide of formula (VII), wherein M is as defined earlier, and the intermediate cyanohydrin is further reacted with amine of formula (V) or its salt. In an alternative method, 2-chlorobenzaldehyde of formula (VI) is added to hydrogen sulfite derivative of formula (VIII) wherein M' represents Na, K, Li and the like; followed by reaction with cyanide of formula (VII), wherein M is as defined earlier, and finally amine of formula (V) or its salt in an *in situ* reaction. Irrespective of the variations in the reaction methodology, the yield of resultant intermediate (IV) obtained is comparable.

The preferred method involves, addition of 2-chlorobenzaldehyde of formula (VI) to hydrogen sulfite derivative of formula (VIII). The salt formed is treated with cyanide of formula (VII), and finally with an amine of formula (V) or its salt in presence of suitable reagent and solvents.

Suitable reagents includes acid catalysts, such as glacial acetic acid (Synthesis, 1989, 616-618), hydrochloric acid, sulfuric acid, methanesulfonic acid, trifluoroacetic acid, polyphosphoric acid and the like.

Suitable solvents can be hydrophilic solvents, either protic or aprotic, includes water, (C₁-C₄) alcohol, tetrahydrofuran, dimethyl formamide, DMSO, dioxane, 1,2-dimethoxyethane,

acetic acid, propionic acid and the like, or a mixture of solvents thereof. The preferred solvent is a mixture of solvents and water in varying ratio. The more preferred reaction medium includes a mixture containing water and (C₁-C₄)alcohol in a ratio varying between 1:1 and 1:10.

5 When the reaction is carried out in aprotic or hydrophobic solvent, a phase transfer catalyst and a biphasic solvent system is necessary. Suitable phase transfer catalyst used in such a case may be tetrabutyl ammonium halide, benzyltrimethylammonium halide, and the like.

10 During the reaction, certain additives may be added. Such suitable additives may be cyclo[(S)-histidine-(S)-phenyl alanine] and the like.

The reaction temperature may range from -30 °C to reflux temperature of the solvent(s) used. The preferred temperature ranges from 0 °C to 100 °C, and more preferably, from 40 °C to 80 °C. However, when HCN (g) (Scheme 2, Intermediate VII, M = H) is used the required temperature is in the range of about -30 °C to -10 °C.

15 This reaction may be carried out in the absence or presence of an inert atmosphere such as N₂, He or Ar. The duration of the reaction may vary from 1 hrs to 3 days, more specifically 2 hrs to 2 days.

20 It is preferable to react a compound of formula (V), hydrogen sulfite derivative (VIII), and cyanide derivative (VII) with respect to 2-chloro benzaldehyde (VI) in the ratio preferably between 1 to 1.2 equivalents. The racemic cyano compound (IV) thus obtained, can be resolved into optically active (+) and (-) forms.

25 The cyano compound (IV) thus obtained can be converted into corresponding acid of formula (III), amide of formula (II) or acid of formula (I) as shown in Scheme 1 (R. C. Larrock, in "Comprehensive Organic Transformations", John Wiley & Sons, Inc, 1999, 2nd Ed., 815 – 818 and references therein).

Yet, another aspect of the present invention is to convert these intermediates II and III, into compounds of formula I, as shown in scheme 1. Each of (±), (+) or (-) the isomer of intermediate of formulae II and III, can be converted into the corresponding isomer of compounds of formula I.

30 The preferred route to obtain the compound of formula (I), involves conversion of either (±), (+) or (-) isomer cyano compound (IV) and its salts, into amide compound of formula (II), in the presence of suitable acids/base reagents in suitable solvents. Later resolving the amide into optically active (+) or (-) form or its salt and the optically active amide is being

converted into optically active ester of formula (I) in presence of suitable catalyst and reagent.

The reaction to convert cyano compound of formula (IV) into amide compound of formula (II) may be carried out in presence of reagents, which include acid or a base. Suitable acids which may be used are, acetic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, chloroacetic acid and the like or anhydrous alcoholic or aqueous solution of mineral acids such as sulfuric acid, HCl, HBr and the like. A base is preferred whenever the starting material is a racemic mixture. Suitable base which may be used are lithium hydroxide, sodium hydroxide, potassium hydroxide, potassium *tert*-butoxide, or mixtures thereof, preferably alkali metal hydroxides. Along with alkali metal hydroxides, excess of hydrogen peroxides or metal peroxides may also be used in the above reaction. Suitable solvent/s for the above reaction may be aqueous, polar or protic solvents such as water, (C₁-C₄)alcohol, acetone, acetic acid, dimethyl formamide, THF, DMSO, dioxane, DME and the like or mixtures thereof; preferably solvent consists of water, methanol or *tert*-BuOH or mixture of these solvents, in a ratio varying between 1:1 to 1:10.

The temperature ranges from 20 °C to 250 °C, preferably, from 50 °C to 150 °C. The reagents used in the above process can be in the range from 0.01 to 1.2 moles equivalents. The reaction may be carried out in the absence or presence of an inert atmosphere such as N₂, He or Ar. The reactions under the basic conditions are preferably under inert atmosphere. The duration of reaction may range from 1/2 hr to 5 days, preferably from 2 hrs to 2 days.

The amide of formula (II), in either racemic or optically active (+) or (-) form, or their salt, can be converted to corresponding methyl ester of formula (I), in presence of at least one equivalent of methanol and acid, in suitable solvent.

Suitable acids which can be used include acetic acid, polyphosphoric acid, *p*-toluenesulfonic acid, trifluoroacetic acid, chloroacetic acid, or mineral acids, which includes, sulfuric acid, HCl, HBr and the like, which could be in different forms like acid dissolved in alcohol, anhydrous acids dissolved or saturated in alcohol and alcohol used may be methanol. The preferable acid is concentrated sulfuric acid in the 1 to 50 equivalent ratio. Suitable solvents for the above transformation may be polar or protic solvent such as hydrophilic solvents including methanol, acetone, acetic acid, THF, DMSO, dioxane, DME and the like or mixtures thereof. The preferable solvent consists of methanol at least in one equivalent and may be in large excess such that it acts as a solvent. Sometimes inert cosolvent, such as toluene, xylene etc. can also be used.

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The temperature ranges from 20 °C to 250 °C, preferably from 50 °C to 150 °C. The reaction may be carried out in the absence or presence of an inert atmosphere such as N₂, He or Ar. The duration of reaction may range from 3 hrs to 5 days, preferably from 4 hrs to 2 days.

5 It is possible to convert compound of formula (IV) in either racemic or optically active (+) or (-) form or its salt is converted into the corresponding acetic acid derivative of formula (III) in presence of suitable solvent and reagent. Suitable solvent/s may be aqueous or alcoholic in nature. Suitable reagents for the above reaction include acids as well as bases.

10 It is also possible to convert the cyano compound of formula (IV) in either racemic or optically active (+) or (-) form or its salts, directly into methyl ester of formula (I), in presence of at least one equivalent of acid and at least one equivalent of methanol in suitable solvents according to methods known in the literature.

15 The acid of formula (III) in either racemic or optically active (+) or (-) form or its salts can be converted into corresponding methyl ester of formula (I), in presence of suitable reagent in suitable solvents and at least one equivalent of methanol.

Suitable reagent which can be used include, thionyl chloride, acid chlorides such as pivaloyl chloride, alkylchloroformates like ethyl or methyl chloroformates and other such reagents which activate the COOH group, in a 1:1 equivalent ratio. Suitable solvent for the above transformations may be polar or protic solvent such as, methanol, acetone, 20 dimethylformamide, THF, DMSO, dichloromethane, dichloroethane, dioxane, DME and the like or mixtures thereof. The preferable solvent consists of methanol in at least one equivalent and may be in large excess such that it acts as a solvent. The temperature ranges from 20 °C to 250 °C, preferably from 50 °C to 150 °C.

25 The reagents used in above process may range from 0.01 moles to equimolar ratios. The reaction may be carried out in the absence or presence of an inert atmosphere such as N₂, He or Ar. The duration of reaction may range from 3 hours to 5 days, preferably from 3 hr to 2 days.

This manufacturing process to prepare the compounds of general formula (I) as shown in scheme 1, has following advantages:

- 30
- 1) It requires less number of steps to prepare the compounds of the formula (I).
 - 2) Simple readily available reagents / chemicals are used.
 - 3) Milder reaction conditions are employed in various steps.
 - 4) It is possible to get chiral/optically active intermediates at every stage (I, II, III, IV, or V)

- 5) It is possible to racemize the unwanted isomers thereby enhancing efficiency and reducing environmental load.
- 6) The above factors contribute to improve cost effectiveness of the process described herein.

5 The compounds of the formulae (I), (II), (III) and (IV) can be resolved by various methods to get optically active compounds of the formulae (I), (II), (III) and (IV), which can give Clopidogrel of desired stereochemistry (R. A. Sheldon, in "Chirotechnology", Marcel Dekker, Inc. NY, Basel, 1993, 173-204 and references therein; A. N. Collins, G. N. Sheldrack and J Crosby, in "Chirality in Industry II", John Wiley & Sons, Inc, 1997, 81-98 and references therein; E. L. Eliel and S. H. Wilen, in "Stereochemistry of Organic Compound", John Wiley & Sons, Inc, 1999, 297-464 and references therein).

The process of resolution comprises of dissolving the racemic mixture (of formulae I, II, III or IV) in suitable solvent and addition of a suitable chiral reagent. Optionally the medium may contain water about < 5 %. Suitable solvent is selected on the basis whether the diastereomeric salt precipitates out differently. The separation of diastereomeric salt may result either spontaneously or by addition of co-solvent or salting out or evaporation of the solvent or addition of a cosolvent. Alternatively, the separation may result simply by stirring at a suitable temperature in a solvent(s) until one of the salts preferentially precipitate out. Purification of diastereomeric salt is possible by refluxing in a suitable solvent. The free base is liberated from its salt using a suitable base reagent. The diastereomeric salt is dissolved or suspended in a mixture of water and organic solvent and is neutralized with a base under stirring. The free base is obtained after separation of aqueous layer and evaporation of the organic solvent.

The solvents used during the resolution can include solvents or mixtures thereof such as (C₁-C₄) alcohol, (C₁-C₄)ketone, dimethylformamide, ethyl acetate, methyl acetate, methyl ethyl ketone, acetonitrile, propionitrile, THF, dioxane and the like; the solvent used optionally may contain water up to 5 %, but presence of water or its amount is not critical. Suitable temperature range for the resolution includes temperature from 0 °C to reflux temperature of the solvent used, preferably 0 °C to 80 °C. The acid chiral reagents, which can be used to form a diastereomeric salt, include tartaric acid, mandelic acid, lactic acid, camphorsulfonic acid, lactic acid, maleic acid, amino acids and the like.

By repeated crystallization from a suitable solvent, the precipitated salt is enriched in the salt of dextrorotatory isomer of the desired diastereomer to yield a product of constant optical rotation.

Suitable base reagent for the hydrolysis of diastereomeric salt includes sodium carbonate, potassium carbonate, sodium hydrogen carbonate and potassium hydrogen carbonate in aqueous media at temperatures varying between 5 °C to 25 °C.

Finally, the desired salt of compound of formula (II), (III), or (IV); or pharmaceutically acceptable salt of compound of formula (I) can be formed from the corresponding stereoisomer and a suitable acid. The optically pure (*S*)-(+)- compound of formula (I), is converted into its bisulfate salt using sulfuric acid 70 % to 98 %, in an appropriate solvent at suitable temperature to afford (+)- Clopidogrel bisulfate, polymorph I as desired.

Alternatively, the diastereomers formed may be separated by conventional methods of purification such as fractional crystallization, column chromatography and the like followed by cleavage of salt to give product of desired stereochemistry. It is preferable to use, such a chiral agent, which can selectively form diastereoisomer with either R or S stereoisomer of intermediate I, II, III or IV. The chiral reagent used may be in 0.5 to 1.1 molar ratio.

Determination of the enantiomeric purity of the (+)-dextrorotatory and (-)-laevorotatory enantiomers may be carried through proton NMR spectroscopy with the addition of a chiral rare earth reagents (shift reagents) or by HPLC using a chiral stationary phase as well as through measurement of optical rotation.

The absolute stereochemistry of the diastereomeric salt of II, III or IV compounds may be determined using conventional methods, such as X-ray crystallography. The absolute stereochemistry of chiral compounds can also be determined by comparing it with the reference standards known in literature.

The pharmaceutically acceptable mineral and organic acid salts of optically active enantiomers of Clopidogrel are prepared using various acidic salts, which forms a part of this invention but are not limited to hydrogen sulfates, hydrohalides, taurocholates and the like.

More specifically the present process of invention results in Clopidogrel bisulfate of melting point 184 ± 3 °C, which is characteristic of Clopidogrel bisulfate form I. Alternatively, Clopidogrel bisulfate form II can also be prepared by known method (WO 99/65915, FR 98 07464).

The process of this invention also includes the process to recycle the unwanted stereoisomer through racemization. The conditions for racemization of all the intermediates of general formula II, III or IV as well as final product I, involves the similar solvent and catalyst in equimolar quantities. Suitable catalyst is generally a base such as LDA (Lithium diisopropylamide), KOH, NaOH, $K^+ - t\text{-BuO}^-$, NaOMe, NaH, KH and the like. Suitable

solvent used during the resolution can include solvents or mixtures thereof such as (C₁-C₄) alcohol, (C₁-C₄)ketone, ethyl acetate, methyl acetate, methyl ethyl ketone, THF, dioxane and the like; the solvent used optionally may contain water up to 5 %. Suitable temperature range for the resolution includes temperature from 0 °C to reflux temperature of the solvent used, preferably 0 ° to 80 °C.

The process described in the present invention is demonstrated in the examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation to the scope of the invention.

EXAMPLE 1

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

To a solution of 8.98 g (86.33 mmole) sodium bisulfite in water (27 mL), o-chlorobenzaldehyde 12.4 g (86.33 mmole) was added resulting in a white precipitate. To the precipitate, 15 g (0.107 moles) of 6,7-dihydro-4H-thieno[3,2-c]pyridine was added, followed by addition of 4.4 g (89.7 mmoles) NaCN (dissolved in 15 mL water). The reaction mixture was heated at 40 - 50 °C for 6 hrs and was quenched by pouring in water (50 mL). The mixture was extracted with 2 x 100 mL of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The yield of the title product is 24 g (97 %).

The product obtained was characterized using IR spectrum, Mass, ¹³C-NMR and ¹H-NMR, which are as given below :

IR spectrum (cm⁻¹) : 2227 (w, CN group)

Mass spectrum (m/z) : 289.1 (M+H)⁺

¹³C-NMR (CDCl₃) : δ 136.46, 132.78, 132.38, 130.69, 130.46, 130.38, 129.90, 126.73, 124.96, 123.01, 115.09, 59.12, 49.30, 47.66, 25.47.

¹H-NMR (CDCl₃) : δ 7.2-7.7 (4H, m), 7.0 (1H, d), 6.69 (1H, d), 5.32 (1H, s), 3.78 (1H, d), 3.65 (1H, d), 2.8-3.0 (4H, m).

EXAMPLE - 2

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

140.5 g (1 mol) of o-chlorobenzaldehyde and 65 g of (1.01 mol) KCN was added to 3.5 L of methanol. 139.05 g (1 mol) of 6,7-dihydro-4H-thieno[3,2-c]pyridine and 190 mL of glacial acetic acid was added to the reaction mixture, which was heated at 60 °C for 20 hrs with

stirring. After 8 hrs, precipitate begins to appear and then the reaction mixture was poured in water and extracted with (2 x 25 mL) ethyl acetate. The solvent was removed under reduced pressure and the residue purified as described in Example 1. The yield of product was 187 g (65 %), having melting point = 123 -124 °C.

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 1.

EXAMPLE-3

(±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetonitrile (IV)

27.6 g (266 mmol) of sodium bisulfite was dissolved in 100 mL water, and 38.2 g (271 mmol) o-chlorobenzaldehyde was added after dissolving in 100 mL methanol. A thick white slurry results, which was heated at 60 °C for 1 hour, followed by addition of, 36.97 g (266 mmol) of 6,7-dihydro-4*H*-thieno[3,2-*c*]pyridine at 40 °C and was stirred for 2 hrs. To this reaction, 17.29 g (266 mmol) of KCN dissolved in 50 mL water was added carefully and heating was continued at 40 °C for 5 - 6 hrs, giving white precipitate. The reaction mixture was worked as described in Example 1 and the yield obtained was 54.6 g (72 %).

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found out to be identical to the product obtained in example 1.

EXAMPLE -4

(±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetonitrile (IV)

4.5 g (25.64 mmol) 6,7-dihydro-4*H*-thieno[3,2-*c*]-5-pyridinium hydrochloride was added (at 10 °C) to solution of potassium cyanide 1.95 g (30 mmol) in 2 mL of ice-cold water, and was followed by dropwise addition of 5 mL concentrated hydrochloric acid at 0 °C. After addition of HCl, 3.3 g (23.47 mmol) o-chlorobenzaldehyde dissolved in 50 mL methanol, was added dropwise. Later the reaction mixture was kept at room temperature for 3 days and afterwards at 50 °C for 3 hrs. The pH was adjusted to 7.5 - 8.0 by dropwise addition of NH₄OH and the product was extracted with ethyl acetate (2 x 50 mL). The solvent was dried over sodium sulfate and evaporated under reduced pressure. The amount of product obtained was 1.67 g (18 %) with melting point = 122 -124 °C.

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 1.

EXAMPLE 5

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

6.25 g (44.46 mmol) o-chlorobenzaldehyde was dissolved in 60 mL of toluene. To the same flask, 10 mL glacial acetic acid and 1.24 g (4.343 mmol) cyclo[(S)-histidine-(S)-phenyl alanine] were added, and the temperature was lowered to -25 °C. This was followed by addition of 7 g (50.35 mmol) 6,7-dihydro-4H-thieno[3,2-c]pyridine and the reaction flask was purged with HCN gas (at the rate of 30 bubbles/min) at -25 °C for 6 hrs and later was stirred at 31 °C for 2 days. The solvent was removed under vacuum, the residue was purified as mentioned in example 1. The amount of product obtained was 5.5 g (43 %) with melting point = 124 -125 °C.

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 1.

EXAMPLE 6

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

As described in Example 5, the adduct was formed between 104.3 g (1 mol) sodium bisulfite and 144.39 g (1.02 mol) o-chlorobenzaldehyde, to which 150 g (1.078 mol) 6,7-dihydro-4H-thieno[3,2-c]pyridine was added at 31 °C to and stirred for 1 hr. 102 g TMS-CN was added dropwise and temperature was maintained at 31 °C for 6 hrs, resulting in a white product, which was isolated and purified according to the procedure in example 1. The yield obtained was 30 g (10 %) having melting point about 123-124 °C.

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 1.

EXAMPLE 7

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

To 19.5 g (250 mmol) KCN dissolved in water (20 mL) and 43 g (250 mmol) 6,7-dihydro-4H-thieno[3,2-c]pyridine was added, followed by dropwise addition of 50 ml concentrated hydrochloric acid. After the addition was complete, a solution of 33 g (230 mmol) o-chlorobenzaldehyde in 100 mL methanol was added dropwise and stirred for 8 hrs at 31 °C. The pH of the reaction mixture was adjusted to 7.5 - 8.0 using NH₄OH and the product was extracted with ethyl acetate (2 x 500 mL) and washed with water (2 x 500 mL), brine (500 mL) and was dried over sodium sulfate. The solvent was evaporated under reduced pressure to give of 50 g (74 %) the product with melting point of about 123-125 °C.

The product obtained was characterized using IR spectrum, Mass, ^{13}C -NMR and ^1H -NMR and was found to be identical to the product obtained in example 1.

EXAMPLE 8

5 (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

To the solution of 35.5 g (342 mmol) sodium bisulfite in 35 mL water, 49.1 g (349 mmol) of o-chloro benzaldehyde was added dropwise, whereupon solid adduct forms instantaneously. To this 50 g (284.9 mmol) 6,7-dihydro-4H-thieno[3,2-c]pyridine hydrochloride was added and refluxed for 5 hrs. The usual workup and purification gave 40 g
10 (40 %) of the product.

The product obtained was characterized using IR spectrum, Mass, ^{13}C -NMR and ^1H -NMR. The product obtained was found to be identical to the product obtained in example 1.

EXAMPLE 9

15 (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

123.83 g (880 mmol) o-chlorobenzaldehyde and 44 g (897 mmol) sodium cyanide were added to in 100 mL of methanol and water (1:1) mixture. To this 150 g (1070 mmol) 6,7-dihydro-4H-thieno[3,2-c]pyridine was added, followed by the addition of 10 mL concentrated hydrochloric acid and was stirred for 2 days at 31 °C temperature. The pH of reaction mixture
20 was adjusted to 7.5 - 8.0 using NH_4OH . The product was extracted with ethyl acetate (2 x 50 mL) and washed with water (2 x 50 mL), brine (50 mL) and was dried over sodium sulfate, and isolated as given in Example 1. The amount of white solid product obtained was 33 g (13 %), which was characterized as usual.

EXAMPLE 10

25 (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

48 g (0.166 mol) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile was suspended in 240 ml *t*-BuOH, and add 18.26 g (0.332 mol) of KOH was added in one lot with stirring. The reaction mixture was refluxed at 80 - 82 °C for 3 hr., then
30 cooled to 30 °C, 240 mL of water was added and stirred for 20 min. The lower aqueous layer was separated and fresh 720 mL chilled water (5 - 10 °C) was added slowly in 15 min. The product was extracted with ethyl acetate (2 x 50 mL) and washed with water (2 x 50 mL), brine (50 mL) and it was dried over sodium sulfate, followed by isolation by evaporating the

solvent under reduced pressure. On treatment with hexane solid was obtained. The yield of product was 48 g (94 %).

The product obtained was characterized using IR spectrum, Mass, ^{13}C -NMR and ^1H -NMR, which are as given below;

5 IR spectrum (cm^{-1}) : 1656 (s, C=O group), 2333.7 (N-H)

Mass spectrum (m/z) : 307.2 (M+H) $^{+}$

^{13}C -NMR (CDCl_3) : δ 173.82, 135.32, 133.42, 133, 130.27, 129.99, 129.4, 126.98, 125.18, 122.98, 69.12, 50.77, 49.10, 25.82.

^1H -NMR (CDCl_3) : δ 7.4 - 7.5 (4H, m), 7.24 (1H, d), 7.0 (1H, s), 6.66 (1H, d), 6.0 (1H, s), 4.88 (1H, d), 3.61 (2H, q), 2.88 (4H, m).

10 Melting point : 125 - 127 $^{\circ}\text{C}$

EXAMPLE 11

($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

15 100 mg (0.3466 mmole) ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile of formula (IV) prepared according to Example 1-9, was dissolved in the 5 mL HCl and 1 mL trifluoroacetic acid and 5 mL *t*-butanol was added and refluxed for 4 hrs. After the reaction was complete, the product was isolated as mentioned in example 11. The yield of the product was 40 mg (38 %).

20 The product obtained was characterized using IR spectrum, Mass, ^{13}C -NMR and ^1H -NMR and was found to be identical to the product obtained in example 10.

EXAMPLE 12

($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

25 In 100 mg (0.346 mmole) ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile of formula (IV) (prepared according to Example 1 to 9, 5 mL formic acid and 5 mL concentrated hydrochloric acid was added and the reaction mixture was stirred for 48 hrs at 25-30 $^{\circ}\text{C}$, and later refluxed at approx. 100 $^{\circ}\text{C}$ for 6 hrs and was stirred for 8 days at 25-30 $^{\circ}\text{C}$. After completion of reaction, the reaction mixture was worked up as mentioned in Example 10. The yield of the product was 50 mg (47 %).

30 The product obtained was characterized using IR spectrum, Mass, ^{13}C -NMR and ^1H -NMR. The product obtained was identical to the product obtained in example 10.

EXAMPLE 13

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

200 mg (0.694 mmole) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile of formula (IV) prepared according to Example 1-9, was added to 5 ml HBr and 5 ml H₂O and was stirred for 72 hrs at room temperature. The reaction mixture was then
5 refluxed for 11 hrs at 100 °C and the product was isolated as mentioned in example 10. The yield of the product was 50 mg (47 %).

The product was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 10.

10 EXAMPLE 14

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

1 g (3.47 mmole) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile, was dissolved in 5 mL H₂SO₄(50 %). To the reaction mixture 0.405 g anhydrous NaCl was added and reflux the reaction at for 2-3 hrs. At the end of reaction, the
15 product was isolated as described in Example 10. The yield of the product was 600 mg (57 %).

The product was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 10.

20 EXAMPLE 15

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

1 g (3.47 mmole) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile was dissolved in the 5 g (5 mmol) HClO₄ and 10 mL H₂O was added to the reaction mixture. The reaction mixture was refluxed at 105 °C for 7 hrs and later stirred at
25 room temperature for 12 hrs. The pH was raised until 10-12, using 10 %w/v NaOH solution and later extracted with 50 mL dichloromethane. The organic layer was isolated, and washed with water and evaporated under reduced pressure. The residue was treated with hexane to give 50 mg (47 % yield) solid, having melting point 125-127 °C.

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 10.
30

EXAMPLE 16

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

1 g (3.47 mmol) of (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile was suspended in 10 mL *t*-BuOH, and 277 mg (6.925 mmol) crushed NaOH was dumped under stirring. The reaction mixture was refluxed at 80 - 82 °C for 4 hrs, followed by cooling to room temperature. The product was isolated by extraction with ethyl acetate. The organic extract was evaporated, and oily material left behind upon hexane treatment yields 400 mg solid (38 %).

