



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

Division de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21 EXPEDIENTE No

06-55464

54 TITULO "PROCESO PARA LA PREPARACION DE
ANINO ALCOHOLES SUSTITUIDOS"

51 CLASIFICACION INTERNACIONAL C07C 213/00, A61K 31/505

71 SOLICITANTE WYETH

DOMICILIO NUEVA JERSEY, ESTADO UNIDO

74 APODERADO ALVARO CORREA ORDONEZ
TP 20281

22 BOGOTA, D C, JUNIO 8, 2006

Publicacion
EN 10 2006

PETITORIO

000001

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Rad: 08-055484-00000-0000

Fec: 2005-06-08 16:04:17 Dep. 2020 NUECREACIONES ICación

Tra. 11 PATENTEYB

Evo: 378 FASENACIONALJ

Act: 411 PRESENTACION

Folios: 89

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

①

SOLICITUD DE

☒

Patente de Invención

☐

Patente de Modelo de Utilidad

☒

Capítulo I

☐

Capítulo II

②

SOLICITANTE
(71)

Nombre WYETH

Dirección Five Giralda Farms, Madison NJ 07940 Estados Unidos de América

Nacionalidad o Domicilio Nueva Jersey Estados Unidos de América
Lugar de Constitución

Teléfono

Fax

E Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre ALVARO CORREA ORDOÑEZ

Dirección Avenida 82 No.10-62 Piso 6

Teléfono 634 1500

Fax 376 2211

E Mail office bogota@bakernet.com

IDENTIFICACION

C.C.

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NIT

☐

C.E.

☐

Otro

☐

Cual

79 143 366 de

Número

Usaquén

TP 20.281

④

INVENTOR (ES)
(72)

Nombre WU Yanzhong RUBEZHOV Arkadiy SCHMID Jean AFRAGOLA Jay Thomas

Dirección 1580 Pelham Parkway South Apartment 4K, Bronx, NY 10461 (US) 3 Fawn Court, West Nyack, NY 10994 (US) 17 Jeffrey Drive Chester NY 10918 (US) 141 Heitman Drive Apartment F Spring Valley NY 10977 (US)

Nacionalidad o Domicilio Estadounidense, estadounidense, canadiense y estadounidense, respectivamente

⑤

PCT (85)

Solicitud Internacional No PCT/US2004/040855

Fecha 07 DIC-04

Publicación Internacional No WO 2005/056514 A2

Fecha 23-JUN-05

⑥

Título (54)

PROCESO PARA LA PREPARACIÓN DE AMINO ALCOHOLES SUSTITUIDOS

⑦

Clasificación Internacional (51)

C07C 213/00

1 A 6 C K 34.085

⑧

Prioridad

SI ☒NO ☐

(33) País de Origen

US

(32) Fecha

08 DIC-03

(31) Número de Solicitud

60/527 930

⑨

Comprobante de pago No 08-41589

Fecha 02-JUN-06

10

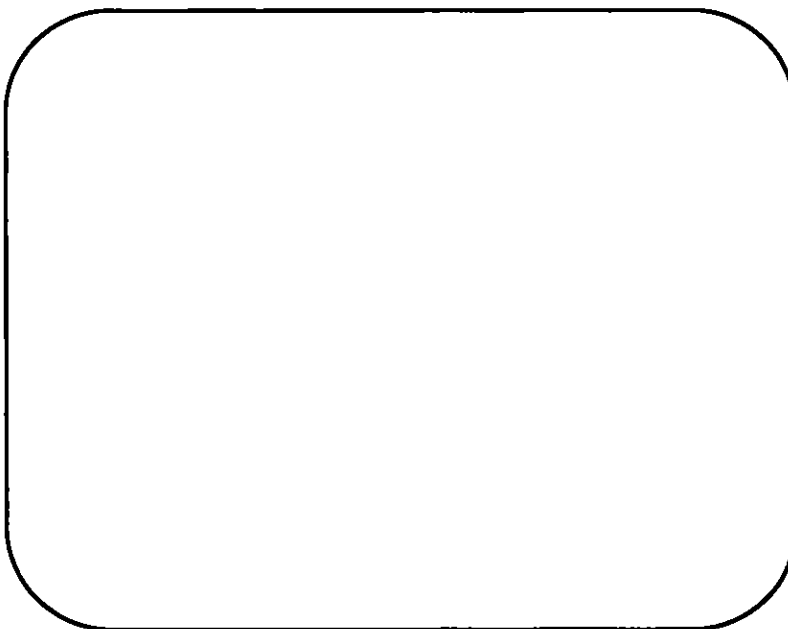
ANEXOS

000007

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes si fuere el caso
- ☒ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional (Resumen descripción reivindicaciones dibujos)
- ☒ Traducción de la solicitud Internacional al castellano (Resumen descripción reivindicaciones dibujos)
- ☐ Copia del examen preliminar Internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar Internacional 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
- ☐ De ser el caso información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso modificaciones efectuadas a la solicitud Internacional
- ☒ Otros Extractos publicación propleitario y temático reporte de búsqueda y republicación WO2005/056541 A3

11

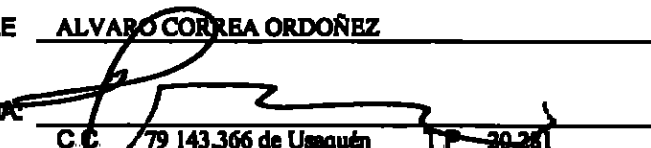
FIGURA CARATERISTICA



12

Solicito la concesión de la patente

NOMBRE ALVARO CORREA ORDOÑEZ

FIRMA 

C.C. 79 143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos ver reverso de esta página

[0 1 0
- 000003

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-055484-00000-0000
Fec: 2008-06-08 10:04:17 Dep: 2020 NUECREACIONES
Tom: 11 PATENTEYII
Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 89

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 41,599
FECHA : JUNIO 2 DE 2006

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	030-00110-6	36559816	02/06/2006	30,057,000 00

C O N C E P T O

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL DE PATENTE DE IN	463,000 00
		TOTAL :	463,000 00

SOM CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE _____

TRADUCCIÓN OFICIAL No 207/06 de un documento escrito en Inglés, el cual para su identificación se sella con el sello del Traductor Esta es una Traducción Oficial efectuada el día 5 de junio de 2006 por la Sra Maria Teresa Lara, c c 41 568 055 de Bogotá, Traductora Oficial según Resolución No 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia

=====

Declaración Juramentada (Affidavit) de WYETH respecto de solicitud de patente para "Proceso para Preparación de Amino Alcoholes Sustituidos"

Certificación notarial suscrita por Barbara A Kiely, Notario Publico del estado de Nueva Jersey, y legalizaciones subsiguientes

AM101562 L1

DECLARACIÓN JURAMENTADA

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE OCTUBRE DE 1998

Yo, Michelle L McGowan, Asociada para Legalizaciones, Wyeth, certifico por la presente que la copia adjunta ha sido comparada con la Cesión original (para el expediente No AM101562 L1 de Wyeth correspondiente a la U S S N 60/527,930, y cualquier equivalente legal de la misma en un país extranjero, para el invento titulado "PROCESO PARA PREPARACIÓN DE AMINO ALCOHOLES SUSTITUIDOS") fechada el 8 de diciembre de 2003 de Yanzhong Wu, Arkadly Rubezhov, Jean Schmid y Jay Thomas Afragola a Wyeth y que la citada copia es fiel copia del original

Dado a los 8 días del mes de febrero de 2006, en Madison, Nueva Jersey, Estados Unidos de América

Wyeth

(Fdo) Michelle L McGowan

Michelle L McGowan
Asociada para Legalizaciones

RECONOCIMIENTO

Estado de Nueva Jersey)
)
 Condado de Morris)

A los 8 días del mes de febrero de 2006, ante mí personalmente compareció Michelle L. McGowan, Asociada para Legalizaciones de Wyeth, a quien conozco y de quien me consta que es la persona descrita en el instrumento anterior y quien lo suscribió, y reconoció ante mí haber suscrito el mismo.

**(Sello notarial
en relieve)**

[Sello] Barbara A Klely ID 33893
Notario Publico de Nueva Jersey
MI comisión expira el 20 de junio de 2009

Expediente No AM101562 L1
Patente

Para ☒ Derechos en los E U y/o ☒ Extranjeros
Para ☒ Solicitud en los E U o ☐ Patente de los E U

Ceslón de Invento

En virtud del pago por la CESIONARIA al CEDENTE de contraprestación válida, el recibo de la cual se reconoce por el presente, el CEDENTE

(1) **Nombre Completo del Inventor** Yanzhong WU
Residencia 1580 Pelham Parkway S , Apt 4K, Bronx, NY 10461
Ciudadanía Estados Unidos de America

(2) Nombre Completo del Inventor Arkadly RUBEZHOV

Residencia 3 Fawn Court, West Nyack, NY 10994

Ciudadanía Estados Unidos de América

(3) Nombre Completo del Inventor Jean SCHMID

Residencia 17 Jeffrey Drive, Chester, NY 10918

Ciudadanía Canadá

(4) Nombre Completo del Inventor Jay Thomas AFRAGOLA

Residencia 141 Heltman Drive, Apt F, Spring Valley, NY 10977

Ciudadanía Estados Unidos de América

por la presente vende, cede y traspasa a la CESIONARIA

Wyeth
Five Giralda Farms
Madison, Nueva Jersey 07940

y los sucesores, cesionarios y representantes legales de la CESIONARIA, todo derecho, título e Interés para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluyendo todo los derechos a reclamar prioridad, en y sobre el invento titulado

PROCESO PARA PREPARACIÓN DE AMINO ALCOHOLES SUSTITUIDOS

e inventado por el CEDENTE y los siguientes Inventores adicionales, en caso de haberlos

y la cual se encuentra en

[marcar y completar (a), (b), (c), (d) o (e)]

(a) ☐ solicitud de patente de los E U de igual fecha que la presente

(b) ☐ solicitud de patente de los E U suscrita el

(c) ☒ solicitud provisional de los E U, no presentada aun, que nombra al(los) inventor(es) anterior(es) para el invento de la referencia

☒ etiqueta de correo expreso no EU673382151US

TERESA LARA R
TRADUCTORA OFICIAL
REGISTRADA EN EL
DEPARTAMENTO DE JUSTICIA

(d) ☐ Solicitud de Patente de los E U No presentada
el

(e) ☐ Patente de los E U No expedida el

[marcar también si se están cediendo solicitud(es) extranjera(s)]

(f) ☒ y cualquier equivalente legal de las mismas en un país
extranjero,

incluyendo el derecho a reclamar prioridad, incluidas todas y cada una de las mejoras allí divulgadas, y en y sobre todas las Patentes que hayan de obtenerse para dicho invento en virtud de la solicitud anterior o cualquier solicitud provisional, no provisional, de continuación, divisional, de renovación o sustituta de la misma posteriormente presentada, y respecto de Patentes cualquier reemisión o reexamen de las mismas

“IA TERESA IUBA R.
TRADUCTORA ESPECIAL
REBOLOZON Y A. PABLO
DE MEXICO”

El CEDENTE pacta por el presente que no se ha hecho ni se hará ni se realizará ninguna cesión, venta, acuerdo o gravamen que pudiese entrar en conflicto con esta cesión

El CEDENTE autoriza a la CESIONARIA a presentar solicitudes y recibir Patentes para dicho invento en cualquiera de dichos países en su propio nombre, o en nombre de la CEDENTE, a su elección

El CEDENTE pacta y acuerda suscribir u obtener cualquier garantía adicional necesaria del título sobre dicho invento y cualquier Patente que pueda emitirse para la misma, en cualquier momento, y a solicitud y por cuenta de la CESIONARIA entregar cualquier testimonio en cualquier interferencia, litigio o proceso relacionado con la misma y otorgar todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título sobre dicho invento o cualquier Patente que pueda otorgarse para la misma en la CESIONARIA, sus sucesores, cesionarios u otros representantes

legales y que, en cualquier momento, a solicitud y por cuenta de la CESIONARIA suscriba cualquier continuación, continuación en parte, solicitud divisional, renovación o sustituta de la misma, y en cuanto a Patentes y reemisión o reexamen de las mismas, o cualquier otra solicitud adicional de Patente para dicho invento o cualquier parte del mismo, todas las cuales solicitudes y cualesquiera Patentes que se expidan sobre las mismas son por la presente cedidas a la CESIONARIA, y hará todo los juramentos o declaraciones lícitos, y realizará todo los actos lícitos requeridos para adquirir las mismas, sin otra compensación, pero por cuenta de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales

El CEDENTE autoriza y solicita al Comisionado de Patentes expedir todas y cada una de las Patentes de los Estados Unidos para dicho invento, resultantes de cualquiera de las anteriores solicitudes para su CESIONARIA

(Fdo) Yanzhong WU
Yanzhong WU

Dic 8, 2003
Fecha

TERESA LARA R.
TRADUCTORA CERTIFICADA
BOLETA N.º 10.810
DE ABOGADO

RECONOCIMIENTO

Estado de Nueva York }
 ss
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, compareció personalmente ante mí Yanzhong WU, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados

(Fdo) Daniel B Moran
Notario Publico

[Sello] DANIEL B MORAN
Notario Publico, Estado de Nueva York
No 01MO4944023
Habilitado en el Condado de Rockland
La comisión expira el 14 de noviembre de 2006

(Fdo) Arkadly RUBEZHOV
Arkadly RUBEZHOV

Dic 8, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss
Condado de Rockland }

A los 8 dias del mes de diciembre de 2003, compareció personalmente ante mí
Arkadly RUBEZHOV, a quien conozco como la misma persona descrita y que
otorgó el Instrumento anterior, y reconoció haber otorgado el mismo, por su
propla voluntad y para los propósitos allí señalados

(Fdo) Janice A White
Notario Publico

[Sello] JANICE A WHITE
NOTARIO PUBLICO-ESTADO DE NUEVA YORK
NO 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

(Fdo) Jean SCHMID
Jean SCHMID

Dic 8, 2003
Fecha

RECONOCIMIENTO

TERESA LARA R.
TRADUCTORA CERTIFICADA
RESOLUCION T.A. P. 876
DE JUSTICIA

Estado de Nueva York }
 ss
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, compareció personalmente ante mi
Jean SCHMID, a quien conozco como la misma persona descrita y que otorgó
el Instrumento anterior, y reconoció haber otorgado el mismo, por su propia
voluntad y para los propósitos allí señalados

(Fdo) Daniel B Moran
Notario Publico

[Sello] DANIEL B MORAN
Notario Publico, Estado de Nueva York
No 01MO4944023
Habilitado en el Condado de Rockland
La comisión expira el 14 de noviembre de 2006

TERESA IUBA R.
TRADUCTORA C.P.E.
RESOLUCION 74. P. 1870
DE MINISTERIA

(Fdo) Jay Thomas Afragola
Jay Thomas AFRAGOLA

Diciembre 8, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss
Condado de Rockland }

A los 8 días del mes de diciembre de 2003, comparecio personalmente ante mí
Jay Thomas AFRAGOLA, a quien conozco como la misma persona descrita y
que otorgó el Instrumento anterior, y reconoció haber otorgado el mismo, por
su propia voluntad y para los propósitos allí señalados

(Fdo) Daniel B Moran
Notario Publico

[Sello] DANIEL B MORAN
Notario Publico, Estado de Nueva York
No 01MO4944023
Habilltado en el Condado de Rockland
La comislón expira el 14 de noviembre de 2006

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

- 1 Pais Estados Unidos de América
- 2 Este documento publico ha sido firmado por Barbara A Kiely
- 3 actuando en calidad de Notario Publico de Nueva Jersey
- 4 lleva el sello/timbre de Barbara A Kiely, Notario

CERTIFICADO

- 5 en Trenton, Nueva Jersey
- 6 el día 10 de febrero de 2006
- 7 por Bradley I Abelow, TESORERO DE NUEVA JERSEY
- 8 No A251419
- 9 Sello/Timbre
- 10 Firma
- (Sello del Estado de Nueva Jersey)
- (Fdo) Bradley Abelow

=====

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación



María Teresa Lara R
c c 41 568 055 de Bogotá
Traductora Oficial segun
Resolución No 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINISTERIO DE JUSTICIA

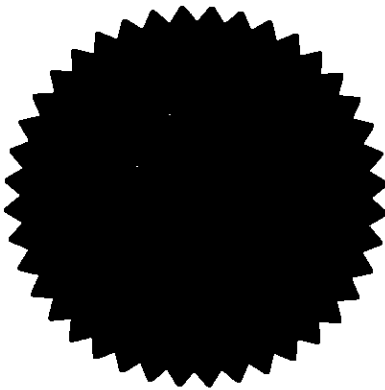
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

- 1 COUNTRY UNITED STATES OF AMERICA
2 THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY
BARBARA A KIELY
3 ACTING IN THE CAPACITY OF
NOTARY PUBLIC OF NEW JERSEY
4 BEARS THE SEAL/STAMP OF
BARBARA A KIELY NOTARY

CERTIFIED

- 5 AT TRENTON NEW JERSEY
6 THE 10TH DAY OF FEBRUARY 2006
7 BY Bradley I Abelow NEW JERSEY TREASURER
8 NO A251419
9 SEAL/STAMP 10 SIGNATURE

*Bradley Abelow*

Teresa Lara R.
TIA TERESA LARA R.
TRADUCTORA OFICIAL
-BOLETA N.º 01076
DE MICHIGAN 207/06

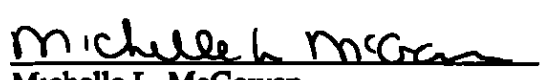
AM101562 L1

AFFIDAVIT

I Michelle L. McGowan Legalization Associate Wyeth, do hereby certify that the attached copy has been compared with the original Assignment (for Wyeth s docket no AM101562 L1 corresponding to U S S N 60/527 930 and any legal equivalent thereof in a foreign country for the invention entitled PROCESS FOR PREPARATION OF SUBSTITUTED AMINO ALCOHOLS) dated December 8 2003 from Yanzhong Wu, Arkadiy Rubezhov Jean Schmid and Jay Thomas Afragola to Wyeth and that the said copy is a true copy of the original

Dated this 8th day of February 2006, at Madison New Jersey United States of America

Wyeth


Michelle L. McGowan
Legalization Associate

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 8th day of February, 2006 before me personally appeared Michelle L. McGowan, Legalization Associate of Wyeth, to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same


Notary Public

Barbara A. Klely ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009

For ☒ U S and/or ☒ Foreign Rights
For ☒ U S Application or ☐ U S Patent

Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration the receipt of which is hereby acknowledged
ASSIGNOR

(1) Full Name of Inventor Yanzhong WU
Residence 1580 Pelham Parkway S Apt 4K Bronx NY 10461
Citizenship United States of America

(2) Full Name of Inventor Arkady RUBEZHOV
Residence 3 Fawn Court West Nyack NY 10994
Citizenship United States of America

(3) Full Name of Inventor Jean SCHMID
Residence 17 Jeffrey Drive Chester NY 10918
Citizenship Canadian Canada JS J.B.M.

(4) Full Name of Inventor Jay Thomas AFRAGOLA
Residence 141 Heltman Drive Apt. F Spring Valley NY 10977
Citizenship United States of America JTA J.B.M.

(5) Full Name of Inventor
Residence
Citizenship

(6) Full Name of Inventor
Residence
Citizenship

hereby sells assigns and transfers to ASSIGNEE

Wyeth
Five Giralda Farms
Madison New Jersey 07940

and the successors assigns and legal representatives of the ASSIGNEE the entire right title and interest for the United States and its territorial possessions and in all foreign countries including all rights to claim priority in and to the invention entitled
PROCESS FOR PREPARATION OF SUBSTITUTED AMINO ALCOHOLS

and invented by ASSIGNOR and the following additional inventors if any

and which is found in

[check and complete (a) (b) (c) (d) or (e)]

- (a) ☐ U S patent application executed on even date herewith
(b) ☐ U S patent application executed on
(c) ☒ U S provisional application not yet filed naming the above inventor(s) for the above-entitled invention
☒ Express mail label no EU673382151US
(d) ☐ U S Patent Application No filed on
(e) ☐ U S Patent No issued on

[also check (f) if foreign application(s) is(are) also being assigned]

- (f) ☒ and any legal equivalent thereof in a foreign country

including the right to claim priority including any and all improvements disclosed therein and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional nonprovisional continuation divisional renewal or substitute thereof and as to Letters Patent any reissue or re-examination thereof

ASSIGNOR hereby covenants that no assignment sale agreement or encumbrance has been or will be made or entered into which would conflict with this assignment

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name or in ASSIGNOR's name at its election

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to at any time upon the request and at the expense of ASSIGNEE deliver any testimony in any interference litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE its successors assigns or other legal representatives and that to at any time upon the request and at the expense of ASSIGNEE execute any continuation continuation in part divisional renewal or substitute thereof and as to Letters Patent and reissue or re-examination thereof or any other additional applications of Letters Patent for said invention or any part thereof all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE and will make all rightful oaths or declarations and do all lawful acts requisite for procuring the same therein without further compensation but at the expense of ASSIGNEE its successors assigns or other legal representatives

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention resulting from any of the aforesaid applications to its ASSIGNEE

Yanzhong WU
Yanzhong WU

Dec 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss.

On the 8th day of December 2003 Yanzhong WU personally appeared before me known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same of his/her own free will and for the purposes set forth

DANIEL B MORAN
Notary Public State of New York
No. 01MO4944023
Qualified in Rockland County
Commission Expires Nov 14 2006

[Signature]
Notary Public

Arkady RUBEZHOV
Arkady RUBEZHOV

Dec 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss.