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 10.

EXAMPLE 17

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

3 g (0.01 mol) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile was suspended in 50 mL acetone. To this solution 1 g (0.023 mol) NaOH dissolved in 10 mL water was added, followed by 5 mL H₂O₂ (0.05 mol, 30 % w/v) in one lot and was refluxed for 3 hrs. The reaction mixture was cooled to room temperature and 5 mL H₂O₂ (0.05 mol, 30 % w/v) was added again and stirred for 12 hrs. The product was isolated by addition of excess water and extracted with 1 L ethyl acetate. The organic extract was evaporated to give 2.8 g crude oily material, which after treatment with hexane, yields 1 g solid (31 %).

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 10.

EXAMPLE 18

(±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

To 10 g (0.0346 mol) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile suspended in 30 ml isopropyl alcohol, 3.9 g (0.0589 mol) crushed KOH (85 %) was added slowly and the mixture was warmed, and 120 ml water was added. The pH of aqueous layer was brought to 7 using dilute hydrochloric acid. The white solid precipitate was filtered and washed with 100 mL water. The yield of product was 9 g (85 %) with melting point : 122 °C.

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR and was found to be identical to the product obtained in example 10.

EXAMPLE 19

(±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide hydrogen sulfate salt (II)

2 g (6.48 mmole) of (±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide of formula (IV), was dissolved in 10 mL acetone. To the reaction mixture 1 mL of sulfuric acid was added and was stirred for 0.5 hr. Later 5 mL of diethyl ether was added and stirred overnight at room temperature to obtain a salt. The salt 2 g (76 %) was isolated by filtration and washed with acetone.

Melting point : 199.1 °C

IR spectrum : 1682.8, 3116 (cm⁻¹).

EXAMPLE 20

(±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetic acid (III)

To 100 mg (0.3466 mmole) (±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl) acetonitrile was dissolved in 2 mL *t*-butanol and add 1.5 mL HCl was added. The reaction mixture was refluxed for 9 hrs at 100 °C. In the end, after the completion of reaction, water was added and pH was brought to 4 with 10 % KOH solution. The product was extracted with 5 mL dichloromethane and proceeded as given in the earlier example. The yield was 40 mg (38 %).

The product obtained was characterized using IR spectrum, Mass, ¹³C -NMR and ¹H-NMR, which are as given below;

IR spectrum (cm⁻¹) : 1637.5 (s, C=O group), 3399.3 (O-H)

Mass peaks (m/z) : 308.1 (M+H)⁺

¹H-NMR (δ ppm) : δ 7.22 - 7.89 (4H, m), δ 7.11 - 7.12 (1H, d), δ 6.61 - 6.63 (1H, d), δ 3.57 - 3.67, (2H, d), δ 4.13 (2H, s), δ 3.32 - 3.42 (2H, s).

EXAMPLE 21

(±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetic acid (III)

5 g (17.33 mmole) (±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetonitrile was added to 100 mL HCl and the mixture was stirred for 2 days and later refluxed for 15 hrs. in the end the reaction mixture was dumped in water, and the pH was raised to 4 using 10 % KOH. The product was extracted with 2 L dichloromethane, washed with water, and the organic layer was evaporated to obtain the residue. Usual purification of the residue gave 2 g of solid (38 %).

The product obtained was characterized using IR spectrum, Mass, ^{13}C -NMR and ^1H -NMR. The product obtained was found identical to the product obtained in example 20.

EXAMPLE 22

5 (±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate (I)

Mix 10 g (32.62 mmole) (±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide (prepared according to example 15), with 19.8 g (161.7 mmole) DMFDMA (Dimethyl formamide dimethylacetal) in 100 mL methanol. The mixture was refluxed at 70 °C for 14 hr. Later the reaction mixture was quenched in water and extracted with ethyl acetate. The organic extract was evaporated under reduced pressure to give 5 g of oily product (48 %). This oil was used without any further treatment to prepare salts of ester (I).

EXAMPLE 23

15 (±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate (I)

15 g (0.0490 mol) of (±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide, was dissolved in 105 mL methanol, with stirring. To the above solution, 45 mL (0.823 mol) of concentrated sulfuric acid (98 %) was added dropwise at room temperature and over a period of 1.5 hour. Later the reaction mixture was refluxed at 80 °C for 26 hour, followed by distillation of methanol. To the residue left behind, 200 mL ethyl acetate was added at temperature between 0 °C to 5 °C along with stirring. After the addition 99 g (1.764 mol) KOH dissolved in 300 mL water was added to the reaction and was stirred for 0.5 hour. Finally, the reaction mixture was filtered and allowed to stand. The organic layer was isolated and dried over anhy. Na_2SO_4 . The solvent was evaporated to obtain oily product. Yield was 10 g (64 %).

EXAMPLE 24

25 (±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate hydrogen sulfate salt (I)

10 g of (±) Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate prepared according to Example 22, was dissolved in 100 mL of ice-cold acetone and 2 mL concentrated sulfuric acid was added at 0 °C to 5 °C. The crystalline white to off white product formed was isolated by filtration and washed with 20 mL of acetone. The product obtained was dried in vacuum oven at 50 °C. The yield of titled product was 7.2 g (56 %).

EXAMPLE 25

(±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate (I)

2 g (0.00652 mol) (±) (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide and 2 mL (0.0308 mol) methane sulfonic acid and 20 mL methanol were mixed and the solution was refluxed at 85 °C for 12 hrs. The excess of solvent was removed under reduced pressure. The pH was adjusted to about 9 with aq. solution of sodium bicarbonate at 0 °C, and the product was extracted with 70 mL ethyl acetate. The combined organic extracts were dried over anhy. Na₂SO₄ and concentrated. The residue obtained was purified by column chromatography using hexane : ethyl acetate as eluent. The product thus obtained was concentrated, was stored under nitrogen atmosphere, and kept in refrigerator before converting into salt. The yield of titled product was 0.419 g (20 %).

EXAMPLE 26

(±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate (I)

1 g (0.00326 mol) (±) (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide was dissolved in 20 mL methanol and refluxed at 85 °C. During the reflux 10 mL polyphosphoric acid was added dropwise over a period of 1 hr and refluxing was continued for 6 hour. The excess of solvent was removed under reduced pressure. To the residue, 50 mL ethyl acetate was added at 0 °C and the reaction mixture was made basic with aq. NaHCO₃, upto pH 9. Out of the two phases separated, the organic layer was isolated, dried over anhydrous Na₂SO₄ and concentrated. The residue obtained was purified by column chromatography using hexane:ethyl acetate (9:1) as eluent. The product obtained was stored under nitrogen atmosphere and kept in refrigerator before converting into salt. The yield of titled product was 310 mg (30 %).

EXAMPLE 27

(±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate (I)

1 g (0.00326 mol) (±) (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide was added to 2 mL toluene at 0 °C along with stirring, followed by dropwise addition of 1 mL titanium tetrachloride, and the reaction was stirred at 0 °C for 1 hour. Later 18 mL of methanol was added, and then the reaction was stirred for 36 hour at 29 °C and later reflux for 3 hrs. The solvent was distilled under reduced pressure and the residue was added to aq. sodium carbonate at 0 °C. the product was extracted with 20 mL ethyl acetate, and the organic layer was isolated, dried over anhy. Na₂SO₄, concentrated and purified by column

chromatography using hexane : ethyl acetate as eluent. The product obtained was stored under nitrogen atmosphere and kept in refrigerator before converting into salt. The yield of titled product was 0.157 g (12-15 %).

EXAMPLE 28

(±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

To 5 g (16.31 mmol) (±) (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide, 25 mL POCl₃ was added under stirring. The contents were refluxed until amide was completely consumed (approx. 4 hr). Afterwards 20 mL methanol and 5 mL concentrated H₂SO₄ were added and stirred at room temperature for 1 hour. Later the reaction mixture was refluxed for 1 hour. The reaction mixture was quenched with aq. Na₂CO₃ at 0 °C, and extracted with 200 mL ethyl acetate. The organic layer was isolated, dried over anhy. Na₂SO₄, concentrated and purified by column chromatography using hexane : ethyl acetate as eluent. The product obtained was stored under nitrogen atmosphere and kept in refrigerator before converting into salt. The yield of titled product was 0.943 g (18%).

EXAMPLE 29

(±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

1 g (0.00326 mol) (±) (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was dissolved in 10 mL methanol. The reaction mixture was saturated with HCl (g) at 0 °C, was stirred at room temperature for 4 hrs, and later was refluxed for 6 hrs. The solvent was removed under reduced pressure. To the residue, 10 mL of ethyl acetate and aqueous NaHCO₃ until pH was 9 (at 0 °C) were added. The organic layer was isolated, dried over anhy. Na₂SO₄, evaporated under reduced pressure. The residue was further purified by column chromatography using hexane : ethyl acetate as eluent. The product obtained was stored under nitrogen atmosphere and kept in refrigerator before converting into salt. The yield of titled product was 0.188 g (18 %).

EXAMPLE 30

(±)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

To 1 g (0.00326 mol) (±) (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide, 3 g (24.2 mmole) DMFDMA (dimethyl formamide dimethyl acetal) and 10 mL methanol were added. The reaction mixture was refluxed at 70 °C for 14 hr, and then poured in water and extracted with ethyl acetate. The combined organic layers are dried over anhy.

Na₂SO₄, evaporated under reduced pressure. The residue was further purified by column chromatography using hexane : ethyl acetate (9:1) as eluent. The yield of titled product was 500 mg (48 %).

EXAMPLE 31

(S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide (II)

a) A solution of 5 g (16.31 mmol) of (±)-(2-chloro-phenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide (prepared as given in Examples 10-15) and 4.15 g (16.2 mmol) (1*S*)-(+)-camphor-10-sulphonic acid monohydrate in 100 mL acetone was stirred at room temperature for 20 h. Subsequently it was kept for 1 week in a freezer. Few crystals appeared concentration of volume by evaporating solvent under reduced pressure and repeated recrystallization in freezer for few days gave 3.3 g (75 % yield) of *(S)*-2-(2-chloro-phenyl)-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyrid-5-yl)acetamide (+)-camphor sulfonic acid salt. The salt was further purified by recrystallization in acetone, until constant specific optical rotation was obtained.

The product obtained was dried suitably. The typical physicochemical characteristics of the product obtained are as follows,

Melting range : 223-225 °C (dec.)

SOR : + 51 ° (C = 1, MeOH)

b) 3.3 g *(S)*-(+)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide 10-*D*-camphor sulfonic acid salt was added to 20 mL saturated aqueous Na₂CO₃ solution and the product was extracted with 20 mL ethyl acetate. The organic layer was isolated, dried over Na₂SO₄ and concentrated under reduced pressure. The product was obtained crude oil, which upon purification gives, 1.6 g of white crystals (64 %).

The product obtained was characterized by different physico-chemical characteristics including IR spectrum, Mass, ¹³C-NMR and ¹H-NMR, which are as given below;

Melting point : 153 - 154 °C

SOR : + 41°(C = 1, MeOH)

Optical purity : 99.5 % by chiral HPLC column.

IR spectrum (cm⁻¹) : 1656 (s, C=O group), 2333.7 (m, C-N), 3357.9 (s, N-H str).

Mass peaks (m/z) : 307.2 (M+H)⁺

¹³C-NMR (CDCl₃) : δ 173.25, 134.84, 132.87, 132.65, 129.98, 129.56, 129.0, 126.72, 124.87, 122.64, 68.65, 50.43, 48.73, 25.28.

¹H-NMR (CDCl₃) : δ 7.4 - 7.5 (4H, m), 7.07 (1H, d), 7.06 (1H, d), 6.66 (1H, d), 6.5 (1H, s), 4.9 (1H, s), 3.6 (2H, q), 2.88 (4H, m).

HPLC purity : 99.85 %

5

EXAMPLE 32

(S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

- a) 2 g (6.5 mmol) of (±)-(2-chloro-phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was added to 30 mL acetone. 0.82 g (3.28 mmol) (1S)-(+)-camphor-10-sulfonic acid monohydrate in 10 mL acetone was added to above solution at 15 - 20 °C in 4 hrs. The reaction mixture was stirred for another 5 min, where a few crystals were formed. The solvent was distilled under reduced pressure and then the reaction mixture was kept in cold condition at temperature below 8 °C. The precipitate formed was filtered and washed with solvent. The yield of titled product was 1.2 g (60 %) with melting range = 223-225 °C and [α]_D = + 51° (C=1, CH₃OH).
- b) To the suspension of 1.1 g of (+)-(S)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (1S)-(+)-camphor-10-sulfonic acid salt in 50 mL water, 50 mL of saturated Na₂CO₃ solution in water was added. The reaction mixture was stirred for some time, and was followed by addition of 100 mL ethyl acetate. The organic layer was isolated, and distilled to get the title product. The amount of product obtained was 600 mg (60 %, based upon the dextroisomer present in the racemic mixture).

The product obtained was characterized by different physico-chemical characteristics, which are as given below;

Melting range : 149 - 153 °C

[α]_D : + 38° (C=1, CH₃OH) with % ee = 97.24 %.

25

EXAMPLE 33

(S)-(+)-(2-chloro-phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

- a) 5 g (16.3 mmol) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was added to 60 mL ethyl acetate. 2 g (8.6 mmol) of (1S)-(+)-camphor-10-sulfonic acid monohydrate was dissolved in minimum amount of water and added to the above solution in one lot, and stirred at 35 - 40 °C for 1 hr. In short time salt forms and was isolated, washed with 50 mL acetone and dried. The amount of product obtained was 1.81 g (36 %).

The product obtained was characterized by different physico-chemical characteristics, which are as given below;

Melting range : 145-149 °C.

$[\alpha]_D$ acetamide: -36.49° (C=1, CH₃OH)

EXAMPLE 35

5 **(S)-(+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate bisulfate (I)**

15 g of (+) (S)-(2-chloro-phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (0.0489 mol), was converted into corresponding ester as given in example 23. The ester can be converted into its hydrogen sulfate salt, according to the procedure given in example 24.

10 The amount of product obtained was 7 g (44.5 %), with melting point = 184 - 185 °C.

The melting point, IR spectrum and XRD of the product obtained resembles that of product obtained in EP 281459 and US 4847265 i.e. now referred as form I polymorph of Clopidogrel bisulfate (WO 99/65915).

15 The product obtained was characterized by different physico-chemical characteristics, as given below;

$[\alpha]_D$: + 55° (C = 1, CH₃OH)

Melting point : 185 °C ± 2°C

IR spectrum : 2980, 1755, 1224, 1175 and 840 respectively with the respective % of percentage

20 ransmittance of approximately: 45; 16; 19; 15; 45.

XRD was found matching with the form I, XRD reported in WO 99/65915.

EXAMPLE 36

25 **(R)-(-)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate bisulfate (I)**

Using 5 g (R)-(-)-(2-chloro-phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide obtained in the above example 34, can be converted into ester as given in Example 23. Later the ester can be converted into hydrogen sulfate salt as given in Example 24. The amount of product obtained was 3.01 g (44 %).

30 The product obtained was characterized by different physico-chemical/purity characteristics, as given below;

$[\alpha]_D$: - 52 ° (C = 1, CH₃OH)

EXAMPLE 37

(S)-(+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl) acetate bisulfate (I)

a) 10 g (0.0185 mol) (1S)-(+)-camphor-10-sulfonic acid salt of (+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was dissolved in 40 ml methanol at 0 °C. To the solution 15 mL (0.28 mol) of conc. H₂SO₄ was added dropwise within 1.5 hr. Gradually the reaction temperature was increased, and it was refluxed for 26 hrs. In the end, the solvent was distilled off under reduced pressure. The residue left behind was mixed with 120 mL of ethyl acetate and the pH was adjusted between 9 to 10 using aq. sodium carbonate for extraction. The organic layer was isolated, dried over anhydrous Na₂SO₄, and evaporated under vacuum. The product obtained was purified by column chromatography using hexane : ethyl acetate (9:1) as eluent. The combined eluent was evaporated at reduced pressure to yield 5.76 g (97 %) of product.

b) 2 g (S)-(+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate was converted into bisulfate salt according to the procedure given in Example 24. The product obtained was 2.2 g (84 %) of product and found identical to that obtained in example 35.

EXAMPLE 38

Polymorph I of (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl) acetate bisulfate salt (I)

52.5 mL of ice-cold acetone was added to 17.5 g (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate while stirring at 0 °C. 3.6 mL of concentrated H₂SO₄ was added dropwise and temperature was kept below 5 °C. 20 mL of acetone was further added and reaction mixture was further stirred for 4 hrs at room temperature. Precipitate was isolated (17 g, 74 %), dried under vacuum at temperature not exceeding 50 °C.

The product obtained was characterized by different physico-chemical characteristics and was found identical to that obtained in example 35, as given below;

Specific optical rotation : + 54° (C = 1, CH₃OH)

Melting point : 185 °C ± 2°C

IR and XRD were found matching to that reported in the literature.

EXAMPLE 39

Polymorph I of (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate bisulfate salt (I)

2.1 g (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate was added 7.6 mL of acetone to obtain a clear solution. To this solution, 0.887 g of H₂SO₄ (80 %) was added slowly and temperature was maintained around 20 °C under nitrogen atmosphere. Later the reaction mixture was cooled upto -20 °C for 2 hrs and then the temperature was brought to room temperature (20 °C). The reaction mixture was stirred at 20 - 25 °C. Precipitate was isolated (600 mg), dried under vacuum at temperature not exceeding 50 °C.

The product obtained was characterized by different physico-chemical characteristics and was found identical to that obtained in example 35, as given below;

SOR (α^D) : + 54.03° (C = 1.89, MeOH)

Melting point : 185 °C $\pm$ 1 °C

Chiral Purity : 99.63 % (ee)

IR and XRD were found matching to that reported in the literature.

EXAMPLE 40

Polymorph I of (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate bisulfate salt (I)

To 2 g (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate was added 5 mL of acetone and stirred at 25-30 °C. The temperature of the reaction mixture was raised from 25 to 65 °C and then kept at 65 °C for 5 min. At temperature 50-52 °C 0.676 g of concentrated H₂SO₄ was added. The reaction mixture was cooled from 52 °C to 5 °C, and additional acetone was added and stirred for 5 min. Later the reaction mixture was stirred at 25 - 30 °C for 12 hrs, the thick precipitate obtained was filtered, washed with 5 mL of acetone and the residue was dried in a vacuum oven. The yield of titled product obtained was 1.27 g (47 %).

The product obtained was characterized by different physico-chemical characteristics and was found identical to that obtained in example 35, as given below;

SOR (α^D) : + 54.03° (C = 1.89, MeOH)

Melting point : 185 °C $\pm$ 1 °C

Chiral Purity : 99.80 % (ee)

IR and XRD were found matching to that reported in the literature.

EXAMPLE 41

Polymorph I of (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate bisulfate salt (I)

To 1.98 g (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate was added 5 mL of acetone and stirred at 25-30 °C. The temperature of the reaction mixture was raised from 25 to 50-52 °C and within one lot 0.7 g of concentrated H₂SO₄ (95 %) was added with constant stirring and the reaction mixture was suddenly cooled to 0 °C to -5 °C for 10 min. Later the reaction mixture was stirred at 25 - 30 °C for 12 hrs, the thick precipitate obtained was filtered, washed with 5mL of acetone and the residue (1.6 g, 62 %) was dried in a vacuum oven.

The product obtained was characterized by different physico-chemical characteristics and was found identical to that obtained in example 35, as given below;

SOR (α^D) : + 55.96° (C = 1.89, MeOH)

Melting point : 185 °C $\pm$ 1 °C

Chiral Purity : 99.85 % (ee)

IR and XRD were found matching to that reported in the literature.

EXAMPLE 42

Racemization of (*R*)-(-)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide (II)

20 g mixture of laevorotatory (*R*)-(-)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide of formula (II) and 11 g of potassium *t*-butoxide in 100 mL of *t*-butanol was stirred at 25 °C to 30 °C for 30 min. After completion of reaction, the reaction mixture was poured in 750 mL cold water to obtain a yellow precipitate. This solid obtained was filtered and dissolved in methylene dichloride. The organic layer was washed with 2 x 100 mL of DM water (2 x 100 mL) and concentrated to give 18 g of the corresponding racemic amide i.e. ($\pm$)-2-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide (II).

The specific optical rotation of racemic amide (II) was $\pm$ 1° (C = 1, CH₃OH).

EXAMPLE 43

Racemization of (*R*)-(-)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide (II)

1 g mixture of laevorotatory (*R*)-(-)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide of formula (II) and 1 g of potassium *t*-butoxide in 20 mL of DMSO was stirred at 50 °C to 60 °C for 3 hours. After completion of reaction, the reaction mixture was poured in 150 mL cold water to obtain a yellow precipitate. This solid obtained was

filtered and dissolved in methylene dichloride. The organic layer was washed with 2 x 25 mL of DM water (2 x 25 mL) and concentrated to give 0.8 g of the corresponding racemic amide i.e. (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide.

The specific optical rotation of racemic amide (II) was $\pm 0.5^\circ$ (C = 1, CH₃OH).

EXAMPLE 44

Racemization of (R)-(-)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

1 g mixture of laevorotatory (R)-(-)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide of formula (II) and 250 mg of sodium hydride in dry tetrahydrofuran was stirred at 25 °C to 30 °C for 3 hours. After completion of reaction, the reaction mixture was poured in 150 mL cold water slowly to obtain a yellow precipitate. This solid obtained was filtered and dissolved in methylene dichloride. The organic layer was washed with 2 x 25 mL of DM water (2 x 25 mL) and concentrated to give 0.95 g of the corresponding racemic amide i.e. (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II).

EXAMPLE 45

Racemization of (R)-(-)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

1 g mixture of laevorotatory (R)-(-)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide of formula (II) and 21 g of potassium *t*-butoxide in 100 mL of DMSO was stirred at 50 °C to 60 °C for 3 hours. After completion of reaction, the reaction mixture was poured in 750 mL cold water to obtain a yellow precipitate. This solid obtained was filtered and dissolved in methylene dichloride. The organic layer was washed with 2 x 100 mL of DM water (2 x 100 mL) and concentrated to give 0.8 g of the corresponding racemic amide i.e. (±)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide.

EXAMPLE 46

(S)-(+)-Methyl 2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

5 g of (+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was dissolved in 35 ml methanol and the solution was chilled to 0 to -5 °C. 15 mL (0.28 mole) of conc. H₂SO₄ (98 %) was added slowly in 1 hr maintaining the temperature till -5 °C. After the completion of addition the reaction mixture was stirred at room temperature for 30 min.

The solution was refluxed at 60 °C for 36 hrs. The reaction mixture was cooled to room temperature and the solvent was distilled off under reduced pressure. The residue was added to 200 mL chilled water was added and cooled to -5 °C. The pH of reaction mixture was adjusted between 9 to 10 using aq. sodium carbonate. The residue was extracted with 100 mL ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, and evaporated under vacuum. The combined eluent was evaporated at reduced pressure to yield 3.2 g of purified product purified by column chromatography, using hexane : ethyl acetate (9:1) as eluent.

EXAMPLE 47

(S)-(+)- Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

5 g of (+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was dissolved in 45 ml methanol, followed by 15 mL of toluene. 5 mL (0.28 mol) of conc. H₂SO₄ was instantly added and another 10 mL of conc. H₂SO₄ was slowly added later, while maintaining the temperature at 90 °C. After that, the reaction mixture was refluxed at 90 °C for 13 hrs. The solvent was distilled off under reduced pressure. To the residue, 50 mL of water was added and the pH of reaction mixture was adjusted between 9 to 10 using aq. sodium carbonate. The residue was extracted with 100 mL ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, and evaporated under vacuum. The combined eluent was evaporated at reduced pressure to yield 2.8 g of crude product purified by column chromatography, using hexane : ethyl acetate (9:1) as eluent.

EXAMPLE 48

(S)-(+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

5 g of (S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was dissolved in 50 ml methanol and the solution was cooled till -15 °C. 15 mL (0.28 mol) of conc. H₂SO₄ (98 %) was added dropwise in 1 hr maintaining the temperature till -15 °C. After the completion of addition the reaction mixture was gradually increased, and stirred at 31 °C for 30 min, and then refluxed at 70 °C for 21 hrs. The solvent was distilled off under reduced pressure and to the residue 50 mL of water was added and stirred for 30 min followed by cooling to -5 °C. The pH of reaction mixture was adjusted between 9 to 10 using aq. sodium carbonate. The residue was extracted with 100 mL ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, and evaporated under vacuum. The yield was 3.8 g of crude product purified by column, using hexane : ethyl acetate (9:1) as eluent.

EXAMPLE 49

(S)-(+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

5 g of (+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide was dissolved in 20 ml methanol and the solution warmed to 65 to 70 °C. 15 mL (0.28 mol) of chilled conc. H₂SO₄ (98 %, -15 °C) was added slowly in 1 hr maintaining the temperature till -15 °C. After the completion of addition the reaction mixture was heated at 70 °C for 16 hrs.

- 5 The solvent was distilled off under reduced pressure and to the residue 50 mL of water was added and stirred for 30 min followed by cooling to -5 °C. The pH of reaction mixture was adjusted between 9 to 10 using aq. sodium carbonate. The residue was extracted with 100 mL ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, and evaporated under vacuum. The combined eluent was evaporated at reduced pressure to yield 2.8 g of crude product purified by column chromatography, using hexane : ethyl acetate (9:1) as eluent to give 2 g of the titled compound (I) and 1 g of the starting material (S)-(+)- (II).

EXAMPLE 50

(S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (II)

- a) A solution of 5 g (16.31 mmol) of (±)-(2-chloro-phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl) acetamide (prepared as given in Examples 10-15) and 4.15 g (16.2 mmol) (1S) (+)-camphor-10-sulphonic acid monohydrate in 100 mL acetone was kept warm for 20 hrs followed by storing it in temperature below 10 °C. A few crystals appeared, the mother liquor was concentrated further and repeated recrystallization, followed by storage in cold condition for few days gave 3.1 g (70 % yield) of (S)-2-(2-chloro-phenyl)-(4,5,6,7-tetrahydrothieno[3,2-c]pyrid-5-yl)acetamide (+)-camphor sulfonic acid salt. The salt was further purified by recrystallization in acetone, until constant specific optical rotation was obtained.

The product obtained was dried suitably. The typical physicochemical characteristics of the product obtained are as follows:

- 25 Melting range : 223-225 °C (dec.)

SOR : + 52° (C = 1, MeOH)

- b) 3.1 g (S)-(+)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide 10-D-camphor sulfonic acid salt was added to 20 mL saturated Na₂CO₃ solution and the product was extracted with 20 mL ethyl acetate. The organic layer was isolated, dried over Na₂SO₄ and concentrated under reduced pressure. The product was obtained crude oil, which upon purification gives, 1.5 g of white crystals (60 %).

EXAMPLE 51

Chiral removal of (-)-stereoisomer from a mixture containing excess of (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

2 g (0.0173 mole) Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (where ee was 80 %) was dissolved in 10 ml acetone and the reaction mixture was stirred for 10 min, followed by reflux. To the reaction mixture, 1.49 g (1S)-(+)-camphor-10-sulfonic acid hydrate in 0.8 mL water was added followed by 1 mL acetone. Then whole reaction mixture was refluxed for 1 hrs and cooled gradually. This was later stirred overnight at room temperature. The clear solution was cooled further at 0 to -5 °C, wherein precipitate was obtained. The salt formed was added to ethyl acetate and water, which was later basified with NaHCO₃, the organic layer was washed with water, concentrated under reduced pressure, to give free base 0.386 g with chiral purity = 99.85 % (+)-isomer (ee = 99.7 %).

EXAMPLE 52

Chiral removal of (-)-stereoisomer from a mixture containing excess of (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

2 g (0.0173 mole) Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (where ee was 90 %) was dissolved in 10 ml acetone and the reaction mixture was stirred for 10 min, followed by reflux. To the reaction mixture, 1.49 g (1S)-(+)-camphor-10-sulfonic acid hydrate in 0.8 mL water was added followed by 1 mL acetone. Then whole reaction mixture was refluxed for 1 hrs and cooled gradually. This was later stirred overnight at room temperature. The clear solution was cooled further at 0 to -5 °C, wherein precipitate was obtained. The salt formed was added to ethyl acetate and water, which was later basified with NaHCO₃, the organic layer was washed with water, concentrated under reduced pressure, to give free base 0.386 g with chiral purity = 99.85 % (+)-isomer (ee = 99.7 %).

EXAMPLE 53

Chiral removal of (-)-stereoisomer from a mixture containing excess of (+)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

2 g (0.0173 mole) Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (where ee was 95 %) was dissolved in 10 ml acetone and the reaction mixture was stirred for 10 min, followed by reflux. To the reaction mixture, 1.49 g (1S)-(+)-camphor-10-sulfonic acid hydrate in 0.8 mL water was added followed by 1 mL acetone. Then whole reaction mixture was refluxed for 1 hrs and cooled gradually. This was later stirred overnight at room temperature. The clear solution was cooled further at 0 to -5 °C, wherein precipitate was obtained. The salt formed was added to ethyl acetate and water, which was later basified

with NaHCO_3 , the organic layer was washed with water, concentrated under reduced pressure, to give free base 0.386 g with chiral purity = 99.85 % (+)-isomer (ee = 99.7 %).

EXAMPLE 54

5 Resolution of ($\pm$)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (I)

33 g (0.1 mol) ($\pm$)-Methyl (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate was dissolved in 200 ml acetone and the reaction mixture was heated to 60 to 70 °C, reflux for 15 min. To the reaction mixture, 25.6 g (1*S*)-(+)-camphor-10-sulfonic acid hydrate dissolved in water was added, wherein formation of salt starts at 60 to 70 °C. After 10 the formation of salt was complete, the reaction mixture was cooled gradually to room temperature and then to 0 °C to 5 °C. The isolation of diastereomeric salt by filtration and washed using acetone, and dried. The yield of the diastereomeric product was 20.5 g (70 %).

The generation of (-) isomer of title compound was carried out using dilute sodium 15 bicarbonate solution and extraction in ethyl acetate, removal of solvent and giving us the title compound 10.9 g (66 %).

EXAMPLE 55

20 Resolution of ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (IV)

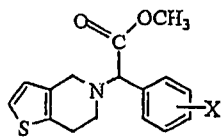
a) To 5 g (0.0173 mol) ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile dissolved in 100 ml acetone, 4.35 g (0.0174 mole) (1*S*)-(+)-camphor-10-sulfonic acid hydrate in 5 mL water was added in one lot at 60 to 62 °C during addition. The mixture is stirred at 60 °C for 60 hr. the stirring was then continued overnight and later kept 25 in refrigerator for 1 day. The diastereomeric salt precipitated was then filtered to yield 730 mg of product.

b) To 730 mg ($\pm$)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (1*S*)-(+)-camphor-10-sulfonic acid salt in 20 mL water, 10 mL (5 %) Na_2CO_3 solution added (pH = 10). After stirring the mixture, 100 mL ethyl acetate was added to it organic layer was 30 then added to it. Organic layer was then separated and distilled off to get product. The yield of product was 400 mg (16 %).

Specific optical rotation(α^D): + 7.5787 ° (C = 1, DMF).

We claim:

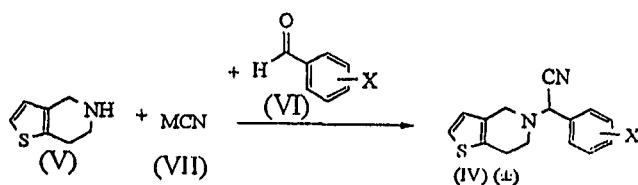
1. A process for the preparation of compound of formula (I),



(I) ($\pm$) or (+) or (-)

- 5 where X represents either hydrogen, fluoro, chloro, bromo or iodo atom, preferably 2-chloro, which comprises:

- i) reacting a compound of formula (V) or its salt,



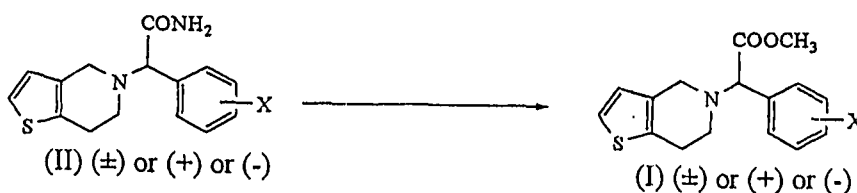
10 with a cyanide of general formula (VII) where M represents alkali metal, trimethylsilyl, Cu, or hydrogen, and followed by addition of compound of general formula (VI), where X is as defined earlier, to obtain a racemic compound of general formula (IV), where X is as defined earlier,

- ii) reacting a compound of general formula (IV), in ($\pm$) form or any of its optically active (+), or (-) forms,



15 with acidic or basic reagents to obtain a compound of formula (II) or its salt with retention of configuration,

- iii) reacting a compound of general formula (II), in either ($\pm$) form or its optically active (+) or (-) forms,



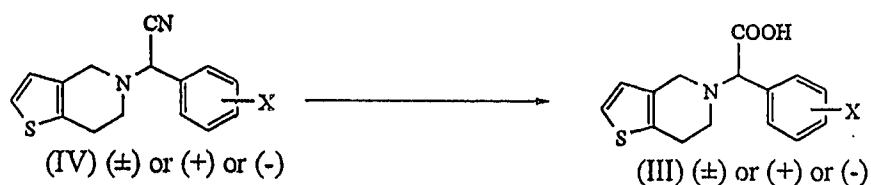
20 with acidic reagents in presence of methanol to obtain a compound of formula (I) or its salt, with retention of configuration,

- iv) finally resolving ($\pm$) the compound of formula (I) or its salt, into its optical isomers.

2. A process according to claim 1, wherein optionally, resolving a racemic compound of formula (IV) into its optical isomers, or else, transforming the racemic compound or its optical isomers into its salts, followed by liberation of the salt from the compound.

3. A process according to claim 1, wherein optionally, resolving a racemic compound of formula (II) into its optical isomers, or else, transforming the racemic compound or its optical isomers into its salts, followed by liberation of the salt from the compound.

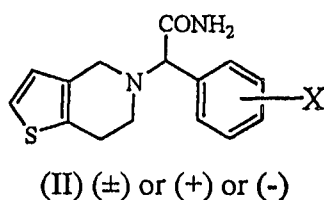
4. A process for the preparation of compound of formula (III) or its salt, where X represents hydrogen, chloro, bromo or iodo atom, preferably 2-chloro, which comprises,



i) reacting a compound of general formula (IV) or their salt, in any of its optical forms, in presence of acidic/basic catalyst in a suitable solvent, giving the corresponding acid of formula (III) or its salt, with configuration same as that of the starting material,

ii) if desired, finally the racemic compound of formula (III) or its salt, are resolved into its corresponding optically pure (+) and (-) forms.

5. A process according to claim 1, wherein a compound of formula (II) (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide, or its optical active isomers or its salts, where X represents a halogen atom such as chloro, bromo, iodo substituent, more preferably 2-chloro, is prepared by a process comprising,



i) treating the compound of formula (IV) or its salt or in any of its optical forms, with basic reagents when the starting material is racemic or else with acidic catalyst when the starting material is optically active, in presence of suitable solvent;

ii) finally forming a salt of the racemic compound of formula (II), which is resolved into its corresponding optically pure (+) and (-) forms.

6. A process according to claim 5, which comprises preparation of compound of formula (II) characterized in that, basic reagent used is lithium hydroxide, potassium hydroxide, sodium hydroxide and potassium *t*-butoxide.

7. A process according to claim 5, which comprises preparation of compound of formula (II), wherein said acidic reagent used is selected from the group consisting of acetic acid, *p*-

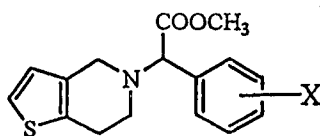
toluenesulfonic acid, trifluoroacetic acid, chloroacetic acid, perchloric acid, formic acid or mineral acids such as anhydrous alcoholic hydrogen halides, or aqueous hydrochloric acid, sulfuric acid, HBr or a mixture thereof.

8. A process according to claim 5, which comprises preparation of compound of formula (II) wherein, the solvent used is water, (C₁-C₄)alcohol, acetone, acetic acid, dimethylformamide, THF, DMSO, dioxane, DME and the like or mixtures thereof, preferably, mixture of water, methanol or *tert*-BuOH.

9. A process according to claim 5 wherein a compound of formula (II) (±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide, is resolved into (-) and its (+) forms using 1-(*R*) or 1-(*S*)-camphorsulfonic-10-acid, tartaric acid, more particularly 1-(*R*) or 1-(*S*)-camphorsulfonic-10-acid, in the presence of solvent such as water, acetone, ethyl acetate or a mixture thereof, and the salt used can be in a molar ratio of 0.5 to 1.1 equivalents.

10. A process according to claim 5, wherein a compound of formula (II) (±)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetamide, is converted into corresponding salt, wherein the salt claimed is D-camphorsulfonate, L-camphor sulfonate, D-tartaric acid, L-tartaric acid or hydrogen sulfate.

11. A process according to claim 1, wherein said compound of formula (I) is Methyl (2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyrid-5-yl)acetate, or its optical active isomers or its salts, where X represents a halogen atom such as chloro, bromo, iodo substituent, more preferably 2-chloro, said process comprising,



(I) (±) or (+) or (-)

i) treating the compound of formula (II) or its salt or in any of its optical forms, with acidic reagents, in presence of suitable solvent;

ii) finally forming a salt of the racemic compound of formula (I), which is resolved into its corresponding optically pure (+) and (-) forms:

12. A process according to claim 11, wherein said acidic reagent used is selected from concentrated sulfuric acid in the range from 1 equivalent to 50 equivalents, preferably the addition is favored at 0 °C to 5 °C or at reflux temperature of the solvent used.

13. A process according to claim 11, wherein, the solvent used is methanol in the range of 3 to 30 volumes, along with other cosolvents such as toluene, DMSO, xylene and the like or mixtures thereof.

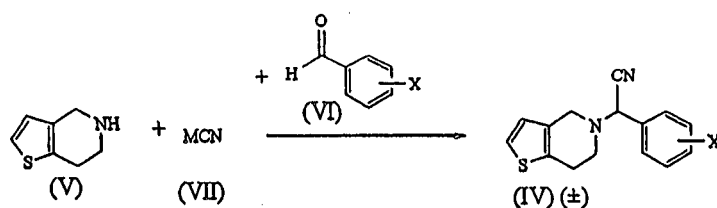
14. A process according to claim 11, wherein the duration of the reaction ranges from 4 hrs to 4 days.

15. A process according to claim 11, wherein the reaction is carried out at a temperature in range from 40 °C to 140 °C.

5 16. A process according to claim 11, wherein a compound of formula (I), is resolved using 1-(*R*) or 1-(*S*)-camphorsulfonic-10-acid, (*R*) or (*S*)-tartaric acid, more particularly 1-(*R*) or 1-(*S*)-camphorsulfonic-10-acid, in the presence of solvent such as water, acetone, ethyl acetate or a mixture thereof.

10 17. A process according to claim 16, wherein a mixture containing the varying ratios of the two enantiomers, (-)-I and (+)-I is chirally enriched to (+)-I-stereoisomer, or chiral removal of (-)-I enantiomer from a variable mixture of (-)-I and (+)-I stereoisomers.

18. A process for the preparation of a compound of formula (IV) and its salts,



where X represents a halogen atom such as chloro, bromo, iodo substituent, more particularly

15 X represents 2-chloro, along with its salts, which comprises,

i) reacting a compound of general formula (V) or its acid addition salt with a cyanide (of general formula (VII) wherein the meaning of M is alkali metal, TMS, Cu, and hydrogen, followed by reaction with a halogenobenzaldehyde of the formula (VI), wherein X is halogen atom, which are resolved into its optical isomers, and if desired, liberating from their salts or transforming into their salts; or

ii) reacting a halogenobenzaldehyde of general formula (VI) wherein the meaning of X is halogen atom with cyanide of general formula (VII) wherein M is as defined earlier, and followed by insitu with the compound of general formula (V) or its acid addition salt; or,

iii) reacting the halogenobenzaldehyde of general formula (VI) wherein the meaning of X is
25 halogen atom, with hydrogen sulfite of general formula (VIII) wherein M is as defined earlier, and finally with cyanide of general formula (VII), wherein M is as defined earlier, and subsequently reacting *in situ* with the compound of general formula (V) or its acid addition salt; and

finally resolving the compound of formula (IV) or its salt, so obtained to its optically pure

30 (+) and (-) form of compound of formula (IV) or its salt.

19. The process according to claim 18, wherein, the reaction is carried out at temperature between 0 °C and 100 °C, whereas with HCN gas, reaction temperature would go further down up to - 30 ° C.

20. The process according to claim 18, wherein the reaction is carried in an aqueous or a non-
5 aqueous medium containing acids such as acetic acid, propionic acid, methanol and HCl/MeOH.

21. The process according to claim 18, wherein a catalyst acid such as dry hydrochloric acid, sulfuric acid, p-toluenesulfonic acid or acetic acid is used.

22. A process according to claim 18, wherein said compound of formula (IV) (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile, is resolved into (-) and
10 its (+) forms using 1(R) or 1(S)-camphorsulfonic-10-acid, tartaric acid, more particularly 1(R) or 1(S)-camphorsulfonic-10-acid, presence of acetone, ethyl acetate or a mixture thereof and water.

23. A process according to claim 18, a compound of formula (IV) (±)-(2-chlorophenyl)-(6,7-
15 dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile, in (±) or (-) or (+) forms are converted into its salt, wherein the salt claimed is D-camphorsulfonate, L-camphor sulfonate, D-tartaric acid, L-tartaric acid or hydrogen sulfate.

24. The process according to claim 18, wherein , racemization of (-) isomer of compound of formula (II) is effected in a mixture which may contain (+) stereoisomer to get (±) compound
20 using a base such as LDA, KOH, NaOH, K-t-BuOH, NaOMe, NaH, KH in a suitable solvent.

25. The process according to claim 1, wherein racemization of (-) isomer of compound of formula (I) is effected in a mixture which may contain (+) stereoisomer to get (±) compound using a base such as LDA, NaOMe, NaH, KH in a suitable solvent.

26. The process according to claim 17, the resolution is carried out in the presence of acetone
25 as a solvent in the range of 5 to 10 volumes, which may contain water upto 5 %.

27. The process according to claim 17, wherein said suitable chiral agent used is in 1:1 molar ratio.

28. The process according to claim 27, wherein, suitable temperature is from 0°C to the reflux temperature of the solvent.

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E-556, Greater Kailash-II
New Delhi-110 048
INDIA

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

Date of mailing
(day/month/year)

02/04/2002

Applicant's or agent's file reference

ZRC-NIPR-002

REPLY DUE

See paragraph 1 below

International application No.

PCT/IN 02/00012

International filing date
(day/month/year)

21/01/2002

Applicant

CADILA HEALTHCARE LTD.

1. ☐ REPLY DUE within _____ ~~1000~~ days from the above date of mailing

☒ NO REPLY DUE

2. COMMUNICATION:

The applicant is informed that establishment of the international search report (ISR) for non first-filings may be delayed due to a current search backlog.

Although the time limit for entering the national phase before designated offices under Article 22(1) PCT and elected offices under Article 39(1) PCT has, with effect from 1 April 2002 (see PCT Gazette 44/2001 Section IV) been set at 30 months from the priority date (before the EPO the time limit is 31 months from the priority date - see Rule 107 EPC as amended with effect from 2 January 2002 - OJ EPO 8-9/2001, 373) not all PCT contracting states have yet made the necessary changes to their national laws and will for the time being continue to require entry to the national phase at 20/21 months from the priority date if a demand has not been filed before the end of 19 months from the priority date - see PCT Gazette/PCT Newsletter available on the WIPO internet site at <http://www.wipo.int/pct/en/index.html> for an up to date list of the applicable time limits.

In these circumstances, the EPO acting as IPEA will accept, without any late payment fee under Rule 58bis PCT, the handling fee and the preliminary examination fee due in respect of the demand relating to the present application, even if they are not paid within the time limit prescribed in Rules 57.3 and 58.1(b) PCT, provided that they are paid within one month from the date of transmittal of the ISR; i.e., the EPO will only send an invitation pursuant to Rule 58bis.1(a) PCT after expiry of this one-month period. In all cases where the EPO has sent an invitation to pay and the applicant has not paid in full the amount due, the demand shall be considered as if it had not been submitted (Rule 58bis.1(b)-(d) PCT). A loss of rights may well be the consequence in designated states where the time limit for entry into the national phase under Article 22 PCT has already expired (see also Article 37(4) PCT).

Note that if the competent IPEA chosen by the applicant is not the EPO and if the fees mentioned above are not paid within the time limit prescribed in Rules 57.3 and 58.1(b) PCT, the competent IPEA is entitled to apply Rule 58bis.1(a) PCT immediately thereafter.

If your application is affected, we apologise for any inconvenience caused.

Finally, applicants are reminded that as of 3 January 2002 a rationalised PCT II procedure may apply, see OJ EPO 11/2001, 539 and that the EPO as ISA will not carry out international search on an application which relates to no more than a method of doing business, see OJ EPO 10/2001, 482. Applicants should also bear in mind the restriction of the EPO's competence as ISA and IPEA in certain technical fields in respect of certain international applications, see OJ EPO 1/2002, 52 and PCT Newsletter 1/2002 for further details.

Name and mailing address of the International Searching Authority



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

Authorized officer

ISA/EP

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF RECEIPT
OF SEARCH COPY

(PCT Rule 25.1)

To:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E-556, Greater Kailash-II
New Delhi-110 048
INDIA

Date of mailing
(day/month/year)

02/04/2002

Applicant's or agent's file reference

ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.

PCT/ IN 02/ 00012

International filing date (day/month/year)

21/01/2002

Priority date (day/month/year)

24/01/2001

Applicant

CADILA HEALTHCARE LTD.

1. Where the International Searching Authority and the Receiving Office are not the same office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the Receiving Office are the same office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

15/03/2002

(date of receipt).

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing in computer readable form.

3. Time limit for establishment of International Search Report

The applicant is informed that the time limit for establishing the International Search Report is 3 months from the date of receipt indicated above or 9 months from the priority date, whichever time limit expires later

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the Receiving Office.

Name and mailing address of the International Searching Authority



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

Authorized officer

ISA/EP

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year) 03 April 2002 (03.04.02)	
Applicant's or agent's file reference ZRC-NIPR-002	IMPORTANT NOTIFICATION
International application No. PCT/IN02/00012	International filing date (day/month/year) 21 January 2002 (21.01.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 January 2001 (24.01.01)
Applicant CADILA HEALTHCARE LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
24 Janu 2001 (24.01.01)	84/MUM/2001	IN	13 Marc 2002 (13.03.02)
22 Octo 2001 (22.10.01)	Not yet allotted	US	NR

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Cécile CHATEL (Fax 338.87.40) Telephone No. (41-22) 338.83.38
--	--

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

SUBRAMANIAM, Harlharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year)

01 August 2002 (01.08.02)

Applicant's or agent's file reference

ZRC-NIPR-002

IMPORTANT NOTICE

International application No.

PCT/IN02/00012

International filing date (day/month/year)

21 January 2002 (21.01.02)

Priority date (day/month/year)

24 January 2001 (24.01.01)

Applicant

CADILA HEALTHCARE LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EA,EC,
EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,
MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,OM,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TN,TR,TT,

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on
01 August 2002 (01.08.02) under No. WO 02/059128

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office. For further details, see PCT Gazette No.44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20,21,30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the PCT Applicant's Guide, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II.)

It is the applicant's sole responsibility to monitor all these limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

Telephone No. (41-22) 338.91.11

PATENT COOPERATION TREATY

Faxed in advance!

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

D/12-11-2002

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash-II
New Delhi-110 048
INDE

Fax no: 91-11-628-6005

Date of mailing
(day/month/year) 06-11-2002Applicant's or agent's file reference
ZRC-NIPR-002REPLY DUE
See paragraph 1 below

International application No.

PCT/ IN 02/ 00012

International filing date (day/month/year)

21/01/2002

Applicant

CADILA HEALTHCARE LTD.

1. ☒ REPLY DUE within 1 , months/days^{XX} from the above date of mailing
☐ NO REPLY DUE

2. COMMUNICATION:

The address on the demand IPEA401 differs from the one on
the request RO101.

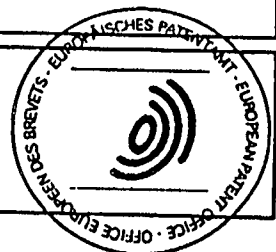
Can you please clarify if address should be with or without
Gandhinagar-Sarkhej Highway.

Name and mailing address of the IPEA/

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Cardenas, Claudette



PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF DEFECTS IN DEMAND

(PCT Rule 60.1(d))

To:

Mme Daniela GRAN
European Patent Office
Erhardtstrasse 27
D-80331 Munich
Germany

In its capacity as International Preliminary Examining Authority

Date of mailing

(day/month/year) 04 October 2002 (04.10.02)

International application No.

PCT/IN02/00012

International filing date

(day/month/year) 21 January 2002 (21.01.02)

Applicant

CADILA HEALTHCARE LTD. et al

The International Bureau hereby notifies the International Preliminary Examining Authority that it has found that the demand is defective for the reasons indicated below:

1. ☐ It does not contain the election of at least one Contracting State bound by Chapter II (Rule 53.2(a)(iv) and 53.7).
2. ☐ It does not permit the identification of the international application to which it relates (Rule 60.1(b)).
3. ☐ It does not contain the required petition (Rules 53.2(a)(i) and 53.3).
4. ☐ It does not contain the required indications concerning the agent as specified in the Annex (Rules 53.2(a)(ii) and 53.5).
5. ☐ It does not contain the required indications concerning the international application as specified in the Annex (Rules 53.2(a)(iii) and 53.6).
6. ☐ It is not submitted in the required language which is _____ (Rule 55.1).
7. ☐ It is not made on the printed form (Rule 53.1(a)).
8. ☐ It is presented as a computer print-out the particulars of which do not comply with the Administrative Instructions (Rule 53.1(a)).
9. ☒ It does not contain the required indications concerning the applicant as specified in the Annex (Rules 53.2(a)(ii) and 53.4).
10. ☐ It does not contain the required signature as specified in the Annex (Rules 53.2(b) and 53.8).