On the 8 day of December 2003 Arkady RUBEZHOV personally appeared before me known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same of his/her own free will and for the purposes set forth

[Signature]
Notary Public

JANICE A. WHITE
NOTARY PUBLIC STATE OF NEW YORK
NO. 01 WH8062804
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-28-2006

Jean Schmid
Jean SCHMID

Dec. 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland }
ss

On the 8th day of December 2003 Jean SCHMID personally appeared before me known by me to be the same person described in and who executed the foregoing Instrument, and acknowledged that he/she executed the same of his/her own free will and for the purposes set forth

DANIEL B. MORAN
Notary Public, State of New York
No. 01MO4944023
Qualified in Rockland County
Commission Expires Nov 14 2006

Daniel B. Moran
Notary Public

Jay Thomas AFRAGOLA
Jay Thomas AFRAGOLA

December 8, 2003
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland }
ss

On the 8th day of December 2003 Jay Thomas AFRAGOLA personally appeared before me known by me to be the same person described in and who executed the foregoing Instrument, and acknowledged that he/she executed the same of his/her own free will and for the purposes set forth

DANIEL B. MORAN
Notary Public, State of New York
No. 01MO4944023
Qualified in Rockland County
Commission Expires Nov 14 2006

Daniel B. Moran
Notary Public

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
23 June 2005 (23.06.2005)

PCT

(10) International Publication Number
WO 2005/056514 A2

(51) International Patent Classification⁷ C07C 213/00

(21) International Application Number⁷
PCT/US2004/040855

(22) International Filing Date: 7 December 2004 (07.12.2004)

(25) Filing Language English

(26) Publication Language: English

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(54) Title: PROCESS FOR PREPARATION OF SUBSTITUTED AMINO ALCOHOLS

(57) Abstract. There is provided a process for the preparation of substituted amino alcohols $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$ from haloalcohols $\text{HO}-(\text{CH}_2)_n-\text{X}$ where X is Cl, Br or I, by reaction with an amine HNR^1R^2 in water as solvent at a temperature range of about 20°C to about 90°C optionally in the presence of a catalytic amount of an iodide source³ metal iodides. The haloalcohols are useful in the preparation of 6-[(substituted)phenyl] triazolopyrimidine compounds which are useful in the treatment of cancer

WO 2005/056514 A2

smo

Described by Kabalka, George W LI Nan-Sheng and Pace R David
 Synthetic Communications (1995) 25(14) 2135-43 is the preparation of amino
 alcohols by the N-t-butoxycarbonyl protection of primary and secondary amines via a
 hydroboration-oxidn reaction sequence

5

Disclosed by Artyushin O I , Petrovskii P V Mastryukova T A. Kabachnik, M
 I Izvestiya Akademii Nauk SSSR Seriya Khimicheskaya (1991) (9) 2154-7 is
 the simple synthesis of 3-(alkylamino)-1-propanols by condensing for example
 10 $\text{NH}_2(\text{CH}_2)_3\text{OH}$ with ClCO_2Me in CH_2Cl_2 containing Na_2CO_3 which gave
 $\text{MeNH}(\text{CH}_2)_3\text{OH}$ in 37% yield

A. Parkkinen et al Journal of Physical Organic Chemistry (1991) 4(1) 53-7
 describes the hydrolytic decomposition of methyltetrahydrooxazines to afford for
 15 example $\text{MeNH}(\text{CH}_2)_3\text{OH}$

Described by Powell John James, Nadine Smith Stuart J Synthesis (1986)
 (4) 338-40 is the preparation of $\text{MeNH}(\text{CH}_2)_3\text{OH}$ by the lithium aluminum hydride
 reduction of formamide $\text{HC(O)NH}(\text{CH}_2)_3\text{OH}$ in the presence of triethanolamine
 20

Kashima Choji Harada Kazuo Omote Yoshimori Canadian Journal of
 Chemistry (1985) 63(2) 288-90 describe the synthetic procedures where in the
 presence of NaH, the methylation of $\text{H}_2\text{NCH}_2\text{CH}_2\text{OH}$ by Me_2SO_4 in THF gave mainly
 25 $\text{H}_2\text{NCH}_2\text{CH}_2\text{OMe}$, $\text{MeNHCH}_2\text{CH}_2\text{OMe}$ and $\text{Me}_2\text{NCH}_2\text{CH}_2\text{OMe}$, whereas with LiH or
 CaH_2 the products were $\text{MeNHCH}_2\text{CH}_2\text{OH}$ and $\text{Me}_2\text{NCH}_2\text{CH}_2\text{OH}$ Similar results
 were obtained with $\text{H}_2\text{N}(\text{CH}_2)_3\text{OH}$ to give $\text{MeHN}(\text{CH}_2)_3\text{OH}$

30 Described by Felfoldi, K. Laszlovik M Bartok, M Karpati, E Acta Physica et
 Chemica (1980) 26(3-4), 163-9 is the preparation of numerous compounds which
 include for example $\text{MeHN}(\text{CH}_2)_3\text{OH}$ by reaction of $\text{Cl}(\text{CH}_2)_3\text{OH}$ with methylamine in
 ethanol in an autoclave in 55% yield. However, the preparation method produces a

flammable solvent and so is not sufficient to prepare the substituted amino alcohols and in particular, 3-methylamino-propan-1-ol

5 Katritzky Alan R Baker Victor J Brito-Palma, Fernando M S Journal of the Chemical Society, Perkin Transactions 2 Physical Organic Chemistry (1972-1999) (1980) (11), 1739-45 describe the preparation for example of MeHN(CH₂)₃OH by reduction of C₂H₅OC(O)(CH₂)₂NHMe with lithium aluminum hydride in 56% yield

10 Described by Jourdain F Pommelet, J C, Tetrahedron Lett 35 10 1994 1545-1548 is the preparation of amino alcohols in which the chloroalcohols are reacted with an excess of amine in the presence of ethanol or aniline in toluene

15 S D Goldberg and W F Whitmore J. Amer Chem Soc. 59, 1937 2280-2282 describe the preparation of monoalkylaminopropanols wherein the aminopropanol is reacted with trimethylene oxide made from trimethylene bromohydrin and 50% sodium hydroxide However the reaction was effected by the action of trimethyleneoxide and trimethylene bromohydrin on the aminopropanol

20 Described by S Searles and V P Gregory J Amer Chem Soc. 76 1954 2789-2790 is the preparation for example wherein 3-methylamino-1-propanol is formed by reaction of a 25% aqueous solution of methylamine and trimethylene oxide in an autoclave at 150°C for 12 hours and then collecting the product by distillation

25 Kurihara et al YKKZAJ Yakugaku Zasshi, 74, 1954 763 Chem Abstr 1955, 11648 describe the preparation of alkylaminopropanols wherein a mixture of sodium ammonium acetate allyl alcohol and alkylamine are reacted in an autoclave at 130-150°C for 7 hours. Prepared using the described conditions is for example 3-methylamino-1-propanol

30

Described by Cherbullez, E et al, HCACAV, Helv Chim. Acta, FR 50, 1967, 331-348 is the alkylation for example of amino-3-propanol-1 with methyl iodide and the product 3-methylamino-propan-1-ol is purified by chromatography

atoms optionally substituted with C₁-C₃ alkyl. Non-limiting representative examples include morpholine, piperidine, pyrrolidine, piperazine, azetidine and N-methyl-piperazine.

5 The term alkyl means a straight or branched alkyl moiety of 1 to 3 carbon atoms.

The term organic solvent means a solvent selected from the group: methanol, ethanol, isopropanol, ethyl acetate, acetonitrile, tetrahydrofuran, diethylether, 1,4-dioxane, toluene and dichloromethane.

10 Dicarboxylic acid salts include the succinate or fumarate salt.

DETAILED DESCRIPTION OF THE INVENTION

15 A process for the preparation of a substituted amino alcohol of the formula HO-(CH₂)_n-NR¹R² wherein R¹ and R² are each independently H or C₁-C₃ alkyl or R¹ and R² when optionally taken together with the nitrogen atom to which each is attached form a 4 to 6 membered saturated heterocyclic ring having 1-2 nitrogen atoms and 0-1 oxygen atoms or 0-1 sulfur atoms, and optionally substituted with R³, n is an integer of 2 to 7, R³ is C₁-C₃ alkyl, comprising the reaction of a haloalcohol of
20 the formula HO-(CH₂)_n-X, where X is Cl, Br or I, with an amine HNR¹R² in water as solvent at a temperature range of about 20°C to about 90°C.

25 Optionally the preparation of substituted amino alcohols of the formula HO-(CH₂)_n-NR¹R² is in the presence of a catalytic amount of an iodide source catalyst which includes alkali metal iodides or tetraalkylammonium iodides.

The preferred iodide source catalysts are alkali metal iodides and the most preferred is sodium and potassium iodide.

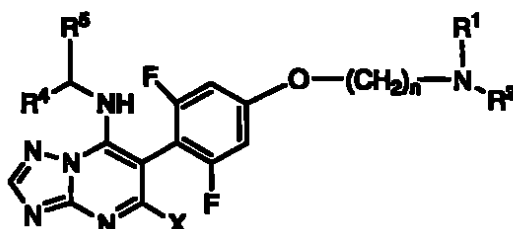
30 An embodiment of this process is wherein the optional amount of an iodide source catalyst used is the catalytic amount in the range of about 1 mole % to about 100 mole %. A preferred range is about 2 mole % to about 10 mole %. The most preferred catalytic amount is about 5 mole %.

atoms and 0-1 oxygen atoms or 0-1 sulfur atoms, and optionally substituted with R³
n is an integer of 2 to 7 R³ is C₁-C₃ alkyl
comprising the steps of

- 5 a reacting a haloalcohol of the formula $\text{HO}-(\text{CH}_2)_n\text{X}$, where X is Cl Br or I with an amine HNR^1R^2 in water to form an aminoalcohol of the formula $\text{HO}-(\text{CH}_2)_n\text{NR}^1\text{R}^2$
- b concentrating
- c adding a base,
- 10 d concentrating
- e extracting with organic solvent;
- f filtering
- g concentrating to a residue and collecting the product
- 15 Optionally the residue collected may be collected and purified by distillation

The process may optionally include an iodide source catalyst.

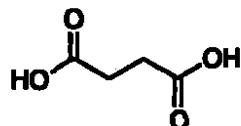
20 Additionally provided is a process for the preparation of a 6-
[(substituted)phenyl]-triazolopyrimidine of the formula



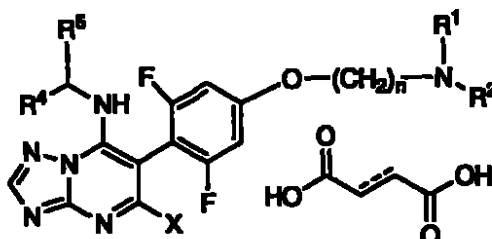
wherein

- R¹ and R² are each independently H or C₁-C₃ alkyl, or**
25 R¹ and R² when optionally taken together with the nitrogen atom to which each is attached form a 4 to 6 membered saturated heterocyclic ring having 1-2 nitrogen atoms and 0-1 oxygen atoms or 0-1 sulfur atoms and optionally substituted with R³.
R⁵ is CF₃ or C₂F₅,
R⁴ is H or C₁-C₃ alkyl
30 R³ is C₁-C₃ alkyl,

- I reacting the 6-[(substituted)phenyl]-triazolopyrimidine product with a dicarboxylic acid of the formula



- wherein the dashed line is an optional bond in t-butylmethyl ether to obtain the 6-[(substituted)phenyl] triazolopyrimidine product dicarboxylic acid salt



- J optionally treating the 6-[(substituted)phenyl]- triazolopyrimidine product dicarboxylic acid salt with water to obtain the 6-[(substituted)phenyl]-triazolopyrimidine as the hydrated salt.

The described process may optionally include an iodide source catalyst.

- Preferably the dicarboxylic acid salt of the 6-[(substituted)phenyl] triazolopyrimidine is the succinic acid salt and more preferably as the anhydrous salt is treated with a saturated atmosphere of (80-100%) relative humidity of water to form the hydrated salt and in particular the dihydrated salt.

- Preferred bases include alkali metal hydroxide alkali metal carbonate or alkali metal bicarbonate

More preferred bases are alkali metal carbonates.

A particularly preferred base is potassium carbonate

Preferred organic solvents include methyl alcohol, isopropyl alcohol or ethyl acetate.

WHAT IS CLAIMED IS

- 1 A process for the preparation of a substituted amino alcohol of the formula
5 $\text{HO}-(\text{CH}_2)_n\text{NR}^1\text{R}^2$ wherein R^1 and R^2 are each independently H or $\text{C}_1\text{-C}_3$ alkyl, or
 R^1 and R^2 when optionally taken together with the nitrogen atom to which each is
attached form a 4 to 6 membered saturated heterocyclic ring having 1-2 nitrogen
atoms and 0-1 oxygen atoms or 0-1 sulfur atoms and optionally substituted with R^3
n is an integer of 2 to 7, R^3 is $\text{C}_1\text{-C}_3$ alkyl comprising the reaction of a haloalcohol of
10 the formula $\text{HO}-(\text{CH}_2)_n\text{-X}$ where X is Cl Br or I with an amine HNR^1R^2 in water as
solvent at a temperature range of about 20°C to about 90°C
- 2 A process according to claim 1 further comprising an iodide source catalyst
- 15 3. A process according to claim 2 wherein the iodide source catalyst is present
in a catalytic amount.
- 4 A process according to claim 2 or claim 3 wherein the iodide source catalyst
is an alkali metal iodide or a tetraalkylammonium iodide
20
- 5 A process according to claim 4 wherein the alkali metal iodide is sodium or
potassium iodide
- 6 A process according to any one of claims 3 to 5 wherein the catalytic
25 amount of iodide source catalyst is present in about 1 mole % to about 100
mole %.
- 7 A process according to claim 6 wherein the catalytic amount of iodide
source catalyst is present in about 5 mole % to 10 mole %
30
- 8 A process according to claim 7 wherein the iodide source catalyst is present
in about 5 mole %

20 A process according to claim 19 wherein the base is an alkali metal hydroxide, alkali metal carbonate or alkali metal bicarbonate

5 21 A process according to claim 20 wherein the base is an alkali metal carbonate

22 A process according to claim 21 wherein the alkali metal carbonate is potassium carbonate

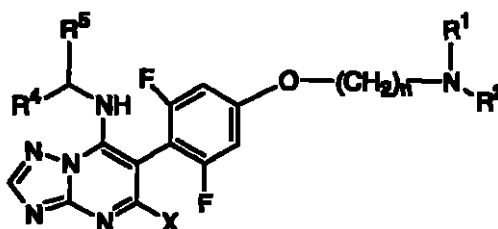
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23 The process according to claim 19 wherein the organic solvent is selected from the group methanol ethanol isopropanol ethyl acetate acetonitrile tetrahydrofuran diethylether 1,4-dioxane toluene and dichloromethane

15 24 A process according to any one of claims 19 to 23 wherein the organic solvent is methyl alcohol isopropyl alcohol and ethyl acetate

25 A process for the preparation of a 6-[(substituted)phenyl] triazolopyrimidine of the formula

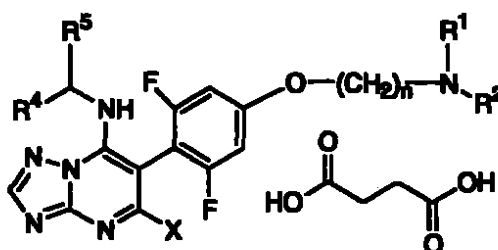
20



wherein

R¹ and R² are each independently H or C₁-C₃ alkyl, or

25 R¹ and R² when optionally taken together with the nitrogen atom to which each is attached form a 4 to 6 membered saturated heterocyclic ring having 1-2 nitrogen atoms and 0-1 oxygen atoms or 0-1 sulfur atoms, and optionally substituted with R³
 R⁵ is CF₃ or C₂F₅,
 R⁴ is H or C₁-C₃ alkyl,



- c optionally treating the 6-[(substituted)phenyl]- triazolopyrimidine product dicarboxylic acid salt with water to obtain the 6-[(substituted)phenyl] triazolopyrimidine as the hydrated salt.

5

- 26 The process according to claim 25 wherein the dihydrated salt is obtained

10

PROCES PARA LA PREPARACIÓN DE
AMINO ALCOHOLES SUSTITUIDOS

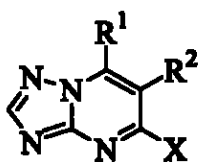
CAMPO DE LA INVENCION

La presente invención se relaciona con un proceso para la preparación de amino alcoholes sustituidos que son útiles para la preparación de inhibidores de tubulina que son útiles en el tratamiento de cáncer

ANTECEDENTES DE LA INVENCION

Subsiste la necesidad en la técnica de agentes citotóxicos para uso en terapia de cáncer. En particular, subsiste la necesidad de agentes citotóxicos que inhiban o traten el crecimiento de tumores que tengan un efecto similar al paclitaxel e interfieran con el proceso de formación de microtúbulo. Adicionalmente, subsiste la necesidad en la técnica de agentes que aceleren la polimerización de tubulina y estabilicen los microtúbulos ensamblados.

Se describe en el caso copendiente referencia No AM 101270, número de solicitud 60/505,544, presentada en septiembre 24, 2003 una serie de compuestos de 6-[fenilo(sustituido)]-triazolopirimidina que tienen la fórmula estructural



(I)

que son inhibidores de microtubulo y útiles en el tratamiento de cáncer

Son útiles en la preparación de los compuestos de 6-[fenilo (sustituido)]-triazolopirimidina anteriormente descritos que son una serie de amino alcoholes sustituidos de la fórmula HO-(CH₂)_n-NR¹R²

Se describe en Kabalka, George W ,Li, Nan-Sheng, and Pace, R David, Synthetic Communication (1995), 25(14), 2135-43 la preparación de amino alcoholes mediante la protección de N-t-butoxicarbonilo de aminas primarias y secundarias por vía de una secuencia de reacción de hidroboración-oxidación

Se describe en Artyushin, O I , Petrovskii P V Mastryukova, T A , Kabachnik, M I Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (1991), (9), 2154-7 una síntesis simple de 3-(alquilamino)-1-propanoles al condensar por ejemplo NH₂(CH₂)₃OH con ClCO₂Me en CH₂Cl₂ que contiene Na₂CO₃ que da MeNH(CH₂)₃OH con 37% de rendimiento

A Parkkinen et al, Journal of Physical Organic Chemistry, (1991), 4(1), 53-7 describe la descomposición hidrolítica de metiltetrahidroozacinas para lograr por ejemplo MeNH(CH₂)₃OH

Se describe en Powell, John, Nadine Smith, Stuart J ,
Synthesis (1986), (4), 338-40 la preparación de $\text{MeNH}(\text{CH}_2)_3\text{OH}$
mediante la reducción de hidruro de litio aluminio de formamida
 $\text{HC}(\text{O})\text{NH}(\text{CH}_2)_3\text{OH}$ en la presencia de trietanolamina

Kashima, Choji, Harada, Kazuo, Omote, Yoshimori, Canadian,
Journal of Chemistry (1985), 63(2), 288-90 describe los
procedimientos sintéticos donde en la presencia de NaH , la
reacción de $\text{H}_2\text{NCH}_2\text{CH}_2\text{OH}$ por Me_2SO_4 en THF da principalmente
 $\text{H}_2\text{NCH}_2\text{CH}_2\text{OMe}$, $\text{MeNHCH}_2\text{CH}_2\text{OMe}$, y $\text{Me}_2\text{NCH}_2\text{CH}_2\text{OMe}$, mientras con LiH o
 CaH_2 los productos fueron $\text{MeNHCH}_2\text{CH}_2\text{OH}$ y $\text{Me}_2\text{NCH}_2\text{CH}_2\text{OH}$ Se
obtuvieron resultados similares con $\text{H}_2\text{N}(\text{CH}_2)_3\text{OH}$ y $\text{MeHN}(\text{CH}_2)_3\text{OH}$

Se describe por Felföldi, K Laszlavik, M, Bartok, M
Karpati, E Acta Physica et Chemica (1980), 163-9 la preparación
de numerosos compuestos que incluyen por ejemplo el $\text{MeHN}(\text{CH}_2)_3\text{OH}$
mediante la reacción de $\text{Cl}(\text{CH}_2)_3\text{OH}$ con metilamina en etanol en un
autoclave con rendimiento del 55% Sin embargo, el método de
preparación produce un solvente inflamable y por lo tanto no es
suficiente para preparar los aminoalcoholes sustituidos y en
particular, 3-metilamino-propan-1-ol

Katritzky, Alan R Baker, Victor J , Brito-Palma, Fernando
M S Journal of the Chemical Society, Perkin Transactions 2
Physical Organic, Chemistry (1972-1999) (1980), (11), 1739-45
describe la preparación por ejemplo de $\text{MeHN}(\text{CH}_2)_3\text{OH}$ mediante la
reducción de $\text{C}_2\text{H}_5\text{OC}(\text{O})(\text{CH}_2)_2\text{NHMe}$ con aluminio hidruro de litio
con 56% de rendimiento

Se describe por Jourdain, F Pommelet, J C Tetrahedron Lett 35, 10, 1994, 1545-1548, la preparación de amino alcoholes en las cuales los cloroalcoholes reaccionan con un exceso de amina en la presencia de etanol o anilina en tolueno

S D Goldberg y W f Whitmore, J Amer Chem Soc , 59, 1937 2280-2282 describe la preparación de monoalquilaminopropanoles en donde el aminopropanol reacciona con óxido de trimetileno hecho de trimetileno bromohidrina y 50% de hidróxido de sodio Sin embargo, la reacción se efectuó mediante la acción de trimetilenooxido y trimetileno bromohidrina sobre el aminopropanol

Se describe por S Searles y V P Gregory, J Amer Chem Soc 76 1954 2789-2790 en la preparación, por ejemplo, en donde 3-metilamino-1-propanol se forma mediante la reacción de solución acuosa al 25% de metilamina y óxido de trimetileno en un autoclave a 150°C durante 12 horas y luego se recolecta el producto mediante destilación

Kurihara et al , YKKZAJ Yakugaku Zasshi, 74, 1954, 763, Chem Abstr , 1955, 11646 describe la preparación de alquilaminopropanoles en donde una mezcla de sodio, acetato de amonio, alil alcohol y alquilamina reaccionan en un autoclave a 130-150°C durante 7 horas Se prepara por ejemplo utilizando las condiciones descritas 3-metilamino-1-propanol