Other observations, if necessary:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer

Sébastien CLAVERI (Fax 338.87.40)

Telephone No.: (41-22) 338.83.38

Form PCT/IB/336 (September 1993)

18-10-2002

NOTIFICATION OF DEFECTS IN DEMAND

PCT/IN02/00012

Continuation of item 4: As to indications concerning the agent (Rule 4.4), the demand:

- a. ☐ does not properly indicate the agent's name (specify):
- b. ☐ does not indicate the agent's address.
- c. ☐ does not properly indicate the agent's address (specify):

Continuation of item 5: As to indications concerning the international application, the demand does not indicate:

- a. ☐ the international filing date.
- b. ☐ the international application number.
- c. ☐ the name of the receiving Office, where the international application number was not known to the applicant at the time the demand was filed.
- d. ☐ the title of the invention.

Continuation of item 9: As to indications concerning the applicant (Rules 4.4 and 4.5), the demand:

- a. ☐ does not indicate all the applicants for the elected States.
- b. ☐ does not properly indicate the applicant's name (specify):
- c. ☐ does not indicate the applicant's address.
- d. ☒ does not properly indicate the applicant's address (specify):
- e. ☐ does not indicate the applicant's nationality.
- f. ☐ does not indicate the applicant's residence.

Continuation of item 10: As to requirements concerning signature (Rules 4.15 and 90.4), the demand:

- a. ☐ is not signed.
- b. ☐ is not signed by all the applicants for the elected States.
- c. ☐ is not accompanied by the statement referred to in the check list in Box No. VI of the demand explaining the lack of the signature of an applicant for the election of the United States of America.
- d. ☐ is signed by what appears to be an agent/common representative but
- ☐ the demand is not accompanied by a power of attorney appointing him.
- ☐ the power of attorney accompanying the demand is not signed by all the applicants for the elected States.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E-556, Greater Kailash-II
New Delhi-110 048
INDIA

Date of mailing
(day/month/year)

17/10/2002

Applicant's or agent's file reference

ZRC-NIPR-002

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/IN 02/00012

International filing date
(day/month/year)

21/01/2002

Applicant

CADILA HEALTHCARE LTD.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90b/s.1 and 90b/s.3, respectively, before the completion of the technical preparations for International publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



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

Authorized officer

John De Bruijn

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16, and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ZRC-NIPR-002	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/IN 02/00012	International filing date (day/month/year) 21/01/2002	(Earliest) Priority Date (day/month/year) 24/01/2001
Applicant CADILA HEALTHCARE LTD.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search 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

2.



Certain claims were found unsearchable (See Box I).

3.



Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 02/00012

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04

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, 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	✓ ALAIN BURGOS, JOHN M. HERBERT AND IAIN SIMPSON: "ortho-Metalaton/Chlorination of Benzoic Acid Derivatives. Preparation of 'benzene-U-13C!-rac-Clopidogrel ('benzene-U-13C!-rac-SR25990C)" J. LABELLED COMPD. RADIOPHARM., vol. 43, no. 9, 2000, pages 891-8, XP008008850 Scheme 2 --- -/--	1-3,5-28

☒ 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

30 September 2002

Date of mailing of the international search report

17/10/2002

Name and mailing address of the ISA

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

Authorized officer

Diederens, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 02/00012

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JERRY MARCH: "Advanced Organic Chemistry" 1992, WILEY & SONS, NEW YORK XP002215119 198280 The HCN can be generated in situ from acetone cyanohydrin (see 6-49), avoiding the use of poisonous HCN. page 812 The addition of HCN ... This is an equilibrium reaction. page 964 Frequently it is the bisulfite addition product that is treated with CN- page 965 6-51 The addition of HCN to C=N and CN Bonds page 966	1-3,5-28
X	--- US 4 529 596 A (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application example 5	4
A	--- NAJER ET AL.: "Nitriles, amides, thioamides et acides alpha-phenyle alpha-tertioaminoacötiques" BULL. SOC. CHIM. FR., 1958, pages 1189-92, XP002215118 Nitrile alpha-phenyle alpha-(tétrahydro-1,2,5,6)pyridinoacétiquw -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00012

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4529596	A	16-07-1985	FR 2530247 A1 20-01-1984
		AT 25384 T	15-02-1987
		AU 554358 B2	21-08-1986
		AU 1663783 A	19-01-1984
		CA 1194875 A1	08-10-1985
		CS 8403815 A2	16-12-1985
		CS 8305281 A2	16-12-1985
		DD 211351 A5	11-07-1984
		DE 3369683 D1	12-03-1987
		DK 304183 A ,B,	14-01-1984
		EG 16540 A	30-12-1990
		EP 0099802 A1	01-02-1984
		ES 523943 D0	01-04-1984
		ES 8403901 A1	01-07-1984
		FI 832543 A ,B,	14-01-1984
		GR 79592 A1	31-10-1984
		HR 980261 A1	30-04-1999
		HU 187111 B	28-11-1985
		IE 55895 B1	14-02-1991
		IL 69049 A	31-03-1986
		JP 1000955 B	10-01-1989
		JP 1518778 C	07-09-1989
		JP 59027895 A	14-02-1984
		KR 8701270 B1	30-06-1987
		MX 9203264 A1	01-07-1992
		NO 832530 A ,B,	16-01-1984
		NZ 204874 A	24-01-1986
		OA 7491 A	31-03-1985
		PH 19375 A	02-04-1986
		PL 242965 A1	16-07-1984
		PT 77018 A ,B	01-08-1983
		SG 95287 G	23-11-1990
		SU 1272994 A3	23-11-1986
		YU 150683 A1	30-04-1986
		YU 197485 A1	31-10-1986
		ZA 8304705 A	28-03-1984

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash-II
New Delhi-110 048
INDE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(c) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

29. 08. 02

Applicant's or agent's file reference
ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.

PCT/ IN 02/ 00012

International filing date (day/month/year)

21/01/2002

Priority date (day/month/year)

24/01/2001

Applicant

CADILA HEALTHCARE LTD.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

19/08/2002

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

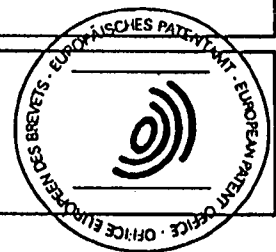


European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

CHURCHER G

Tel. (+49-89) 2399-2545



Form PCT/IPEA/402 (July 1998) P20452

(26/08/2002)

PATENT COOPERATION TREATY

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year)

04 July 2002 (04.07.02)

Applicant's or agent's file reference

ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.

PCT/IN02/00012

International filing date (day/month/year)

21 January 2002 (21.01.02)

Applicant

CADILA HEALTHCARE LTD. et al

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1. ☒ Correction of priority claim. In accordance with the applicant's notice received on: 05 June 2002 (05.06.02), the following priority claim has been corrected to read as follows:
US 22 October 2001 (22.10.01) 10/054,101
- ☐ even though the indication of the number of the earlier application is missing.
- ☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. ☐ Addition of priority claim. In accordance with the applicant's notice received on: , the following priority claim has been added:
- ☐ even though the indication of the number of the earlier application is missing.
- ☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. ☐ As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. ☐ Priority claim considered not to have been made.
- ☐ The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
- ☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
- ☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.
- The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(1B).
5. ☐ In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s):
6. A copy of this notification has been sent to the receiving Office and
- ☒ to the International Searching Authority (where the international search report has not yet been issued).
- ☒ the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Mougamadou ABIDINE (Fax 338.87 40)

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year) 04 July 2002 (04.07.02)	
Applicant's or agent's file reference ZRC-NIPR-002	IMPORTANT NOTIFICATION
International application No. PCT/IN02/00012	International filing date (day/month/year) 21 January 2002 (21.01.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 January 2001 (24.01.01)
Applicant CADILA HEALTHCARE LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
24 Janu 2001 (24.01.01)	84/MUM/2001	IN	13 Marc 2002 (13.03.02)
22 Octo 2001 (22.10.01)	10/054,101	US	05 June 2002 (05.06.02)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Mougamadou ABIDINE (Fax 338.87 40) Telephone No. (41-22) 338.83.38
--	---

PATENT COOPERATION TREATY

PCT

INVITATION TO CORRECT PRIORITY CLAIM

(PCT Rules 4.10, 26bis.1, 26bis.2(a) and (b))

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing

(day/month/year) 27 February 2002 (27.02.02)

Applicant's or agent's file reference

ZRC-NIPR-002

REPLY DUE

See item I

International application No.

PCT/IN02/00012

International filing date

(day/month/year) 21 January 2002 (21.01.02)

Applicant

CADILA HEALTHCARE LTD.

The applicant is hereby invited, within the time limit indicated below, to correct, by a notice submitted to the International Bureau, defects in the priority claim(s), as indicated in the Annex:

1. Time limit to respond to this invitation (Rule 26bis.1(a)):

- within 16 months from the (earliest) priority date; or

- if the (earliest) priority date is changed as a result of the correction or addition of the (earliest) priority claim, within 16 months from that (earliest) priority date so changed,

whichever expires first, provided that such a notice may, in any event, be submitted until the expiration of four months from the international filing date.

Failure to respond to this invitation within the prescribed time limit may result in the priority claim concerned to be considered, for the purposes of the procedure under the PCT, not to have been made (Rule 26bis.2(b)).

2. In the case where multiple priorities have been claimed, this invitation relates to the following priority claim(s):

US

22 October 2001 (22.10.01)

Not yet allotted

3. A copy of this invitation is being sent to the receiving Office.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Jean-Marc VIVET (Fax 338.87.40)

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

The International Bureau has found the following defects in the priority claim(s):

1. Failure to Comply with the Requirements of Rule 4.10

a. ☐ National application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☒ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the country party to the Paris Convention for the Protection of Industrial Property, or of the Member of the World Trade Organization that is not party to that Convention, in which the earlier national application was filed.
- ☐ The country indicated is neither a party to the Paris Convention for the Protection of Industrial Property nor a Member of the World Trade Organization.

b. ☐ Regional application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the authority entrusted with the granting of regional patents under the applicable regional patent treaty.
- ☐ The authority indicated as the authority entrusted with the granting of regional patents does not grant regional patents.
- ☐ The priority claim in relation to the ARIPO application does not indicate either at least one country party to the Paris Convention for the Protection of Industrial Property, or at least one Member of the World Trade Organization, for which the earlier application was filed.

c. ☐ International application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the receiving Office with which it was filed.

2. Inconsistency with the Corresponding Indications in the Priority Document*

a. ☐ Inconsistency with regard to the filing date of the earlier application:

The request indicates:

The priority document indicates:

b. ☐ Inconsistency with regard to the number of the earlier application:

The request indicates:

The priority document indicates:

c. ☐ Inconsistency with regard to the country party to the Paris Convention for the Protection of Industrial Property or the Member of the World Trade Organization in which the national application was filed:

The request indicates:

The priority document indicates:

d. ☐ Inconsistency with regard to the authority entrusted with the granting of regional patents under the applicable regional patent treaty:

The request indicates:

The priority document indicates:

e. ☐ Inconsistency with regard to the receiving Office with which the International application was filed:

The request indicates:

The priority document indicates:

* Even if this defect is not corrected in response to this invitation, the priority claim concerned will not be considered not to have been made (Rule 26bis.2(b)).

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year) 27 February 2002 (27.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference ZRC-NIPR-002	International application No. PCT/IN02/00012

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

CADILA HEALTHCARE LTD. (for all designated States except US)
PANDEY, Bipin et al (for US)

International filing date : 21 January 2002 (21.01.02)

Priority date(s) claimed : 24 January 2001 (24.01.01)

22 October 2001 (22.10.01)

Date of receipt of the record copy
by the International Bureau : 14 February 2002 (14.02.02)

List of designated Offices :

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

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, SI, SK, SL, TJ, TM, TN, TR,

TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Jean-Marc VIVET (Fax 338.87.40)

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 27 February 2002 (27.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference ZRC-NIPR-002	International application No. PCT/IN02/00012

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase
- ☐ confirmation of precautionary designations
- ☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

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SUBRAMANIAM, NATARAJ & ASSOCIATES

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ZRC-NIPR-002

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Netherlands
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(Tel No. +31 70 340 2040)

16 December 2002

ORIGINAL BY COURIER

Dear Sir,

Re: CADILA HEALTHCARE LIMITED
PCT INTERNATIONAL APPLICATION No. PCT/IN00/00012
Filed on 21 January 2001
Priority Dates: 24/01/2001 (IN)
22/10/2001 (US)

We respectfully refer to the written opinion transmitted to us by Official communication dated 24 October 2002. The applicants have been afforded time up to 24 December 2002 to submit a reply.

The applicants respectfully submit that the claimed invention is novel and inventive over the prior art cited (whether taken individually or in combination) for the reasons submitted hereunder. It is therefore, respectfully requested that a favourable examination report is issued.

Taking the issues raised by the Hon'ble European Patent Office seriatim:

Re: Item I (Basis of the opinion)

The applicants have no comments with respect to the basis of the opinion

Re: Item V (Reasoned Statement)

The documents referred to have been noted. The applicants most respectfully submit that the documents cited in the International Search Report and relied upon in the Written Opinion do not affect the novelty or inventiveness of the invention covered by this PCT International application. Detailed explanation is given below:

The PCT International application is question relates to a process of manufacturing Clopidogrel. The aim of a process chemist is always to develop a better and more efficient process, with high yield, with enhanced operational simplicity (for example, crystallizing the desired isomer in the first step), reducing the number of steps as even altering the sequence of already known steps, increasing the overall yield as also improving the yield of each individual step, overcoming the drawbacks of existing processes, devising moderate reaction conditions, providing a clean product with lesser side products and impurities, providing an optically pure product without any contamination, recycling the unwanted isomer thereby reducing waste thus making it environment friendly, avoiding tedious column chromatography, devising reaction conditions to reduce the reaction time, devising a safer reaction scheme using less hazardous reactants as also milder reaction conditions and so on.

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All these above factors contribute to inventiveness and make a chemical process cost effective and commercially viable. If any one or more of the above mentioned objectives are fulfilled by an inventive process it should become a patentable subject matter. It is respectfully submitted that the following submissions will make it clear that the claimed process is novel and inventive:

The Learned Examiner's reasoning on the grounds of obviousness and novelty are based on the following documents:

1. Burgos et. al., *J of Labelled Compounds Radiopharm.* 43, 891-898 (2000) (XP008008850)
2. Jerry March: "Advanced Organic Chemistry" 1992, Wiley & Sons., New York (XP002215119 198280)
3. U. S. Pat. 4,529,596 (Aubert et. al.)
4. Najer et. al., *Bull. Soc. Chim. Fr.*, 1189-92 (1958) (XP002215118)

A. The article of reference no. 1, (XP008008850), describes a method of preparing [benzene-U-¹³C]-*rac*-Clopidogrel by *ortho*-Metalation / Chlorination of Benzoic acid derivatives using Strecker synthesis.

In connection with this document, it is respectfully submitted as follows:

1) Strecker synthesis:

Strecker reaction is a fairly old reaction as will be clear from

1. A Strecker, *Ann*, **75**, 27 (1850)
2. A. Strecker, *Ann*, **91**, 349 (1854)
3. Liebigs *Ann. Chem.*, **155**, 177 (1870) and relevant pages of Merck Index (Annexure 1).

However, in the referred citation, acetone cyanohydrin has been used as the source of cyanide while the applicants have used NaCN or KCN as the cyanide source. The source of cyanide being NaCN or KCN was also known from the very long time. Even the use of NaHSO₃ is known for several decades in prior art.

The prior art in question ((XP008008850)) suffers from some serious drawbacks such as:

- a) Low yield - 31%
- b) Presence of impurities of adducts formed from cyclic amine and acetone cyanohydrin (pages 894-895).
- c) Use of column chromatography for separation
- d) Scale of synthesis i.e. product isolated is only 744 mg.

The applicants' invention overcomes the above-mentioned problems and has the following advantages:

- a) Very high yield- 97% (Example 1)
- b) No impurity formation with the applicants' "cyano" source.
- c) No column chromatography required.
- d) Scale of synthesis - 24 gm product isolated (reported in our application, Example No.1).

In fact, the synthesis has been done at Kilogram level.

The applicants have also employed several variations of Strecker synthesis (see Ex. 1-9) with reactants, solvents etc., each providing different yield but all consistently much higher than reported in the prior art. Hence the applicants have advantageously used the ideas/concepts of known knowledge to develop a better process with high yield, no impurity and with reduced steps (not requiring column chromatography as was done in the referred prior art).

The learned Examiner will note that the applicants' claimed invention "yields unexpectedly improved properties, which is not present in the prior art." Therefore, it is respectfully submitted that the applicants' invention is novel and inobvious. (Patent Law Basics,

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Rosenberg, West Group, page 6-7;) (Annexure II). The improved properties in applicants' invention are better yields and operational simplicity.

The fact that inventing a process which improves the yield considerably or reduces the presence of impurities in the desired product, by minor modification of reactants, reaction conditions, etc., is a sufficient ground for the claimed process to be non-obvious and hence patentable is further corroborated by the following examples.

a) US 6,355,827, Komoschinski et. al., describes an improved process for preparing 2-cyanoindan-1-ones, where MeOH as solvent has been replaced by DMF:H₂O and the yield was improved from 70 % to 95%. (Annexure III)

In the applicants' present invention, the yield has improved from 31% to 97%.

b) US 6,201,135, Maywald et. al., describes a process of separating impurities from 3-(2'-acetoxy-ethyl-dihydro-2(3H)-furanone, according to a known process but uses a different purification process to get the purified product. (Annexure IV)

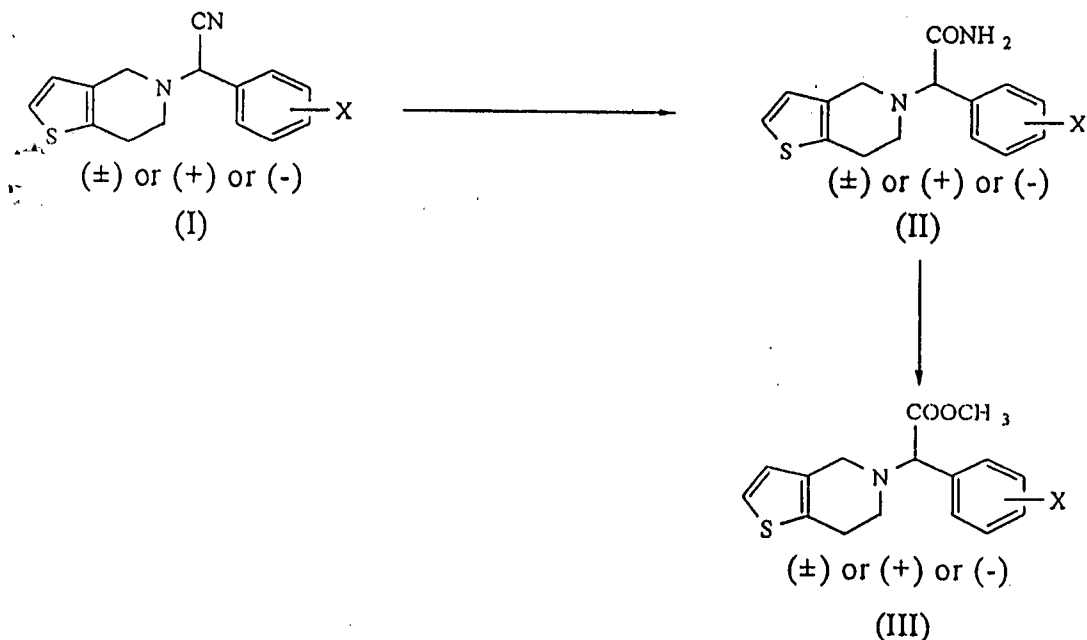
Similarly through the claimed process, the applicants obtain a pure product without involving further purification step.

c) US 6,037,503, Oren et. al., describes a process for the preparation of p-fluorophenol, where the "hydroxyl ion" source has been changed from Ca(OH)₂ to NaOH with a view to minimize impurities, get a high conversion and a clean reaction. (Annexure V)

The applicants' process also changes the source of CN⁽⁻⁾ from acetone cyanohydrin to NaCN or KCN, with a view to eliminate impurities, get a high conversion and consequently a better yield and a clean reaction.

d) US 6,107,490, Murthy et. al., describes a process for preparing 4-methyl-5-hydroxymethyl imidazole, where the reaction medium has been changed from base/water to K₂CO₃/isopropanol thereby improving the yield. (Annexure VI)

II) Conversion of nitrile to ester via amide:



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According to Burgos et. al. ((XP008008850)), the conversion was not carried out through saponification of the nitrile to amide, as there was a problem of retro-Strecker reaction (Burgos et. al., *J of Labelled Compounds Radiopharm.* 43, (2000) page 895, lines 2-4). Hence Burgos et. al. has carried out HCl promoted hydrolysis to amide in order to avoid retro Strecker and finally yielding low amount of product.

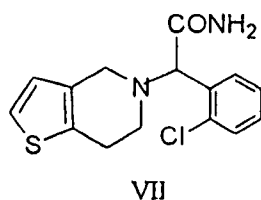
However, the applicants' process describes a modified process where saponification of nitrile (I) with KOH-t-BuOH yields amide (II) in high yield (94%) and without any retro-Strecker reaction (Example 10 of our specification). The high yield and cleanliness of the reaction is indeed noteworthy. Also, Example 18 (with KOH / isopropanol) of applicants' specification describes a process where the pure product precipitates out of the reaction mixture without extraction, simply by adding water, which offers advantage of operational simplicity.

A further problem with Burgos et. al's process is that it requires a long time (48 hours), azeotropic drying of reaction mass (page 897), whereas in the present process the reaction time required is 3 hours (Ex. 10, applicants' specification), and offers considerable advantage of operational simplicity, where the desired product precipitates out by simply adding water and without any extractive workup. All these issues i.e. time, operational simplicity, purity and avoidance of extractive workup adds up to better yields and commercial viability. Indeed such advantage of operational simplicity is not disclosed anywhere in the referred prior art.

The applicants would like to draw attention to the fact that they have actually solved the problems faced by the prior art and have improved the process significantly by doing what was stated as non-viable in the prior art. "Doing what the prior art references try to avoid is the antithesis of obviousness." (Patent Law Basics, Rosenberg, West Group, page 9-63). Also, for the present invention to be obvious, "there must be reasonable expectation of success" - US Manual of Patent Examination Procedure, (Patent Law Basics, Rosenberg, West Group, page 9-31), from what has been described in the prior art. However, in the present case the prior art in essence will discourage people from using saponification for obtaining the amide.

The applicants would also take this opportunity to highlight some other major features of their claimed invention.

The applicants' resolution process of ($\pm$) amide (VII), with 1S(+) CSA is not only unprecedented but it is technologically most desirable from the process perspective, since the desired dextro rotatory isomer (+) amide precipitates quantitatively in the very first attempt as diastereoisomer, without any contamination of unwanted (-) isomer or ($\pm$) isomer. (Ex. 31 of the applicants' specification). The optical purity of our product is 99.5%. There is no need for removal of impurity.



The applicants would like to draw the learned Examiner's attention to the following patent nos. US 4,546,201; US 4,515,811; GB 1,426,186 & GB 1,422,015 (Annexures VII, VIII, IX and X) all of which relate to the process of optical resolution of ($\pm$) 2-(6'-methoxy-2'-naphthyl) propanoic acid (Naproxen). The objective of all these patents have been to discover resolving agents and identify critical process parameters which avoids multiple crystallization and provides higher proportion of the desired d-isomer in a single crystallization step with improved quality (no contamination of unwanted l-isomer).

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Once again, the resolution of racemic ($\pm$) Naproxen in four patents confirms the applicants' contention that although conceptually one can argue that based on prior art, it is "obvious to try" but experience suggests that nobody could guarantee that such an experiment would have been expected to succeed.

"The governing standard is not whether a particular approach leading to an invention would be 'obvious to try', but whether such an experiment would have been expected to succeed" (Patent Law Basics, Rosenberg, West Group, page 9-58).

Besides there are other non-obvious features of the applicants' process:

- i) The applicants' resolving agent for cyclic amide is (+) CSA, which has not been reported for this synthesis.
- ii) The applicants' resolution of cyclic amide is unprecedented and its properties e.g. SOR (specific optical rotation) of diastereoisomer of VII with S(+) CSA = $+51^\circ$ (C=1, MeOH) and SOR of (+) amide (VII) = $+41^\circ$ (C=1, MeOH) are hitherto unknown (see Ex. 31)
- iii) The applicants' invention is, *inter alia*, that (+) nitrile (IV) gives (+) amide (V) and (+) amide gives (+) ester (I) is novel and non-obvious. No prior art can predict this.
- iv) The applicants process for converting (+) amide to (+) ester is both high yielding and without racemization.

In this context, it is relevant to note the drawbacks of the prior art reported by Burgos et. al.'s process ((XP008008850)), for conversion of racemic amide to racemic ester where a drastic condition of long reflux of 144 hours leads to only partial conversion of starting material, and low yield (overall 7%, page 895) of ester, with 26 % unreacted amide isolated by column chromatography.

- v) The applicants' process of conversion of diastereoisomeric salt of (+) amide / (+) CSA to (+) ester without any racemization in 97% yield in 26 hours (Ex. 37) is indeed unique and unprecedented. The very concept of converting a diastereoisomeric salt to the desired compound is new, novel and non-obvious.

vi) The applicants' process also reports the racemization of the unwanted isomer and its recycling (see Ex. 43, 44, 45 & relevant claims (24, 25) which is not disclosed in any of the cited prior art. The applicants would like to state that the process of recycling and reuse of waste products has been considered a patentable invention as is evident from the grant of the following patents- (Annexures XII and XII):

- a) US 6,114,523, Allegrini et. al., describes a "Process of recycle and reuse of
- b) waste products in Diltiazem synthesis.
- c) US 5,082, 970, Braish, describes a "Process for recycling an amine isomer" which is involved in the synthesis of Sertraline.

The grant of above patents are noteworthy because such recycling of unwanted products not only add to the cost effectiveness of the process, but also decreases load on the environment by minimizing waste.

Besides, for process patents, where a process consists of more than a single step, the arrangement, order or sequence in which these component steps are to be performed may itself be of patentable significance. Thus, the patentability of a multi-step process may reside solely in the arrangement of its constituent steps - although each of the individual steps being old, the particular order constituting a new combination (Patent Law Basics, Rosenberg, West Group, page 6-6).

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In this context, the applicants' strategy of resolving the coupled cyclic nitrile (I) and / or amide (II), to their respective dextrorotatory isomers and then converting them to the final product S(+)-Clopidogrel, constitutes a new arrangement of its constituent steps - even if some of the racemic ($\pm$) intermediates e.g. labeled coupled nitrile and labeled coupled amide are known in the prior art.

The inventive merit of this strategy becomes more significant as this strategy will require less reagents for further transformation and will also reduce wastage of costly intermediates. It is a common knowledge that the cost of intermediates keeps on increasing as we proceed from starting material to final product in a multi-step synthesis. One would therefore, like to use cheaper intermediates by introducing resolution in the beginning of the synthetic ladder than resolving the costly final product at the end.

In conclusion the applicants would like to draw the attention of the Learned Examiner to the following facts which clearly shows the substantial improvement of their process over all known prior arts:

Our overall yield of 66.3%, in four steps is as follows:

- i) In the Strecker step - 97 % (Ex. 1)
- ii) Conversion of nitrile to amide - 94% (Ex. 10)
- iii) Resolution to diastereoisomers - 75% (Ex. 31)
- iv) Diastereoisomer to ester - 97% (Ex. 37)

With applicants' success with racemization and recycling of unwanted isomers, the resolution step yield goes above 95% from 75%, which further pushes our overall yield to not less than 84%.

On the contrary, Burgos et. al. report a 7 % overall yield for racemic ($\pm$) ester, Thus, on the ground of simple yield improvement also, one can not extrapolate and the applicants' invention is therefore, non obvious.

That increasing the yield of a known process is a patentable subject matter has been recognized by the patent office as is evident from US 6,355,827, Komoschinski et. al., (prior art yield was 70%, whereas improved yield is 95%), with a small modification of reaction conditions (change of solvent from methanol to a mixture of DMF/H₂O in 95:5) for the same reaction and same reagents (yield improvement only 1.35 fold). Compared to that our invention gives a 28 fold yield improvement, from not more than 3% (prior art) to not less than 84 %.

B. With respect to the citations from J. D. March (XP002215119 198280) the applicants would like to state the following:

i. According to the citation on page 842, the cyanide source referred to is acetone cyanohydrin. This reagent has been used in the process described by Burgos et. al. (*J of Labelled Compounds Radiopharm.* 43, 891-898 (2000); page 895) whereby the yield reported was very poor (31%; page 897). The applicants have not used acetone cyanohydrin as our source of cyanide. **The applicants have employed sodium cyanide as the nitrile source which results in a substantially higher yield of 97% (Example 1).** In fact, the applicants have not used any of the nitrile sources referred to in the citation of J. D. March. Based on simply the high degree of yield improvement the applicants' process becomes non-obvious.

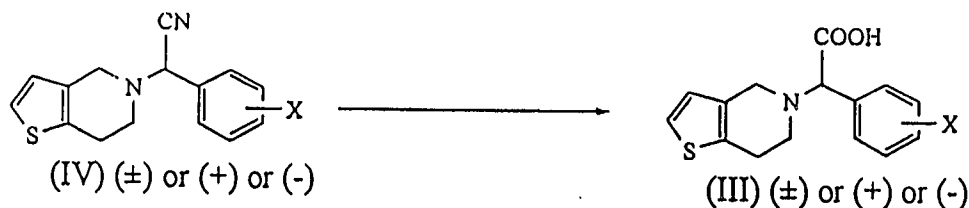
ii. The citations on pages 964, 965 (6-49), and 966 (6-51) speaks of the further fundamental reaction mechanism involved in the addition of HCN to an aldehyde, ketone or to a -C=N bond. It is also stated that "it is the bisulfite addition product that is treated with CN⁻" (page 965, 3rd line). Here again the applicants would like to state that their invention is an improved process for preparing a compound of industrial significance and for achieving this

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they have used known methodologies, reactants, reagents, reaction conditions etc. in a specific sequence whereby they have overcome the drawbacks of the prior art and also increased the efficiency and yield of the final product as well as intermediates to a level not reported anywhere in the prior art. Thus a citation which merely describes the mechanism involved and the preferable sequence of a very well known reaction generally, cannot render the applicants' invention obvious.

Thus it is the applicants' contention that the references of J. D. March merely teaches the general mechanism involved in the addition of a nitrile to an aldehyde, ketone or a $-C=N$ group but does in no way teaches their invention. Hence, it is the applicants' contention that our invention doesn't become obvious based on these cited documents.

C. The learned Examiner further states that Claim number 4 of the present invention lacks novelty because of Example no. 5 of US 4,529,596 (Aubert et. al.). However, the referred example describes a process of preparing α -[4,5,6,7-tetrahydro-thieno-[3,2-c]-5-pyridyl]-o-chlorophenylacetic acid from the corresponding ester compound using alkaline hydrolysis. However, the applicants' method of preparing the acid (III) as claimed in Claim 5 of the specification is by hydrolysis of the corresponding cyano compound (IV) in the presence of a suitable acidic/basic catalyst, in a suitable solvent.



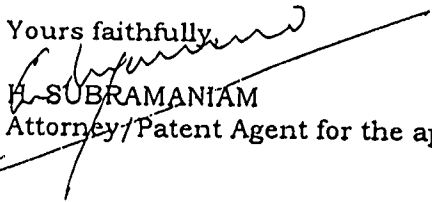
The applicants would like to state here that they have not claimed the compound of formula (III), which is widely known from long time as the first metabolite of Clopidogrel formed in the body. The process of preparation of (III) according to the applicants' application is in no way taught by the referred example. Hence, it is respectfully submitted that the cited reference does affect the novelty of our process, which is unique.

D. The last reference cited by the learned Examiner is the article by Najer et. al. (Bull. Soc. Chim. Fr., 1958, pages 1189-92) which according to the Examiner generally describes the state of the art which is of not much significance. We accept the learned Examiner's observation and do not have any comments to make.

In view of the above, it is respectfully requested that a favourable Examination report is issued.

No amendments are made to the claims or description at present.

Yours faithfully,


H. SUBRAMANIAM

Attorney/Patent Agent for the applicants

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash-II
New Delhi-110 048
INDE

WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference ZRC-NIPR-002		Date of mailing (day/month/year) 24/10/2002
International application No. PCT/ IN 02/ 00012		REPLY DUE within 2/ 00 months/days from the above date of mailing
International filing date (day/month/year) 21/01/2002	Priority date (day/month/year) 24/01/2001	
International Patent Classification (IPC) or both national classification and IPC C07D495/04		
Applicant CADILA HEALTHCARE LTD.		

- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
 - ☒ Basis of the opinion
 - ☐ Priority
 - ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application
- The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **24/05/2003**

Name and mailing address of the IPEA/  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer Examiner Formalities officer (incl. extension of time limits) Tel. (+49-89) 2399 2828
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Form PCT/IPEA/408 (cover sheet) (march 2002)



I. Basis of the opinion

1. The basis of this written opinion is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claims references).
2. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

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) ZRC-NIPR-002

Box No. I TITLE OF INVENTION	
PROCESS FOR PREPARING CLOPIDOGREL	
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.)	
CADILA HEALTHCARE LTD. Zydus Tower, Satellite Cross Roads Ahemdabad-380 015 Gujarat	
Telephone No. + 91 79 375 0603	
Facsimile No. + 91 79 375 0606	
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.)	
PANDEY, Bipin Zydus Tower, Satellite Cross Roads Ahemdabad-380 015 Gujarat	
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.)	
SUBRAMANIAM, Hariharan; NATARAJ, Guruswamy PRITHVIRAJ, Susheela, Attorneys- at-law & Patent Agents of SUBRAMANIAM, NATARAJ & ASSOCIATES E-556, Greater Kallash-II New Delhi-110 048	
Telephone No. +91 11 628 6012	
Facsimile No. +91 11 628 6005	
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.) LOHRAY, Vidya Bhushan Zydus Tower, Satellite Cross Roads Ahemdabad-380 015 Gujarat	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.) LOHRAY, Braj Bhushan Zydus Tower, Satellite Cross Roads Ahemdabad-380 015 Gujarat	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.) (Empty)	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.) (Empty)	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 | ☒ MG Madagascar | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MN Mongolia | ☒ UZ Uzbekistan |
| ☒ EE Estonia | ☒ MW Malawi | ☒ VN Viet Nam |
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| ☒ FI Finland | ☒ MZ Mozambique | ☒ ZA South Africa |
| ☒ GB United Kingdom | ☒ NO Norway | ☒ ZM Zambia |
| ☒ GD Grenada | | ☒ ZW Zimbabwe |
| ☒ GE Georgia | | |
| ☒ 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.)

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) 24 January 2001	84/MUM/2001	IN		
item (2) 22 October 2001	Not yet allotted	U.S.A		
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(h)(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)		
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			:

This international application contains: (a) the following number of sheets in paper form: <table style="width: 100%;"> <tr> <td>request (including declaration sheets) :</td> <td style="text-align: right;">5</td> </tr> <tr> <td>description (excluding sequence listing part) :</td> <td style="text-align: right;">35</td> </tr> <tr> <td>claims :</td> <td style="text-align: right;">5</td> </tr> <tr> <td>abstract :</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings :</td> <td style="text-align: right;">_____</td> </tr> <tr> <td>Sub-total number of sheets :</td> <td style="text-align: right;">46</td> </tr> </table> sequence listing part of description (<i>actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below</i>) : Total number of sheets : (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 (<i>additional copies to be indicated under Item 9(ii), in right column</i>):	request (including declaration sheets) :	5	description (excluding sequence listing part) :	35	claims :	5	abstract :	1	drawings :	_____	Sub-total number of sheets :	46	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): <table style="width: 100%;"> <tr> <td>1. ☒ fee calculation sheet</td> <td style="text-align: right;">: 1</td> </tr> <tr> <td>2. ☐ original separate power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>4. ☐ copy of general power of attorney; reference number, if any: _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;">:</td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s): _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>7. ☐ translation of international application into (language): _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;">:</td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (ii) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td> <td style="text-align: right;">:</td> </tr> <tr> <td>10. ☐ other (<i>specify</i>): _____</td> <td style="text-align: right;">:</td> </tr> </table>	1. ☒ fee calculation sheet	: 1	2. ☐ original separate power of attorney	:	3. ☐ original general power of attorney	:	4. ☐ copy of general power of attorney; reference number, if any: _____	:	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) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) 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 (<i>specify</i>): _____	:
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description (excluding sequence listing part) :	35																																						
claims :	5																																						
abstract :	1																																						
drawings :	_____																																						
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2. ☐ original separate power of attorney	:																																						
3. ☐ original general power of attorney	:																																						
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(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 (<i>specify</i>): _____	:																																						
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 <i>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).</i> SUBRAMANIAM, HARIHARAN Attorney-at-law, Regd. Patent Agent Patent Agent for the Applicants																																							

For receiving Office use only	
1. Date of actual receipt of the purported international application: 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 /	2. Drawings: ☐ received: ☐ not received: 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:

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International Application No.

Applicant's or agent's
file reference

ZRC-NIPR-002

Date stamp of the receiving Office

Applicant CADILA HEALTH CARE LTD, applicants for all designated States except U.S.A,
PANDEY, Bipin; LOHRAY, Vidya Bhushan & LOHRAY, Braj Bhushan, applicants only for U.S.A

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE Rs. 5000.00 T

2. SEARCH FEE USD. 866.00 S

International search to be carried out by EP
(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets }
Where item (b) of Box No. IX does not apply, enter Total number of sheets }

b1 first 30 sheets USD 407.00 b1

b2 15 x 9 = USD 135.00 b2
number of sheets in excess of 30 fee per sheet

b3 additional component (only if sequence listing part of description
is filed in computer readable form under Section 801(a)(i), or
both in that form and on paper, under Section 801(a)(ii)):

400 x = b3
fee per sheet

Add amounts entered at b1, b2 and b3 and enter total at B USD 542.00 B

Designation Fees

The international application contains 115 designations.

5 x 88 = USD 440.00 D
number of designation fees payable (maximum 5) amount of designation fee

Add amounts entered at B and D and enter total at I USD 982.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

Rs. 3000.00 P

4. FEE FOR PRIORITY DOCUMENT (If applicable)

5. TOTAL FEES PAYABLE Rs. 8000.00 + USD 1848.00
Add amounts entered at T, S, I and P, and enter total in the TOTAL box TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☐ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons
☐ cheque ☐ bank draft ☐ revenue stamps ☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

- ☐ Authorization to charge the total fees indicated above.
☐ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.
☐ Authorization to charge the fee for priority document.

Receiving Office: RO/

Deposit Account No.:

Date:

Name:

Signature:

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059128 A3

(51) International Patent Classification⁷: C07D 495/04

(21) International Application Number: PCT/IN02/00012

(22) International Filing Date: 21 January 2002 (21.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

84/MUM/2001 24 January 2001 (24.01.2001) IN
10/054,101 22 October 2001 (22.10.2001) US

(71) Applicant (for all designated States except US): CADILA HEALTHCARE LTD. [IN/IN]; Zydus Tower, Satellite Cross Roads, Gandhinagar-Sarkhej Highway, Ahmedabad 380 015, Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PANDEY, Bipin [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad-380 015, Gujarat (IN). LOHRAY, Vidya, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN). LOHRAY, Braj, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN).

(74) Agents: SUBRAMANIAM, Hariharan et al.; Subramaniam, Nataraj & Associates, E- 556, Greater Kailash - II, New Delhi 110 048, Maharashtra (IN).

(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, SI, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (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, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

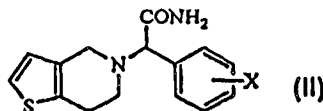
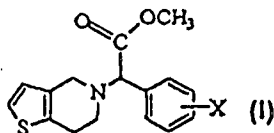
Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
19 December 2002

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

(54) Title: PROCESS FOR PREPARING CLOPIDOGREL



chlorine, bromine or iodine. The present invention also describes a process for preparing the compounds of general formula (II), in either racemic or optically active (+) or (-) forms and their salts, where X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine. The compounds represented by formulae (I) and (II) have one asymmetric carbon and hence, the optically active compounds of formula (I) or of formula (ii), may be obtained either by resolving the racemic intermediate/final product or using an optically active intermediate. The compounds of the invention are pharmacologically active and have significant anti-aggregating and anti-thrombotic properties.

(57) Abstract: The present invention discloses a process for the preparation of thieno[3,2-c]pyridine derivatives of general formula (I), in either racemic or optically active (+) or (-) forms and their salts, wherein X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine,

WO 02/059128 A3

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/IN 02/00012

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JERRY MARCH: "Advanced Organic Chemistry" 1992, WILEY & SONS, NEW YORK XP002215119 198280 The HCN can be generated in situ from acetone cyanohydrin (see 6-49), avoiding the use of poisonous HCN. page 812 The addition of HCN ... This is an equilibrium reaction. page 964 Frequently it is the bisulfite addition product that is treated with CN- page 965 6-51 The addition of HCN to C=N and CN Bonds page 966 ---	1-3,5-28
X	US 4 529 596 A (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application example 5 ---	4
A	NAJER ET AL.: "Nitriles, amides, thioamides et acides alpha-phenyle alpha-tertioaminoacötiques" BULL. SOC. CHIM. FR., 1958, pages 1189-92, XP002215118 Nitrile alpha-phenyle alpha-(tétrahydro-1,2,5,6)pyridinoacétiquw -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00012

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4529596	A	16-07-1985	FR 2530247 A1	20-01-1984
			AT 25384 T	15-02-1987
			AU 554358 B2	21-08-1986
			AU 1663783 A	19-01-1984
			CA 1194875 A1	08-10-1985
			CS 8403815 A2	16-12-1985
			CS 8305281 A2	16-12-1985
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			DE 3369683 D1	12-03-1987
			DK 304183 A ,B,	14-01-1984
			EG 16540 A	30-12-1990
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			GR 79592 A1	31-10-1984
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			NZ 204874 A	24-01-1986
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			PH 19375 A	02-04-1986
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			YU 150683 A1	30-04-1986
			YU 197485 A1	31-10-1986
			ZA 8304705 A	28-03-1984

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash II
New Delhi 110 048
INDE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

Date of mailing (day/month/year)	20.03.2003
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Applicant's or agent's file reference ZRC-NIPR-002	IMPORTANT NOTIFICATION
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International application No. PCT/IN02/00012	International filing date (day/month/year) 21/01/2002	Priority date (day/month/year) 24/01/2001
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Applicant

CADILA HEALTHCARE LTD.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/	Authorized officer
 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 - 3016	Cardenas, C Tel.+31 70 340-3370



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-NIPR-002	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IN02/00012	International filing date (day/month/year) 21/01/2002	Priority date (day/month/year) 24/01/2001
International Patent Classification (IPC) or national classification and IPC C07D495/04		
Applicant CADILA HEALTHCARE LTD.		

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 report
- 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 Article 35(2) 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 19/08/2002	Date of completion of this report 20.03.2003
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 - 3016	Authorized officer Diederer, J Telephone No. +31 70 340 1097 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IN02/00012

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:

1-35 as originally filed

Claims, No.:

1-28 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)):

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/IN02/00012

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

6. Additional observations, if necessary:

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	1-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations
see separate sheet

168
195

Reference is made to the following documents:

D1: ALAIN BURGOS, JOHN M. HERBERT AND IAIN SIMPSON: 'ortho-Metalaton/Chlorination of Benzoic Acid Derivatives. Preparation of [benzene- U-13C]-rac-Clopidogrel ([benzene-U-13C]-rac-SR25990C)' J. LABELLED COMPD. RADIOPHARM., vol. 43, no. 9, 2000, pages 891-8, XP008008850

D2: JERRY MARCH: 'Advanced Organic Chemistry' 1992, WILEY & SONS, NEW YORK XP002215119 198280

D3: US-A-4 529 596 (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application

Re Item V

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

Article 33(3) PCT

The present application does not comply with Article 33(3) PCT as it is considered that the disclosure does not involve an inventive step.

Claim 1:

Claim deals with a process to prepare compounds of Formula I by a reaction of compounds V with MCN (VII) and aldehydes VI, subsequent hydrolysis to form II and then conversion to compounds I by reaction with methanol in acidic media.

The closest prior art document is D1. D1 discloses in Scheme 2, a synthesis of Clopidogrel by reaction of aldehyde 3 with thienopyridine 6 in the presence of acetone cyanohydrine to form compound 7 which is hydrolysed and esterified with MeOH. Acetone cyanohydrin is in equilibrium with acetone and HCN (as is general knowledge, disclosed in e.g. D2: 6-49). The difference of D1 with claim 1 of the present application is an extra resolution step (step 4). This resolution step does not render the claim inventive as it is a general method in the art to separate enantiomers by resolution. All the other dependent claims do not seem to contain features which, in combination with claim 1, render those claims inventive. Referring to the letter by the applicant it has to

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IN02/00012

be noted that claim 1 deals *inter alia* with HCN, not only with NaCN or KCN.

Claim 4:

Claim 4 deals with an hydrolysis of nitrile compounds IV. The closest prior art is D3 which discloses a similar hydrolysis of a thienopyridine ester under basic conditions to form a compound of Formula III. The difference is that in D3 a thienopyridine ester is hydrolysed whereas in the present application a thienopyridine nitrile is hydrolysed. It is however common knowledge that also nitrile compounds may be hydrolysed under the conditions as mentioned in claim 4. A skilled person would, starting from D3, easily substitute the ester with a nitrile group to come to the solution as presented in claim 4.

Claim 18

Claim 18 deals with three different processes to prepare compounds of formula IV. The closest prior art document is D1. In Scheme 2 nitrile 7 is produced by reaction of aldehyde 3 with thienopyridine 6, followed by addition of acetone cyanohydrin (HCN in situ). The difference of D1 with the second option of claim 18 (ii) is that the order of adding the reagents is different. It does not seem to make any difference at first sight and it is therefore obvious to change the order to render claim 18 novel. All the other dependent claims do not seem to contain features which, in combination with claim 18, render those claims inventive.

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This international application contains: (a) the following number of sheets in paper form: <table style="width: 100%;"> <tr> <td>request (including declaration sheets)</td> <td style="text-align: right;">5</td> </tr> <tr> <td>description (excluding sequence listing part)</td> <td style="text-align: right;">35</td> </tr> <tr> <td>claims</td> <td style="text-align: right;">5</td> </tr> <tr> <td>abstract</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings</td> <td style="text-align: right;">_____</td> </tr> <tr> <td>Sub-total number of sheets</td> <td style="text-align: right;">46</td> </tr> </table> sequence listing part of description (<i>actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below</i>) : _____ Total number of sheets : _____ (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 (<i>additional copies to be indicated under Item 9(ii), in right column</i>): _____	request (including declaration sheets)	5	description (excluding sequence listing part)	35	claims	5	abstract	1	drawings	_____	Sub-total number of sheets	46	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): <table style="width: 100%;"> <tr> <td>1. ☒ fee calculation sheet</td> <td style="text-align: right;">1</td> </tr> <tr> <td>2. ☐ original separate power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>4. ☐ copy of general power of attorney; reference number, if any: _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;">:</td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s): _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>7. ☐ translation of international application into (language): _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;">:</td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (ii) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td> <td style="text-align: right;">:</td> </tr> <tr> <td>10. ☐ other (<i>specify</i>): _____</td> <td style="text-align: right;">:</td> </tr> </table>	1. ☒ fee calculation sheet	1	2. ☐ original separate power of attorney	:	3. ☐ original general power of attorney	:	4. ☐ copy of general power of attorney; reference number, if any: _____	:	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) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) 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 (<i>specify</i>): _____	:
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1. ☒ fee calculation sheet	1																																						
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3. ☐ original general power of attorney	:																																						
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5. ☐ statement explaining lack of signature	:																																						
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(ii) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	:																																						
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10. ☐ other (<i>specify</i>): _____	:																																						
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 <i>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).</i> SUBRAMANIAM, HARIHARAN Attorney-at-law, Regd. Patent Agent Patent Agent for the Applicants																																							

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

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FEE CALCULATION SHEET

Annex to the Request

Applicant's or agent's file reference		ZRC-NIPR-002		For receiving Office use only	
				International Application No.	
				Date stamp of the receiving Office	
Applicant CADILA HEALTH CARE LTD, applicants for all designated States except U.S.A, PANDEY, Bipin; LOHRAY, Vidya Bhushan & LOHRAY, Braj Bhushan, applicants only for U.S.A					
CALCULATION OF PRESCRIBED FEES					
1. TRANSMITTAL FEE		Rs. 5000.00		T	
2. SEARCH FEE		USD. 866.00		S	
International search to be carried out by EP (If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)					
3. INTERNATIONAL FEE					
Basic Fee					
Where item (b) of Box No. IX applies, enter Sub-total number of sheets } Where item (b) of Box No. IX does not apply, enter Total number of sheets }					
b1 first 30 sheets		USD 407.00		b1	
b2 15 number of sheets in excess of 30		x 9 fee per sheet		= USD 135.00 b2	
b3 additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii):					
400 x				= b3	
Add amounts entered at b1, b2 and b3 and enter total at B		USD 542.00		B	
Designation Fees					
The international application contains 115 designations.					
5 number of designation fees payable (maximum 5)		x 88 amount of designation fee		= USD 440.00 D	
Add amounts entered at B and D and enter total at I		USD 982.00		I	
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)					
		Rs. 3000.00		P	
4. FEE FOR PRIORITY DOCUMENT (if applicable)					
5. TOTAL FEES PAYABLE		Rs. 8000.00 + USD 1848.00		TOTAL	
Add amounts entered at T, S, I and P, and enter total in the TOTAL box					
☐ The designation fees are not paid at this time.					
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(19) World Intellectual Property Organization
International Bureau



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10/054,101 22 October 2001 (22.10.2001) US

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(74) Agents: SUBRAMANIAM, Hariharan et al.; Subrama-
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(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,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (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, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

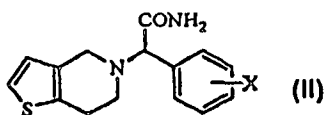
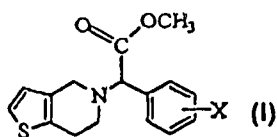
Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
19 December 2002

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 CLOPIDOGREL



(57) Abstract: The present invention discloses a
process for the preparation of thieno[3,2-c]pyridine
derivatives of general formula (I), in either racemic
or optically active (+) or (-) forms and their salts,
wherein X, the substituent on benzene ring represents
either a hydrogen or halogen atom such as fluorine,

chlorine, bromine or iodine. The present invention also describes a process for preparing the compounds of general formula (II),
in either racemic or optically active (+) or (-) forms and their salts, where X, the substituent on benzene ring represents either a
hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine. The compounds represented by formulae (I) and (II) have
one asymmetric carbon and hence, the optically active compounds of formula (I) or of formula (ii), may be obtained either by
resolving the racemic intermediate/final product or using an optically active intermediate. The compounds of the invention are
pharmacologically active and have significant anti-aggregating and anti-thrombotic properties.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/IN 02/00012

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JERRY MARCH: "Advanced Organic Chemistry" 1992, WILEY & SONS, NEW YORK XP002215119 198280 The HCN can be generated in situ from acetone cyanohydrin (see 6-49), avoiding the use of poisonous HCN. page 812 The addition of HCN ... This is an equilibrium reaction. page 964 Frequently it is the bisulfite addition product that is treated with CN- page 965 6-51 The addition of HCN to C=N and CN Bonds page 966 --- US 4 529 596 A (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application example 5 ---	1-3,5-28
A	NAJER ET AL.: "Nitriles, amides, thioamides et acides alpha-phenyle alpha-tertioaminoacötiques" BULL. SOC. CHIM. FR., 1958, pages 1189-92, XP002215118 Nitrile alpha-phenyle alpha-(tétrahydro-1,2,5,6)pyridinoacétiquw -----	4 1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00012

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4529596	A	16-07-1985	FR 2530247 A1	20-01-1984
			AT 25384 T	15-02-1987
			AU 554358 B2	21-08-1986
			AU 1663783 A	19-01-1984
			CA 1194875 A1	08-10-1985
			CS 8403815 A2	16-12-1985
			CS 8305281 A2	16-12-1985
			DD 211351 A5	11-07-1984
			DE 3369683 D1	12-03-1987
			DK 304183 A ,B,	14-01-1984
			EG 16540 A	30-12-1990
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			NO 832530 A ,B,	16-01-1984
			NZ 204874 A	24-01-1986
			OA 7491 A	31-03-1985
			PH 19375 A	02-04-1986
			PL 242965 A1	16-07-1984
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			YU 150683 A1	30-04-1986
			YU 197485 A1	31-10-1986
			ZA 8304705 A	28-03-1984

PATENT COOPERATION TREATY

195
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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash II
New Delhi 110 048
INDE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing (day/month/year)	20.03.2003
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Applicant's or agent's file reference ZRC-NIPR-002		IMPORTANT NOTIFICATION
International application No. PCT/IN02/00012	International filing date (day/month/year) 21/01/2002	Priority date (day/month/year) 24/01/2001
Applicant CADILA HEALTHCARE LTD.		