Se describe por Cherbuliez, E et al , HCACAV Helv, Chim Acta, FR, 50, 1967, 331-346 la alquilación por ejemplo de

amino-3-propanol-1 con yoduro de metilo y el producto 3-metilamino-propan-1-ol se purifica mediante cromatografía

Aunque los procesos anteriormente descritos pueden ser utilizados para preparar amino alcoholes sustituidos subsiste la necesidad de un proceso más simple que se pueda utilizar para preparaciones mayores a escala

RESUMEN DE LA INVENCION

La presente invención suministra un proceso para producir una serie de amino alcoholes sustituidos de la fórmula $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$ donde R^1 y R^2 son cada uno independientemente H o alquilo C_1-C_3 o

R^1 y R^2 cuando se toman opcionalmente juntos con el átomo de nitrógeno el cual cada uno está unido forman un anillo heterocíclico saturado de 4 a 6 miembros que tiene 1-2 átomos de hidrógeno y 0-1 átomos de oxígeno 0-1 átomos de azufre, y opcionalmente sustituido con R^3 , R^3 es alquilo C_1-C_3 , que comprende hacer reaccionar un haloalcohol de la fórmula $\text{X}-(\text{CH}_2)_n-\text{OH}$ en donde X es bromo, cloro o yodo y n es un entero de 2 a 7 con una amina HNR^1R^2 en una solución acuosa

El proceso descrito puede contener opcionalmente un catalizador con fuente de yodo

DEFINICIONES

El término base significa un hidróxido de metal alcalino, carbonato de metal alcalino o bicarbonato de metal alcalino

El término hidróxido de metal alcalino significa hidróxido de litio, potasio o sodio

El término carbonato de metal alcalino significa carbonato de litio, potasio o sodio

El término bicarbonato de metal alcalino significa bicarbonato de litio, potasio o sodio

El término yoduro de metal alcalino significa yoduro de litio, potasio o sodio

El término hidruro de metal alcalino significa hidruro de litio, potasio o sodio

El término catalizador de fuente de yodo significa yoduro de metal alcalino o yoduro de tetraalquilamonio

El término anillo heterocíclico como se utiliza aquí significa un anillo heterocíclico saturado que tiene 4 a 6 miembros que tienen 1-2 átomos de nitrógeno, 0-1 átomos de oxígeno o 0-1 átomos de azufre opcionalmente sustituido con el alquilo C₁-C₃. Ejemplos representativos no limitantes incluyen

morfolina, piperidina, pirrolidina, piperazina, azetidina y N-metil-piperazina

El término alquilo significa una porción alquilo recta o ramificada de 1 a 3 átomos de carbono

El término solvente orgánico significa un solvente seleccionado del grupo metanol, etanol, isopropanol, etil acetato, acetonitrilo, tetrahidrofurano, dietileter, 1,4-dioxano, tolueno, y diclorometano

Las sales de ácido dicarboxílico incluyen la sal succinato o fumarato

DESCRIPCIÓN DETALLADA DE LA INVENCION

Un proceso para la preparación de un amino alcohol sustituido de fórmula $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$ donde R^1 y R^2 son cada uno independientemente H o alquilo C_1-C_3 o R^1 y R^2 cuando se toman opcionalmente juntos con el átomo de nitrógeno al cual cada uno está unido forman un anillo heterocíclico saturado de 4 a 6 miembros que tiene 1-2 átomos de nitrógeno y 0-1 átomo de oxígeno o 0-1 átomo de azufre, y opcionalmente sustituido por R^3 , n es un entero de 2 a 7 R^3 es alquilo C_1-C_3 , que comprende la reacción de un haloalcohol de fórmula $\text{HO}-(\text{CH}_2)_n-\text{X}$, donde X es Cl, Br, o I, con una amina HNR^1R^2 , el agua como solvente en un rango de temperatura de aproximadamente 20°C a aproximadamente 90°C

Opcionalmente la preparación de los amino alcoholes sustituidos de la fórmula $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$ están en la presencia de una cantidad catalítica de catalizador con fuente de yodo que incluye yoduro de metal alcalino o yoduro de tetralquilamonio

Los catalizadores como fuente de yodo preferidos son yoduro de metal alcalino y el más preferido es el yoduro de sodio y potasio

Una modalidad de este proceso es aquella en la cual una cantidad opcional de un catalizador con fuente de yodo utilizado es la cantidad catalítica en el rango de aproximadamente 1 mol % a aproximadamente 100 moles %. Un rango preferido es de aproximadamente 2 moles % a aproximadamente 10 moles %. La cantidad catalítica más preferida es aproximadamente 5 moles %

Otra modalidad de este proceso es en donde la proporción en mol de haloalcohol a amina está en el rango de aproximadamente 1:1 a aproximadamente 1:15. Una proporción de mol preferida de halo alcohol a amina está en el rango de aproximadamente 1:2 a aproximadamente 1:8. La proporción en mol más preferida de haloalcohol a amina es aproximadamente 1:4.

El proceso se puede llevar a cabo en un rango de temperatura de aproximadamente 15°C a aproximadamente 90°C. Un rango de temperatura preferido es aproximadamente 200°C a aproximadamente 50°C. La temperatura más preferida es aproximadamente 25°C.

El proceso se puede llevar a cabo en el rango de aproximadamente 8 h a aproximadamente 72 h. Un rango de tiempo preferido es aproximadamente 10 h a aproximadamente 24 h. El tiempo más preferido para ser llevado a cabo el proceso es aproximadamente 15 h.

Una modalidad preferida es donde n es 2 a 4.

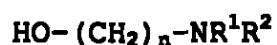
Una modalidad particularmente preferida es donde n es 3.

Una modalidad de proceso es donde R^1 y R^2 son cada una independientemente H o alquilo C_1-C_3 .

Una modalidad de este proceso es donde R^1 es H y R^2 es metilo.

Una modalidad de este proceso es donde X es Cl.

Un proceso para la preparación de amino alcohol de la fórmula



En donde

R^1 y R^2 son cada uno independientemente h o alquilo C_1-C_3 o

R^1 y R^2 cuando se toman opcionalmente juntos con el átomo de nitrógeno al cual cada uno está unido forman un anillo

heterocíclico saturado de 4 a 6 miembros Que tiene 1-2 átomos de nitrógeno y un 0-1 átomos de oxígeno o 0-1 átomos de azufre, y opcionalmente sustituido por R^3 n es un entero de 2 a 7, R^3 es alquilo C_1-C_3

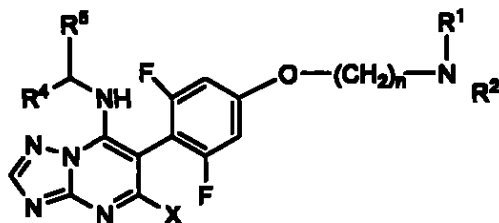
que comprende las etapas de

- a Hacer reaccionar un haloalcohol de la fórmula $HO-(CH_2)_n-$, donde X es Cl, Br o I, con una amina HNR^1R^2 , en agua para formar un aminoalcohol de fórmula $HO-(CH_2)_n-NR^1R^2$,
- b Concentrar,
- c agregando una base,
- d concentrar,
- e extrayendo con solvente orgánico,
- f filtrando,
- g concentrando a un residuo y recolectando el producto

Opcionalmente el residuo recolectado se puede recolectar y purificar mediante destilación

El proceso puede incluir opcionalmente un catalizador con fuente de yodo

Adicionalmente, se suministra un proceso para la preparación de 6-[fenilo(sustituido)]-triazolopirimidina de formula



En donde

R¹ y R² cada son cada uno independientemente H o alquilo C₁-C₃

R¹ y R² cuando se toman opcionalmente juntos con el átomo de nitrógeno al cual cada uno está unido y forman un anillo heterocíclico saturado de 4 a 6 miembros que tiene 1-2 átomos de nitrógeno y 0-1 átomos de oxígeno o 0-1 átomos de azufre, y opcionalmente sustituido con R³,

R⁵ es CF₃ o C₂F₅,

R⁴ es H o alquilo C₁-C₃,

R³ es alquilo C₁-C₃,

n es un entero de 2 a 4,

X es Cl o Br,

o una sal de ácido de carboxílico farmacéuticamente aceptable o hidrato de esta

que comprende

a hacer reaccionar un haloalcohol de la fórmula HO-(CH₂)_n-X, donde X es Cl, Br o I, con una amina HNR¹R², en agua para formar un aminoalcohol de la fórmula HO-(CH₂)_n-NR¹R²

b concentrar,

c agregar una base,

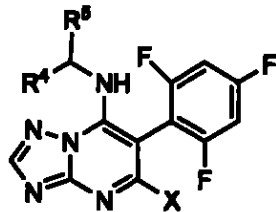
d concentrar,

e extraer con solvente orgánico

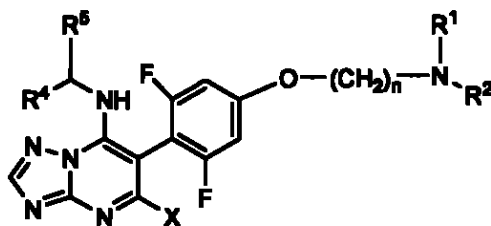
f filtrar

g concentrar a un residuo y recolectar el amino alcohol de la fórmula $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$,

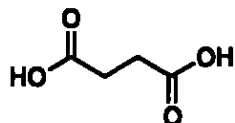
h hacer reaccionar el aminoalcohol $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$ con un hidruro de metal alcalino durante aproximadamente 390 minutos en tetrahidrofurano a aproximadamente 10 a 40°C, agregando el producto amina



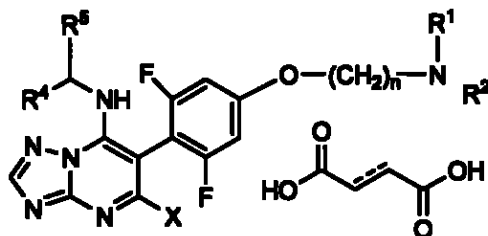
y calentando a aproximadamente 60°C durante aproximadamente 12 a 20 h para obtener el producto 6-[fenilo (sustituido)]-triazolopirimidina



i hacer reaccionar el producto 6-[fenilo(sustituido)]-triazolopirimidina con un ácido dicarboxílico de la fórmula



En donde la línea punteada es un enlace opcional, en t-butilmetil éter para obtener la sal de ácido dicarboxílico del producto 6-[fenilo(sustituido)]-triazolopirimidina



j Opcionalmente tratar la sal de ácido dicarboxílico del producto 6-[fenilo(sustituido)]-triazolopirimidina con agua para obtener el 6-[fenilo(sustituido)]-triazolopirimidina como la sal hidratada

El proceso descrito puede opcionalmente incluir un catalizador con fuente de yodo

Preferiblemente la sal de ácido dicarboxílico de 6-[fenilo(sustituido)]-triazolopirimidina es sal de ácido succínico y más preferiblemente como la sal anhidro se trata con una atmósfera saturada de (80-100%) de humedad relativa de agua para formar la sal hidratada y en particular la sal hidratada

Las bases preferidas incluyen hidróxido de metal alcalino, carbonato de metal alcalino o bicarbonato de metal alcalino

Las bases más preferidas son carbonatos de metal alcalino

Una base más preferida es carbonato de potasio

Los solventes orgánicos preferidos incluyen metil alcohol, isopropil alcohol o etil acetato

Los siguientes ejemplos se presentan para ilustrar ciertas modalidades de la presente invención, pero no debe ser considerado como limitante del alcance de la invención

Ejemplo 1

En un metal de 3L, se disolvió 3-cloro-1-propanol (50 0g 0 53 mol, 90%, Aldrich C4,640-3) en solución de metilamina (1L, 40% en peso en agua, Aldrich 42,646-6) y se calentó hasta reflujo durante 3 días. La reacción se enfrió a temperatura ambiente de cuarto y el solvente se redujo *in vacuo* a ~150 mL. A la mezcla de reacción, se agregó carbonato de potasio (50g) y el resto del solvente se removió. El residuo se suspendió en metanol (200 mL) y se filtró a través de un tarugo de sílica gel (200 g). El tarugo se lavó con metanol (2 x 100 mL), se combinaron las capas orgánicas, los solventes se removieron para dar un aceite naranja. El aceite se destiló a ~1-2 mm de Hg desde temperatura ambiente de cuarto a 60°C con un baño de aceite y una trampa de destilación. La destilación logró 3-metilamino-propan-1-ol como un líquido claro, incoloro (22 0 g), BP 165-167°C (760 torr), $C_4H_{11}NO$, MW 89 14

Ejemplo 2

Una mezcla de 30 g de yoduro de sodio, 500 g de 3-cloro-1-propanol 4000 mL de solución de metilamina (40% en peso en agua,

Aldrich 42, 646-6) se agita a temperatura ambiente de cuarto durante 17 h. El solvente se reduce *in vacuo* a ~700-800 ml. A la mezcla de reacción se agrega carbonato de potasio (500 g) y el resto de agua se remueve a un residuo que es destilado con tolueno para lograr un residuo. El residuo es suspendido en metanol (2000 mL), filtrado y la torta lavada con metanol (2 x 1000 mL). Las capas de metanol son combinadas, y los solventes son removidos para dar un aceite. El aceite es destilado para lograr 3-metilamino-propan-1-ol como un líquido claro, incoloro (352.0 g), BP 90-95°C (8 mm), $C_4H_{11}NO$, MW 89.14 A.

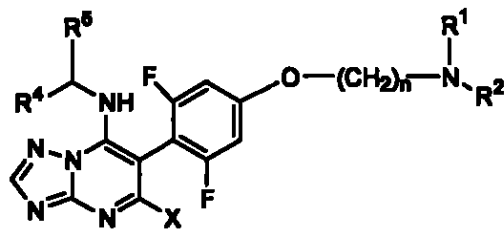
REIVINDICACIONES

- 1 Un proceso para la preparación de una aminoalcohol sustituido de la fórmula $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$ en donde R^1 y R^2 son cada uno independientemente H o alquilo C_1-C_3 , o R^1 y R^2 cuando se toman opcionalmente junto con el átomo de nitrógeno el cual está cada uno unido forman un anillo heterocíclico saturado de 4 a 6 miembros que tiene 1-2 átomos de nitrógeno y 0-1 átomos de oxígeno o 0-1 átomos de azufre, y opcionalmente sustituido con R^3 , n es un entero de 2 a 7, R^3 es alquilo C_1-C_3 , que comprende la reacción de un alcohol de la fórmula $\text{HO}-(\text{CH}_2)_n-\text{X}$, donde X es Cl, Br o I, con una amina NHR^1R^2 en agua como solvente en un rango de temperatura de aproximadamente 20°C a aproximadamente 90°C
- 2 Un proceso de acuerdo con la reivindicación 1 que comprende además un catalizador con fuente de yoduro
- 3 Un proceso de acuerdo con la reivindicación 2 en donde el catalizador con fuente yoduro está presente en una cantidad catalítica
- 4 Un proceso de acuerdo con la reivindicación 2 o reivindicación 3 en donde el catalizador con fuente yoduro es un yoduro de metal alcalino o un yoduro de tetraalquilaminio

- 5 Un proceso de acuerdo con la reivindicación 4 en donde el yoduro de metal alcalino es yoduro de sodio o potasio
- 6 Un proceso de acuerdo con una cualquiera de las reivindicaciones 3 a 5 en donde la cantidad catalítica de catalizador con fuente yoduro está presente en aproximadamente 1 mol% a aproximadamente 100 moles %
- 7 Un proceso de acuerdo con la reivindicación 6 en donde la cantidad catalítica de catalizador con fuente yoduro está presente en aproximadamente 5 moles % a 10 moles %
- 8 Un proceso de acuerdo con la reivindicación 7 en donde el catalizador con fuente yoduro está presente en aproximadamente 5 moles %
- 9 Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 8 en donde el rango de temperatura es aproximadamente 20 a aproximadamente 50°C
- 10 Un proceso de acuerdo con la reivindicación 9 en donde la temperatura es aproximadamente 25°C
- 11 Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 10 en donde X es Cl
- 12 Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 11 en donde n es 2 a 4

- 13 Un proceso de acuerdo con la reivindicación 12 en donde n es 3
- 14 un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 13 en donde la proporción de mol de haloalcohol a amina está en el rango de aproximadamente 1 1 a 1 15
- 15 Un proceso de acuerdo con la reivindicación 14 en donde la proporción en mol de haloalcohol a amina está en el rango de aproximadamente 1 2 a aproximadamente 1 8
- 16 Un proceso de acuerdo con la reivindicación 14 en donde la proporción en mol de haloalcohol a amina es aproximadamente 1 4
- 17 Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 16 en donde R^1 y R^2 son cada uno independientemente H o alquilo C_1-C_3
- 18 Un proceso de acuerdo con la reivindicación 17 en donde R^1 es H y R^2 es metilo
- 19 Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 18 en la cual el producto de reacción de aminoalcohol es sometido a las etapas que comprenden

- a concentrar,
 - b agregar una base
 - c concentrar
 - d extraer con solvente orgánico,
 - e filtrar,
 - f concentrar a un residuo y recolectar el producto
- 20 Un proceso de acuerdo con la reivindicación 19 en donde la base es un hidróxido de metal alcalino, carbonato de metal alcalino o bicarbonato de metal alcalino
- 21 Un proceso de acuerdo con la reivindicación 20 en donde la base es un carbonato de metal alcalino
- 22 Un proceso de acuerdo con la reivindicación 21 en donde el carbonato de metal alcalino es carbonato de potasio
- 23 El proceso de acuerdo con la reivindicación 19 en donde el solvente orgánico se selecciona del grupo metanol, etanol, isopropanol, etil acetato, acetonitrilo, tetrahidrofurano, dietileter, 1,4-dioxano, tolueno y diclorometano
- 24 Un proceso de acuerdo con una cualquiera de las reivindicaciones 19 a 23 en donde el solvente orgánico es metil alcohol, isopropil alcohol y etil acetato
- 25 Un proceso para la preparación de una 6-[fenilo(sustituido)]-triazolopirimidina de la fórmula

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En donde

R¹ y R² son cada uno independientemente H o alquilo C₁-C₃,
o

R¹ y R² cuando se toman opcionalmente junto con el átomo de nitrógeno al cual cada uno está unido y forman un anillo heterocíclico saturado de 4 a 6 miembros que tiene 1-2 átomos de nitrógeno y 0-1 átomos de oxígeno o 0-1 átomos de azufre, y opcionalmente sustituido con R³,

R⁵ es CF₃ o C₂F₅,

R⁴ es H o alquilo C₁-C₃,

R³ es alquilo C₁-C₃,

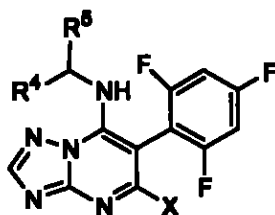
n es un entero de 2,3 o 4,

X es Cl o Br

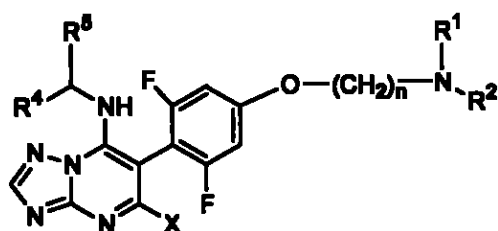
o una sal de ácido de carboxílico farmacéuticamente aceptable o hidrato de esta

Que comprende

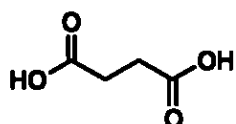
a hacer reaccionar un aminoalcohol HO-(CH₂)_n-NR¹R² preparado mediante un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 25 con un hidruro de metal alcalino durante aproximadamente 30 minutos en tetrahidrofurano aproximadamente 10 a 50°C, agregando el producto amina



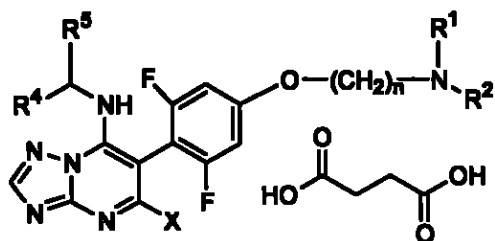
y calentar a aproximadamente 60°C durante aproximadamente 12 a 20 horas para obtener el producto 6-[fenilo(sustituido)]-triazolopirimidina



b hacer reaccionar el producto 6-[fenilo(sustituido)]-triazolopirimidina con un ácido dicarboxílico de la fórmula



en donde la línea punteada es un enlace opcional, en t-butil metil éter para obtener la sal de ácido dicarboxílico del producto 6-[fenilo(sustituido)]-triazolopirimidina



c tratar opcionalmente la sal de ácido dicarboxílico del producto 6-[fenilo(sustituido)]-triazolopirimidina con agua para obtener el 6-[fenilo(sustituido)]-triazolopirimidina como la sal hidratada

26 El proceso de acuerdo con la reivindicación 25 en donde se obtiene la sal hidratada

RESUMEN

Se suministra un proceso para la preparación de amino alcoholes sustituidos $\text{HO}-(\text{CH}_2)_n-\text{NR}^1\text{R}^2$ de haloalcoholes $\text{HO}-(\text{CH}_2)_n-\text{X}$, donde X es Cl, Br, o I, mediante la reacción con una amina HNR^1R^2 , en agua como solvente a temperatura en el rango de aproximadamente 20°C a aproximadamente 90°C opcionalmente en la presencia de una cantidad catalítica de unos yoduros metálicos fuente de yoduro

Los haloalcoholes son útiles en la preparación de compuestos 6-[fenilo(sustituido)]-triazolopirimidina que son útiles en el tratamiento de cáncer

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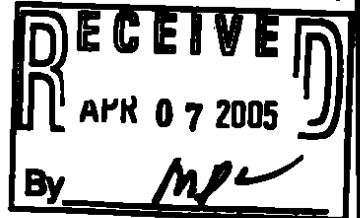
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Applicant

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Declarations under Rule 4.17

(22) International Filing Date: 7 December 2004 (07.12.2004)

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW. ARIPO patents (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patents (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patents (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patents (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data
60/527 930 8 December 2003 (08.12.2003) US

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW. ARIPO patents (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patents (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patents (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patents (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): WYETH [US/US] Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors, and

(75) Inventors/Applicants (for US only): WU, Yanzhong [US/US] 1580 Pelham Parkway South, Apartment 4K, Bronx, NY 10461 (US); RUBEZHOV Arkady [US/US] 3 Fawn Court, West Nyack, NY 10994 (US); SCHMID, Jean [CA/US] 17 Jeffroy Drive, Chester, NY 10918 (US); AFRAGOLA, Jay Thomas [US/US] 141 Heitman Drive, Apartment F Spring Valley, NY 10977 (US).