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
- 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/  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 - 3016	Authorized officer Cardenas, C Tel.+31 70 340-3370
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-NIPR-002	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IN02/00012	International filing date (day/month/year) 21/01/2002	Priority date (day/month/year) 24/01/2001
International Patent Classification (IPC) or national classification and IPC C07D495/04		
Applicant CADILA HEALTHCARE LTD.		
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 report - 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 Article 35(2) 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 19/08/2002	Date of completion of this report 20.03.2003	
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 - 3016	Authorized officer Diederer, J Telephone No. +31 70 340 1097 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IN02/00012

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:

1-35 as originally filed

Claims, No.:

1-28 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)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IN02/00012

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

6. Additional observations, if necessary:

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	1-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

**2. Citations and explanations
see separate sheet**

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IN02/00012

Reference is made to the following documents:

D1: ALAIN BURGOS, JOHN M. HERBERT AND IAIN SIMPSON: 'ortho-Metalaton/Chlorination of Benzoic Acid Derivatives. Preparation of [benzene- U-13C]-rac-Clopidogrel ([benzene-U-13C]-rac-SR25990C)' J. LABELLED COMPD. RADIOPHARM., vol. 43, no. 9, 2000, pages 891-8, XP008008850

D2: JERRY MARCH: 'Advanced Organic Chemistry' 1992, WILEY & SONS, NEW YORK XP002215119 198280

D3: US-A-4 529 596 (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application

Re Item V

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

Article 33(3) PCT

The present application does not comply with Article 33(3) PCT as it is considered that the disclosure does not involve an inventive step.

Claim 1:

Claim deals with a process to prepare compounds of Formula I by a reaction of compounds V with MCN (VII) and aldehydes VI, subsequent hydrolysis to form II and then conversion to compounds I by reaction with methanol in acidic media.

The closest prior art document is D1. D1 discloses in Scheme 2, a synthesis of Clopidogrel by reaction of aldehyde 3 with thienopyridine 6 in the presence of acetone cyanohydrine to form compound 7 which is hydrolysed and esterified with MeOH. Acetone cyanohydrin is in equilibrium with acetone and HCN (as is general knowledge, disclosed in e.g. D2: 6-49). The difference of D1 with claim 1 of the present application is an extra resolution step (step 4). This resolution step does not render the claim inventive as it is a general method in the art to separate enantiomers by resolution. All the other dependent claims do not seem to contain features which, in combination with claim 1, render those claims inventive. Referring to the letter by the applicant it has to

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IN02/00012

be noted that claim 1 deals *inter alia* with HCN, not only with NaCN or KCN.

Claim 4:

Claim 4 deals with an hydrolysis of nitrile compounds IV. The closest prior art is D3 which discloses a similar hydrolysis of a thienopyridine ester under basic conditions to form a compound of Formula III. The difference is that in D3 a thienopyridine ester is hydrolysed whereas in the present application a thienopyridine nitrile is hydrolysed. It is however common knowledge that also nitrile compounds may be hydrolysed under the conditions as mentioned in claim 4. A skilled person would, starting from D3, easily substitute the ester with a nitrile group to come to the solution as presented in claim 4.

Claim 18

Claim 18 deals with three different processes to prepare compounds of formula IV. The closest prior art document is D1. In Scheme 2 nitrile 7 is produced by reaction of aldehyde 3 with thienopyridine 6, followed by addition of acetone cyanohydrin (HCN in situ). The difference of D1 with the second option of claim 18 (ii) is that the order of adding the reagents is different. It does not seem to make any difference at first sight and it is therefore obvious to change the order to render claim 18 novel. All the other dependent claims do not seem to contain features which, in combination with claim 18, render those claims inventive.

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TRADUCCIÓN OFICIAL No. 02/329 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido de conformidad con el Certificado de Idoneidad Profesional No. 0045 expedido por la Universidad Nacional de Colombia.

(Se traducen los sellos sobre un poder otorgado por la compañía CADILA HEALTHCARE LIMITED con fecha Septiembre 21, 2002, escrito en inglés y español, y Legalización No. 516875 Ministerio de Relaciones Exteriores).

(En ingles y español, poder)

(Sello: No. de Serie 313, 2002, (Firma) R. J. BRAHMBHATT, NOTARIO, GOBIERNO DE GUJARAT)

(Sello Notarial a Tinta, Mi Comisión vence 10/07/2007, (Firmado) R.J. BRAHMBHATT, Notario, Gobierno de Gujarat)

(Sellos a tinta de la Cámara de Comercio e Industria de Nueva Delhi, 26 de Septiembre 2002)

(Sellos a Notariales a tinta del Gobierno de Gujarat, 21 de Septiembre 2002)

(Estampillas)

(Sello Notarial a Tinta, Ante mi, (Firmado) R.J. BRAHMBHATT, Notario, Gobierno de Gujarat)

Al respaldo: (Sellos a Tinta autenticando la firma del Funcionario de la Cámara

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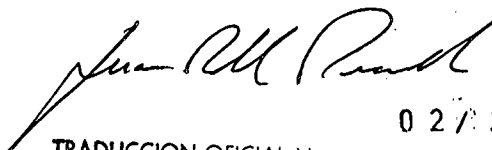
de Comercio, Septiembre 27, 2002)

En Español, legalización de la firma anterior por el Consulado de Colombia en Nueva Delhi, India No. 19/2002 de Octubre 3, 2002. Pagado el Impuesto de Timbre y los Derechos Consulares por US\$ 108.00.

Legalización de la firma del Cónsul por el Jefe de Legalizaciones del Ministerio de Relaciones Exteriores de Colombia No. 516875, con fecha Octubre 17, 2002.

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Bogotá, Octubre 25 de 2002.


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**MINISTERIO DE
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BOGOTÁ D.C.

COLOMBIA

Carrera 11 n° 93-43, Of. 404 Bogotá Colombia Tel: (57 1) 6350813 Fax: (57 1) 6350824 Email: clarkemodetclarkemodet.com.co

H. J. BRAHMBHATT
NOTARY
GOVT. OF GUJARAT

PODER

Yo (nosotros), abajo firmante(s)

Arun Madhusudan Parikh

en mi (nuestro) carácter de representante(s) legales de

Cadila Healthcare Limited

una sociedad organizada y existente de acuerdo con las leyes de *India*.

y en actual cumplimiento de su objeto social, con domicilio en *Zydus tower Satellite Road, Ahmedabad, India*
Pin 380015

por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñanzas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.

2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.

3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.

4) Ejercer acciones de oposición, observación,

POWER OF ATTORNEY

I (we), the undersigned

ARUN MADHUSUDAN PARIKH

legal representative(s) of

CADILA HEALTHCARE LIMITED

an organization existing under the laws of

INDIA

and in present execution of its business activity, domiciled at

ZYDUS TOWER, SATELLITE ROAD, AHMEDABAD, GUJARAT, INDIA.

PIN: 380015

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, extensions, assignments, changes of name and/or domicile, agreements and licenses.

2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.

3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or extensions, assignments, changes of name and/or domicile, agreements and licenses.

4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the

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reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).

5) Registrar nombres de dominio ante la entidad competente.

6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.

7) Ratificar o no la agencia oficiosa.

8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.

5) To register domain names before the competent entity.

6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related object and waive or renounce the rights granted or in process of granting, admit the facts of the case.

7) To ratify or not the officious agency.

8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extra-judicial attorneys, substitute this Power of Attorney and to revoke such substitutions.

Granted and signed at

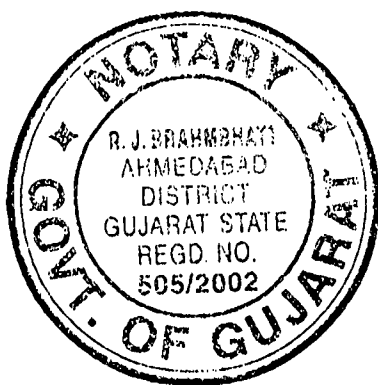
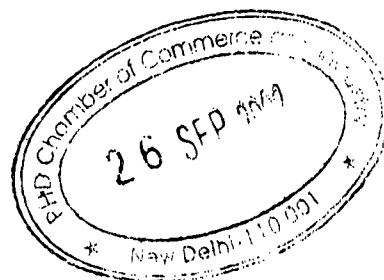
on this 21st day of
of SEPTEMBER, 2002.

Dado y firmado en

a los 21 días de Sept. 2002

Firma/ Signature

[Signature]

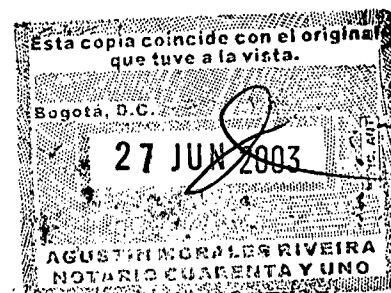


BEFORE ME
[Signature]
R.J. BRAHMBHATT
NOTARY
C. OF GUJARAT

ATTESTED

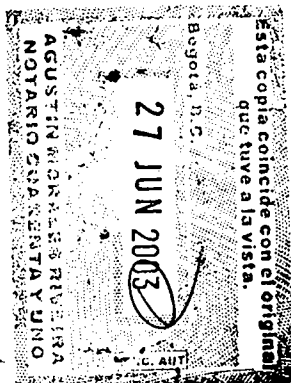
Addl./Joint/Sr. Asstt. Secretary General Admn. Officer
P.W. Chandra - Commerce and Industry
New Delhi

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A circular stamp from the U.S. Department of State, Office of External Affairs. The text "U.S. DEPARTMENT OF STATE" is curved along the top, and "OFFICE OF EXTERNAL AFFAIRS" is curved along the bottom. In the center, the year "1989" is printed. A small, dark, irregular mark is visible in the center of the stamp.

100-443887-100





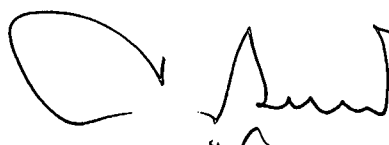
No.19/2002

EL SUSCRITO MINISTRO Plenipotenciario ENCARGADO DE LAS
FUNCIONES CONSULARES ANTE LA EMBAJADA DE COLOMBIA EN NUEVA
DELHI INDIA,
VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

CERTIFICA:

QUE EL SEÑOR A.K. GHOSH, FUNCIONARIO CONSULAR DEL
MINISTERIO DE RELACIONES EXTERIORES DE INDIA, QUIEN
AUTENTICO LA FIRMA DEL SEÑOR ARUN MADHUSUDAN PARIKH,
FIRMANTE DEL PRESENTE DOCUMENTO, EJERCIÓ EN LA FECHA
LAS FUNCIONES INDICADAS Y SU FIRMA CORRESPONDE A LA
REGISTRADA EN ESTE CONSULADO; QUE LA COMPAÑIA CADILA
HEALTHCARE LIMITED" ESTA CONSTITUIDA DE ACUERDO CON LAS
LEYES DE LA INDIA Y CUMPLE SU OBJETO CONFORME A LAS
MISMAS. DOMICILIADA EN AHMEDABAD GUJARAT, INDIA; QUE EL
SEÑOR ARUN MADHUSUDAN PARIKH, EN SU CARACTER DE VICE-
PRESIDENTE Y REPRESENTANTE LEGAL DE LA EMPRESA ARRIBA
MENCIONADA, ESTA FACULTADO PARA FIRMAR EL PRESENTE
DOCUMENTO.

DADO EN NUEVA DELHI A LOS TRES (3) DIAS DEL MES DE OCTUBRE
DE DOS MIL DOS (2002).


LUIS GUILLERMO BECERRA
Ministro Plenipotenciario
Cónsul de Colombia



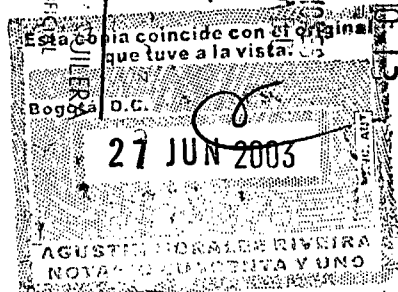
518875
Luis G. Becerra
COPIA FIRMADA POR EL
DOCUMENTO DESEMPLEADO
LAS FUNCIONES INDICADAS

MINISTERIO DE RELACIONES
EXTERIORES

PAGADO IMPUESTO DE TIMBRE Y
DERECHOS CONSULARES: US \$108.00
(Ciento ocho Dólares Americanos)

UNIVERSIDAD NACIONAL DE COLOMBIA

TRADUCCION OFICIAL No. 1
JUAN PABLO PIEDRAHITA
TRADUCCION OFICIAL No. 1
C. IDONIDAD 045



NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2002 OCT 17 A 10:13

Jefe de Legación
SARAFI DE BOGOTÁ

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ZRC-NIPR-002	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/IN 02/00012	International filing date (day/month/year) 21/01/2002	(Earliest) Priority Date (day/month/year) 24/01/2001
Applicant CADILA HEALTHCARE LTD.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search 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

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 02/00012

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04

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, 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	✓ ALAIN BURGOS, JOHN M. HERBERT AND IAIN SIMPSON: "ortho-Metalaton/Chlorination of Benzoic Acid Derivatives. Preparation of 'benzene-U-13C!-rac-Clopidogrel ('benzene-U-13C!-rac-SR25990C)" J. LABELLED COMPD. RADIOPHARM., vol. 43, no. 9, 2000, pages 891-8, XP008008850 Scheme 2 --- -/--	1-3,5-28

☒ 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

30 September 2002

Date of mailing of the international search report

17/10/2002

Name and mailing address of the ISA

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

Authorized officer

Diederen, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 02/00012

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JERRY MARCH: "Advanced Organic Chemistry" 1992, WILEY & SONS, NEW YORK XP002215119 198280 The HCN can be generated in situ from acetone cyanohydrin (see 6-49), avoiding the use of poisonous HCN. page 812 The addition of HCN ... This is an equilibrium reaction. page 964 Frequently it is the bisulfite addition product that is treated with CN- page 965 6-51 The addition of HCN to C=N and CN Bonds page 966	1-3,5-28
X	--- US 4 529 596 A (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application example 5	4
A	--- NAJER ET AL.: "Nitriles, amides, thioamides et acides alpha-phenyle alpha-tertioaminoacötiques" BULL. SOC. CHIM. FR., 1958, pages 1189-92, XP002215118 Nitrile alpha-phenyle alpha-(tétrahydro-1,2,5,6)pyridinoacétiquw -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00012

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4529596	A	16-07-1985	FR 2530247 A1 20-01-1984
			AT 25384 T 15-02-1987
			AU 554358 B2 21-08-1986
			AU 1663783 A 19-01-1984
			CA 1194875 A1 08-10-1985
			CS 8403815 A2 16-12-1985
			CS 8305281 A2 16-12-1985
			DD 211351 A5 11-07-1984
			DE 3369683 D1 12-03-1987
			DK 304183 A ,B, 14-01-1984
			EG 16540 A 30-12-1990
			EP 0099802 A1 01-02-1984
			ES 523943 D0 01-04-1984
			ES 8403901 A1 01-07-1984
			FI 832543 A ,B, 14-01-1984
			GR 79592 A1 31-10-1984
			HR 980261 A1 30-04-1999
			HU 187111 B 28-11-1985
			IE 55895 B1 14-02-1991
			IL 69049 A 31-03-1986
			JP 1000955 B 10-01-1989
			JP 1518778 C 07-09-1989
			JP 59027895 A 14-02-1984
			KR 8701270 B1 30-06-1987
			MX 9203264 A1 01-07-1992
			NO 832530 A ,B, 16-01-1984
			NZ 204874 A 24-01-1986
			OA 7491 A 31-03-1985
			PH 19375 A 02-04-1986
			PL 242965 A1 16-07-1984
			PT 77018 A ,B 01-08-1983
			SG 95287 G 23-11-1990
			SU 1272994 A3 23-11-1986
			YU 150683 A1 30-04-1986
			YU 197485 A1 31-10-1986
			ZA 8304705 A 28-03-1984

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash-II
New Delhi-110 048
INDE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(c) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

29. 08. 02

Applicant's or agent's file reference

ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.

PCT/ IN 02/ 00012

International filing date (day/month/year)

21/01/2002

Priority date (day/month/year)

24/01/2001

Applicant

CADILA HEALTHCARE LTD.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

19/08/2002

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(c)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

CHURCHER G

Tel. (+49-89) 2399-2545



PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 402 and 409)

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year)

04 July 2002 (04.07.02)

Applicant's or agent's file reference

ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.

PCT/IN02/00012

International filing date (day/month/year)

21 January 2002 (21.01.02)

Applicant

CADILA HEALTHCARE LTD. et al

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1. ☒ **Correction of priority claim.** In accordance with the applicant's notice received on: 05 June 2002 (05.06.02), the following priority claim has been corrected to read as follows:

US 22 October 2001 (22.10.01) 10/054,101

☐ even though the indication of the number of the earlier application is missing.☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

2. ☐ **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:

☐ even though the indication of the number of the earlier application is missing.☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

3. ☐ As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:

4. ☐ **Priority claim considered not to have been made.**

☐ The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(IB).

5. ☐ In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s):

6. A copy of this notification has been sent to the receiving Office and

☒ to the International Searching Authority (where the international search report has not yet been issued).☒ the designated Offices (which have already been notified of the receipt of the record copy).The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Mougamadou ABIDINE (Fax 338.87 40)

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year) 04 July 2002 (04.07.02)	IMPORTANT NOTIFICATION	
Applicant's or agent's file reference ZRC-NIPR-002		
International application No. PCT/IN02/00012		International filing date (day/month/year) 21 January 2002 (21.01.02)
International publication date (day/month/year) Not yet published		Priority date (day/month/year) 24 January 2001 (24.01.01)
Applicant CADILA HEALTHCARE LTD. et al		

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
24 Janu 2001 (24.01.01)	84/MUM/2001	IN	13 Marc 2002 (13.03.02)
22 Octo 2001 (22.10.01)	10/054,101	US	05 June 2002 (05.06.02)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Mougamadou ABIDINE (Fax 338.87 40) Telephone No. (41-22) 338.83.38
--	---

PATENT COOPERATION TREATY

PCT

INVITATION TO CORRECT PRIORITY CLAIM

(PCT Rules 4.10, 26bis.1, 26bis.2(a) and (b))

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year) 27 February 2002 (27.02.02)	
Applicant's or agent's file reference ZRC-NIPR-002	REPLY DUE See item 1
International application No. PCT/IN02/00012	International filing date (day/month/year) 21 January 2002 (21.01.02)
Applicant CADILA HEALTHCARE LTD.	

The applicant is hereby invited, within the time limit indicated below, to correct, by a notice submitted to the International Bureau, defects in the priority claim(s), as indicated in the Annex:

- Time limit to respond to this invitation (Rule 26bis.1(a)):
 - within 16 months from the (earliest) priority date; or
 - if the (earliest) priority date is changed as a result of the correction or addition of the (earliest) priority claim, within 16 months from that (earliest) priority date so changed,
 whichever expires first, provided that such a notice may, in any event, be submitted until the expiration of four months from the international filing date.

Failure to respond to this invitation within the prescribed time limit may result in the priority claim concerned to be considered, for the purposes of the procedure under the PCT, not to have been made (Rule 26bis.2(b)).

- In the case where multiple priorities have been claimed, this invitation relates to the following priority claim(s):

US	22 October 2001 (22.10.01)	Not yet allotted
----	----------------------------	------------------

- A copy of this invitation is being sent to the receiving Office.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Jean-Marc VIVET (Fax 338.87.40) Telephone No. (41-22) 338.83.38
--	--

The International Bureau has found the following defects in the priority claim(s):

1. Failure to Comply with the Requirements of Rule 4.10

a. ☐ National application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☒ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the country party to the Paris Convention for the Protection of Industrial Property, or of the Member of the World Trade Organization that is not party to that Convention, in which the earlier national application was filed.
- ☐ The country indicated is neither a party to the Paris Convention for the Protection of Industrial Property nor a Member of the World Trade Organization.

b. ☐ Regional application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the authority entrusted with the granting of regional patents under the applicable regional patent treaty.
- ☐ The authority indicated as the authority entrusted with the granting of regional patents does not grant regional patents.
- ☐ The priority claim in relation to the ARIPO application does not indicate either at least one country party to the Paris Convention for the Protection of Industrial Property, or at least one Member of the World Trade Organization, for which the earlier application was filed.

c. ☐ International application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the receiving Office with which it was filed.

2. Inconsistency with the Corresponding Indications in the Priority Document*

a. ☐ Inconsistency with regard to the filing date of the earlier application:

The request indicates:

The priority document indicates:

b. ☐ Inconsistency with regard to the number of the earlier application:

The request indicates:

The priority document indicates:

c. ☐ Inconsistency with regard to the country party to the Paris Convention for the Protection of Industrial Property or the Member of the World Trade Organization in which the national application was filed:

The request indicates:

The priority document indicates:

d. ☐ Inconsistency with regard to the authority entrusted with the granting of regional patents under the applicable regional patent treaty:

The request indicates:

The priority document indicates:

e. ☐ Inconsistency with regard to the receiving Office with which the international application was filed:

The request indicates:

The priority document indicates:

* Even if this defect is not corrected in response to this invitation, the priority claim concerned will not be considered not to have been made (Rule 26bis.2(b)).

The International Bureau has found the following defects in the priority claim(s):

1. Failure to Comply with the Requirements of Rule 4.10

- a. ☐ **National application**
- ☐ Missing indication of the filing date of the earlier application.
 - ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
 - ☒ Missing indication of the number of the earlier application.*
 - ☐ Missing indication of the country party to the Paris Convention for the Protection of Industrial Property, or of the Member of the World Trade Organization that is not party to that Convention, in which the earlier national application was filed.
 - ☐ The country indicated is neither a party to the Paris Convention for the Protection of Industrial Property nor a Member of the World Trade Organization.
- b. ☐ **Regional application**
- ☐ Missing indication of the filing date of the earlier application.
 - ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
 - ☐ Missing indication of the number of the earlier application.*
 - ☐ Missing indication of the authority entrusted with the granting of regional patents under the applicable regional patent treaty.
 - ☐ The authority indicated as the authority entrusted with the granting of regional patents does not grant regional patents.
 - ☐ The priority claim in relation to the ARIPO application does not indicate either at least one country party to the Paris Convention for the Protection of Industrial Property, or at least one Member of the World Trade Organization, for which the earlier application was filed.
- c. ☐ **International application**
- ☐ Missing indication of the filing date of the earlier application.
 - ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
 - ☐ Missing indication of the number of the earlier application.*
 - ☐ Missing indication of the receiving Office with which it was filed.