(74) Agent: CALNAN, William, H., Wyeth Patent Law Department, Five Giralda Farms, Madison, NJ 07940 (US).

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

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(88) Date of publication of the international search report.
11 August 2005

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,

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 PREPARATION OF SUBSTITUTED AMINO ALCOHOLS

(57) Abstract: There is provided a process for the preparation of substituted amino alcohols HO-(CH₂)_nNR¹R² from haloalcohols HO-(CH₂)_nX where X is Cl, Br or I, by reaction with an amine HNR¹R² in water as solvent at a temperature range of about 20°C to about 90°C optionally in the presence of a catalytic amount of an iodide source.3 metal iodides. The haloalcohols are useful in the preparation of 6-[(substituted)phenyl]-triazolopyrimidine compounds which are useful in the treatment of cancer.

WO 2005/056514 A3

INTERNATIONAL SEARCH REPORT

00005453

Info Application No
PCT/US2004/040855

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07C213/04

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 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal BEILSTEIN Data WPI Data PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY vol 80, 1958, pages 5203-5208, XP002328566 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 5207, right-hand column - page 5208, left-hand column	2-8,25 26
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 70 1948, pages 3100-3102, XP002328567 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 3101, right-hand column, last paragraph	2-8,25 26
	-/-	

☒ 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
- T* 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
- Z* document member of the same patent family

Date of the actual completion of the international search

19 May 2005

Date of mailing of the international search report

01/06/2005

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Paludarium 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-8040, Tx 31 851 epo nl,
Fax (+31-70) 340-8018

Authorized officer

Seymour, L

INTERNATIONAL SEARCH REPORT

Title of Application No
PCT/US2004/040855

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY vol 70 1948, pages 3862-3864, XP002328603 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 3862, right-hand column	2-8,25 26
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY vol 72, 1950, pages 1331-1334, XP002328568 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 1333 left-hand column	2-8,25, 26
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 58 1936, pages 1079-1081 XP002328569 USAMERICAN CHEMICAL SOCIETY WASHINGTON, DC	1 9-24
Y	paragraph AMINOALCOHOLS!	2-8,25, 26
X	DATABASE BEILSTEIN 1988, XP002328570 Database accession no 6210465 (REACTION ID) abstract	1,9-24
Y	& JUSTUS LIEBIGS ANNALEN DER CHEMIE , vol 121, 1862, page 227, DEVERLAG CHEMIE GMBH WEINHEIM	2-8,25, 26
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 77, 1955, pages 3648-3649, XP002328585 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC page 3648, right-hand column, last paragraph	1,9-24
Y	DE 10 18 868 B (SOCIETE DES USINES CHIMIQUES) 7 November 1957 (1957-11-07) example 6	2-8
A	WO 02/14381 A (UNIVERSITY OF ALBERTA, HALL, DENNIS, G) 21 February 2002 (2002-02-21) example 3	2-8
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INTERNATIONAL SEARCH REPORT

Intern	Application No
PCT/US2004/040855	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/48893 A (AMERICAN CYANAMID COMPANY) 30 September 1999 (1999-09-30) page 10, line 12 - page 11 line 1, example 4 —————	25,26

3

INTERNATIONAL SEARCH REPORT

00005163

Information on patent family members

Int. Application No.
PCT/US2004/040855

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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WO 9948893	A	30-09-1999	US 5981534 A AT 239727 T AT 228133 T AU 752669 B2 AU 3098599 A AU 735730 B2 AU 6867198 A BG 64197 B1 BG 103805 A BR 9808531 A BR 9909009 A CA 2287470 A1 CA 2324154 A1 CN 1302299 A ,C CN 1528762 A CZ 20003472 A3 CZ 292092 B6 DE 69814375 D1 DE 69814375 T2 DE 69903988 D1 DE 69903988 T2 DK 975635 T3 DK 945453 T3 EA 2906 B1 EA 3281 B1 EE 9900486 A EP 0975635 A1 EP 0945453 A1 EP 1066291 A1 ES 2188094 T3 HU 0001993 A2 HU 0101751 A2 IL 132238 A JP 11322750 A JP 2001520650 T JP 2003522100 T NO 994973 A NZ 500143 A PL 343176 A1 PT 945453 T SI 975635 T1 SK 141499 A3 WO 9948893 A1 US 6284762 B1	09-11-1999 15-05-2003 15-12-2002 26-09-2002 18-10-1999 12-07-2001 11-11-1998 30-04-2004 30-06-2000 23-05-2000 28-11-2000 22-10-1998 30-09-1999 04-07-2001 15-09-2004 16-01-2002 16-07-2003 12-06-2003 24-12-2003 02-01-2003 27-03-2003 02-06-2003 16-12-2002 31-10-2002 24-04-2003 15-06-2000 02-02-2000 29-09-1999 10-01-2001 16-06-2003 28-10-2000 28-10-2001 29-05-2003 24-11-1999 30-10-2001 22-07-2003 13-10-1999 29-06-2001 30-07-2001 31-03-2003 31-10-2003 11-09-2001 30-09-1999 04-09-2001

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INTERNATIONAL SEARCH REPORT

mention of patent family members

Inventor: Application No
PCT/US2004/040855

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9948893 A		ZA 200005867 A NZ 506912 A	22-10-2001 28-03-2003

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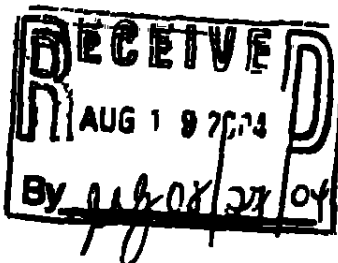


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 United States Patent and Trademark Office
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 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPL. NO.	FILING OR 371 (a) DATE	ART. UNIT	FILE FEE REC'D	ATTY. DOCKET NO.	DRAWINGS	TOT. CLMS	IND. CLMS
60/527 930	12/08/2003		180	AM101582 L1			

25281
 WYETH
 PATENT LAW GROUP
 5 GIRALDA FARMS
 MADISON NJ 07940



CONFIRMATION N 4831

FILING RECEIPT



OC000000013557807

Also 2004

Date Mailed 08/17/2004

ELZAGETI L. C. GLU...D

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-748-9185. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Yanzhong Wu Bronx NY ✓
 Arkady Rubazhov West Nyack NY ✓
 Jean Schmid Chester NY ✓
 Jay Thomas Afragola Spring Valley NY ✓

If Required, Foreign Filing License Granted 08/18/2004

Projected Publication Date: None application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Process for preparation of substituted amino alcohols

DOCKETED
 DUE DATE
 STAT DATE
 BY [signature]

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

CC PEARL RIVER

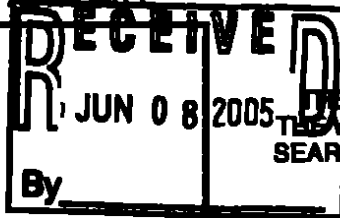
PATENT COOPERATION TREATY

00006057

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
WYETH
Patent Law Department
Attn Calnan William H
Five Giralda Farms
Madison New Jersey 07940
UNITED STATES OF AMERICA



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 01/06/2005	
Applicant's or agent's file reference AM101562	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2004/040855	International filing date (day/month/year) 07/12/2004
Applicant WYETH	

- 1 ☒ The applicant is hereby notified that the International search report and the written opinion of the International Searching Authority have been established and are 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 and the written opinion of the International Searching Authority are 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. Reminders

Shortly after the expiration of 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.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, 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), otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II National Chapters and the WIPO Internet site.

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) 340-3018	Authorized officer Federico Bonomelli Jb 11.9.05
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CC PEARL 011-01
16:14:10

NOTES TO FORM PCT/ISA/220

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64 58

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, Articles "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 letter 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 25 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 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 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.

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 to 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 Office. 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.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101562	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below	
International application No. PCT/US2004/040855	International filing date (day/month/year) 07/12/2004	(Earliest) Priority Date (day/month/year) 08/12/2003
Applicant WYETH		

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 6 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, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority because the applicant failed to suggest a figure.

☐ as selected by this Authority because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

000064 38

Int. Patent Application No.
PCT/US2004/040855

61

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D487/04 C07C213/04		
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 C07C Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BEILSTEIN Data, WPI Data, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 80, 1958, pages 5203-5208, XP002328566 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 5207, right-hand column - page 5208, left-hand column	2-8,25, 26
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 70, 1948, pages 3100-3102, XP002328567 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 3101, right-hand column, last paragraph	2-8,25, 26
-/-		
☒ 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. Δ document member of the same patent family		
Date of the actual completion of the international search 19 May 2005		Date of mailing of the international search report 01/06/2005
Name and mailing address of the ISA European Patent Office, P.B. 6816 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl Fax (+31-70) 340-3016		Authorized officer Seymour, L

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 70, 1948, pages 3862-3864, XP002328603 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 3862, right-hand column	2-8,25, 26
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 72, 1950, pages 1331-1334, XP002328568 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	page 1333, left-hand column	2-8,25, 26
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 58, 1936, pages 1079-1081, XP002328569 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC	1,9-24
Y	paragraph 'AMINOALCOHOLS'	2-8,25 26
X	DATABASE BEILSTEIN 1988, XP002328570 Database accession no 6210465 (REACTION ID) abstract	1,9-24
Y	& JUSTUS LIEBIGS ANNALEN DER CHEMIE , vol 121, 1862, page 227, DEVERLAG CHEMIE GMBH WEINHEIM	2-8,25, 26
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , vol 77, 1955, pages 3648-3649, XP002328585 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC page 3648, right-hand column, last paragraph	1,9-24
Y	DE 10 18 868 B (SOCIETE DES USINES CHIMIQUES) 7 November 1957 (1957-11-07) example 6	2-8
A	WO 02/14381 A (UNIVERSITY OF ALBERTA HALL, DENNIS, G) 21 February 2002 (2002-02-21) example 3	2-8
A	US 4 874 785 A (SMITH ET AL) 17 October 1989 (1989-10-17) examples 3,4	2-8
	-/-	

INTERNATIONAL SEARCH REPORT

00008572

63

Int. Patent Application No.
PCT/US2004/040855

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/48893 A (AMERICAN CYANAMID COMPANY) 30 September 1999 (1999-09-30) page 10, line 12 - page 11, line 1, example 4 	25, 26

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No
PCT/US2004/040855

00006723
69

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 1018868	B	07-11-1957	NONE
WO 0214381	A	21-02-2002	AU 8739901 A 25-02-2002 WO 0214381 A2 21-02-2002 CA 2419238 A1 21-02-2002 US 2004039129 A1 26-02-2004
US 4874785	A	17-10-1989	US 4883917 A 28-11-1989 US 4824867 A 25-04-1989 US 4874788 A 17-10-1989 US 4874784 A 17-10-1989 US 4874789 A 17-10-1989 US 5047577 A 10-09-1991
WO 9948893	A	30-09-1999	US 5981534 A 09-11-1999 AT 239727 T 15-05-2003 AT 228133 T 15-12-2002 AU 752669 B2 26-09-2002 AU 3098599 A 18-10-1999 AU 735730 B2 12-07-2001 AU 6867198 A 11-11-1998 BG 64197 B1 30-04-2004 BG 103805 A 30-06-2000 BR 9808531 A 23-05-2000 BR 9909009 A 28-11-2000 CA 2287470 A1 22-10-1998 CA 2324154 A1 30-09-1999 CN 1302299 A ,C 04-07-2001 CN 1528762 A 15-09-2004 CZ 20003472 A3 16-01-2002 CZ 292092 B6 16-07-2003 DE 69814375 D1 12-06-2003 DE 69814375 T2 24-12-2003 DE 69903988 D1 02-01-2003 DE 69903988 T2 27-03-2003 DK 975635 T3 02-06-2003 DK 945453 T3 16-12-2002 EA 2906 B1 31-10-2002 EA 3281 B1 24-04-2003 EE 9900486 A 15-06-2000 EP 0975635 A1 02-02-2000 EP 0945453 A1 29-09-1999 EP 1066291 A1 10-01-2001 ES 2188094 T3 16-06-2003 HU 0001993 A2 28-10-2000 HU 0101751 A2 28-10-2001 IL 132238 A 29-05-2003 JP 11322750 A 24-11-1999 JP 2001520650 T 30-10-2001 JP 2003522100 T 22-07-2003 NO 994973 A 13-10-1999 NZ 500143 A 29-06-2001 PL 343176 A1 30-07-2001 PT 945453 T 31-03-2003 SI 975635 T1 31-10-2003 SK 141499 A3 11-09-2001 WO 9948893 A1 30-09-1999 US 6284762 B1 04-09-2001

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis 1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/040855

International filing date (day/month/year)
07 12 2004

Priority date (day/month/year)
08 12 2003

International Patent Classification (IPC) or both national classification and IPC
C07D487/04 C07C213/04

Applicant
WYETH

1 This opinion contains indications relating to the following items

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis 1(a)(i) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2 FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3 For further details, see notes to Form PCT/ISA/220

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/US2004/040855

Box No. 1 Basis of the opinion

- 1 With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b))
- 2 With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search
- 3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished
- 4 Additional comments

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/US2004/040855

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability, citations and explanations supporting such statement**

1 Statement

Novelty (N)	Yes	Claims	2-8,25,26
	No	Claims	1,9-24
Inventive step (IS)	Yes	Claims	
	No	Claims	1,26
Industrial applicability (IA)	Yes	Claims	1,26
	No	Claims	

2 Citations and explanations

see separate sheet

**WRITTEN PINION F THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No

PCT/US2004/040855

Re Item V**1 Reference is made to the following documents**

- D1 J Amer Chem Soc , vol 80, 1958, pages 5203-5208, XP002328566
D2 J Amer Chem Soc , vol 70, 1948, pages 3100-3102, XP002328567
D3 J Amer Chem Soc , vol 70 1948 pages 3862-3864, XP002328603
D4 J Amer Chem Soc , vol 72, 1950 pages 1331 1334 XP002328568
D5 J Amer Chem Soc. vol 58 1936 pages 1079-1081 XP002328569
D6 Database Beilstein 1988 accession no 6210465 (reaction ID)
D7 J Amer Chem Soc vol 77, 1955, pages 3648-3649 XP002328585
D8 DE 10 18 868 B D9 US-A-4 874 785
D10 WO 02/14381 A D11 WO 99/48893 A

2 The present application does not meet the criteria of Article 33(1) PCT because the subject-matter of claims 1,9-24 is not new in the sense of Article 33(2) PCT Documents D1-D5 all disclose reactions falling within the scope of said claims

- D1 p 5208 synthesis of 3-ethylaminopropanol
D2 p 3102 synthesis of 2 (2,4-dimethylpyrrolidino)ethanol and 2-(2,5-dimethylpyrrolidino)ethanol
D3 p 3862, synthesis of 3-(pyrrolidino)propanol
D4, p 1333, synthesis of 3-(2-methylpyrrolidino)propanol
D5 p 1080, synthesis of 3-(dimethylamino)propanol
D6, synthesis of 2-aminoethanol

Documents D7 D11 are not novelty destroying

The synthesis of 3-pipendinopropanol disclosed in D7 only differs from the present reaction in that the solvent is aqueous alcohol rather than water as specified in claim 1

The reaction disclosed in the last paragraph of example 6 of D8 only differs from the present reaction owing to the fact that the diethylamine starting material is substituted at the ethyl group

**WRITTEN FINAL
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No

PCT/US2004/040855

In examples 3 and 4 of D9, a quaternary compound is produced

- In D10, the amine starting material is a polymer

In D11 aminoalcohols are not produced

- 3 The present application does not meet the criteria of Article 33(1) PCT because the subject-matter of the present claims does not involve an inventive step in the sense of Article 33(3) PCT

The problem underlying the present application lies in the provision of an alternative synthesis of aminoalcohols

Novel claims 2-8 differ from the processes of D1-D6 in that they are conducted in the presence of an iodide source acting as a catalyst

This modification is already known from D8 for a closely analogous reaction (see example 6) Moreover, the use of iodide salts to catalyse the reaction of halohydrins is generally known in the art (see e.g. D9 examples 3 and 4 and D10 example 3)

The solution proposed in said claims cannot therefore be considered as involving an inventive step (Article 33(3) PCT)

The additional step claimed in claim 25 is also not regarded as being inventive since the reaction of alcohols, in the presence of an alkali metal hydride, with trifluorophenyl substrates of the type claimed is already known from D11 (see p 10 | 12 p 11 | 1 and example 4)

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 claims 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 48.4)

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.

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

If, at the time of filing any amendments under Article 18, 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 68.2(a), first sentence).

Consequences 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 18 may have to be furnished to the designated/selected Offices, instead of, or in addition to, the translation of the claims as filed.

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

PATENT CO-OPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43b/s.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/040855

International filing date (day/month/year)
07 12 2004

Priority date (day/month/year)
08 12 2003

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, C07C213/04

Applicant
WYETH

1 This opinion contains indications relating to the following items

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2 FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3 For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCH AUTHORITY**International application No.
PCT/US2004/040855**Box No. I Basis of the opinion**

- 1 With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b))
- 2 With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search
- 3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments

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83

**WRITTEN PINION F THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/040855

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	2-8,25,28
	No	Claims	19-24
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

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No

PCT/US2004/040855**Re Item V****1 Reference is made to the following documents**

D1 J Amer Chem Soc. vol 80, 1958 pages 5203-5208 XP002328586
D2 J Amer Chem Soc., vol 70 1948 pages 3100-3102, XP002328587
D3 J Amer Chem Soc., vol 70 1948 pages 3862-3864, XP002328603
D4 J Amer Chem Soc., vol 72 1950 pages 1331 1334, XP002328588
D5 J Amer Chem Soc vol 58 1936 pages 1079-1081, XP002328589
D6 Database Beilstein 1988 accession no 6210465 (reaction ID)
D7 J Amer Chem Soc. vol 77 1955 pages 3648-3649 XP002328585
D8 DE 10 18 868 B D9 US-A-4 874 785
D10 WO 02/14381 A D11 WO 99/48893 A

- 2 The present application does not meet the criteria of Article 33(1) PCT because the subject matter of claims 1-9-24 is not new in the sense of Article 33(2) PCT Documents D1-D5 all disclose reactions falling within the scope of said claims**
- D1 p 5208 synthesis of 3-ethylaminopropanol
D2, p 3102 synthesis of 2-(2,4-dimethylpyrrolidino)ethanol and 2-(2,5-dimethylpyrrolidino)ethanol
D3, p 3862 synthesis of 3-(pyrrolidino)propanol
D4 p 1333 synthesis of 3-(2-methylpyrrolidino)propanol
D5, p 1080 synthesis of 3-(dimethylamino)propanol
D6 synthesis of 2-aminoethanol

Documents D7-D11 are not novelty destroying

The synthesis of 3-piperidinopropanol disclosed in D7 only differs from the present reaction in that the solvent is aqueous alcohol rather than water as specified in claim 1

The reaction disclosed in the last paragraph of example 6 of D8 only differs from the present reaction owing to the fact that the diethylamine starting material is substituted at the ethyl group

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/040855

In examples 3 and 4 of D9 a quaternary compound is produced

In D10 the amine starting material is a polymer

In D11 aminoalcohols are not produced

3. The present application does not meet the criteria of Article 33(1) PCT because the subject-matter of the present claims does not involve an inventive step in the sense of Article 33(3) PCT

The problem underlying the present application lies in the provision of an alternative synthesis of aminoalcohols.

Novel claims 2-8 differ from the processes of D1-D6 in that they are conducted in the presence of an iodide source acting as a catalyst.

This modification is already known from D8 for a closely analogous reaction (see example 6). Moreover, the use of iodide salts to catalyse the reaction of halohydrins is generally known in the art (see e.g. D9 examples 3 and 4 and D10 example 3).

The solution proposed in said claims cannot therefore be considered as involving an inventive step (Article 33(3) PCT).

The additional step claimed in claim 25 is also not regarded as being inventive, since the reaction of alcohols, in the presence of an alkali metal hydride with trifluorophenyl substrates of the type claimed is already known from D11 (see p. 10 | 12, p. 11 | 1 and example 4).

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 18. 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 these 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 18

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 18 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 18, 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 10 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 48.1).

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 48.2).

Where a demand for international preliminary examination has been 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 203(b)).

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

What documents must accompany the amendments?

Letter (Section 203(c)):

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 18(1)" (see below under "Statement under Article 18(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.

78

Retiro folios 87, 88 y 89
Extracto y Tapetas

87
79



Industria y Comer

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Rad: 06-055464- -00000-0000

Rec. 2006-08-08 16:04:17 Dep. 2020 NUECREACIONES

Tm. 11 PATENTE/VI

Env. 378 FASENACIONAL

Act 411 PRESENTACION

Folios. 60

**Delegatura de Propiedad Industrial
División de Nuevas Creaciones**

**REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL
TRAMITE**

	USUARIO	RADICADOR
PATENTE DE INVENCION (✓) MODELO DE UTILIDAD ()	()	()
Indicación de que se solicita la concesión de una patente	(✓)	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud	(✓)	()
Descripción de la invención	(✓)	()
-Dibujos de ser estos pertinentes.	(✓)	()
-Comprobante de Pago de las tasas establecidas	(✓)	()
COMPLETA () INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()		
-Indicación de que se solicita el registro de Diseño Industrial	()	()
Datos de identificación del solicitante o de la persona que se 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 se solicita el registro de Diseño Industrial	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()
-Representación gráfica del Esquema Trazado	()	()
-Comprobante de Pago de las tasas establecidas	()	()
COMPLETA () INCOMPLETA ()	()	()

Firma Responsable

Fecha


Junio 8, 2006