2. Inconsistency with the Corresponding Indications in the Priority Document*

- a. ☐ Inconsistency with regard to the filing date of the earlier application:
The request indicates:
The priority document indicates:
- b. ☐ Inconsistency with regard to the number of the earlier application:
The request indicates:
The priority document indicates:
- c. ☐ Inconsistency with regard to the country party to the Paris Convention for the Protection of Industrial Property or the Member of the World Trade Organization in which the national application was filed:
The request indicates:
The priority document indicates:
- d. ☐ Inconsistency with regard to the authority entrusted with the granting of regional patents under the applicable regional patent treaty:
The request indicates:
The priority document indicates:
- e. ☐ Inconsistency with regard to the receiving Office with which the International application was filed:
The request indicates:
The priority document indicates:

* Even if this defect is not corrected in response to this invitation, the priority claim concerned will not be considered not to have been made (Rule 26bis.2(b)).

The International Bureau has found the following defects in the priority claim(s):

1. Failure to Comply with the Requirements of Rule 4.10

a. ☐ National application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☒ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the country party to the Paris Convention for the Protection of Industrial Property, or of the Member of the World Trade Organization that is not party to that Convention, in which the earlier national application was filed.
- ☐ The country indicated is neither a party to the Paris Convention for the Protection of Industrial Property nor a Member of the World Trade Organization.

b. ☐ Regional application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the authority entrusted with the granting of regional patents under the applicable regional patent treaty.
- ☐ The authority indicated as the authority entrusted with the granting of regional patents does not grant regional patents.
- ☐ The priority claim in relation to the ARIPO application does not indicate either at least one country party to the Paris Convention for the Protection of Industrial Property, or at least one Member of the World Trade Organization, for which the earlier application was filed.

c. ☐ International application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the receiving Office with which it was filed.

2. Inconsistency with the Corresponding Indications in the Priority Document*

a. ☐ Inconsistency with regard to the filing date of the earlier application:

The request indicates:

The priority document indicates:

b. ☐ Inconsistency with regard to the number of the earlier application:

The request indicates:

The priority document indicates:

c. ☐ Inconsistency with regard to the country party to the Paris Convention for the Protection of Industrial Property or the Member of the World Trade Organization in which the national application was filed:

The request indicates:

The priority document indicates:

d. ☐ Inconsistency with regard to the authority entrusted with the granting of regional patents under the applicable regional patent treaty:

The request indicates:

The priority document indicates:

e. ☐ Inconsistency with regard to the receiving Office with which the international application was filed:

The request indicates:

The priority document indicates:

* Even if this defect is not corrected in response to this invitation, the priority claim concerned will not be considered not to have been made (Rule 26bis.2(b)).

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year) 27 February 2002 (27.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference ZRC-NIPR-002	International application No. PCT/IN02/00012

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

CADILA HEALTHCARE LTD. (for all designated States except US)
PANDEY, Bipin et al (for US)

International filing date : 21 January 2002 (21.01.02)
Priority date(s) claimed : 24 January 2001 (24.01.01)
22 October 2001 (22.10.01)

Date of receipt of the record copy
by the International Bureau : 14 February 2002 (14.02.02)

List of designated Offices :

AP : GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA : AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP : AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
OA : BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
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,SI,SK,SL,TJ,TM,TN,TR,
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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer: Jean-Marc VIVET (Fax 338.87.40) Telephone No. (41-22) 338.83.38
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Form PCT/IB/301 (April 2000)

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Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 27 February 2002 (27.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference ZRC-NIPR-002	International application No. PCT/IN02/00012

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase
- ☐ confirmation of precautionary designations
- ☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. It is **the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

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SUBRAMANIAM, NATARAJ & ASSOCIATES

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ZRC-NIPR-002

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16 December 2002

ORIGINAL BY COURIER

Dear Sir,

Re: CADILA HEALTHCARE LIMITED
PCT INTERNATIONAL APPLICATION No. PCT/IN00/00012
Filed on 21 January 2001
Priority Dates: 24/01/2001 (IN)
22/10/2001 (US)

We respectfully refer to the written opinion transmitted to us by Official communication dated 24 October 2002. The applicants have been afforded time up to 24 December 2002 to submit a reply.

The applicants respectfully submit that the claimed invention is novel and inventive over the prior art cited (whether taken individually or in combination) for the reasons submitted hereunder. It is therefore, respectfully requested that a favourable examination report is issued.

Taking the issues raised by the Hon'ble European Patent Office seriatim:

Re: Item I (Basis of the opinion)

The applicants have no comments with respect to the basis of the opinion

Re: Item V (Reasoned Statement)

The documents referred to have been noted. The applicants most respectfully submit that the documents cited in the International Search Report and relied upon in the Written Opinion do not affect the novelty or inventiveness of the invention covered by this PCT International application. Detailed explanation is given below:

The PCT International application is question relates to a process of manufacturing Clopidogrel. The aim of a process chemist is always to develop a better and more efficient process, with high yield, with enhanced operational simplicity (for example, crystallizing the desired isomer in the first step), reducing the number of steps as even altering the sequence of already known steps, increasing the overall yield as also improving the yield of each individual step, overcoming the drawbacks of existing processes, devising moderate reaction conditions, providing a clean product with lesser side products and impurities, providing an optically pure product without any contamination, recycling the unwanted isomer thereby reducing waste thus making it environment friendly, avoiding tedious column chromatography, devising reaction conditions to reduce the reaction time, devising a safer reaction scheme using less hazardous reactants as also milder reaction conditions and so on.

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All these above factors contribute to inventiveness and make a chemical process cost effective and commercially viable. If any one or more of the above mentioned objectives are fulfilled by an inventive process it should become a patentable subject matter. It is respectfully submitted that the following submissions will make it clear that the claimed process is novel and inventive:

The Learned Examiner's reasoning on the grounds of obviousness and novelty are based on the following documents:

1. Burgos et. al., *J of Labelled Compounds Radiopharm.* 43, 891-898 (2000) (XP008008850)
2. Jerry March: "Advanced Organic Chemistry" 1992, Wiley & Sons., New York (XP002215119 198280)
3. U. S. Pat. 4,529,596 (Aubert et. al.)
4. Najer et. al., *Bull. Soc. Chim. Fr.*, 1189-92 (1958) (XP002215118)

A. The article of reference no. 1, (XP008008850), describes a method of preparing [benzene-U-¹³C]-*rac*-Clopidogrel by *ortho*-Metalation / Chlorination of Benzoic acid derivatives using Strecker synthesis.

In connection with this document, it is respectfully submitted as follows:

I) Strecker synthesis:

Strecker reaction is a fairly old reaction as will be clear from

1. A Strecker, *Ann*, **75**, 27 (1850)
2. A. Strecker, *Ann*, **91**, 349 (1854)
3. Liebigs *Ann. Chem.*, **155**, 177 (1870) and relevant pages of Merck Index (Annexure 1).

However, in the referred citation, acetone cyanohydrin has been used as the source of cyanide while the applicants have used NaCN or KCN as the cyanide source. The source of cyanide being NaCN or KCN was also known from the very long time. Even the use of NaHSO₃ is known for several decades in prior art.

The prior art in question ((XP008008850)) suffers from some serious drawbacks such as:

- a) Low yield - 31%
- b) Presence of impurities of adducts formed from cyclic amine and acetone cyanohydrin (pages 894-895).
- c) Use of column chromatography for separation
- d) Scale of synthesis i.e. product isolated is only 744 mg.

The applicants' invention overcomes the above-mentioned problems and has the following advantages:

- a) Very high yield- 97% (Example 1)
- b) No impurity formation with the applicants' "cyano" source.
- c) No column chromatography required.
- d) Scale of synthesis - 24 gm product isolated (reported in our application, Example No.1).

In fact, the synthesis has been done at Kilogram level.

The applicants have also employed several variations of Strecker synthesis (see Ex. 1-9) with reactants, solvents etc., each providing different yield but all consistently much higher than reported in the prior art. Hence the applicants have advantageously used the ideas/concepts of known knowledge to develop a better process with high yield, no impurity and with reduced steps (not requiring column chromatography as was done in the referred prior art).

The learned Examiner will note that the applicants' claimed invention "yields unexpectedly improved properties, which is not present in the prior art." Therefore, it is respectfully submitted that the applicants' invention is novel and inobvious. (Patent Law Basics,

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Rosenberg, West Group, page 6-7;) (Annexure II). The improved properties in applicants' invention are better yields and operational simplicity.

The fact that inventing a process which improves the yield considerably or reduces the presence of impurities in the desired product, by minor modification of reactants, reaction conditions, etc., is a sufficient ground for the claimed process to be non-obvious and hence patentable is further corroborated by the following examples.

a) US 6,355,827, Komoschinski et. al., describes an improved process for preparing 2-cyanoindan-1-ones, where MeOH as solvent has been replaced by DMF:H₂O and the yield was improved from 70 % to 95%. (Annexure III)

In the applicants' present invention, the yield has improved from 31% to 97%.

b) US 6,201,135, Maywald et. al., describes a process of separating impurities from 3-(2'-acetoxy-ethyl-dihydro-2(3H)-furanone, according to a known process but uses a different purification process to get the purified product. (Annexure IV)

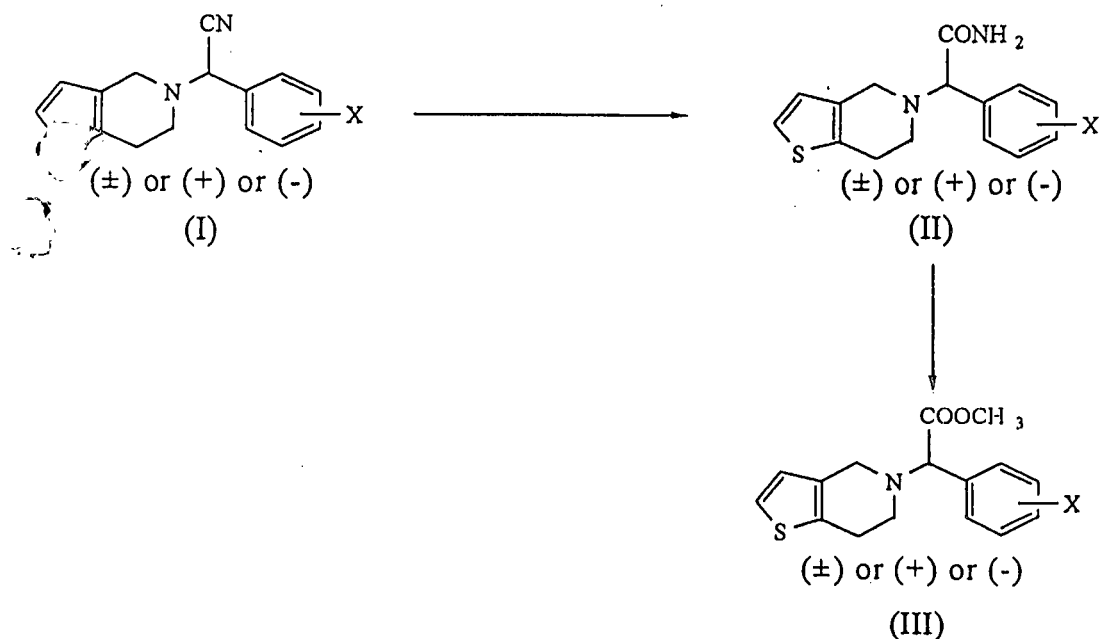
Similarly through the claimed process, the applicants obtain a pure product without involving further purification step.

c) US 6,037,503, Oren et. al., describes a process for the preparation of p-fluorophenol, where the "hydroxyl ion" source has been changed from Ca(OH)₂ to NaOH with a view to minimize impurities, get a high conversion and a clean reaction. (Annexure V)

The applicants' process also changes the source of CN⁽⁻⁾ from acetone cyanohydrin to NaCN or KCN, with a view to eliminate impurities, get a high conversion and consequently a better yield and a clean reaction.

d) US 6,107,490, Murthy et. al., describes a process for preparing 4-methyl-5-hydroxymethyl imidazole, where the reaction medium has been changed from base/water to K₂CO₃/isopropanol thereby improving the yield. (Annexure VI)

II) Conversion of nitrile to ester via amide:



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According to Burgos et. al. ((XP008008850)), the conversion was not carried out through saponification of the nitrile to amide, as there was a problem of retro-Strecker reaction (Burgos et. al., *J of Labelled Compounds Radiopharm.* 43, (2000) page 895, lines 2-4). Hence Burgos et. al. has carried out HCl promoted hydrolysis to amide in order to avoid retro Strecker and finally yielding low amount of product.

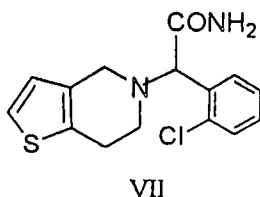
However, the applicants' process describes a modified process where saponification of nitrile (I) with KOH-t-BuOH yields amide (II) in high yield (94%) and without any retro-Strecker reaction (Example 10 of our specification). The high yield and cleanliness of the reaction is indeed noteworthy. Also, Example 18 (with KOH / isopropanol) of applicants' specification describes a process where the pure product precipitates out of the reaction mixture without extraction, simply by adding water, which offers advantage of operational simplicity.

A further problem with Burgos et. al's process is that it requires a long time (48 hours), azeotropic drying of reaction mass (page 897), whereas in the present process the reaction time required is 3 hours (Ex. 10, applicants' specification), and offers considerable advantage of operational simplicity, where the desired product precipitates out by simply adding water and without any extractive workup. All these issues i.e. time, operational simplicity, purity and avoidance of extractive workup adds up to better yields and commercial viability. Indeed such advantage of operational simplicity is not disclosed anywhere in the referred prior art.

The applicants would like to draw attention to the fact that they have actually solved the problems faced by the prior art and have improved the process significantly by doing what was stated as non-viable in the prior art. "Doing what the prior art references try to avoid is the antithesis of obviousness." (Patent Law Basics, Rosenberg, West Group, page 9-63). Also, for the present invention to be obvious, "there must be reasonable expectation of success" - US Manual of Patent Examination Procedure, (Patent Law Basics, Rosenberg, West Group, page 9-31), from what has been described in the prior art. However, in the present case the prior art in essence will discourage people from using saponification for obtaining the amide.

The applicants would also take this opportunity to highlight some other major features of their claimed invention.

The applicants' resolution process of ($\pm$) amide (VII), with 1S(+) CSA is not only unprecedented but it is technologically most desirable from the process perspective, since the desired dextro rotatory isomer (+) amide precipitates quantitatively in the very first attempt as diastereoisomer, without any contamination of unwanted (-) isomer or ($\pm$) isomer. (Ex. 31 of the applicants' specification). The optical purity of our product is 99.5%. There is no need for removal of impurity.



The applicants would like to draw the learned Examiner's attention to the following patent nos. US 4,546,201; US 4,515,811; GB 1,426,186 & GB 1,422,015 (Annexures VII, VIII, IX and X) all of which relate to the process of optical resolution of ($\pm$) 2-(6'-methoxy-2'-naphthyl) propanoic acid (Naproxen). The objective of all these patents have been to discover resolving agents and identify critical process parameters which avoids multiple crystallization and provides higher proportion of the desired d-isomer in a single crystallization step with improved quality (no contamination of unwanted l-isomer).

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Once again, the resolution of racemic ($\pm$) Naproxen in four patents confirms the applicants' contention that although conceptually one can argue that based on prior art, it is "obvious to try" but experience suggests that nobody could guarantee that such an experiment would have been expected to succeed.

"The governing standard is not whether a particular approach leading to an invention would be 'obvious to try', but whether such an experiment would have been expected to succeed" (Patent Law Basics, Rosenberg, West Group, page 9-58).

Besides there are other non-obvious features of the applicants' process:

- i) The applicants' resolving agent for cyclic amide is (+) CSA, which has not been reported for this synthesis.
- ii) The applicants' resolution of cyclic amide is unprecedented and its properties e.g. SOR (specific optical rotation) of diastereoisomer of VII with S(+) CSA = $+51^\circ$ (C=1, MeOH) and SOR of (+) amide (VII) = $+41^\circ$ (C=1, MeOH) are hitherto unknown (see Ex. 31)
- iii) The applicants' invention is, *inter alia*, that (+) nitrile (IV) gives (+) amide (V) and (+) amide gives (+) ester (I) is novel and non-obvious. No prior art can predict this.
- iv) The applicants process for converting (+) amide to (+) ester is both high yielding and without racemization.

In this context, it is relevant to note the drawbacks of the prior art reported by Burgos et. al.'s process ((XP008008850)), for conversion of racemic amide to racemic ester where a drastic condition of long reflux of 144 hours leads to only partial conversion of starting material, and low yield (overall 7%, page 895) of ester, with 26 % unreacted amide isolated by column chromatography.

- v) The applicants' process of conversion of diastereoisomeric salt of (+) amide / (+) CSA to (+) ester without any racemization in 97% yield in 26 hours (Ex. 37) is indeed unique and unprecedented. The very concept of converting a diastereoisomeric salt to the desired compound is new, novel and non-obvious.

- vi) The applicants' process also reports the racemization of the unwanted isomer and its recycling (see Ex. 43, 44, 45 & relevant claims (24, 25) which is not disclosed in any of the cited prior art. The applicants would like to state that the process of recycling and reuse of waste products has been considered a patentable invention as is evident from the grant of the following patents- (Annexures XII and XII):

- a) US 6,114,523, Allegrini et. al., describes a "Process of recycle and reuse of
- b) waste products in Diltiazem synthesis.
- c) US 5,082, 970, Braish, describes a "Process for recycling an amine isomer" which is involved in the synthesis of Sertraline.

The grant of above patents are noteworthy because such recycling of unwanted products not only add to the cost effectiveness of the process, but also decreases load on the environment by minimizing waste.

Besides, for process patents, where a process consists of more than a single step, the arrangement, order or sequence in which these component steps are to be performed may itself be of patentable significance. Thus, the patentability of a multi-step process may reside solely in the arrangement of its constituent steps – although each of the individual steps being old, the particular order constituting a new combination (Patent Law Basics, Rosenberg, West Group, page 6-6).

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In this context, the applicants' strategy of resolving the coupled cyclic nitrile (I) and / or amide (II), to their respective dextrorotatory isomers and then converting them to the final product S(+)-Clopidogrel, constitutes a new arrangement of its constituent steps - even if some of the racemic ($\pm$) intermediates e.g. labeled coupled nitrile and labeled coupled amide are known in the prior art.

The inventive merit of this strategy becomes more significant as this strategy will require less reagents for further transformation and will also reduce wastage of costly intermediates. It is a common knowledge that the cost of intermediates keeps on increasing as we proceed from starting material to final product in a multi-step synthesis. One would therefore, like to use cheaper intermediates by introducing resolution in the beginning of the synthetic ladder than resolving the costly final product at the end.

In conclusion the applicants would like to draw the attention of the Learned Examiner to the following facts which clearly shows the substantial improvement of their process over all known prior arts:

Our overall yield of 66.3%, in four steps is as follows:

- i) In the Strecker step - 97 % (Ex. 1)
- ii) Conversion of nitrile to amide - 94% (Ex. 10)
- iii) Resolution to diastereoisomers - 75% (Ex. 31)
- iv) Diastereoisomer to ester - 97% (Ex. 37)

With applicants' success with racemization and recycling of unwanted isomers, the resolution step yield goes above 95% from 75%, which further pushes our overall yield to not less than 84%.

On the contrary, Burgos et. al. report a 7 % overall yield for racemic ($\pm$) ester, Thus, on the ground of simple yield improvement also, one can not extrapolate and the applicants' invention is therefore, non obvious.

That increasing the yield of a known process is a patentable subject matter has been recognized by the patent office as is evident from US 6,355,827, Komoschinski et. al., (prior art yield was 70%, whereas improved yield is 95%), with a small modification of reaction conditions (change of solvent from methanol to a mixture of DMF/H₂O in 95:5) for the same reaction and same reagents (yield improvement only 1.35 fold). Compared to that our invention gives a 28 fold yield improvement, from not more than 3% (prior art) to not less than 84 %.

B. With respect to the citations from J. D. March (XP002215119 198280) the applicants would like to state the following:

i. According to the citation on page 842, the cyanide source referred to is acetone cyanohydrin. This reagent has been used in the process described by Burgos et. al. (*J of Labelled Compounds Radiopharm.* 43, 891-898 (2000); page 895) whereby the yield reported was very poor (31%; page 897). The applicants have not used acetone cyanohydrin as our source of cyanide. **The applicants have employed sodium cyanide as the nitrile source which results in a substantially higher yield of 97% (Example 1).** In fact, the applicants have not used any of the nitrile sources referred to in the citation of J. D. March. Based on simply the high degree of yield improvement the applicants' process becomes non-obvious.

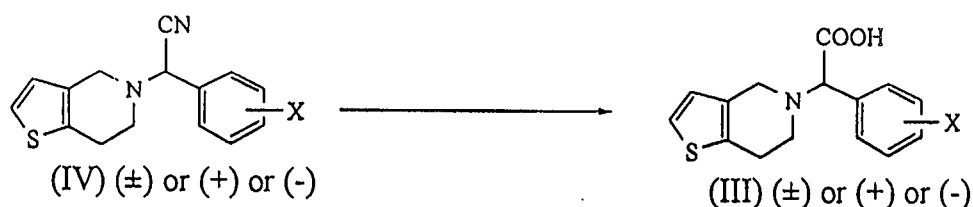
ii. The citations on pages 964, 965 (6-49), and 966 (6-51) speaks of the further fundamental reaction mechanism involved in the addition of HCN to an aldehyde, ketone or to a -C=N bond. It is also stated that "it is the bisulfite addition product that is treated with CN⁻" (page 965, 3rd line). Here again the applicants would like to state that their invention is an improved process for preparing a compound of industrial significance and for achieving this

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they have used known methodologies, reactants, reagents, reaction conditions etc. in a specific sequence whereby they have overcome the drawbacks of the prior art and also increased the efficiency and yield of the final product as well as intermediates to a level not reported anywhere in the prior art. Thus a citation which merely describes the mechanism involved and the preferable sequence of a very well known reaction generally, cannot render the applicants' invention obvious.

Thus it is the applicants' contention that the references of J. D. March merely teaches the general mechanism involved in the addition of a nitrile to an aldehyde, ketone or a $-C=N$ group but does in no way teaches their invention. Hence, it is the applicants' contention that our invention doesn't become obvious based on these cited documents.

C. The learned Examiner further states that Claim number 4 of the present invention lacks novelty because of Example no. 5 of US 4,529,596 (Aubert et. al.). However, the referred example describes a process of preparing α -[4,5,6,7-tetrahydro-thieno-[3,2-c]-5-pyridyl]-o-chlorophenylacetic acid from the corresponding ester compound using alkaline hydrolysis. However, the applicants' method of preparing the acid (III) as claimed in Claim 5 of the specification is by hydrolysis of the corresponding cyano compound (IV) in the presence of a suitable acidic/basic catalyst, in a suitable solvent.



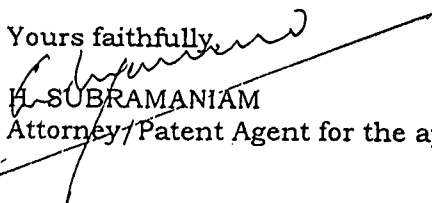
The applicants would like to state here that they have not claimed the compound of formula (III), which is widely known from long time as the first metabolite of Clopidogrel formed in the body. The process of preparation of (III) according to the applicants' application is in no way taught by the referred example. Hence, it is respectfully submitted that the cited reference does affect the novelty of our process, which is unique.

D. The last reference cited by the learned Examiner is the article by Najer et. al. (Bull. Soc. Chim. Fr., 1958, pages 1189-92) which according to the Examiner generally describes the state of the art which is of not much significance. We accept the learned Examiner's observation and do not have any comments to make.

In view of the above, it is respectfully requested that a favourable Examination report is issued.

No amendments are made to the claims or description at present.

Yours faithfully,


H. SUBRAMANIAM

Attorney/Patent Agent for the applicants

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash-II
New Delhi-110 048
INDE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)		24/10/2002
Applicant's or agent's file reference ZRC-NIPR-002		REPLY DUE within 2/00 months/days from the above date of mailing
International application No. PCT/ IN 02/ 00012	International filing date (day/month/year) 21/01/2002	Priority date (day/month/year) 24/01/2001
International Patent Classification (IPC) or both national classification and IPC C07D495/04		
Applicant CADILA HEALTHCARE LTD.		

- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
 - ☒ Basis of the opinion
 - ☐ Priority
 - ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application
- The applicant is hereby invited to reply to this opinion.

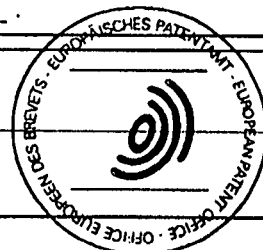
When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 24/05/2003

Name and mailing address of the IPEA/  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer Examiner Formalities officer (incl. extension of time limits) Tel. (+49-89) 2399 2828
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I. Basis of the opinion

1. The basis of this written opinion is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claims references).
2. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

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) ZRC-NIPR-002

Box No. I TITLE OF INVENTION	
PROCESS FOR PREPARING CLOPIDOGREL	
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.) CADILA HEALTHCARE LTD. Zydus Tower, Satellite Cross Roads Ahemdabad-380 015 Gujarat	
Telephone No. + 91 79 375 0603 Facsimile No. + 91 79 375 0606 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.) PANDEY, Bipin Zydus Tower, Satellite Cross Roads Ahemdabad-380 015 Gujarat	
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.) SUBRAMANIAM, Hariharan; NATARAJ, Guruswamy PRITHVIRAJ, Susheela, Attorneys- at-law & Patent Agents of SUBRAMANIAM, NATARAJ & ASSOCIATES E-556, Greater Kailash-II New Delhi-110 048	
Telephone No. +91 11 628 6012 Facsimile No. +91 11 628 6005 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)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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.)

LOHRAY, Vidya Bhushan
Zydus Tower, Satellite Cross Roads
Ahemdabad-380 015
Gujarat

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.)

LOHRAY, Braj Bhushan
Zydus Tower, Satellite Cross Roads
Ahemdabad-380 015
Gujarat

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.)

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.

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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 | ☒ MG Madagascar | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MN Mongolia | ☒ UZ Uzbekistan |
| ☒ EE Estonia | ☒ MW Malawi | ☒ VN Viet Nam |
| ☒ ES Spain | ☒ MX Mexico | ☒ YU Yugoslavia |
| ☒ FI Finland | ☒ MZ Mozambique | ☒ ZA South Africa |
| ☒ GB United Kingdom | ☒ NO Norway | ☒ ZM Zambia |
| ☒ GD Grenada | | ☒ ZW Zimbabwe |
| ☒ GE Georgia | | |
| ☒ 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(h) 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.)

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) 24 January 2001	84/MUM/2001	IN		
item (2) 22 October 2001	Not yet allotted	U.S.A		
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)	
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		:

This international application contains: (a) the following number of sheets in paper form: <table style="width: 100%;"> <tr> <td>request (including declaration sheets)</td> <td style="text-align: right;">5</td> </tr> <tr> <td>description (excluding sequence listing part)</td> <td style="text-align: right;">35</td> </tr> <tr> <td>claims</td> <td style="text-align: right;">5</td> </tr> <tr> <td>abstract</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings</td> <td style="text-align: right;">_____</td> </tr> <tr> <td>Sub-total number of sheets</td> <td style="text-align: right;">46</td> </tr> </table> sequence listing part of description (<i>actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below</i>) : _____ Total number of sheets : _____ (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 (<i>additional copies to be indicated under item 9(ii), in right column</i>): _____	request (including declaration sheets)	5	description (excluding sequence listing part)	35	claims	5	abstract	1	drawings	_____	Sub-total number of sheets	46	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): <table style="width: 100%;"> <tr> <td>1. ☒ fee calculation sheet</td> <td style="text-align: right;">1</td> </tr> <tr> <td>2. ☐ original separate power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>4. ☐ copy of general power of attorney; reference number, if any: _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;">:</td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s): _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>7. ☐ translation of international application into (language): _____</td> <td style="text-align: right;">:</td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;">:</td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (ii) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter</td> <td style="text-align: right;">:</td> </tr> <tr> <td> (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td> <td style="text-align: right;">:</td> </tr> <tr> <td>10. ☐ other (<i>specify</i>): _____</td> <td style="text-align: right;">:</td> </tr> </table>	1. ☒ fee calculation sheet	1	2. ☐ original separate power of attorney	:	3. ☐ original general power of attorney	:	4. ☐ copy of general power of attorney; reference number, if any: _____	:	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) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) 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 (<i>specify</i>): _____	:
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claims	5																																						
abstract	1																																						
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(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 (<i>specify</i>): _____	:																																						
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 <i>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).</i> SUBRAMANIAM, HARIHARAN Attorney-at-law, Regd. Patent Agent Patent Agent for the Applicants																																							
For receiving Office use only <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; padding: 5px;"> 1. Date of actual receipt of the purported international application: _____ </td> <td rowspan="3" style="width: 40%; padding: 5px; vertical-align: top;"> 2. Drawings: ☐ received: ☐ not received: </td> </tr> <tr> <td style="padding: 5px;"> 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: _____ </td> </tr> <tr> <td style="padding: 5px;"> 4. Date of timely receipt of the required corrections under PCT Article 11(2): _____ </td> </tr> <tr> <td style="padding: 5px;"> 5. International Searching Authority (if two or more are competent): ISA / </td> <td style="padding: 5px;"> 6. ☐ Transmittal of search copy delayed until search fee is paid </td> </tr> </table>		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																																
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3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: _____																																							
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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: _____																																							

PCT

FEE CALCULATION SHEET

Annex to the Request

Applicant's or agent's file reference		ZRC-NIPR-002		For receiving Office use only	
Applicant		CADILA HEALTH CARE LTD, applicants for all designated States except U.S.A, PANDEY, Bipin; LOHRAY, Vidya Bhushan & LOHRAY, Braj Bhushan, applicants only for U.S.A		International Application No.	
				Date stamp of the receiving Office	
CALCULATION OF PRESCRIBED FEES					
1. TRANSMITTAL FEE		Rs. 5000.00		T	
2. SEARCH FEE		USD, 866.00		S	
International search to be carried out by <u>EP</u> <i>(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)</i>					
3. INTERNATIONAL FEE Basic Fee Where item (b) of Box No. IX applies, enter Sub-total number of sheets } Where item (b) of Box No. IX does not apply, enter Total number of sheets }					
b1 first 30 sheets		USD 407.00		b1	
b2 15		x 9		= USD 135.00 b2	
number of sheets in excess of 30 fee per sheet					
b3 additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):					
400 x				= b3	
fee per sheet					
Add amounts entered at b1, b2 and b3 and enter total at B		USD 542.00		B	
Designation Fees The international application contains <u>115</u> designations.					
5		x 88		= USD 440.00 D	
number of designation fees payable (maximum 5) amount of designation fee					
Add amounts entered at B and D and enter total at I		USD 982.00		I	
<i>(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)</i>					
Rs. 3000.00				P	
4. FEE FOR PRIORITY DOCUMENT (if applicable)					
5. TOTAL FEES PAYABLE		Rs. 8000.00 + USD 1848.00			
Add amounts entered at T, S, I and P, and enter total in the TOTAL box		TOTAL			
☐ The designation fees are not paid at this time.					
MODE OF PAYMENT ☐ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons ☐ cheque ☐ bank draft ☐ revenue stamps ☐ other (specify):					
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT <i>(This mode of payment may not be available at all receiving Offices)</i>					
☐ Authorization to charge the total fees indicated above. ☐ <i>(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. ☐ Authorization to charge the fee for priority document.		Receiving Office: RO/ _____ Deposit Account No.: _____ Date: _____ Name: _____ Signature: _____			

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059128 A3

(51) International Patent Classification⁷: C07D 495/04

(21) International Application Number: PCT/IN02/00012

(22) International Filing Date: 21 January 2002 (21.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
84/MUM/2001 24 January 2001 (24.01.2001) IN
10/054,101 22 October 2001 (22.10.2001) US

(71) Applicant (for all designated States except US): CADILA HEALTHCARE LTD. [IN/IN]; Zydus Tower, Satellite Cross Roads, Gandhinagar-Sarkhej Highway, Ahmedabad 380 015, Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PANDEY, Bipin [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad-380 015, Gujarat (IN). LOHRAY, Vidya, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN). LOHRAY, Braj, Bhushan [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN).

(74) Agents: SUBRAMANIAM, Hariharan et al.; Subramaniam, Nataraj & Associates, E- 556, Greater Kailash - II, New Delhi 110 048, Maharashtra (IN).

(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, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (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, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

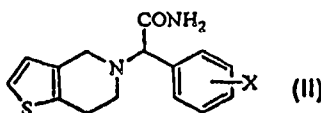
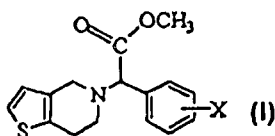
Published:

--- with international search report
--- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
19 December 2002

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

(54) Title: PROCESS FOR PREPARING CLOPIDOGREL



(57) Abstract: The present invention discloses a process for the preparation of thieno[3,2-c]pyridine derivatives of general formula (I), in either racemic or optically active (+) or (-) forms and their salts, wherein X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine,

chlorine, bromine or iodine. The present invention also describes a process for preparing the compounds of general formula (II), in either racemic or optically active (+) or (-) forms and their salts, where X, the substituent on benzene ring represents either a hydrogen or halogen atom such as fluorine, chlorine, bromine or iodine. The compounds represented by formulae (I) and (II) have one asymmetric carbon and hence, the optically active compounds of formula (I) or of formula (ii), may be obtained either by resolving the racemic intermediate/final product or using an optically active intermediate. The compounds of the invention are pharmacologically active and have significant anti-aggregating and anti-thrombotic properties.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/IN 02/00012

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JERRY MARCH: "Advanced Organic Chemistry" 1992, WILEY & SONS, NEW YORK XP002215119 198280 The HCN can be generated in situ from acetone cyanohydrin (see 6-49), avoiding the use of poisonous HCN. page 812 The addition of HCN ... This is an equilibrium reaction. page 964 Frequently it is the bisulfite addition product that is treated with CN- page 965 6-51 The addition of HCN to C=N and CN Bonds page 966 --- US 4 529 596 A (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application example 5 ---	1-3,5-28
A	NAJER ET AL.: "Nitriles, amides, thioamides et acides alpha-phenyle alpha-tertioaminoacötiques" BULL. SOC. CHIM. FR., 1958, pages 1189-92, XP002215118 Nitrile alpha-phenyle alpha-(tétrahydro-1,2,5,6)pyridinoacétiquw -----	4 1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00012

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 452956	A	16-07-1985	FR 2530247 A1	20-01-1984
			AT 25384 T	15-02-1987
			AU 554358 B2	21-08-1986
			AU 1663783 A	19-01-1984
			CA 1194875 A1	08-10-1985
			CS 8403815 A2	16-12-1985
			CS 8305281 A2	16-12-1985
			DD 211351 A5	11-07-1984
			DE 3369683 D1	12-03-1987
			DK 304183 A ,B,	14-01-1984
			EG 16540 A	30-12-1990
			EP 0099802 A1	01-02-1984
			ES 523943 D0	01-04-1984
			ES 8403901 A1	01-07-1984
			FI 832543 A ,B,	14-01-1984
			GR 79592 A1	31-10-1984
			HR 980261 A1	30-04-1999
			HU 187111 B	28-11-1985
			IE 55895 B1	14-02-1991
			IL 69049 A	31-03-1986
			JP 1000955 B	10-01-1989
			JP 1518778 C	07-09-1989
			JP 59027895 A	14-02-1984
			KR 8701270 B1	30-06-1987
			MX 9203264 A1	01-07-1992
			NO 832530 A ,B,	16-01-1984
			NZ 204874 A	24-01-1986
			OA 7491 A	31-03-1985
			PH 19375 A	02-04-1986
			PL 242965 A1	16-07-1984
			PT 77018 A ,B	01-08-1983
			SG 95287 G	23-11-1990
			SU 1272994 A3	23-11-1986
			YU 150683 A1	30-04-1986
			YU 197485 A1	31-10-1986
			ZA 8304705 A	28-03-1984

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash II
New Delhi 110 048
INDE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 20.03.2003

Applicant's or agent's file reference
ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.
PCT/IN02/00012

International filing date (day/month/year)
21/01/2002

Priority date (day/month/year)
24/01/2001

Applicant
CADILA HEALTHCARE LTD.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/



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 - 3016

Authorized officer

Cardenas, C

Tel. +31 70 340-3370



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-NIPR-002	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IN02/00012	International filing date (day/month/year) 21/01/2002	Priority date (day/month/year) 24/01/2001
International Patent Classification (IPC) or national classification and IPC C07D495/04		
Applicant CADILA HEALTHCARE LTD.		

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.

This report contains indications relating to the following items:

- I ☒ Basis of the report
- 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 Article 35(2) 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 19/08/2002	Date of completion of this report 20.03.2003
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 - 3016	Authorized officer Diederer, J Telephone No. +31 70 340 1097 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IN02/00012

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:

1-35 as originally filed

Claims, No.:

1-28 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)):

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IN02/00012

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

6. Additional observations, if necessary:

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	1-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IN02/00012

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Reference is made to the following documents:

D1: ALAIN BURGOS, JOHN M. HERBERT AND IAIN SIMPSON: 'ortho-Metalaton/Chlorination of Benzoic Acid Derivatives. Preparation of [benzene- U-13C]-rac-Clopidogrel ([benzene-U-13C]-rac-SR25990C)' J. LABELLED COMPD. RADIOPHARM., vol. 43, no. 9, 2000, pages 891-8, XP008008850

D2: JERRY MARCH: 'Advanced Organic Chemistry' 1992, WILEY & SONS, NEW YORK XP002215119 198280

D3: US-A-4 529 596 (AUBERT DANIEL ET AL) 16 July 1985 (1985-07-16) cited in the application

Re Item V

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

Article 33(3) PCT

The present application does not comply with Article 33(3) PCT as it is considered that the disclosure does not involve an inventive step.

Claim 1:

Claim deals with a process to prepare compounds of Formula I by a reaction of compounds V with MCN (VII) and aldehydes VI, subsequent hydrolysis to form II and then conversion to compounds I by reaction with methanol in acidic media.

The closest prior art document is D1. D1 discloses in Scheme 2, a synthesis of Clopidogrel by reaction of aldehyde 3 with thienopyridine 6 in the presence of acetone cyanohydrine to form compound 7 which is hydrolysed and esterified with MeOH. Acetone cyanohydrin is in equilibrium with acetone and HCN (as is general knowledge, disclosed in e.g. D2: 6-49). The difference of D1 with claim 1 of the present application is an extra resolution step (step 4). This resolution step does not render the claim inventive as it is a general method in the art to separate enantiomers by resolution. All the other dependent claims do not seem to contain features which, in combination with claim 1, render those claims inventive. Referring to the letter by the applicant it has to

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IN02/00012

be noted that claim 1 deals *inter alia* with HCN, not only with NaCN or KCN.

Claim 4:

Claim 4 deals with an hydrolysis of nitrile compounds IV. The closest prior art is D3 which discloses a similar hydrolysis of a thienopyridine ester under basic conditions to form a compound of Formula III. The difference is that in D3 a thienopyridine ester is hydrolysed whereas in the present application a thienopyridine nitrile is hydrolysed. It is however common knowledge that also nitrile compounds may be hydrolysed under the conditions as mentioned in claim 4. A skilled person would, starting from D3, easily substitute the ester with a nitrile group to come to the solution as presented in claim 4.

Claim 18

Claim 18 deals with three different processes to prepare compounds of formula IV. The closest prior art document is D1. In Scheme 2 nitrile 7 is produced by reaction of aldehyde 3 with thienopyridine 6, followed by addition of acetone cyanohydrin (HCN in situ). The difference of D1 with the second option of claim 18 (ii) is that the order of adding the reagents is different. It does not seem to make any difference at first sight and it is therefore obvious to change the order to render claim 18 novel. All the other dependent claims do not seem to contain features which, in combination with claim 18, render those claims inventive.

PATENT COOPERATION TREATY

244
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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E-556, Greater Kailash-II
New Delhi-110 048
INDIA

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

Date of mailing
(day/month/year)

02/04/2002

Applicant's or agent's file reference

ZRC-NIPR-002

REPLY DUE

See paragraph 1 below

International application No.

PCT/IN 02/00012

International filing date
(day/month/year)

21/01/2002

Applicant

CADILA HEALTHCARE LTD.

1. ☐ REPLY DUE within _____ ~~XXXX~~ days from the above date of mailing

☒ NO REPLY DUE

2. COMMUNICATION:

The applicant is informed that establishment of the international search report (ISR) for non first-filings may be delayed due to a current search backlog.

Although the time limit for entering the national phase before designated offices under Article 22(1) PCT and elected offices under Article 39(1) PCT has, with effect from 1 April 2002 (see PCT Gazette 44/2001 Section IV) been set at 30 months from the priority date (before the EPO the time limit is 31 months from the priority date - see Rule 107 EPC as amended with effect from 2 January 2002 - OJ EPO 8-9/2001, 373) not all PCT contracting states have yet made the necessary changes to their national laws and will for the time being continue to require entry to the national phase at 20/21 months from the priority date if a demand has not been filed before the end of 19 months from the priority date - see PCT Gazette/PCT Newsletter available on the WIPO internet site at <http://www.wipo.int/pct/en/index.html> for an up to date list of the applicable time limits.

In these circumstances, the EPO acting as IPEA will accept, without any late payment fee under Rule 58bis PCT, the handling fee and the preliminary examination fee due in respect of the demand relating to the present application, even if they are not paid within the time limit prescribed in Rules 57.3 and 58.1(b) PCT, provided that they are paid within one month from the date of transmittal of the ISR; i.e., the EPO will only send an invitation pursuant to Rule 58bis.1(a) PCT after expiry of this one-month period. In all cases where the EPO has sent an invitation to pay and the applicant has not paid in full the amount due, the demand shall be considered as if it had not been submitted (Rule 58bis.1(b)-(d) PCT). A loss of rights may well be the consequence in designated states where the time limit for entry into the national phase under Article 22 PCT has already expired (see also Article 37(4) PCT).

Note that if the competent IPEA chosen by the applicant is not the EPO and if the fees mentioned above are not paid within the time limit prescribed in Rules 57.3 and 58.1(b) PCT, the competent IPEA is entitled to apply Rule 58bis.1(a) PCT immediately thereafter.

If your application is affected, we apologise for any inconvenience caused.

Finally, applicants are reminded that as of 3 January 2002 a rationalised PCT II procedure may apply, see OJ EPO 11/2001, 539 and that the EPO as ISA will not carry out international search on an application which relates to no more than a method of doing business, see OJ EPO 10/2001, 482. Applicants should also bear in mind the restriction of the EPO's competence as ISA and IPEA in certain technical fields in respect of certain international applications, see OJ EPO 1/2002, 52 and PCT Newsletter 1/2002 for further details.

Name and mailing address of the International Searching Authority



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

Authorized officer

ISA/EP

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF RECEIPT
OF SEARCH COPY

(PCT Rule 25.1)

To:
SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E-556, Greater Kailash-II
New Delhi-110 048
INDIA

Date of mailing
(day/month/year)

02/04/2002

Applicant's or agent's file reference

ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.

PCT/IN 02/ 00012

International filing date (day/month/year)

21/01/2002

Priority date (day/month/year)

24/01/2001

Applicant

CADILA HEALTHCARE LTD.

1. Where the International Searching Authority and the Receiving Office are not the same office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the Receiving Office are the same office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

15/03/2002

(date of receipt).

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing in computer readable form.

3. Time limit for establishment of International Search Report

The applicant is informed that the time limit for establishing the International Search Report is 3 months from the date of receipt indicated above or 9 months from the priority date, whichever time limit expires later

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the Receiving Office.

Name and mailing address of the International Searching Authority



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

Authorized officer

ISA/EP

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDEDate of mailing (day/month/year)
03 April 2002 (03.04.02)Applicant's or agent's file reference
ZRC-NIPR-002

IMPORTANT NOTIFICATION

International application No.
PCT/IN02/00012International filing date (day/month/year)
21 January 2002 (21.01.02)International publication date (day/month/year)
Not yet publishedPriority date (day/month/year)
24 January 2001 (24.01.01)

Applicant

CADILA HEALTHCARE LTD. et al

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority datePriority application No.Country or regional Office
or PCT receiving OfficeDate of receipt
of priority document24 Janu 2001 (24.01.01)
22 Octo 2001 (22.10.01)84/MUM/2001
Not yet allottedIN
US13 Marc 2002 (13.03.02)
NRThe International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Cécile CHATEL (Fax 338.87.40)

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E- 556, Greater Kailash - II
New Delhi 110 048
Maharashtra
INDE

Date of mailing (day/month/year)

01 August 2002 (01.08.02)

Applicant's or agent's file reference

ZRC-NIPR-002

IMPORTANT NOTICE

International application No.

PCT/IN02/00012

International filing date (day/month/year)

21 January 2002 (21.01.02)

Priority date (day/month/year)

24 January 2001 (24.01.01)

Applicant

CADILA HEALTHCARE LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EA,EC,
EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,
MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,OM,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TN,TR,TT,

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the International application (Rule 49.1(a-bis)).

Enclosed with this notice is a copy of the International application as published by the International Bureau on

01 August 2002 (01.08.02) under No. WO 02/059128

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into national phase**

The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph** be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office. For further details, see PCT Gazette No.44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20,21,30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the PCT Applicant's Guide, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II.)

It is the applicant's sole responsibility to monitor all these limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

J. Zahra

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.91.11

PATENT COOPERATION TREATY

Faxed in advance!

PCT

9/12/2002

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLEFrom the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Subramaniam, Hariharan
SUBRAMANIAM, NATARAJ & ASSOCIATES
E-556, Greater Kailash-II
New Delhi-110 048
INDE

Fax no: 91-11-628-6005

Date of mailing
(day/month/year) 06-11-2002Applicant's or agent's file reference
ZRC-NIPR-002REPLY DUE
See paragraph 1 belowInternational application No.
PCT/IN 02/ 00012International filing date (day/month/year)
21/01/2002

Applicant

CADILA HEALTHCARE LTD.

1. ☒ REPLY DUE within 1 , months/days^{XX} from the above date of mailing
☐ NO REPLY DUE

2. COMMUNICATION:

The address on the demand IPEA401 differs from the one on
the request RO101.

Can you please clarify if address should be with or without
Gandhinagar-Sarkhej Highway.

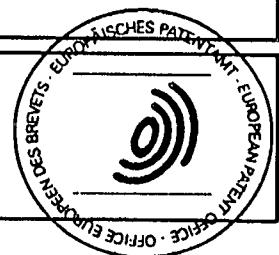
Name and mailing address of the IPEA/



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Cardenas, Claudette



PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF DEFECTS IN DEMAND

(PCT Rule 60.1(d))

To:

Mme Daniela GRAN
European Patent Office
Erhardtstrasse 27
D-80331 Munich
Germany

in its capacity as International Preliminary Examining Authority

Date of mailing

(day/month/year) 04 October 2002 (04.10.02)

International application No.

PCT/IN02/00012

International filing date

(day/month/year) 21 January 2002 (21.01.02)

Applicant

CADILA HEALTHCARE LTD. et al

The International Bureau hereby notifies the International Preliminary Examining Authority that it has found that the demand is defective for the reasons indicated below:

1. ☐ It does not contain the election of at least one Contracting State bound by Chapter II (Rule 53.2(a)(iv) and 53.7).
2. ☐ It does not permit the identification of the international application to which it relates (Rule 60.1(b)).
3. ☐ It does not contain the required petition (Rules 53.2(a)(i) and 53.3).
4. ☐ It does not contain the required indications concerning the agent as specified in the Annex (Rules 53.2(a)(ii) and 53.5).
5. ☐ It does not contain the required indications concerning the international application as specified in the Annex (Rules 53.2(a)(iii) and 53.8).
6. ☐ It is not submitted in the required language which is _____ (Rule 55.1).
7. ☐ It is not made on the printed form (Rule 53.1(a)).
8. ☐ It is presented as a computer print-out the particulars of which do not comply with the Administrative Instructions (Rule 53.1(a)).
9. ☒ It does not contain the required indications concerning the applicant as specified in the Annex (Rules 53.2(a)(ii) and 53.4).
10. ☐ It does not contain the required signature as specified in the Annex (Rules 53.2(b) and 53.8).

Other observations, if necessary:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer

Sébastien CLAVERI (Fax 338.87.40)

Telephone No.: (41-22) 338.83.38

Form PCT/IB/336 (September 1993)

18-10-2002

NOTIFICATION OF DEFECTS IN DEMAND

PCT/IN02/00012

Continuation of item 4: As to indications concerning the agent (Rule 4.4), the demand:

- a. ☐ does not properly indicate the agent's name (specify):
- b. ☐ does not indicate the agent's address.
- c. ☐ does not properly indicate the agent's address (specify):

Continuation of item 5: As to indications concerning the international application, the demand does not indicate:

- a. ☐ the international filing date.
- b. ☐ the international application number.
- c. ☐ the name of the receiving Office, where the international application number was not known to the applicant at the time the demand was filed.
- d. ☐ the title of the invention.

Continuation of item 9: As to indications concerning the applicant (Rules 4.4 and 4.5), the demand:

- a. ☐ does not indicate all the applicants for the elected States.
- b. ☐ does not properly indicate the applicant's name (specify):
- c. ☐ does not indicate the applicant's address.
- d. ☒ does not properly indicate the applicant's address (specify):
- e. ☐ does not indicate the applicant's nationality.
- f. ☐ does not indicate the applicant's residence.

Continuation of item 10: As to requirements concerning signature (Rules 4.15 and 90.4), the demand:

- a. ☐ is not signed.
- b. ☐ is not signed by all the applicants for the elected States.
- c. ☐ is not accompanied by the statement referred to in the check list in Box No. VI of the demand explaining the lack of the signature of an applicant for the election of the United States of America.
- d. ☐ is signed by what appears to be an agent/common representative but
- ☐ the demand is not accompanied by a power of attorney appointing him.
- ☐ the power of attorney accompanying the demand is not signed by all the applicants for the elected States.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:
SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E-556, Greater Kailash-II
New Delhi-110 048
INDIA

Date of mailing
(day/month/year) 17/10/2002

Applicant's or agent's file reference
ZRC-NIPR-002

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
CT/ IN 02/ 00012

International filing date
(day/month/year) 21/01/2002

Applicant

CADILA HEALTHCARE LTD.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

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

Authorized officer

John De Bruijn

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16, and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

COMPLETA (X)

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 y 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:

Eduard Navarro

02-07-2003

Fecha: