



Industria y Comercio

SUPERINTENDENCIA

OL

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

06-122180

21. EXPEDIENTE No.

54. TÍTULO II DERIVADOS DE AMINO-5,5-DIFENILMIDAZOLONA
PARA LA INHIBICIÓN DE B-SECRETASA'

51. CLASIFICACIÓN INTERNACIONAL CO7D 401/10

71. SOLICITANTE WYETH

DOMICILIO NEW JERSEY, ESTADOS UNIDOS

74. APODERADO ALVARO CORREA CRDÓNEZ
T.P. 20201

22. BOGOTÁ, D. C., 4 DICIEMBRE, 2006.

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-122180-00000-0000
Es: Feb: 2006-12-04 16:31:26 Dep. 2020 NUECREACIONES
Trib. 11 PATENTEYII
3a: 278 FASE NACIONAL
Act 411 PRESENTACION
Forma 236

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1

SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☒ X

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.

☒ X

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

79.143.388 de
Usaquén

TP 20.261

4

INVENTOR (ES)
(72)

Nombre: MALAMAS, Michael Sotillos; ERDEI, James Joseph; NAWAN, Iwan Suwandi; ZHOU, Ping; YAN, Ymfa; QUAGLIATO, Dominick A.

Dirección: 2443 Oleander Circle, Jamison, PA 18929 Estados Unidos de América; 304B Cherry Street, Philadelphia, PA 19016 Estados Unidos de América; 29 Rue Chapall, Somerset, NJ 08873 Estados Unidos de América; 28 Marion Drive, Plainsboro, NJ 08538 Estados Unidos de América; 382 Wren Lane, Bedminster, NJ 07921 Estados Unidos de América; 9 Cory Lane, Bridgewater, NJ 08807 Estados Unidos de América, respectivamente.

Nacionalidad o Domicilio: Estadounidenses

5 PCT (85)

Solicitud Internacional No. PCT/US2005/020720

Fecha 14-JUN-2005

Publicación Internacional No. WO 2006/009653

Fecha 28-ENE-2006

6 Título (54)

DERIVADOS DE AMINO-5,5-DIFENILIMIDAZOLONA PARA LA INHIBICIÓN DE β -SECRETASA

7

Clasificación Internacional (51)

C07D 401/10, 403/10, 405/14; A61K 31/4178; A61P 25/28

8

Prioridad

SI ☒ X

NO ☐

(33) País de Origen

US

(32) Fecha

16-JUN-2004

(31) Número de Solicitud

60/580,286

9

Comprobante de pago No. 06-78528

Fecha 11-OCT-2006

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

10

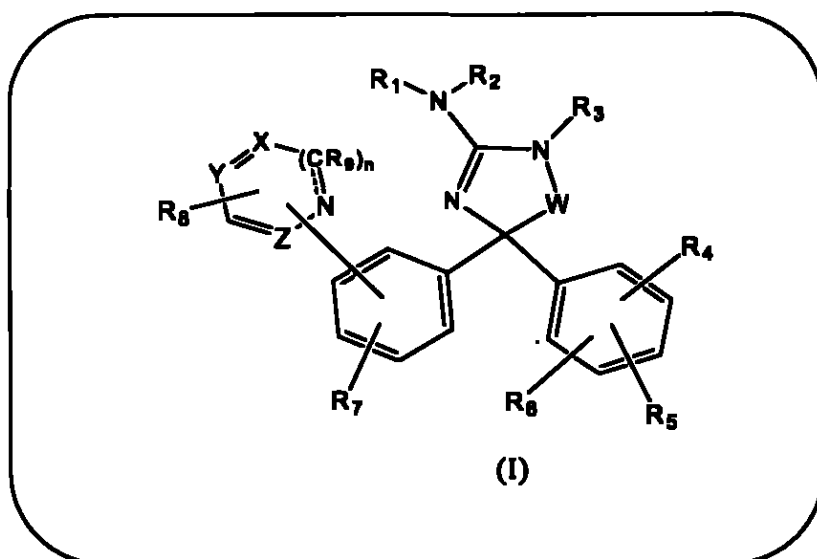
ANEXOS

00002

- ☒ 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, Reporte de búsqueda, opinión escrita y presentación de Documento de Prioridad.

11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.388 de Usaquén

T.P. 20.261

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

023 3
00003

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 78,528
FECHA : OCTUBRE 11 DE 2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-122180-00000-0000
Fec: 2006-12-04 16:31:25 Dep. 2020 NUECREACIONES
TIB 11 PATENTE/II
No. 578 FASE NACIONAL I
A01411 PRESENTACION FORM 236

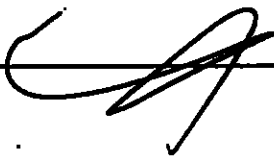
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ORLANDO LINARES	CONSIGNACION	BANCO POPULAR	050-00110-6	55795232	11/10/2006	48,609,000.00

***** CONCEPTO *****

CANT. REMISIVO	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 : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

nnnnn/

TRADUCCIÓN OFICIAL No. 478/06 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 23 de noviembre de 2006 por la Sra. María 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.

=====

Poder otorgado por WYETH respecto de la solicitud de patente titulada "DERIVADOS DE LA AMINO-5, 5-DIFENILIMIDAZOLONA PARA LA INHIBICIÓN DE LA BETA-SECRETASA". Certificación notarial suscrita por Michelle McGowan, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

EL PODER NO SE TRADUCE POR ENCONTRARSE EN INGLÉS Y ESPAÑOL EN EL DOCUMENTO ORIGINAL.

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

CERTIFICACIÓN NOTARIAL

A los 31 días del mes de julio de 2006, la suscrita Notario,

DA FE

1. Que William H. Calnan, mayor y domiciliado en Five Giralda Farms, Madison, Nueva Jersey 07940, Estados Unidos de América, suscribió de su puño y letra el documento que antecede.
2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.
3. Que el otorgante ha suscrito el referido documento en su carácter de Secretario Asistente de la persona jurídica WYETH.

4. Que la persona jurídica WYETH, con sede en Five Giralda Farms, Madison, NJ 07940, Estados Unidos de América, está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se ha otorgado el poder está comprendido entre los que constituyen su objeto social.
5. Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.
6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia: Acta de reunión de la Junta Directiva celebrada el 27 de abril de 2006.

(Fdo.) Michelle L. McGowan
Notario Público

[Sello] MICHELLE L. McGOWAN
Notario Público, Estado de Nueva Jersey
No. 2108903
Habilitada en el Condado de Morris
La comisión expira el 9 de febrero de 2011

(Sello notarial
en relieve)

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por: Michelle L. McGowan
3. actuando en calidad de: Notario Público de Nueva Jersey
4. lleva el sello/timbre de: Michelle L. McGowan, Notario

TERESA LARA
TRADUCTORA CERTIFICADA
RESOLUCION 100 PAREC
DE MINISTERIO

CERTIFICADO

5. en Trenton, Nueva Jersey
6. el día 8 de agosto de 2006
7. por Bradley Abelow, TESORERO DE NUEVA JERSEY
8. No. A267492
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.

TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINISTERIO DE JUSTICIA

María Teresa Lara R.

María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

7.

00007

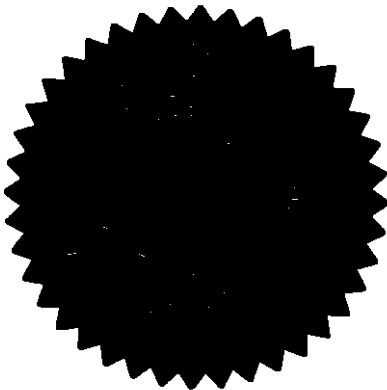
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MICHELLE L MC GOWAN
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MICHELLE L MC GOWAN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 8TH DAY OF AUGUST 2006
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A267492
9. SEAL/STAMP:
10. SIGNATURE



Bradley Abelow

Teresa Lora

TERESA LORA R.
TRADUCTORA OFICIAL
RESOLUCION No. 1197
DE MINISTERIA

478/06

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 8th Floor
Bogotá, Colombia

NIT: 990.088.840-3
Tel: +57 1 634 1800
Fax: +57 1 378 2211
www.bekernet.com

POWER OF ATTORNEY

The undersigned.

WYETH

with offices at

Five Giralda Farms, Madison, NJ 07940,
United States of America

declares that it hereby grants to

**ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA**

All members of the law firm Raisbeck, Lara, Rodríguez & Rueda, with domicile at Av. 82 No. 10 - 62, 6th floor, of Bogotá D. C., Colombia, and for so long as they remain members of the law firm, a full and sufficient power of attorney with respect to Colombian patent application(s) based on PCT/US2005/020720 and entitled "AMINO-5, 5-DIPHENYLIMIDAZOLONE DERIVATIVES FOR THE INHIBITION OF BETA-SECRETASE" and to obtain patent protection therefor, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of a patent(s) based upon said patent application(s) in Colombia, including filing of assignments, change of name or address, voluntary cancellation; and defending oppositions, cancellations, nullity, writ mandamus, and in general the civil and administrative processes relating to those rights.

I hereby ratify all lawful actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 31st day of July of 2006

WYETH


William H. Calman; Assistant Secretary

PODER DE ABOGADO

La abajo firmada,

WYETH

con oficinas en

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

declara por el presente que otorga a

**ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA**

Todos miembros de la firma de abogados Raisbeck, Lara, Rodríguez & Rueda, con domicilio en la Av. 82 No. 10 - 62 Piso 6 en Bogotá D. C., Colombia, para tan largo como ellos se quedan miembros de dijo el bufete de abogados, poder especial amplio y suficiente con respecto a la solicitud(es) de patente en Colombia basada(s) en PCT/US2005/020720 y titulada "AMINO-5, 5-DIPHENYLIMIDAZOLONE DERIVATIVES FOR THE INHIBITION OF BETA-SECRETASE", y para obtener la protección de patente de la misma, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de la(s) patente(s) de invención en Colombia basada(s) en la mencionada solicitud de patente, incluyendo presentación de traspasos, cambio de nombre o dirección, cancelación voluntaria; y defensa en oposiciones, cancelaciones, nulidades, la tutela, y en general procesos civiles y administrativos relacionados con estos derechos.

Igualmente, ratifico todo lo actuado en derecho hasta el momento en nombre de esta compañía por cualquiera de los mencionados apoderados en los casos mencionados.

Dado y firmado en

A los _____ días del mes de _____ de 2006

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this 31st day of July
2006, the undersigned Notary

CERTIFIES

1. That **William H. Calnan**

of legal age and located at

Five Giralda Farms, Madison, New Jersey 07940 U.S.A.

set his hand on the foregoing document.
2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.
3. That the grantor has executed the foregoing document as

Assistant Secretary

of the judicial person **WYETH**
4. That the judicial person **WYETH**
having its home office in
Five Giralda Farms, Madison, NJ 07940,
United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.
5. That the grantor has in fact the referred to authority and that his/her representation is legal.
6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
Minutes from the Board of Director's Meeting held on April 27, 2006.

Michelle L. McGowan
Notary Public
MICHELLE L. MCGOWAN
Notary Public, State of New Jersey
No. 2108903
Qualified in Morris County
Commission Expires Feb. 9, 2011

CERTIFICACION NOTARIAL

A los _____ días del mes de _____
de 2006, el suscrito Notario

DA FE

1. Que

mayor y domiciliado en

suscribió de su puño y letra el documento que antecede.
2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.
3. Que el otorgante ha suscrito el referido documento en su carácter de

de la persona jurídica **WYETH**
4. Que la persona jurídica **WYETH**
con sede en
Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.
5. Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.
6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:

El Notario Público

no not

TRADUCCIÓN OFICIAL No. 487/06 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 28 de noviembre de 2006 por la Sra. María 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 cesión del invento "Derivados de la amino-5, 5-difenilimidazolona para la Inhibición de la beta-secretasa". Certificación notarial suscrita por Winlfred A. Ventura, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

AM101475

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, Asociada para Legalizaciones, Wyeth, certifico por la presente que la copia adjunta ha sido comparada con la Cesión original (para la Solicitud de Patente Internacional PCT/US2005/020720, la cual reclama prioridad con base en la solicitud provisional de los E.U. número 60/580,286, y cualquier equivalente legal de la misma en un país extranjero, para el Invento titulado: "DERIVADOS DE LA AMINO-5, 5-DIFENILIMIDAZOLONA PARA LA INHIBICIÓN DE LA BETA-SECRETASA") fechada el 20 de octubre de 2006 de James Joseph Erdel; y fechada el 23 de octubre de 2006 de Michael Sotirios Malamas, Iwan Suwandi Gunawan y Dominick Anthony Quagliato; y fechada el 31 de octubre de 2006 de Ping Zhou y Yinfa Yan, a Wyeth, y que la citada copia es fiel copia del original.

Dado a los 2 días del mes de noviembre de 2006, en Madison, Nueva Jersey, Estados Unidos de América.

Wyeth

(Fdo.) Michelle L. McGowan
Michelle L. McGowan
Asociada para Legalizaciones

PARA USO EN COLOMBIA

TERESA LARA E.
TRADUCTORA OFICIAL
RESOLUCION NO. 01016
DE 1998

RECONOCIMIENTO

Estado de Nueva Jersey)
)
Condado de Morris)

A los 2 días del mes de noviembre 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.

(Fdo.) Winifred A. Ventura
Notario Público

(Sello notarial
en relieve)

[Sello]

WINIFRED A. VENTURA
NOTARIO PÚBLICO, Estado de Nueva Jersey
No. 2334651
Habilitada en el Condado de Union
La comisión expira el 19 de septiembre de 2010

MANA TERESA LARA R.
TRADUCTORA OFICIAL
RECONOCIDA POR EL GOBIERNO
DE LOS ESTADOS UNIDOS

Expediente No: AM101475
Patente

Cesión de Invento

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

(1) Nombre Completo del Inventor: Michael Sotírios MALAMAS
Residencia: 2443 Oleander Circle, Jamison, PA 18929
Ciudadanía: Estados Unidos de América

(2) Nombre Completo del Inventor: James Joseph ERDEI
Residencia: 304B Cherry Street, Philadelphia, PA 19016
Ciudadanía: Estados Unidos de América

(3) Nombre Completo del Inventor: Iwan Suwandi GUNAWAN
Residencia: 29 Rue Chagall, Somerset, NJ 08873
Ciudadanía: Estados Unidos de América

(4) Nombre Completo del Inventor: Ping ZHOU
Residencia: 28 Marion Drive, Plainsboro, NJ 08536
Ciudadanía: Estados Unidos de América

(5) Nombre Completo del Inventor: Yinfa YAN
Residencia: 362 Wren Lane, Bedminster, NJ 07921
Ciudadanía: Estados Unidos de América

(6) Nombre Completo del Inventor: Dominick Anthony QUAGLIATO
Residencia: 9 Cory Lane, Bridgewater, NJ 08807
Ciudadanía: Estados Unidos de América

por la presente vende, cede y traspasa a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, Nueva Jersey 07940

y a 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:

DERIVADOS DE LA AMINO-5, 5-DIFENILIMIDAZOLONA PARA LA INHIBICIÓN DE LA BETA-SECRETASA

el cual se encuentra en

- (a) [X] la Sollicitud de Patente Internacional PCT/US2005/020720 presentada el 14 de junio de 2005, la cual reclama prioridad con base en la solicitud provisional de los E.U. No. 60/580,286 presentada el 16 de junio de 2004,

MARIA TERESA LARA L.
TRADUCTORA OFICIAL
REGISTRADA EN EL
DE MEXICO

(b) [X] y cualquier equivalente legal de la misma en un país designado, de dicha Solicitud de Patente Internacional,

incluido el derecho a reclamar prioridad con base en la solicitud provisional de los Estados Unidos número 60/580,286, incluidos todos y cada uno de los inventos allí descritos, y en y sobre todas las solicitudes de patente presentadas en los países designados de dicha Solicitud de Patente Internacional, incluido el derecho a cualesquiera continuaciones, continuaciones en parte, divisionales, renovaciones o sustitutos de la misma posteriormente presentados, y en cuanto a Patentes, cualesquiera reexpediciones, reexámenes o prórrogas de las mismas.

ADICIONALMENTE, el Cedente pacta y acuerda otorgar u obtener el otorgamiento de cualquier garantía adicional del título sobre cualquiera de las solicitudes de patente anteriores, y las solicitudes de patente en los países designados de dicha Solicitud de Patente Internacional, o los inventos descritos en la misma, y, en cualquier momento, y a solicitud y por cuenta de la Cesionaria, entregar, o disponer la entrega, de cualquier testimonio en cualquier interferencia, litigio o proceso relacionado con la misma y otorgar, o disponer el otorgamiento, de todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título sobre dichos inventos o cualquier Patente que pueda otorgarse para los mismos a la Cesionaria, sus sucesores, cesionarios u otros representantes legales y que otorgará, o dispondrá el otorgamiento, de todos los juramentos o declaraciones lícitos, y realizará todos los actos lícitos requeridos para adquirir los mismos, sin otra compensación, pero por cuenta de la Cesionaria, sus sucesores, cesionarios u otros representantes legales.

La CEDENTE pacta por el presente que no se ha efectuado ni se efectuará ni celebrará ninguna cesión, venta, acuerdo o gravamen que pudiera entrar en conflicto con esta cesión.

(Fdo.) Michael Sotirios Malamas
Michael Sotirios MALAMAS

Octubre 23, 2006
Fecha

RECONOCIMIENTO

Estado de Nueva Jersey }
ss:
Condado de Middlesex }

A los 23 días del mes de octubre de 2006, compareció personalmente ante mí Michael Sotirios MALAMAS, a quien conozco como la misma persona descrita en el instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Karolina Piorek
Notario Público

[Sello] KAROLINA PIOREK
NOTARIO PÚBLICO DE NUEVA JERSEY
Mi comisión expira el 22 de agosto de 2010

TERESA LARA R.
TRADUCTORA OFICIAL
DE DOCUMENTOS
DE INMIGRACIÓN

(Fdo.) James Joseph Erdel
James Joseph ERDEI

Octubre 20 de 2006
Fecha

RECONOCIMIENTO

Estado de Nueva Jersey }
ss:
Condado de Middlesex }

A los 20 días del mes de octubre de 2006, compareció personalmente ante mí James Joseph ERDEI, a quien conozco como la misma persona descrita en el instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Karolina Piorek
Notario Público

[Sello] KAROLINA PIOREK
NOTARIO PÚBLICO DE NUEVA JERSEY
Mi comisión expira el 22 de agosto de 2010

15-

~~015~~

(Fdo.) Karolína Plorek
Notario Público

YANA TERESA LARA L.
TRADUCTORA OFICIAL
RESOLUCION No. 07919
DE MANUFACTURA

Octubre 31, 2006
Fecha

(Fdo.) Karolina Plorek
Notario Público

**[Sello] KAROLINA PIOREK
NOTARIO PÚBLICO DE NUEVA JERSEY
Mi comisión expira el 22 de agosto de 2010**

(Fdo.) Yinfa Yan

Yinfa YAN

Octubre 31, 2006

Fecha

RECONOCIMIENTO

Estado de Nueva Jersey }

ss:

Condado de Middlesex }

A los 31 días del mes de octubre de 2006, compareció personalmente ante mí Yinfa YAN, a quien conozco como la misma persona descrita en el Instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Karolina Piorek

Notario Público

[Sello]

KAROLINA PIOREK
NOTARIO PÚBLICO DE NUEVA JERSEY
Mi comisión expira el 22 de agosto de 2010

(Fdo.) Dominick Anthony Quagliato

Dominick Anthony QUAGLIATO

Octubre 23, 2006

Fecha

RECONOCIMIENTO

Estado de Nueva Jersey }

ss:

Condado de Middlesex }

A los 23 días del mes de octubre de 2006, compareció personalmente ante mí Dominick Anthony QUAGLIATO, a quien conozco como la misma persona descrita en el Instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Karolina Piorek

Notario Público

[Sello]

KAROLINA PIOREK
NOTARIO PÚBLICO DE NUEVA JERSEY
Mi comisión expira el 22 de agosto de 2010

YANA TERESA LARA L.
TRADUCTORA OPORTUN
RESOLUCION No. 0748
DE MIDDLESEX

AP STILLE
(Convention de La Haye du 5 octobre 1961)

- 1. País: Estados Unidos de América
- 2. Este documento público ha sido firmado por: Winifred A. Ventura
- 3. actuando en calidad de: Notario Público de Nueva Jersey
- 4. lleva el sello/timbre de: Winifred A. Ventura, Notario

CERTIFICADO

- 5. en Trenton, Nueva Jersey
- 6. el día 21 de noviembre de 2006
- 7. por Bradley Abelow, TESORERO DE NUEVA JERSEY
- 8. No. A276569
- 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 según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia


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

18
#2
nnn13
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
WINIFRED A VENTURA
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
WINIFRED A VENTURA, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 21ST DAY OF NOVEMBER 2006
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A276569
9. SEAL/STAMP:
10. SIGNATURE

Bradley Abelow



Terresalva R.
TERESA TERESA LUNA R.
TRADUCTORA OFICIAL
RESOLUCION DEL OFICIO 487/06
DE REGISTRO

AM101475

AFFIDAVIT

I, Michelle L. McGowan, Legalization Associate, Wyeth, do hereby certify that the attached copy has been compared with the original Assignment (for International Patent Application PCT/US2005/020720, which claims priority from U.S. provisional application number 60/580,286, and any legal equivalent thereof in a foreign country, for the invention entitled: "AMINO-5, 5-DIPHENYLMIDAZOLONE DERIVATIVES FOR THE INHIBITION OF BETA-SECRETASE") dated October 20, 2006 from James Joseph Erdei; and dated October 23, 2006 from Michael Sotirios Malamas, Iwan Suwandi Gunawan and Dominick Anthony Quagliato; and dated October 31, 2006 from Ping Zhou and Yinfa Yan to Wyeth and that the said copy is a true copy of the original.

Dated this 2nd day of November, 2006, at Madison, New Jersey, United States of America.

Wyeth

Michelle L. McGowan
Michelle L. McGowan
Legalization Associate

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 2nd day of November, 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 she acknowledged to me that she executed the same.

Winifred A. Ventura
Notary Public

WINIFRED A. VENTURA
NOTARY PUBLIC, State of New Jersey
No. 2294851
Qualified in Union County
Commission Expires September 18, 2010

nnn20

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: Michael Sotirios MALAMAS
Residence: 2443 Oleander Circle, Jamison, PA 18929
Citizenship: USA

- (2) Full Name of Inventor: James Joseph ERDEI
Residence: 304B Cherry Street, Philadelphia, PA 19016
Citizenship: USA

- (3) Full Name of Inventor: Iwan Suwandi GUNAWAN
Residence: 29 Rue Chagall, Somerset, NJ 08873
Citizenship: USA

- (4) Full Name of Inventor: Ping ZHOU
Residence: 28 Marion Drive, Plainsboro, NJ 08536
Citizenship: USA

- (5) Full Name of Inventor: Yinfa YAN
Residence: 362 Wren Lane, Bedminister, NJ 07921
Citizenship: USA

- (6) Full Name of Inventor: Dominick Anthony QUAGLIATO
Residence: 9 Cory Lane, Bridgewater, NJ 08807
Citizenship: USA

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:

AMINO-5, 5-DIPHENYLIMIDAZOLONE DERIVATIVES FOR THE INHIBITION OF BETA-SECRETASE

which is found in

- (a) ☒ International Patent Application PCT/US2005/020720 filed June 14, 2005 which claims priority from U.S. provisional application number 60/580,286 filed 16 June 2004,
- (b) ☒ and any legal equivalent thereof in a designated country of said International Patent Application,

Including the right to claim priority from United States provisional application number 60/580,286, including any and all inventions described therein, and in and to all patent applications filed in the designated countries of said International Patent Application, including the right to any subsequently filed continuations, continuations-in-part, divisional, renewals, or substitutes thereof, and as to Letters Patents any reissues, reexaminations or extensions thereof.

IN ADDITION, Assignor covenants and agrees to execute or cause the execution of any further assurance of title to any of the foregoing patent applications, and patent applications in the designated countries of said International Patent Application, or inventions described therein, and to, at any time, upon the request and at the expense of Assignee deliver, or cause to be delivered, any testimony in any interference, litigation or proceeding related thereto and execute, or cause to be executed, all papers that may be necessary or desirable to perfect the title to said inventions or any Letters Patent which may be granted therefor in Assignee, its successors, assigns or any other legal representatives and will make, or cause to be made, 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 hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

Michael Sotirios Malamas
Michael Sotirios MALAMAS

October 23, 2006
Date

ACKNOWLEDGMENT

State of New Jersey }
County of Hudson } ss:

On the 23rd day of October 2006, Michael Sotirios MALAMAS 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.

Kawira P. P. P.
Notary Public for the State of New Jersey
Commission Expires 6/23/2010

James Joseph ERDEI
James Joseph ERDEI

October 20th, 2006
Date

ACKNOWLEDGMENT

State of New Jersey }
County of Middlesex }

On the 20th day of October 2006, James Joseph ERDEI 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.

Kawiana Pirek
Notary Public
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 8/22/2010

Ivan Surwandi GUNAWAN
Ivan Surwandi GUNAWAN

October 23, 2006
Date

ACKNOWLEDGMENT

State of New Jersey }
County of Middlesex }

On the 23rd day of October 2006, Iwan Surwandi GUNAWAN 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.

Kawiana Pirek
Notary Public
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 8/22/2010

Ping ZHOU
Ping ZHOU

Oct. 31, 2006
Date

ACKNOWLEDGMENT

State of New Jersey }
County of Middlesex } ss:

On the 31st day of October 2006, Ping ZHOU 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.

Kawline Proulx

Notary Public
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 6/28/2010

Yinfa YAN
Yinfa YAN

Oct. 31, 2006
Date

ACKNOWLEDGMENT

State of New Jersey }
County of Middlesex } ss:

On the 31st day of October 2006, Yinfa YAN 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.

Kawline Proulx

Notary Public
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 6/28/2010

1. ~~00000~~

Oct. 23, 2006
Date

88:

On the 23rd day of October 2006, Dominick Anthony QUAGLIATO 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.

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(74) Agent: LENCSES, Barbara, L.; Wyeth, Patent Law De-
partment, Five Giralda Farms, Madison, NJ 07940, (US).

(21) International Application Number:
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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, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
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(71) Applicant (for all designated States except US): WYETH
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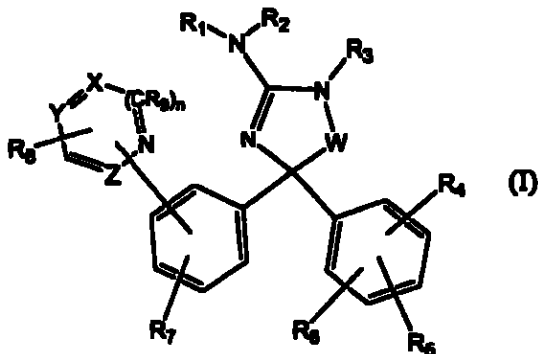
(72) Inventors; and

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NAWAN, Iwan Suwandi [US/US]; 29 Rue Chagall,
Somerset, NJ 08873 (US). ZHOU, Ping [US/US]; 28
Marion Drive, Plainsboro, NJ 08536 (US). YAN, Yinfu
[CN/US]; 362 Wren Lane, Belminister, NJ 07921 (US).
QUAGLIATO, Dominick, A. [US/US]; 9 Cory Lane,
Bridgewater, NJ 08807 (US).

Published:
with international search report

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

(54) Title: AMINO-5,5-DIPHENYLIMIDAZOLONE DERIVATIVES FOR THE INHIBITION OF BETA-SECRETASE



(57) Abstract: The present invention provides a compound of for-
mula (I) and the use thereof for the therapeutic treatment, preven-
tion or amelioration of a disease or disorder characterized by elevated
β-amyloid deposits or β-amyloid levels in a patient.

WO 2006/009653 A1

AMINO-5,5-DIPHENYLIMIDAZOLONE DERIVATIVES FOR THE INHIBITION OF BETA-SECRETASE

5

BACKGROUND OF THE INVENTION

Alzheimer's disease (AD), a progressive degenerative disease of the brain primarily associated with aging, is a serious healthcare problem. Clinically, AD is characterized by the of loss of memory, cognition, reasoning, judgment, and orientation. Also affected, as the disease progresses, are motor, sensory, and linguistic abilities until global impairment of multiple cognitive functions occurs. These cognitive losses take place gradually, but typically lead to severe impairment and eventual death in 4-12 years. Patients with AD display characteristic β -amyloid deposits in the brain and in cerebral blood vessels (β -amyloid angiopathy) as well as neurofibrillary tangles. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of patients with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), and other neurodegenerative disorders. Neurofibrillary tangles also occur in other dementia-inducing disorders.

The family of proteins known as β -amyloid are thought to be causal for the pathology and subsequent cognitive decline in Alzheimer's disease. Proteolytic processing of the amyloid precursor protein (APP) generates amyloid β (A-beta) peptide; specifically, A-beta is produced by the cleavage of APP at the N-terminus by β -secretase and at the C-terminus by one or more γ -secretases. Aspartyl protease enzyme, or β -secretase enzyme (BACE), activity is correlated directly to the generation of A-beta peptide from APP (Sinha, et al, *Nature*, 1999, 402, 537-540). Increasingly, studies indicate that the inhibition of the β -secretase enzyme, inhibits

the production of A-beta peptide. The inhibition of β -secretase and consequent lowering of A-beta peptide may lead to the reduction of β -amyloid deposits in the brain and β -amyloid levels in the cerebral blood vessels and to an effective treatment of a disease or disorder caused thereby.

5 Therefore, it is an object of this invention to provide compounds which are inhibitors of β -secretase and are useful as therapeutic agents in the treatment, prevention or amelioration of a disease or disorder characterized by elevated β -amyloid deposits or β -amyloid levels in a patient.

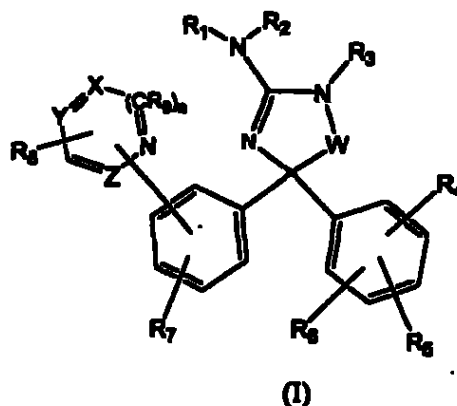
10 It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment, prevention or amelioration of a disease or disorder characterized by elevated β -amyloid deposits or β -amyloid levels in a patient.

It is a feature of this invention that the compounds provided may also be useful to further study and elucidate the β -secretase enzyme.

15 These and other objects and features of the invention will become more apparent by the detailed description set forth hereinbelow.

SUMMARY OF THE INVENTION

20 The present invention provides a compound of formula I



wherein W is CO, CS or CH₂;

X is N, NO or CR₁₀;

25 Y is N, NO or CR₁₁;

Z is N, NO or CR₁₆ with the proviso that no more than two of X, Y or Z may be N or NO;

R₁ and R₂ are each independently H, COR₂₀, CO₂R₂₁ or an optionally substituted C₁-C₆alkyl group;

5 R₃ is H, OR₁₂ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl or aryl(C₁-C₆)alkyl group each optionally substituted;

10 R₄ and R₅ are each independently H, halogen, NO₂, CN, OR₁₃, NR₁₄R₁₅ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl or C₃-C₆cycloalkyl group each optionally substituted or when attached to adjacent carbon atoms R₄ and R₅ may be taken together with the atoms to which they are attached to form an optionally substituted 5- to 7-membered ring optionally containing one or two heteroatoms selected from O, N or S;

15 R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₆ are each independently H, halogen, NO₂, CN, OR₁₆, NR₁₇R₁₈ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl or C₃-C₆cycloalkyl group each optionally substituted;

n is 0 or 1;

— is a single bond when n is 0 or a double bond when n is 1;

20 R₁₂, R₁₃, R₁₆, R₂₀ and R₂₁ are each independently H or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl or aryl group each optionally substituted; and

R₁₄, R₁₅, R₁₇ and R₁₈ are each independently H or C₁-C₆alkyl; or a tautomer thereof, a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

25 The present invention also provides therapeutic methods and pharmaceutical compositions useful for the treatment, prevention or amelioration of a disease or disorder characterized by increased β -amyloid deposits or increased β -amyloid levels in a patient.

30

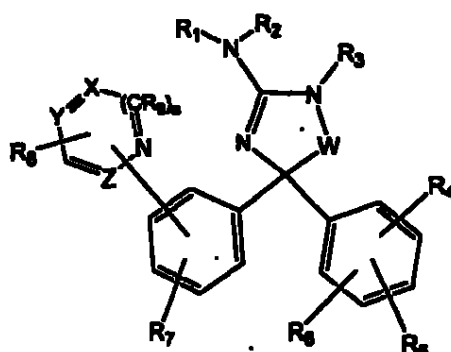
DETAILED DESCRIPTION OF THE INVENTION

Alzheimer's disease (AD) is a major degenerative disease of the brain which presents clinically by progressive loss of memory, cognition, reasoning, judgement

and emotional stability and gradually leads to profound mental deterioration and death. The exact cause of AD is unknown, but increasing evidence indicates that amyloid beta peptide (A-beta) plays a central role in the pathogenesis of the disease. (D. B. Schenk; R. E. Rydel *et al*, Journal of Medicinal Chemistry, 1995, 21,4141 and
5 D. J. Selkoe, Physiology Review, 2001, 81, 741). Patients with AD exhibit characteristic neuropathological markers such as neuritic plaques (and in β -amyloid angiopathy, deposits in cerebral blood vessels) as well as neurofibrillary tangles detected in the brain at autopsy. A-beta is a major component of neuritic plaques in AD brains. In addition, β -amyloid deposits and vascular β -amyloid angiopathy also
10 characterize individuals with Downs Syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch type and other neurodegenerative and dementia-inducing disorders. Over expression of the amyloid precursor protein (APP), altered cleavage of APP to A-beta or a decrease in the clearance of A-beta from a patient's brain may increase the levels of soluble or fibrillar forms of A-beta in the brain. The
15 β -site APP cleaving enzyme, BACE1, also called memapsin-2 or Asp-2, was identified in 1999 (R. Vassar, B. D. Bennett, *et al*, Nature, 1999, 402, 537). BACE1 is a membrane-bound aspartic protease with all the known functional properties and characteristics of β -secretase. Parallel to BACE1, a second homologous aspartyl protease named BACE2 was found to have β -secretase activity *in vitro*. Low
20 molecular weight, non-peptide, non-substrate-related inhibitors of BACE1 or β -secretase are earnestly sought both as an aid in the study of the β -secretase enzyme and as potential therapeutic agents.

Surprisingly, it has now been found that amino-5,5-diphenylimidazolone, -imidazothione and -imidazole compounds of formula I demonstrate inhibition of β -
25 secretase and the selective inhibition of BACE1. Advantageously, said compounds may be used as effective therapeutic agents for the treatment, prevention or amelioration of a disease or disorder characterized by elevated β -amyloid deposits or β -amyloid levels in a patient. Accordingly, the present invention provides a compound of formula I

20



(I)

wherein W is CO, CS or CH₂;

X is N, NO or CR₁₀;

Y is N, NO or CR₁₁;

5 Z is N, NO or CR₁₉ with the proviso that no more than two of X, Y or Z may be N or NO;

R₁ and R₂ are each independently H, COR₂₀, CO₂R₂₁, or an optionally substituted C₁-C₄alkyl group;

10 R₃ is H, OR₁₂ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl or aryl(C₁-C₆)alkyl group each optionally substituted;

15 R₄ and R₅ are each independently H, halogen, NO₂, CN, OR₁₃, NR₁₄R₁₅ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl or C₃-C₆cycloalkyl group each optionally substituted or when attached to adjacent carbon atoms R₄ and R₅ may be taken together with the atoms to which they are attached to form an optionally substituted 5-

20 to 7-membered ring optionally containing one or two heteroatoms selected from O, N or S;

R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₉ are each independently H, halogen, NO₂, CN,

OR₁₆, NR₁₇R₁₈ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl or C₃-C₆cycloalkyl group each optionally substituted;

25 n is 0 or 1;

== is a single bond when n is 0 or a double bond when n is 1;

R₁₂, R₁₃, R₁₆, R₂₀ and R₂₁ are each independently H or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl or aryl group each optionally substituted; and

R₁₄, R₁₅, R₁₇ and R₁₈ are each independently H or C₁-C₄alkyl; or

a tautomer thereof, a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

X is N, NO or CR₁₀; preferably N or CR₁₀. Y is N, NO or CR₁₁; preferably CR₁₁. Z is N, NO or CR₁₀; preferably CR₁₀. The symbol n is 0 or 1, preferably 1. R₆,
5 R₇, R₈, R₉, R₁₀, R₁₁ and R₁₈ are each independently H, halogen, NO₂, CN, OR₁₈, NR₁₇R₁₈ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl or C₃-C₆cycloalkyl group each optionally substituted; preferably H, halogen, C₁-C₄alkyl or C₁-C₄alkoxy. The ring containing X, Y and Z substitutes the phenyl group, preferably at the 3-position thereof. The ring member of the ring containing X, Y and Z that is linked to
10 the phenyl group is preferably the carbon atom linked to Y and Z.

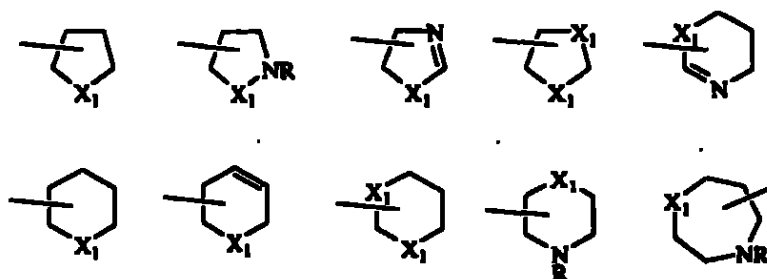
R₁ and R₂ are each independently H, COR₂₀, CO₂R₂₁, or an optionally substituted C₁-C₄alkyl group; preferably H or an optionally substituted C₁-C₄alkyl group; more preferably H, a C₁-C₄alkyl group or a C₁-C₄haloalkyl group; advantageously H.

15 W is preferably CO.

R₄ and R₅ are each independently H, halogen, NO₂, CN, OR₁₃, NR₁₄R₁₅ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl or C₃-C₆cycloalkyl group each optionally substituted or when attached to adjacent carbon atoms R₄ and R₅ may be taken together with the atoms to which they are attached to form an optionally
20 substituted 5- to 7-membered ring optionally containing one or two heteroatoms selected from O, N or S. Preferably R₄ and R₅ are each independently H, halogen, CN, OR₁₃, or a C₁-C₆alkyl, C₁-C₆haloalkyl, or C₃-C₆cycloalkyl group each optionally substituted or, when attached to adjacent carbon atoms, R₄ and R₅ may be taken together with said adjacent carbon atoms to form an optionally substituted 5- to 7-
25 membered ring optionally containing one or two heteroatoms selected from O, N or S, the ring preferably containing two oxygen atoms as heteroatoms. More preferably R₄ and R₅ are each independently H, halogen, CN, OR₁₃, or a C₁-C₆alkyl, C₁-C₆haloalkyl, or C₃-C₆cycloalkyl group or, when attached to adjacent carbon atoms, R₄ and R₅ may be taken together with said adjacent carbon atoms to form a 5- to 7-
30 membered ring optionally containing one or two heteroatoms selected from O, N or S, the ring being optionally substituted by 1, 2 or 3 halogen atoms. Advantageously at least one of R₄ and R₅ is OR₁₃ or R₄ and R₅ when taken together represent a divalent radical which is a methylenedioxy or ethylenedioxy radical optionally

substituted by one or more halogen atoms. R_{13} is H or a C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or aryl group each optionally substituted; preferably C_1 - C_6 alkyl substituted by 0, 1, 2 or 3 substituents independently selected from halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkoxycarbonyl, alkanoyl, alkanoyloxy, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocyclyl and cycloalkyl groups.

As used in the specification and claims, the term halogen designates F, Cl, Br or I and the term cycloheteroalkyl designates a five- to seven-membered cycloalkyl ring system containing 1 or 2 heteroatoms, which may be the same or different, selected from N, O or S and optionally containing one double bond. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the following rings wherein X₁ is NR, O or S; and R is H or an optional substituent as described hereinbelow:



Similarly, as used in the specification and claims, the term heteroaryl designates a five- to ten-membered aromatic ring system containing 1, 2 or 3 heteroatoms, which may be the same or different, selected from N, O or S. Such heteroaryl ring systems include pyrrolyl, azoly, oxazoly, thiazoly, imidazoly, furyl, thienyl, quinoliny, isoquinoliny, indoly, benzothieryl, benzofuranyl, benzisoxazoly or the like. The term aryl designates a carbocyclic aromatic ring system such as phenyl, naphthyl, anthracenyl or the like. The term aryl(C₁-C₄)alkyl designates an aryl group as defined hereinabove attached to a C₁-C₄alkyl group which may be straight or branched. Said aryl(C₁-C₄)alkyl groups include benzyl, phenethyl, naphthylmethyl, or the like. The term haloalkyl as used herein designates a C_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different and the term haloalkoxy as used herein designates an OC_nH_{2n+1} group having from

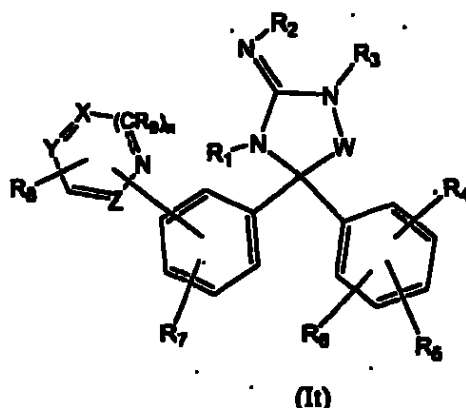
one to $2n+1$ halogen atoms which may be the same or different. Preferably the term haloalkyl designates CF_3 and the term haloalkoxy designates OCF_3 .

In the specification and claims, when the terms C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, cycloheteroalkyl, aryl, aryl(C_1 - C_4)alkyl or heteroaryl are designated as being optionally substituted, the substituent groups which are optionally present may be one or more of those customarily employed in the development of pharmaceutical compounds or the modification of such compounds to influence their structure/activity, persistence, absorption, stability or other beneficial property. Specific examples of such substituents include halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocyclidyl or cycloalkyl groups, preferably halogen atoms or lower alkyl or lower alkoxy groups. Typically, 0-3 substituents may be present. When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, more preferably up to 4 carbon atoms.

Pharmaceutically acceptable salts may be any acid addition salt formed by a compound of formula I and a pharmaceutically acceptable acid such as phosphoric, sulfuric, hydrochloric, hydrobromic, citric, maleic, malonic, mandelic, succinic, fumaric, acetic, lactic, nitric, sulfonic, p-toluene sulfonic, methane sulfonic acid or the like.

Compounds of the invention include amides, esters, carbamates or other conventional prodrug forms, which in general, are functional derivatives of the compounds of the invention and which are readily converted to the inventive active moiety *in vivo*. Correspondingly, the method of the invention embraces the treatment of the various conditions described hereinabove with a compound of formula I or with a compound which is not specifically disclosed but which, upon administration, converts to a compound of formula I *in vivo*. Also included are metabolites of the compounds of the present invention defined as active species produced upon introduction of these compounds into a biological system.

Compounds of the invention may exist as one or more tautomers. One skilled in the art will recognize that compounds of formula I may also exist as the tautomer it as shown below.



(Ii)

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Tautomers often exist in equilibrium with each other. As these tautomers interconvert under environmental and physiological conditions, they provide the same useful biological effects. The present invention includes mixtures of such tautomers as well as the individual tautomers of Formula I and Formula II.

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The compounds of the invention may contain one or more asymmetric carbon atoms or one or more asymmetric (chiral) centers and may thus give rise to optical isomers and diastereomers. Thus, the invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure stereoisomers; as well as other mixtures of the R and S stereoisomers. One skilled

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in the art will appreciate that one stereoisomer may be more active or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich or selectively prepare said stereoisomers. Accordingly, the

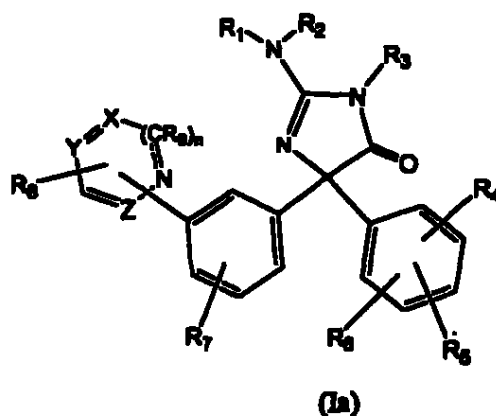
present invention comprises compounds of Formula I, the stereoisomers thereof, the tautomers thereof and the pharmaceutically acceptable salts thereof. The compounds of the invention may be present as a mixture of stereoisomers, individual stereoisomers, or as an optically active or enantiomerically pure form.

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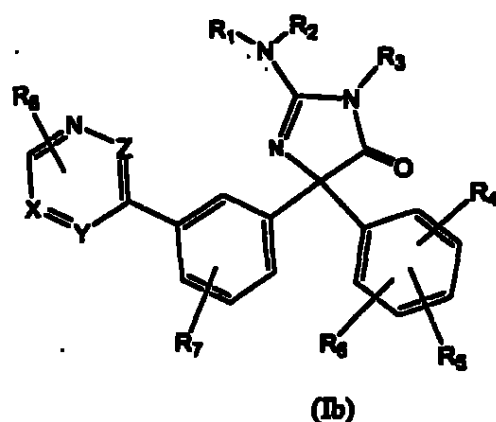
Preferred compounds of the invention are those compounds of formula I wherein W is CO. Another group of preferred compounds of the invention are those compounds of formula I wherein R₁ and R₂ are H and R₃ is C₁-C₄ alkyl. Also preferred are those formula I compounds wherein n is 1. A further group of preferred

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compounds of the invention are those compounds of formula I wherein the nitrogen-containing 5-membered or 6-membered heteroaryl ring is attached to the phenyl ring in the 3-position of the phenyl ring; this preferred group of formula I compounds is designated in the specification and claims as formula Ia. The formula Ia compound is shown below.



More preferred compounds of the invention are those compounds of formula Ia wherein the nitrogen-containing heteroaryl ring is a 6-membered ring and is attached to the phenyl ring in the 3-position of said heteroaryl ring; this more preferred group of formula I compounds is designated in the specification and claims as formula Ib. Formula Ib is shown below.



Another group of more preferred compounds of the invention are those compounds of formula Ib wherein R3 is methyl. A further group of more preferred compounds of

the invention are those compounds of formula Ib wherein Y is CR₁₁; R₁ and R₂ are H; and R₃ is methyl.

Examples of preferred compounds of formula I include:

- 2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-(4-methoxy-3-methylphenyl)-3-methyl-
 3,5-dihydro-4H-imidazol-4-one;
 (5S)-2-amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-
 methyl-3,5-dihydro-4H-imidazol-4-one;
 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-
 dihydro-4H-imidazol-4-one;
 (5S)-2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-
 dihydro-4H-imidazol-4-one;
 (5R)-2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-5-[4-
 (trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one;
 4-[2-amino-4-(4-methoxy-3-methylphenyl)-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-4-
 yl]-2-pyridin-3-ylbenzonitrile;
 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(4-methyl-3-pyridin-3-ylphenyl)-
 3,5-dihydro-4H-imidazol-4-one;
 2-amino-5-[4-methoxy-3-(trifluoromethyl)phenyl]-3-methyl-5-(3-pyridin-3-ylphenyl)-
 3,5-dihydro-4H-imidazol-4-one;
 2-amino-3-ethyl-5-(4-methoxy-3-methylphenyl)-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-
 4H-imidazol-4-one;
 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrazin-2-ylphenyl)-3,5-
 dihydro-4H-imidazol-4-one;
 2-amino-3-methyl-5-(3-pyrimidin-2-ylphenyl)-5-[4-(trifluoromethoxy)phenyl]-3,5-
 dihydro-4H-imidazol-4-one;
 2-amino-5-(4-hydroxy-3-methylphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-
 4H-imidazol-4-one;
 2-amino-5-[4-methoxy-3-(trifluoromethyl)phenyl]-3-methyl-5-(3-pyrazin-2-ylphenyl)-
 3,5-dihydro-4H-imidazol-4-one;
 (5R)-2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-
 dihydro-4H-imidazol-4-one;
 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-
 4H-imidazol-4-one;

- 2-amino-5-(3,4-diethoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(3,4-dimethoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 5 2-amino-5-(3-cyclopentyl-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(4-methoxy-3-propoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(3-butoxy-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 10 2-amino-5-(3-isopropoxy-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(1,3-benzodioxol-5-yl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 15 2-amino-5-(2,3-dihydro-1-benzofuran-5-yl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 5-[2-amino-1-methyl-5-oxo-4-(3-pyridin-3-ylphenyl)-4,5-dihydro-1H-imidazol-4-yl]-2-methoxybenzonitrile;
- 20 2-amino-5-(3-fluoro-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 25 2-amino-5-(3-chloro-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-3-methyl-5-(3-pyridin-3-ylphenyl)-5-(3,4,5-trimethoxyphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyridin-4-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 30 2-amino-5-(3-ethoxy-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;

2-amino-3-methyl-5-(3-pyridin-3-ylphenyl)-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one;

2-amino-3-methyl-5-(3-pyridin-3-ylphenyl)-5-[(4-trifluoromethoxy-3-trifluoromethyl)phenyl]-3,5-dihydro-4H-imidazol-4-one;

5 2-amino-5-(3,4-diethoxyphenyl)-5-(4-fluoro-3-pyridin-3-ylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one;

2-amino-5-(3-chloro-4-trifluoromethoxyphenyl)-5-(4-fluoro-3-pyridin-3-ylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one;

a tautomer thereof; a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

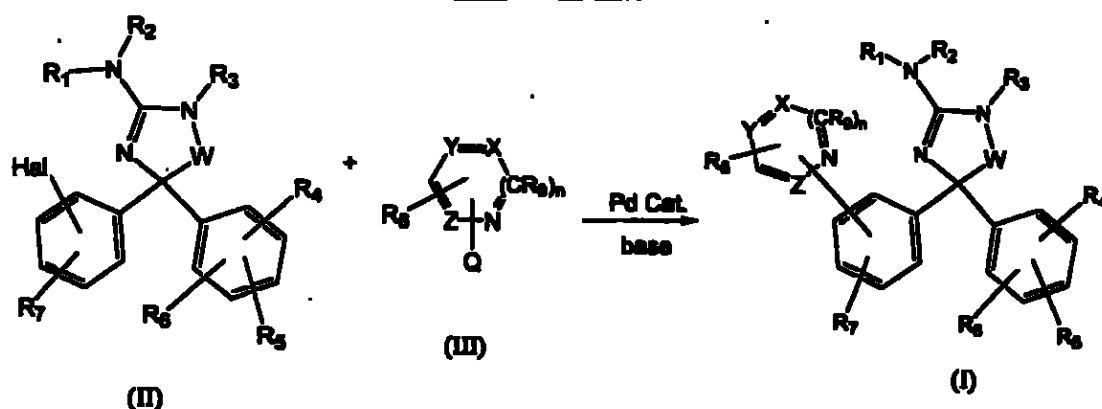
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Advantageously, the present invention provides a process for the preparation of a compound of formula I which comprises reacting a compound of formula II wherein Hal is Cl or Br with a compound of formula III wherein Q is B(OH)₂, Sn(Bu)₃ or Sn(CH₃)₃ in the presence of a palladium catalyst and an inorganic base optionally

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in the presence of a solvent. The process is shown in flow diagram I, wherein Hal and Q are as defined hereinabove.

Flow Diagram I



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Palladium catalysts suitable for use in the process of the invention include Pd(0) or Pd(II) catalysts such as dichlorobis(tri-o-tolylphosphine)palladium(II), Pd(OCOCH₃)₂/tri-o-tolylphosphine, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0)/triphenylphosphine, or the like.

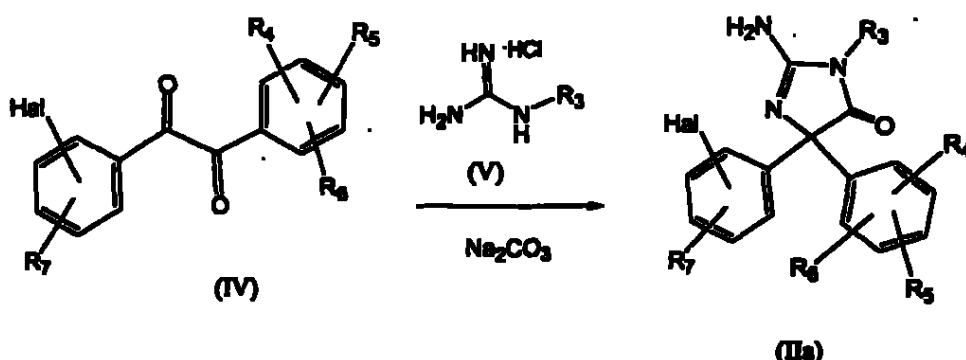
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Inorganic bases suitable for use in the inventive process include Na or K hydroxides, carbonates or bicarbonates, preferably Na₂CO₃ or K₂CO₃.

Solvents suitable for use in the inventive process include polar or non-polar organic solvents such as toluene, diethoxy ethyl ether, dioxane, ethyleneglycol dimethyl ether or any non-reactive organic solvent which is capable of solubilizing the formula II or formula III compounds.

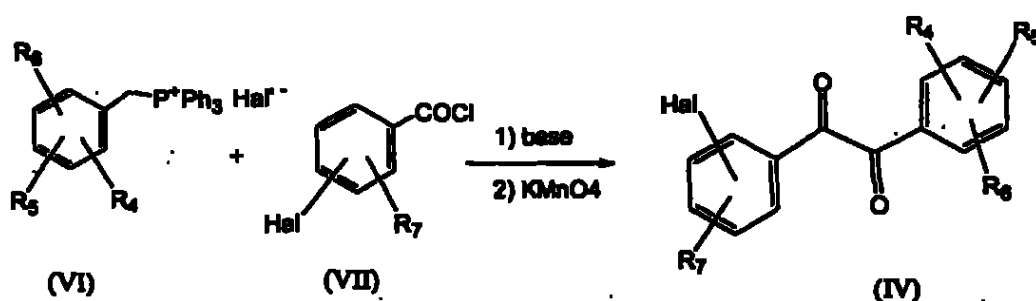
- 5 Compounds of formula II may be prepared using conventional synthetic methods and, if required, standard separation or isolation techniques. For example, compounds of formula II wherein W is CO and R₁ and R₂ are H (IIa), may be prepared by reacting a diketone of formula IV with a substituted guanidine of formula V in the presence of a base such as Na₂CO₃ to give the desired compound of
10 formula IIa. The reaction is shown in flow diagram II wherein Hal is Cl or Br.

Flow Diagram II



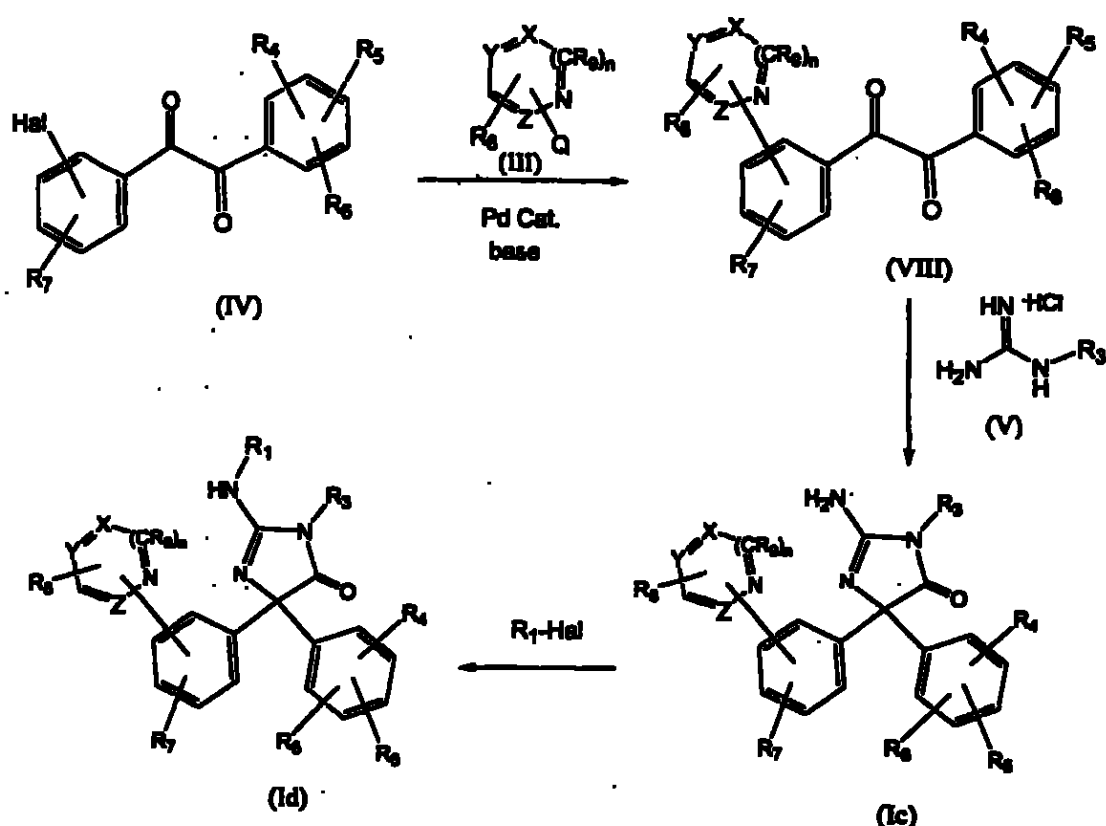
- 15 Compounds of formula IV may be prepared by reacting a triphenylphosphonium salt of formula VI with a benzoyl chloride of formula VII in the presence of a base such as Na₂CO₃ to form the corresponding triphenylphosphine ylide and oxidizing said ylide with KMnO₄ in the presence of MgSO₄ to give the desired diketone of formula IV. The reaction is shown in flow diagram III wherein Hal
20 and Hal' are each independently Cl or Br and Ph represents a phenyl group.

Flow Diagram III



- Alternatively, compounds of formula I wherein W is CO and R₁ and R₂ are H (Ic) may be prepared by reacting a diketone of formula IV with a compound of formula III in the presence of a palladium catalyst and an inorganic base to give the diketone of formula VIII and reacting said formula VIII diketone with a substituted guanidine of formula V (as shown in flow diagram II hereinabove) to give the desired compound of formula Ic. Compounds of formula I wherein R₁ is other than H (Id) may be prepared using standard alkylation techniques such as reacting the compound of formula Ic with an alkyl halide, R₁-Hal, to give the compound of formula I wherein R₁ is other than H and R₂ is H (Id). The reaction is shown in flow diagram IV wherein Q is B(OH)₂, Sn(Bu)₃ or Sn(CH₃)₃ and Hal is Cl or Br.

Flow Diagram IV



- Compounds of formula I wherein W is CO and R₁ and R₂ are other than H may be prepared by reacting said formula Id compound with a second alkyl halide, R₂-Hal, to give the desired formula I compound wherein R₁ and R₂ are other than H.
- Advantageously, the compounds of the invention are useful for the treatment, prevention or amelioration of a disease or disorder characterized by elevated β-amyloid deposits or β-amyloid levels in a patient, including Alzheimer's disease, Downs Syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch type or other neurodegenerative or dementia-inducing disorders. Accordingly, the present invention provides a method for the treatment, prevention or amelioration of a disease or disorder characterized by elevated β-amyloid deposits or β-amyloid levels in a patient which comprises providing said patient with a therapeutically effective amount of a compound of formula I as described hereinabove. The compound may be provided by oral or parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The term "providing" as used herein with respect to providing a compound or substance embraced by the invention, designates either directly administering such a compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

5 As described herein, a therapeutically or prophylactically useful amount of a compound of the invention is that amount of a compound which alleviates the symptoms of the disease, e.g., AD, or which prevents the onset of symptoms, or the onset of more severe symptoms. The useful amounts of a compound may vary depending upon the formulation and route of delivery. For example, higher amounts
10 may be delivered orally than when the compound is formulated for injection or inhalation, in order to deliver a biologically equivalent amount of the drug. Suitably, an individual dose (i.e., per unit) of a compound of the invention is in the range from about 1 µg/kg to about 10 g/kg. Desirably, these amounts are provided on a daily basis. However, the dosage to be used in the treatment or prevention of a specific
15 cognitive deficit or other condition may be subjectively determined by the attending physician. The variables involved include the specific cognitive deficit and the size, age and response pattern of the patient. For example, based upon the activity profile and potency of the compounds of this invention, a starting dose of about 375 to 500 mg per day with gradual increase in the daily dose to about 1000 mg per day may
20 provide the desired dosage level in the human.

In actual practice, the compounds of the invention are provided by administering the compound or a precursor thereof in a solid or liquid form, either neat or in combination with one or more conventional pharmaceutical carriers or excipients. Accordingly, the present invention provides a pharmaceutical
25 composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as described hereinabove.

Solid carriers suitable for use in the composition of the invention include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aides, binders, tablet-disintegrating
30 agents or encapsulating materials. In powders, the carrier may be a finely divided solid which is in admixture with a finely divided compound of formula I. In tablets, the formula I compound may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. Said

powders and tablets may contain up to 99% by weight of the formula I compound. Solid carriers suitable for use in the composition of the invention include calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Any pharmaceutically acceptable liquid carrier suitable for preparing solutions, suspensions, emulsions, syrups and elixirs may be employed in the composition of the invention. Compounds of formula I may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a pharmaceutically acceptable oil or fat, or a mixture thereof. Said liquid composition may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers, osmo-regulators, or the like. Examples of liquid carriers suitable for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) or their derivatives, or oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier may also be an oily ester such as ethyl oleate or isopropyl myristate.

Compositions of the invention which are sterile solutions or suspensions are suitable for intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions may also be administered intravenously. Inventive compositions suitable for oral administration may be in either liquid or solid composition form.

Alternatively, the use of sustained delivery devices may be desirable, in order to avoid the necessity for the patient to take medications on a daily basis. "Sustained delivery" is defined as delaying the release of an active agent, i.e., a compound of the invention, until after placement in a delivery environment, followed by a sustained release of the agent at a later time. Those of skill in the art know suitable sustained delivery devices. Examples of suitable sustained delivery devices include, e.g., hydrogels (see, e.g., US Patent Nos. 5,266,325; 4,959,217; and 5,292,515); an osmotic pump, such as described by Alza (US Patent Nos. 4,295,987 and 5,273,752) or Merck (European Patent No. 314,206), among others; hydrophobic membrane

materials, such as ethylenemethacrylate (EMA) and ethylenevinylacetate (EVA); bioresorbable polymer systems (see, e.g., International Patent Publication No. WO 98/44984, Bioxid and Cellomeda; US Patent Nos. 5,756,127 and 5,854,388); other bioresorbable implant devices have been described as being composed of, for
5 example, polyesters, polyanhydrides, or lactic acid/glycolic acid copolymers (see, e.g., US Patent No. 5,817,343 (Alkermes Inc.)). For use in such sustained delivery devices, the compounds of the invention may be formulated as described herein.

In another aspect, the invention provides a pharmaceutical kit for delivery of a product. Suitably, the kit contains packaging or a container with the compound
10 formulated for the desired delivery route. For example, if the kit is designed for administration by inhalation, it may contain a suspension containing a compound of the invention formulated for aerosol or spray delivery of a predetermined dose by inhalation. Suitably, the kit contains instructions on dosing and an insert regarding the active agent. Optionally, the kit may further contain instructions for monitoring
15 circulating levels of product and materials for performing such assays including, e.g., reagents, well plates, containers, markers or labels, and the like. Such kits are readily packaged in a manner suitable for treatment of a desired indication. For example, the kit may also contain instructions for use of the spray pump or other delivery device.

20 Other suitable components to such kits will be readily apparent to one of skill in the art, taking into consideration the desired indication and the delivery route. The doses may be repeated daily, weekly, or monthly, for a predetermined length of time or as prescribed.

For a more clear understanding, and in order to illustrate the invention more
25 clearly, specific examples thereof are set forth hereinbelow. The following examples are merely illustrative and are not to be understood as limiting the scope and underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the examples set forth hereinbelow and the foregoing
30 description. Such modifications are also intended to fall within the scope of the appended claims.

Unless otherwise noted, all parts are parts by weight. The terms HNMR and HPLC designate proton nuclear magnetic resonance and high performance liquid

chromatography, respectively. The terms EtOAc and THF designate ethyl acetate and tetrahydrofuran, respectively. In the structures, the term Ph designates a phenyl group.

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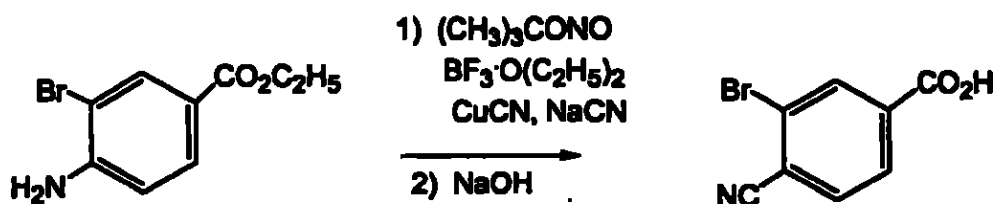
EXAMPLE 1**Preparation of Ethyl 4-amino-3-bromobenzoate**

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A solution of bromine (7.0 mL, 137.3 mmol) in dichloromethane is added dropwise to a cold (-10 °C) solution of ethyl 4-aminobenzoate (22.0 g, 133.3 mmol) in dichloromethane. The reaction mixture is allowed to come to room temperature, stirred for 18 h and diluted with water. The organic phase is separated, washed
10 twice with brine, dried over MgSO₄ and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (SiO₂, 8/1 hexanes/EtOAc as eluent) to afford the title compound as a white solid, 28.6 g (88% yield), identified by HNMR and mass spectral analyses. MS *m/e* 242 (M-H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 1.28 (t, *J* = 7.01 Hz, 3 H), 4.22 (q, *J* = 7.16 Hz, 2 H), 6.18 (brs, 2 H), 6.81 (d, *J* = 7.91 Hz, 1H),
15 7.65 (dd, *J* = 8.54, 1.98 Hz 1 H), 7.89 (d, *J* = 1.83 Hz, 1H).

EXAMPLE 2**Preparation of 3-Bromo-4-cyanobenzoic acid**

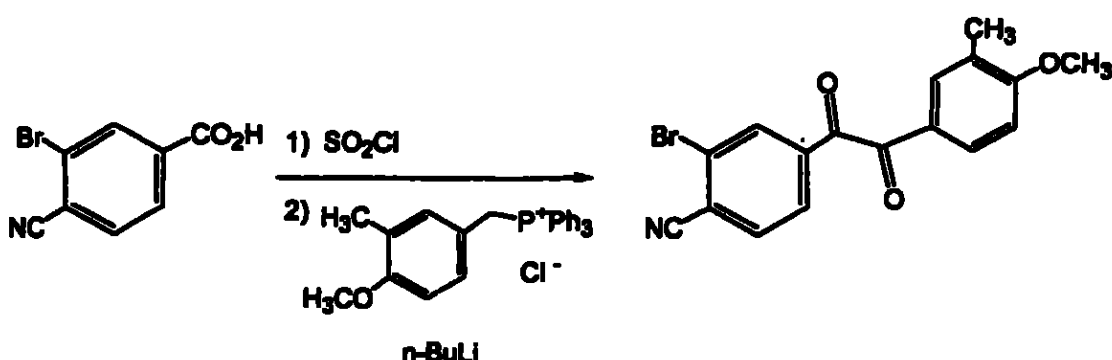
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A solution of ethyl 4-amino-3-bromobenzoate (23.5 g, 96.3 mmol) in methylene chloride at -10° C is treated dropwise with *tert*-butyl nitrite (14.0 mL, 118.4
25 mmol), followed by boron trifluoride diethyl etherate (18.4 mL, 146.5 mmol). The reaction mixture is allowed to come to room temperature, stirred for 4 h, diluted with ethyl ether and filtered. The filtercake is dried, dispersed in toluene, cooled to 0° C, treated with a solution of copper (I) cyanide (11.5 g, 129.2 mmol) and sodium

cyanide (15.8 g, 323.1 mmol) in water, stirred at 0° C for 30 min., warmed to 60° C, stirred for 1 h, cooled to room temperature and diluted with EtOAc and water. The organic phase is separated, dried over MgSO₄ and concentrated *in vacuo*. The resultant residue is crystallized from ethyl ether/hexanes to give the ethyl ester of the title compound as an off-white solid, 18.6 g (76% yield). A solution of this ester (8.5 g, 33.6 mmol) in THF is treated with a solution of NaOH (30 mL, 2.5 N) and ethanol, stirred for 20 h, acidified with 2N HCl and extracted with ethyl ether. The ether extracts are combined, dried over MgSO₄ and concentrated *in vacuo*. The resultant residue is crystallized from ethyl ether/hexanes to afford the title compound as a beige solid, 6.81 g (90% yield), identified by HNMR and mass spectral analyses. MS *m/e* 223 (M-H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 8.05 (dd, *J* = 9.76, 1.37 Hz 1 H), 8.09 (d, *J* = 8.08 Hz, 1H), 8.29 (d, *J* = 1.37 Hz, 1H).

15

EXAMPLE 3**Preparation of 2-Bromo-4-[(4-methoxy-3-methylphenyl)(oxo)acetyl]benzonitrile**

A suspension of 3-bromo-4-cyanobenzoic acid (1.65 g, 7.28 mmol) in thionyl chloride (10 mL) is treated with 3 drops of N,N-dimethylformamide, heated at reflux temperature for 1 h and concentrated *in vacuo*. This acid chloride residue is re-evaporated 3X with toluene to remove any remaining thionyl chloride. A mixture of 3-methyl-4-methoxybenzyl triphenylphosphonium chloride (6.3 g, 14.55 mmol) in toluene at 0° C is treated dropwise with n-butyllithium (6.1 mL, 2.5 M in hexanes), allowed to come to room temperature, stirred for 2 h, cooled to 0° C, treated dropwise

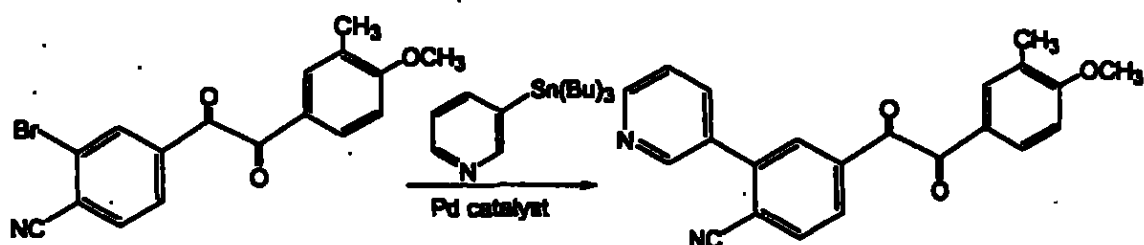
37

nnn 48

with a solution of the above-obtained acid chloride in toluene, allowed to come to room temperature, stirred for 2 h, quenched with water and concentrated *in vacuo*. The resultant residue is dispersed in acetone and water, treated with MgSO_4 (7.5 g, 62.5 mmol) and KMnO_4 (2.18 g, 13.8 mmol), vigorously stirred at 45° C for 18 h and
 5 filtered. The filtrate is diluted with EtOAc, washed sequentially with water and brine, dried over MgSO_4 and evaporated to dryness. This residue is purified by flash chromatography (SiO_2 , 2/1 hexanes/EtOAc as eluent) to afford the title compound as a yellow solid, 1.8 g (69% yield), identified by HNMR and mass spectral analyses.
 MS *m/e* 357 ($\text{M}+\text{H}^+$); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.21 (s, 3H), 3.93 (s, 3H),
 10 7.15 (d, $J = 8.54$ Hz, 1H), 7.81 (d, $J = 1.38$ Hz, 1H), 7.85 (dd, $J = 8.54, 2.14$ Hz, 1H), 8.03 (dd, $J = 8.08, 1.52$ Hz 1 H), 8.18 (d, $J = 8.08$ Hz, 1H), 8.30 (d, $J = 1.38$ Hz, 1H).

EXAMPLE 4

15 Preparation of 4-[(4-Methoxy-3-methylphenyl)(oxo)acetyl]-2-pyridin-3-ylbenzonitrile

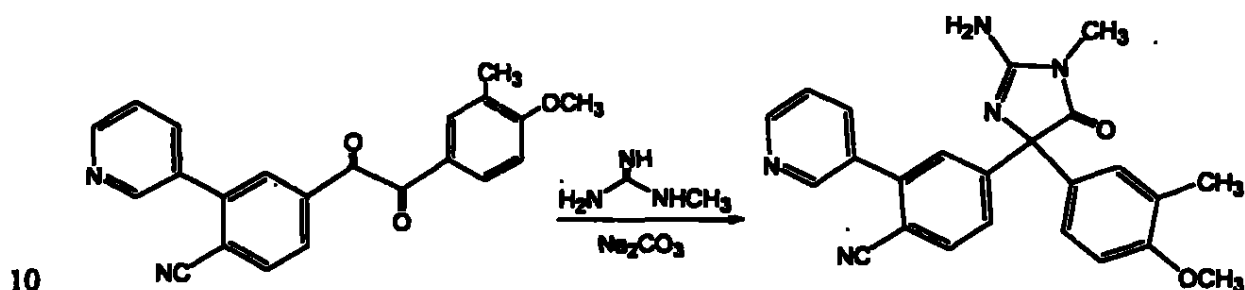


20

A mixture of 2-bromo-4-[(4-methoxy-3-methylphenyl)(oxo)acetyl]benzonitrile (200 mg, 0.56 mmol) and 3-(tributylstannyl)pyridine (288 mg, 0.73 mmol) in 1,2-diethoxyethane is treated with dichlorobis(tri-*o*-tolylphosphine)palladium(II) (39.6 mg, 0.05 mmol), heated at 145° C, stirred for 30 min. and filtered to remove the catalyst.
 25 The filtrate is evaporated to dryness. The resultant residue is purified by flash chromatography (SiO_2 , 2/1 hexanes/EtOAc as eluent) and crystallization from ethyl ether/hexanes to afford the title compound as a yellow solid, 181 mg (91% yield), identified by HNMR and mass spectral analyses. MS *m/e* 357 ($\text{M}+\text{H}^+$); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.21 (s, 3H), 3.93 (s, 3H), 7.18 (d, $J = 8.69$ Hz, 1H), 7.81 (m, 1H),

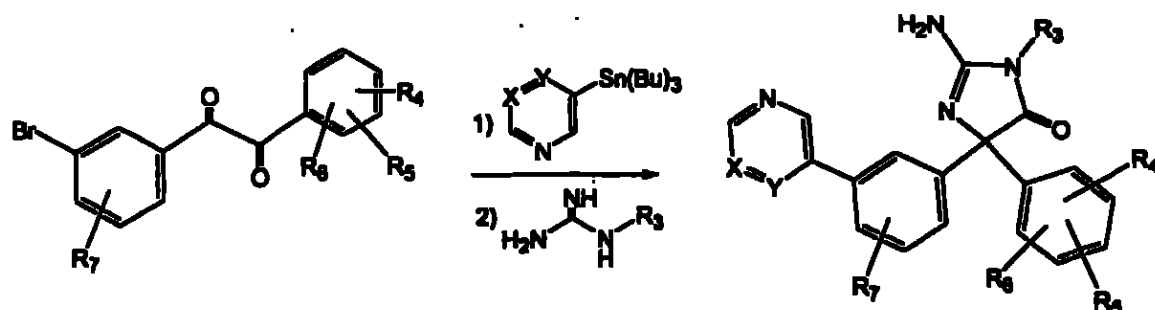
7.82 (d, $J = 8.54$, 1H), 7.84 (dd, $J = 8.54$, 1.99 Hz 1 H), 8.07 (dd, $J = 7.76$, 1.67 Hz, 1H), 8.12 (m, $J = 1.38$ Hz, 2H), 8.25 (d, $J = 8.08$ Hz, 1H), 8.74 (m, 1H), 8.85 (d, 1.68 Hz, 1H).

5

EXAMPLE 5**Preparation of 4-[(2-amino-4-(4-methoxy-3-methylphenyl)-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-4-yl)-2-pyridin-3-yl]benzonitrile**

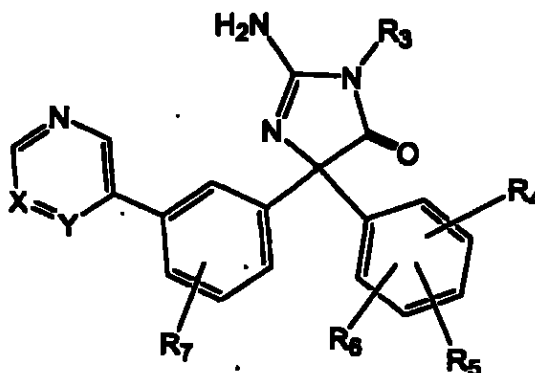
A mixture of 4-[(4-methoxy-3-methylphenyl)(oxo)acetyl]-2-pyridin-3-ylbenzonitrile (160 mg, 0.45 mmol) and 1-methylguanidine hydrochloride (222 mg, 2.02 mmol) in dioxane and ethyl alcohol is treated with Na_2CO_3 (214 mg, 2.02 mmol) in water, stirred at 85°C for 3 h and concentrated *in vacuo*. The resultant residue is partitioned between chloroform and water. The phases are separated and the organic phase is dried over MgSO_4 and concentrated *in vacuo*. This residue is purified by flash chromatography (SiO_2 , 15/1 EtOAc/methanol as eluent) and crystallization from CHCl_3 /hexanes to give the title compound as a white solid, 138 mg (75% yield), identified by HNMR and mass spectral analyses. MS m/e 412 ($\text{M}+\text{H}^+$); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.09 (s, 3H), 2.98 (s, 3H), 3.74 (s, 3H), 6.74 (brs, 2H), 6.86 (d, $J = 8.69$ Hz, 1H), 7.22 (s, 1H), 7.26 (d, $J = 8.54$ Hz, 1H), 7.58 (m, 1H), 7.69 (s, 1H), 7.70 (s, 1H), 7.9-8.0 (m, 2H), 8.7 (m, 2H).

25

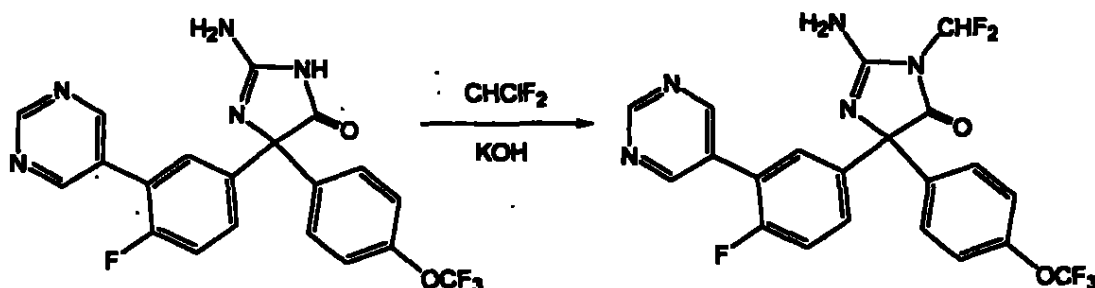
EXAMPLES 6-33**Preparation of Amino-5,5-diphenylimidazolone Derivatives**

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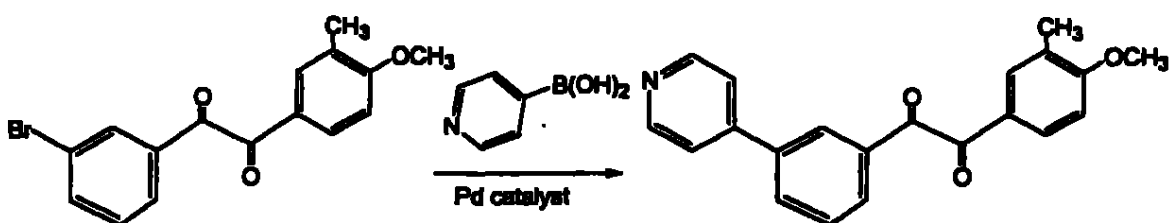
Using essentially the same procedures described in Examples 4 and 5 hereinabove and employing the appropriate dione substrate, tributylstannyl-pyridine or -pyrimidine intermediate and desired guanidine reagent, the compounds shown on Table I are obtained and identified by HNMR and mass spectral analyses.

Table I

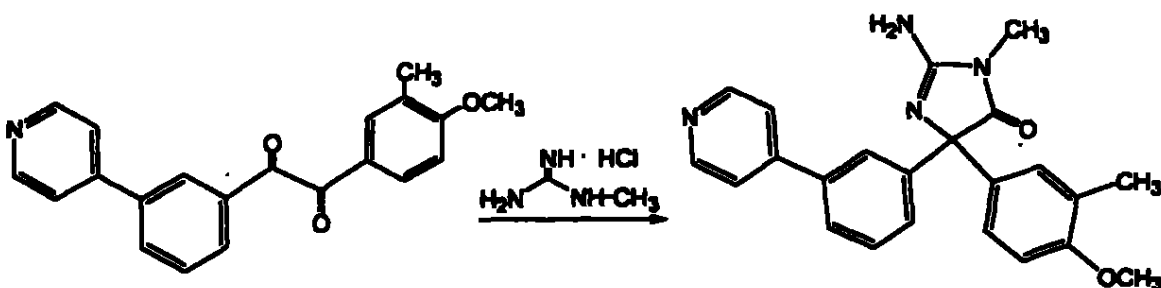
Ex. No	R ₃	R ₄	R ₅	R ₆	R ₇	X	Y	mp °C
6	CH ₃	3-CH ₃	4-OCH ₃	H	4-CH ₃	CH	CH	—
7	CH ₃	3-CF ₃	4-OCH ₃	H	H	CH	CH	—
8	C ₂ H ₅	3-CH ₃	4-OCH ₃	H	H	CH	CH	—
9	CH ₃	3-CH ₃	4-OCH ₃	H	H	CH	N	—
10	CH ₃	3-CH ₃	4-OH	H	H	CH	CH	—
11	CH ₃	3-CF ₃	4-OCH ₃	H	H	CH	N	—
12	CH ₃	3-CH ₃	4-OCH ₃	H	H	N	CH	126

EXAMPLE 34**Preparation of 2-Amino-3-difluoromethyl-5-[4-fluoro-3-(pyrimidin-5-yl)phenyl]-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one**

A solution of 2-amino-5-[4-fluoro-3-(pyrimidin-5-yl)phenyl]-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one (0.398 g, 0.92 mmol) in dimethylformamide is treated with KOH (0.057 g, 1.01 mmol), cooled to -45°C , and bubbled with chlorodifluoromethane (1.40 g, 17.6 mmol). The reaction vessel is sealed and heated at 70°C for 18 h. The reaction is cooled to room temperature, quenched by careful addition to water, extracted with ethyl acetate, diluted with brine and extracted again with ethyl acetate. The combined extracts are washed with brine, dried over sodium sulfate and concentrated. The resultant residue is purified twice by flash chromatography (silica, 95:5:0.5 to 90:10:0.5 methylene chloride/methanol/concentrated ammonium hydroxide and 100:0 to 98:2 methylene chloride/methanol as eluents) to afford the title compound as a white solid, 0.064 g (14% yield), mp $82-84^{\circ}\text{C}$. Identified by HNMR, infrared and mass spectral analyses. ^1H NMR (500 MHz, CDCl_3) δ 9.21 (s, 1H), 8.89 (s, 2H), 7.64–7.60 (m, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 7.23–7.18 (m, 3H), 6.95 (t, $J = 58$ Hz, 1H), 4.92 (br s, 2H); IR (ATR) 3497, 3309, 3149, 1761, 1678, 1497, 1449, 1416, 1252, 1212, 1162 cm^{-1} ; ESI MS m/z 482 [$\text{C}_{21}\text{H}_{13}\text{F}_8\text{N}_5\text{O}_2 + \text{H}$] $^{+}$;

EXAMPLE 35**Preparation of 1-(4-Methoxy-3-methylphenyl)-2-(3-pyridin-4-ylphenyl)ethane-1,2-dione**

A solution of 1-(3-bromo-phenyl)-2-(4-methoxy-3-methylphenyl)ethane-1,2-dione (0.25 g, 0.75 mmol) in dioxane is treated sequentially with tri-*o*-tolylphosphine (57 mg, 0.187 mmol), palladium (II) acetate (21 mg, 0.093 mmol), pyridine-4-boronic acid (139 mg, 1.125 mmol) and H₂O, stirred at 100° C for 4 h, cooled to room temperature and filtered. The filtrate is evaporated *in vacuo*. The resultant residue is purified by flash chromatography on silica gel (hexanes/EtOAc 3/7 as eluent), to afford the title compound as a yellow solid, 0.145 g (58% yield), identified by HNMR and mass spectral analyses. *MS m/e* (M+H)⁺ 332; ¹H NMR (400 MHz, CDCl₃) δ 2.28 (s, 3H) 3.95 (s, 3H) 6.94 (d, 1H) 7.68 (m, 3H) 7.84 (m, 2H) 7.88 (m, 1H) 8.08 (m, 1H) 8.30 (m, 1H) 8.75 (m, 2H).

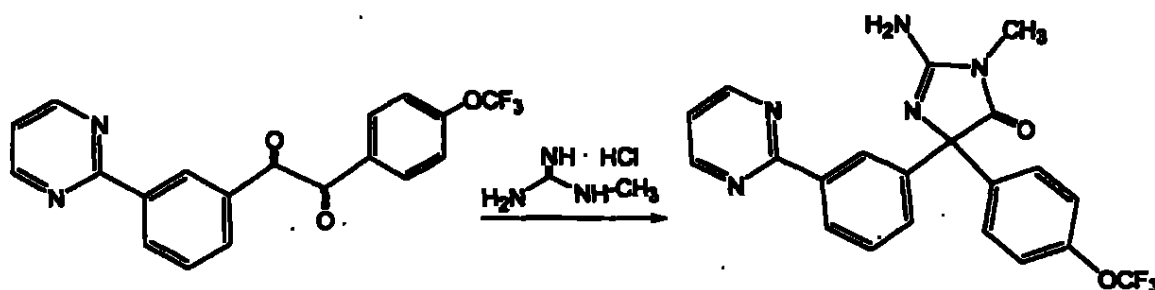
EXAMPLE 36**Preparation of 2-Amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyridin-4-ylphenyl)-3,5-dihydro-4H-imidazol-4-one**

Using essentially the same procedure described in Example 5 hereinabove, and employing 1-(4-methoxy-3-methylphenyl)-2-(3-pyridin-4-ylphenyl)ethane-1,2-

dione and 1-methylguanidine hydrochloride as reactants, the title compound is obtained as a white solid, 0.15 g (90% yield), mp 175° C, identified by HNMR and mass spectral analyses. *MS m/e* (M)⁺ 387; ¹H NMR (400 MHz, DMSO-d₆) δ 2.05 (s, 3H) 3.00 (s, 3H) 3.75 (s, 3H) 6.60 (bs, 2H) 6.82 (d, 1H) 7.20 (m, 1H) 7.25 (m, 1H) 7.40 (m, 1H) 7.50 (m, 3H) 7.62 (m, 1H) 7.8 (m, 1H) 8.6 (m, 2H).

EXAMPLE 37

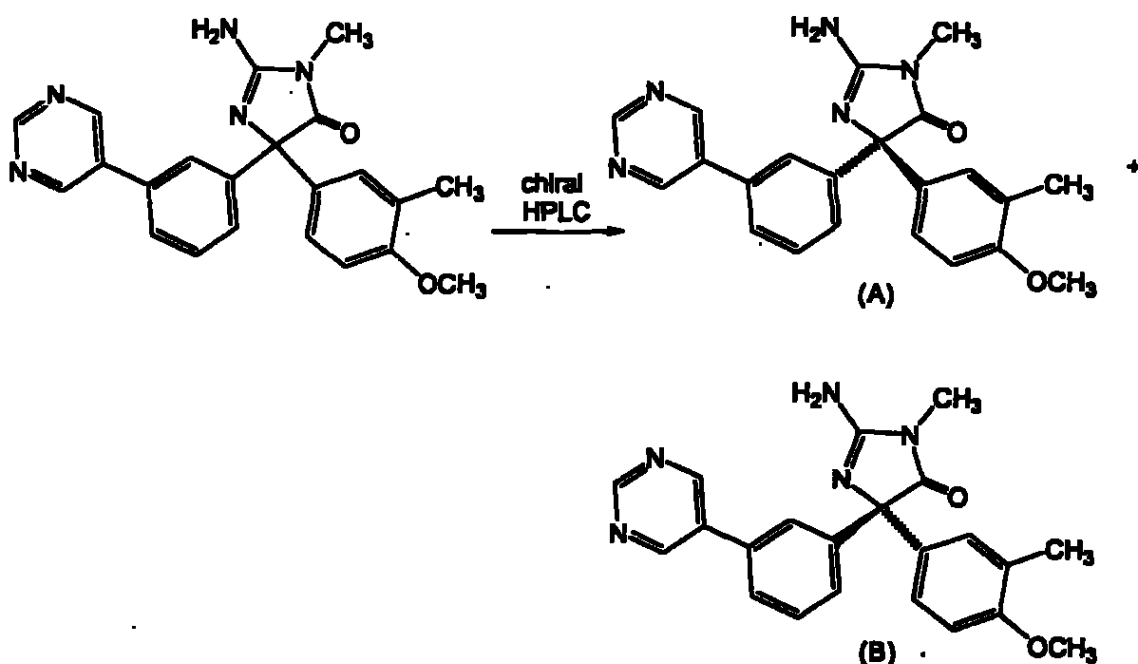
Preparation of 2-Amino-3-methyl-5-(3-pyrimidin-2-ylphenyl)-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one



Using essentially the same procedure described in Example 36 hereinabove and employing 1-(3-pyrimidin-2-ylphenyl)-2-[4-(trifluoromethoxy)phenyl]ethane-1,2-dione and methylguanidine hydrochloride as reactants, the title compound is obtained as a white solid, identified by HNMR and mass spectral analyses. *MS m/e* 428 (M+H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 3.01 (s, 1H), 6.79 (brs, 2H), 7.33-7.49 (m, 2H), 7.58-7.66 (m, 3H), 8.27 (m, 2H), 7.59 (d, J = 7.77 Hz, 1H), 7.98 (d, J = 7.47 Hz, 1H), 8.26 (s, 1H), 8.61 (t, J = 1.67 Hz, 1H), 8.90 (d, J = 4.88 Hz, 2H).

EXAMPLE 38

Preparation of (5R)-2-Amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one (A) and (5S)-2-Amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one (B)



Racemic 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one is resolved using chiral HPLC technique on a Chiralcel AD, 2x25 cm and using as mobile phase 50% IPA/DEA in 7200/DEA with a flow rate of 10mL/min. The R-isomer, title compound A, is obtained, after crystallization from chloroform/hexane as a white solid, 98% ee; identified by HNMR and mass spectral analyses. MS m/e 388 ($M+H$)⁺; ¹H NMR (400 MHz, DMSO- d_6) δ 2.07 (s, 3H), 2.97 (s, 3H), 3.72 (s, 3H), 6.63 (brs, 2H), 6.85 (d, J = 8.39 Hz, 1H), 7.21 (s, 1H), 7.25 (dd, J = 7.88, 1.01, 1H), 7.46 (t, J = 7.55 Hz, 1H), 7.52 (d, J = 7.89 Hz, 1H), 7.63 (dd, J = 7.54, 0.84 Hz, 1H), 7.75 (s, 1H), 8.99 (s, 2H), 9.18 (s, 1H). $[\alpha]_D^{25}$ = +40.2 (c = 1% in CH₃OH)

The S-isomer, title compound B, is obtained, after crystallization from chloroform/hexane as a white solid, 95% ee; identified by HNMR and mass spectral

41

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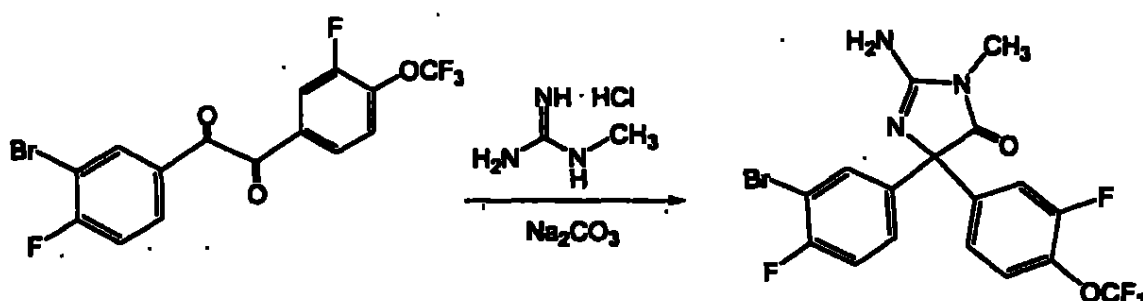
analyses. MS m/e 388 (M+H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 2.07 (s, 3H), 2.97 (s, 3H), 3.72 (s, 3H), 6.63 (brs, 2H), 6.85 (d, J = 8.39 Hz, 1H), 7.21 (s, 1H), 7.25 (dd, J = 7.88, 1.01, 1H), 7.46 (t, J = 7.55 Hz, 1H), 7.52 (d, J = 7.89 Hz, 1H), 7.63 (dd, J = 7.54, 0.84 Hz, 1H), 7.75 (s, 1H), 8.99 (s, 2H), 9.18 (s, 1H).

$[\alpha]_D^{25}$ = -79.6 (c = 0.67% in CH₃OH).

Absolute configuration for each of title compound A and B is determined by x-ray crystallography.

EXAMPLE 39

Preparation of 2-Amino-5-(3-bromo-4-fluorophenyl)-5-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-methyl-3,5-dihydroimidazol-4-one

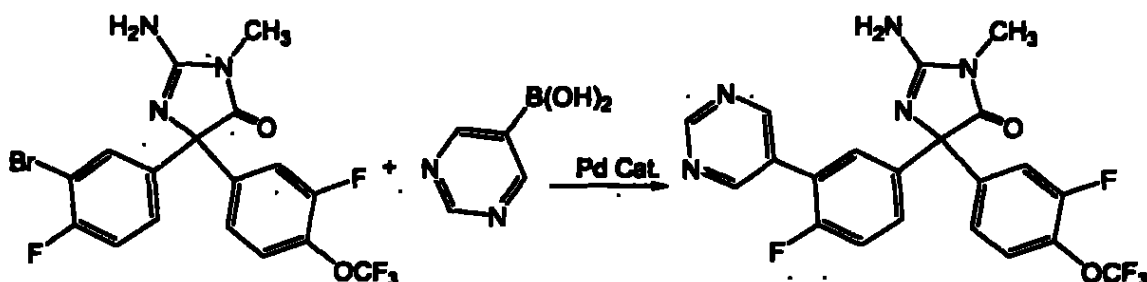


A mixture of 1-(3-bromo-4-fluorophenyl)-2-[3-fluoro-4-(trifluoromethoxy)phenyl]ethane-1,2-dione (0.594 g, 1.45 mmol) and 1-methylguanidine hydrochloride (0.716 g, 6.53 mmol) in dioxane and ethanol is stirred at room temperature for 5 min., treated with a solution of sodium carbonate (0.692 g, 6.53 mmol) in water (5 mL), heated at 85° C with stirring for 45 min., cooled to room temperature, and concentrated *in vacuo*. The resultant residue is partitioned between methylene chloride and water. The organic phase is separated, washed with sequentially with water and brine, dried over sodium sulfate and concentrated *in vacuo*. This residue is purified by flash chromatography (silica, 95:5:0.5 methylene chloride/methanol/concentrated ammonium hydroxide as eluent) to afford a viscous oil. This oil is dissolved in a minimal amount of methylene chloride, treated with hexanes and then concentrated to afford the title product as an off-white solid, 0.30g (45% yield), identified by HNMR and mass spectral analyses. ¹H NMR (500 MHz,

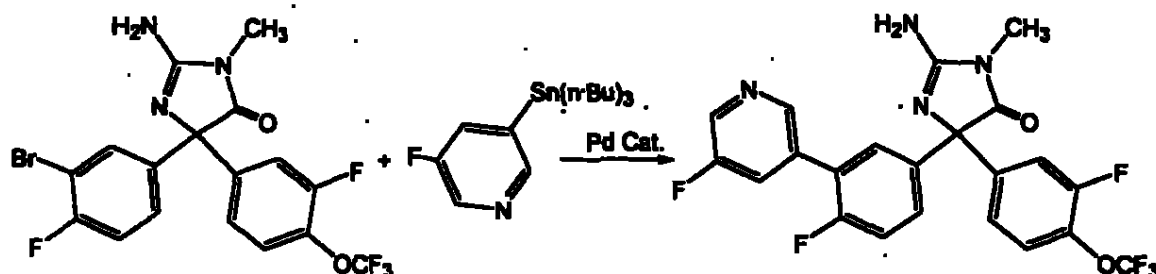
CD₃OD) δ 7.64 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.43–7.37 (m, 2H), 7.33 (dd, *J* = 11.5, 2.1 Hz, 1H), 7.30 (m, 1H), 7.18 (t, *J* = 8.6 Hz, 1H), 3.11 (s, 3H); ESI MS *m/z* 464 [C₁₇H₁₁BrF₅N₃O₂ + H]⁺.

EXAMPLE 40

Preparation of 2-Amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-methyl-3,5-dihydro-imidazol-4-one



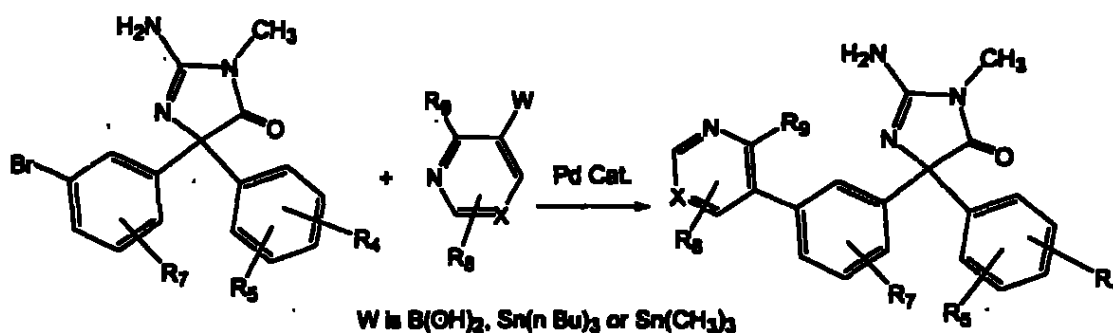
A mixture of ethylene glycol dimethyl ether, tris(dibenzylideneacetone)-dipalladium(0) (0.015 g, 16.5 μmol) and triphenylphosphine (0.008 g, 32.0 μmol) under nitrogen is stirred for 5 min, treated with 2-amino-5-(3-bromo-4-fluorophenyl)-5-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-methyl-3,5-dihydroimidazol-4-one (0.154 g, 0.33 mmol), 5-pyrimidine boronic acid (0.046 g, 0.37 mmol), sodium carbonate (0.105 g, 0.99 mmol) and water, heated at reflux temperature for 1.25 h, cooled to room temperature and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica, 95:5:0.5 methylene chloride/methanol/concentrated ammonium hydroxide as eluent) to afford a viscous oil. This oil is suspended in a mixture of methylene chloride/hexanes and concentrated to afford the title compound as an off-white solid, 0.045 g (29% yield), mp 102–110° C, identified by HNMR and mass spectral analyses. ¹H NMR (500 MHz, CD₃OD) δ 9.15 (s, 1H), 8.95 (s, 2H), 7.62–7.56 (m, 2H), 7.39–7.27 (m, 4H), 3.12 (s, 3H); IR 3353, 3061, 2956, 1732, 1666, 1498, 1470, 1416, 1251, 1216, 1170 cm⁻¹; ESI MS *m/z* 464 [C₂₁H₁₄F₅N₃O₂ + H]⁺; HPLC (Method 2) 95.0% (AUC) *t_R* = 13.78 min.

EXAMPLE 41**Preparation of 2-Amino-5-[4-fluoro-3-(5-fluoropyridin-3-yl)phenyl]-5-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-methyl-3,5-dihydro-imidazol-4-one**

A mixture of 2-amino-5-(3-bromo-4-fluorophenyl)-5-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-methyl-3,5-dihydroimidazol-4-one (0.17 g, 0.366 mmol), 5-fluoropyridin-3-yl-tri(n-butyl)stannate (0.212 g, 0.55 mmol) and bis(triphenylphosphino)palladium(II) chloride (0.013 g, 0.018 mmol) in dimethyl formamide is degassed, heated at 150° C for 1 h, cooled to room temperature and diluted with ethyl acetate and 2% aqueous lithium chloride. The organic phase is separated, washed with 2% aqueous lithium chloride, dried over sodium sulfate and concentrated *in vacuo*. Purification of the resultant residue by flash chromatography (silica, 97:3:0.25 methylene chloride/methanol/concentrated ammonium hydroxide as eluent) affords the title compound as a white solid, 0.130 g (74% yield), mp 91–97°C; identified by HNMR and mass spectral analyses. ¹H NMR (300 MHz, CD₃OD) 8.55 (m, 1H), 8.49 (d, *J* = 3.0 Hz, 1H), 7.83 (d, *J* = 9.6 Hz, 1H), 7.60–7.21 (m, 6H), 3.13 (s, 3H); IR (ATR) 3352, 3070, 1732, 1669, 1598, 2502, 1479, 1421, 1252, 1217, 1171, 863, 817, 794, 703 cm⁻¹; ESI MS *m/z* 481

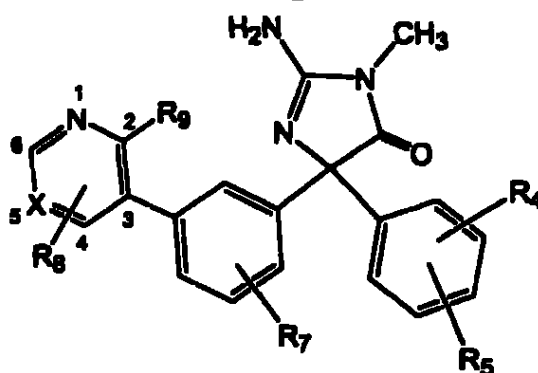
EXAMPLES 42-50

Preparation of 2-Amino-5,5-diphenylimidazolone Derivatives



Using essentially the same procedures described hereinabove for examples 40 and 41 and employing the appropriate 2-amino-5-(3-bromophenyl)-5-(substituted-phenyl)imidazolone substrate and pyridinyl or pyrimidinyl reagent, the compounds shown on Table II were obtained and identified by HNMR and mass spectral analyses.

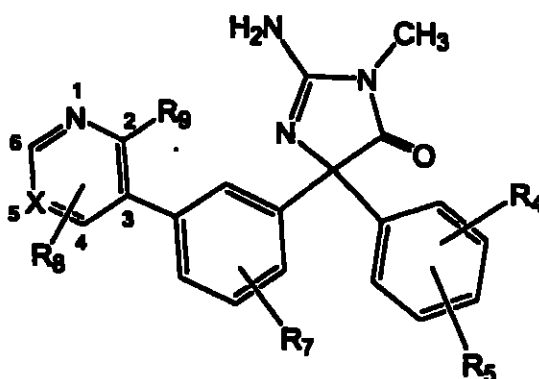
Table II



Ex.No	R ₄	R ₅	R ₇	R ₈	R ₉	X	mp °C
42	3-F	4-OCF ₃	4-F	H	H	C-Cl	201-203
43	3-F	4-OCF ₃	4-F	F	H	CH	75-80
44	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	H	N	100-105
46	H	4-OCF ₃	4-F	H	H	C-Cl	241-243
47	H	4-OCF ₃	4-F	H	H	C-F	216-218
48	H	4-OCF ₃	2-F	H	H	N	130-135
49	H	4-OCF ₃	4-Cl	H	H	N	124-129
50	H	4-OCF ₃	4-F	H	H	CH	134

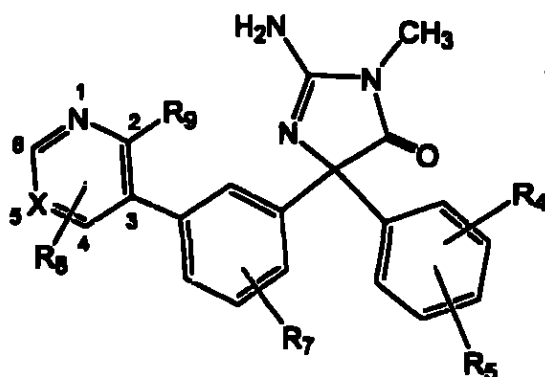
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Table II, cont.d



Ex.No	R ₄	R ₃	R ₇	R ₆	R ₅	X	mp °C
51	H	4-OCF ₃	H	H	H	C-OCH ₃	212
52	H	4-OCF ₃	H	OCH ₃	H	CH	96
53	H	4-OCF ₃	3-F	H	H	N	228
54	3-CH ₃	4-OCH ₃	4-F	H	H	N	118
55	3-CH ₃	4-OCH ₃	4-F	F	H	CH	113
56	3-CF ₃	4-OCH ₃	4-F	H	H	N	115
57	3-CF ₃	4-OCH ₃	4-F	H	6-F	CH	135
58	3-CF ₃	4-OCH ₃	4-F	F	H	CH	118
59	3-CH ₃	4-OCH ₃	H	F	H	CH	125
60	H	4-OCH ₃	4-F	H	H	C-F	—
61	3-CH ₃	4-OCH ₃	4-F	H	H	C-F	—
62	H	4-OCH ₃	4-F	F	H	CH	—
63	H	4-OCH ₃	4-F	H	H	N	—
64	H	4-OCF ₃	H	H	6-OCH ₃	CH	—
65	H	4-OCF ₃	H	H	6-F	CH	—
66	H	4-OCF ₃	H	F	H	CH	—
67	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	H	C-OCH ₃	—
68	3-OC ₂ H ₅	4-OC ₂ H ₅	H	OCH ₃	H	CH	—
69	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	6-F	CH	—
70	3-OC ₂ H ₅	4-OC ₂ H ₅	H	F	H	CH	—
71	H	4-OCF ₃	4-F	H	H	C-OCH ₃	—
72	H	4-OCF ₃	4-F	OCH ₃	H	CH	—
73	H	4-OCF ₃	4-F	H	6-F	CH	—
74	H	4-OCF ₃	4-F	F	H	CH	—
75	3-CH ₃	4-OCH ₃	H	OCH ₃	H	CH	—

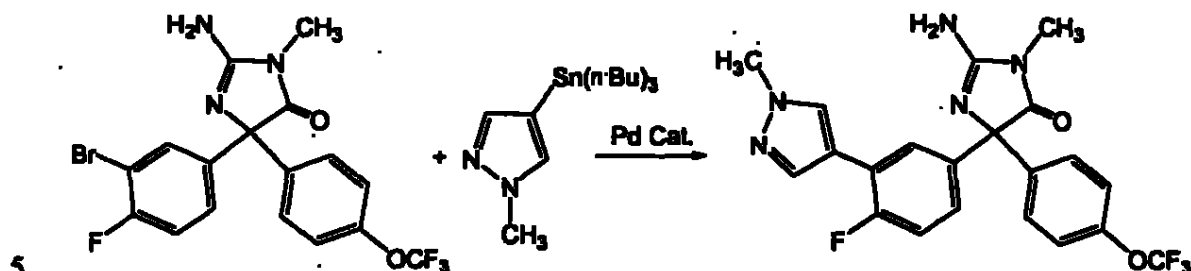
Table II, cont.d



Ex.No.	R4	R5	R7	R9	R8	X	mp °C
77	H	4-OCF ₃	4-F	H	H	N	—
78	3-F	4-OCF ₃	4-F	H	4-F	CH	93-96
79	3-C ₂ H ₅	3-C ₂ H ₅	4-F	F	H	CH	95-100
80	H	4-OCH ₃	4-F	H	H	C-Cl	—
81	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	4-F	CH	—
82	H	4-OCF ₃	H	H	4-F	CH	—
83	H	4-OCH ₃	4-F	H	4-F	CH	—
84	H	4-OCF ₃	6-F	H	H	CH	—
85	H	4-OCF ₃	2-F	H	H	CH	239
86	3-OC ₂ H ₅	4-OC ₂ H ₅	4-F	H	H	N	95-98
87	H	4-OCHF ₂	4-F	H	H	C-F	—
88	H	4-OCHF ₂	4-F	H	6-F	CH	—
89	H	4-OCHF ₂	H	F	H	CH	—
90	H	4-OCHF ₂	H	H	6-F	CH	—
91	H	4-OCHF ₂	H	F	H	C-F	—
92	H	4-OCHF ₂	4-F	F	H	C-F	—
93	H	4-SCF ₃	4-F	F	H	CH	95
94	H	4-SCF ₃	4-F	H	H	N	183
95	H	4-OCHF ₂	4-F	H	H	CH	104-106
96	H	4-OCHF ₂	4-F	F	H	CH	106-110
97	H	4-OCHF ₂	4-F	H	H	N	103-105
99	3-OC ₂ H ₅	4-OC ₂ H ₅	4-F	H	H	CH	93-95

44.

n n n n n

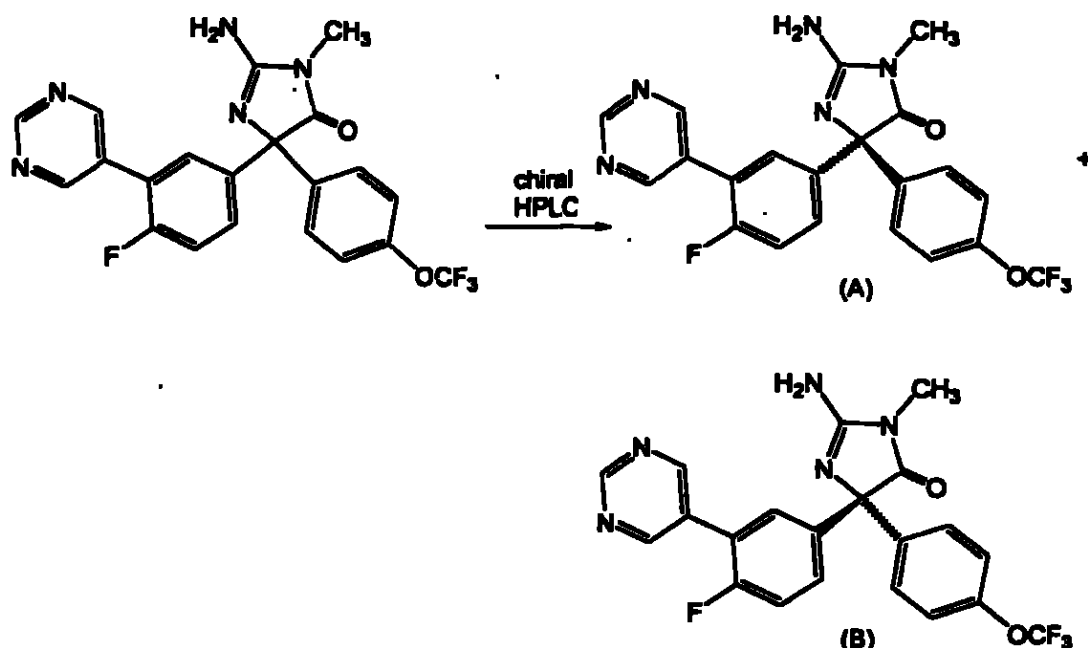
EXAMPLE 100**Preparation of 2-Amino-5-[4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl]-3-methyl-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one**

Using essentially the same procedure described in Example 41
 hereinabove and employing 2-amino-5-(3-bromo-4-fluorophenyl)-3-methyl-5-
 [4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one and 1-methyl-4-
 (tributylstannyl)-1H-pyrazole as reactants, the title product is obtained as a
 10 white solid, identified by HNMR and mass spectral analyses. ¹H NMR (300
 MHz, DMSO-d₆) δ 2.95 (s, 3H), 3.92 (s, 3H), 6.7 (brs, 2H), 7.15 (t, 1H), 7.28
 (m, 3H), 7.5 (m, 2H), 7.65 (m, 2H), 8.0 (d, 1H) MS m/e (M+H)⁺ 448

15

EXAMPLE 101

Preparation of (5S)-2-Amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-5-[4-
(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one (A) and
(5R)-2-Amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-5-[4-
 20 **(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one (B)**



Racemic 2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one is resolved using chiral
 5 HPLC technique on a Chiralcel AD, 2x25 cm and using as mobile phase EtOH with a flow rate of 11mL/min. The S-isomer, title compound A, is obtained, after crystallization from chloroform/hexanes, as a white solid, 98.8% ee; identified by HNMR and mass spectral analyses. ¹H NMR (300 MHz, DMSO-d₆) δ 2.95 (s, 3H), 3.95 (m, 4H), 6.72 (brs, 2H), 7.25 (d, 2H), 7.32 (t, 1H), 7.55-7.6 (m, 3H), 7.65 (dd, 1H), 8.9 (s, 2H), 9.2 (s, 1H) MS m/e (M+H)⁺ 446
 10

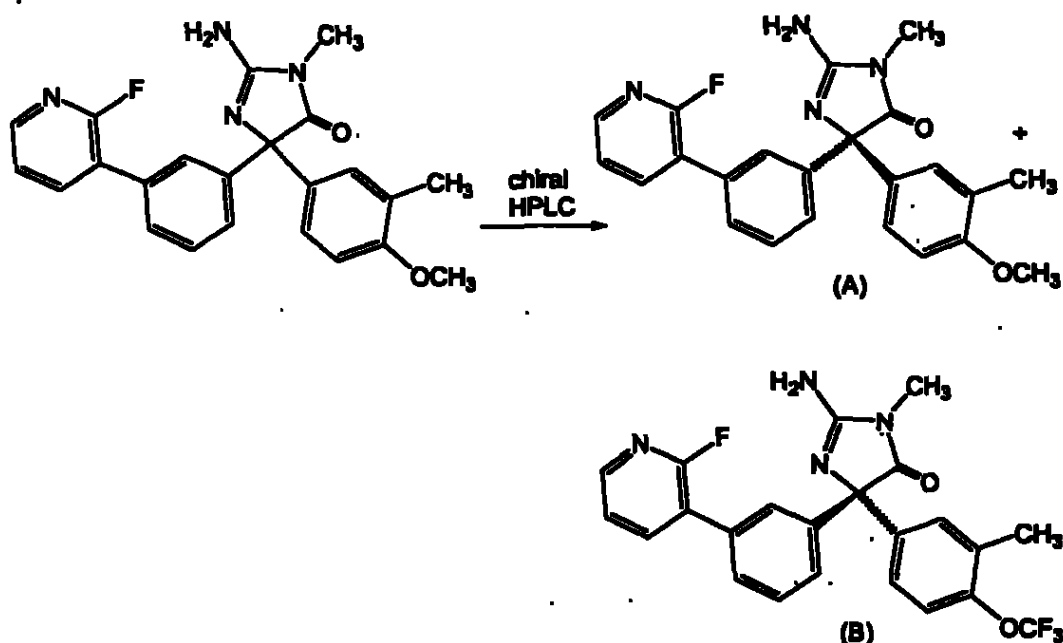
The R-isomer, title compound B, is obtained, after crystallization from chloroform/hexanes, as a white solid, 98.4% ee; identified by HNMR and mass spectral analyses. ¹H NMR (300 MHz, DMSO-d₆) δ 2.95 (s, 3H), 3.95 (m, 4H), 6.72 (brs, 2H), 7.25 (d, 2H), 7.32 (t, 1H), 7.55-7.6 (m, 3H), 7.65 (dd, 1H), 8.9 (s, 2H), 9.2 (s, 1H) MS m/e (M+H)⁺ 446
 15

EXAMPLE 102

Preparation of (5R)-2-Amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one (A) and
 20

nnns₄

(5S)-2-Amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one (B)



5

Racemic 2-amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one is resolved using chiral HPLC technique on a Chiralcel AD, 2x25 cm and using as mobile phase 9% EtOH/DEA in hexane/DEA with a flow rate of 25mL/min. The R-isomer, title compound A, is obtained, after crystallization from chloroform/hexanes, as a white solid, 100% ee; identified by HNMR and mass spectral analyses. ¹H NMR (300 MHz, DMSO-d₆) δ 2.05 (s, 3H), 2.96 (s, 3H), 3.67 (s, 3H), 6.62 (brs, 2H), 6.6 (d, 1H), 7.25-7.35 (m, 2H), 7.35-7.5 (m, 2H), 7.65 (m, 1H), 7.95 (m, 2H), 8.4 (dd, 1H)

10

MS m/e (M+H)⁺ 405 [α]_D²⁵ = +22 (c = 1% in CH₃OH)

15

The S-isomer, title compound B, is obtained, after crystallization from chloroform/hexanes, as a white solid, 98% ee; identified by HNMR and mass spectral analyses. ¹H NMR (300 MHz, DMSO-d₆) :

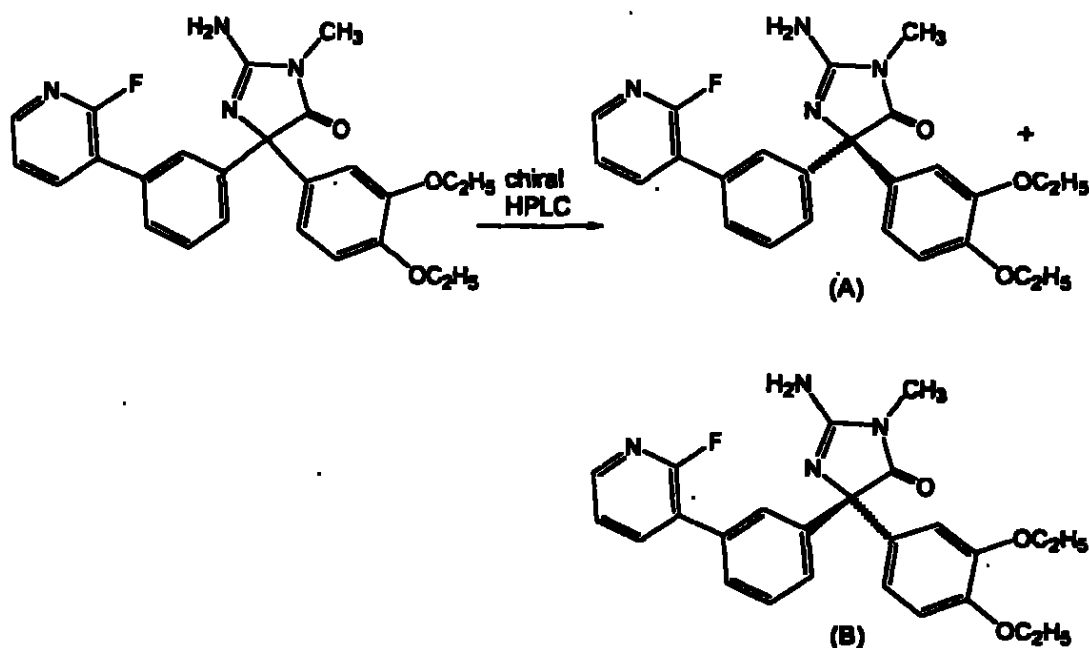
δ 2.05 (s, 3H), 2.96 (s, 3H), 3.67 (s, 3H), 6.62 (brs, 2H), 6.6 (d, 1H), 7.25-7.35 (m, 2H), 7.35-7.5 (m, 2H), 7.65 (m, 1H), 7.95 (m, 2H), 8.4 (dd, 1H)

20

MS m/e (M+H)⁺ 405 [α]_D²⁵ = -9.5 (c = 0.4% in CH₃OH)

EXAMPLE 103

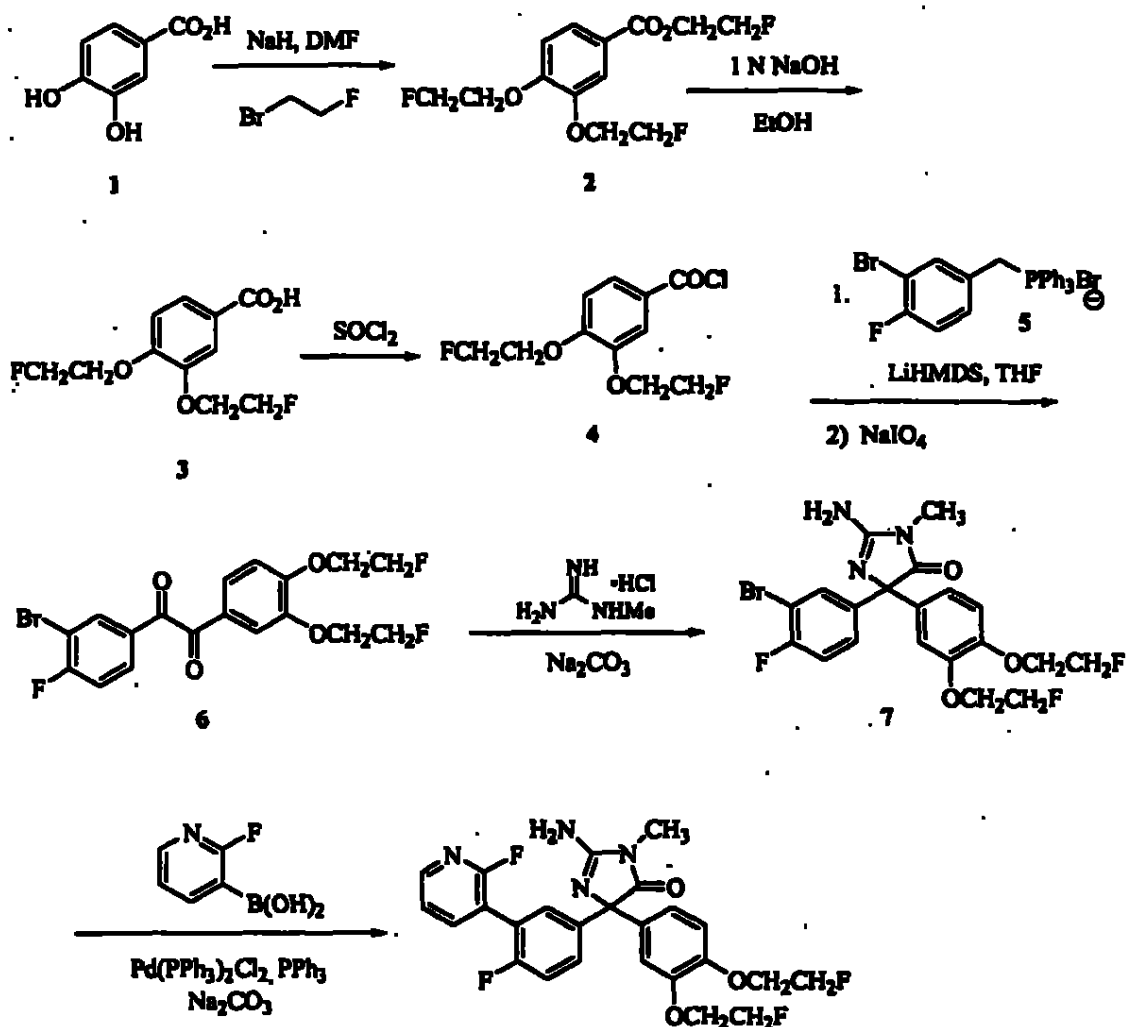
Preparation of (5R)-2-Amino-5-(3,4-diethoxyphenyl)-5-[3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one (A) and
(5S)-2-Amino-5-(3,4-diethoxyphenyl)-5-[3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-
3,5-dihydro-4H-imidazol-4-one (B)



Racemic 2-amino-5-(3,4-diethoxyphenyl)-5-[3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one is resolved using chiral HPLC technique on a Chiralcel AD, 0.46 x 25 cm column and using as mobile phase 25% EtOH in hexanes/DEA. The R-isomer, title compound A, is obtained and identified by HNMR and mass spectral analyses. ¹H NMR (DMSO-d₆, 300 MHz) δ 1.22 (m, 6H), 2.95 (s, 3H), 3.95 (m, 4H), 6.6 (brs, 2H), 6.85 (d, 1H), 7.0 (m, 2H), 7.37 -7.45 (m, 3H), 7.48 (d, 1H), 7.63 (s, 1H), 7.96 (m, 1H), 8.2 (d, 1H) MS m/e (M+H)⁺ 449
 [α]_D²⁵ = +7.4 (c = 1% in CH₃OH)

The S-isomer, title compound B, is obtained and identified by HNMR and mass spectral analyses. ¹H NMR (DMSO-d₆, 300 MHz) δ 1.22 (m, 6H), 2.95 (s, 3H), 3.95 (m, 4H), 6.6 (brs, 2H), 6.85 (d, 1H), 7.0 (m, 2H), 7.37 -7.45 (m, 3H), 7.48 (d, 1H), 7.63 (s, 1H), 7.96 (m, 1H), 8.2 (d, 1H) MS m/e (M+H)⁺ 449
 [α]_D²⁵ = -9.8 (c = 1% in CH₃OH)

nnncg

EXAMPLE 104**Preparation of 2-Amino-5-[3,4-bis-(2-fluoro-ethoxy)-phenyl]-5-[4-fluoro-3-(2-fluoro-pyridin-3-yl)-phenyl]-3-methyl-3,5-dihydro-imidazol-4-one****Step a) Preparation of compound 2**

Sodium hydride (1.82 g of a 60% dispersion in oil, 45.5 mmol) was washed with hexanes, suspended in DMF (5 mL) and treated dropwise with a solution of 1 (2.0 g, 13.0 mmol) in DMF (15 mL) over a period of 10 min at room temperature. After stirring for an additional 1.5 h at room temperature, the mixture was treated with a solution of 1-bromo-2-fluoro ethane in DMF (15 mL) and the mixture stirred at room

temperature for 18 h, then heated at 60 °C for an additional 4 h. The mixture was cooled to room temperature and diluted with ethyl acetate (100 mL) and water (100 mL). The organic layer was separated and washed with 1 N NaOH (100 mL), 5 % aqueous lithium chloride (2 × 100 mL), brine (100 mL), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (silica, 1:3 ethyl acetate/hexanes) afforded 2 (1.00 g, 26%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.74 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 4.84 (m, 2H), 4.75 (m, 3H), 4.67 (m, 1H), 4.58 (m, 1H), 4.52 (m, 1H), 4.36 (m, 2H), 4.30 (m, 2H); ESI MS *m/z* 293 [C₁₃H₁₅F₃O₄ + H]⁺.

10 **Step b) Preparation of compound 3**

A mixture of 2 (1.00 g, 3.42 mmol) in ethanol (10 mL) and 1 N NaOH (10 mL) was heated at 75 °C for 1 h. The mixture was cooled to room temperature, concentrated, diluted with water (10 mL) and acidified with 6 N HCl. The solids that formed were collected by filtration and dried to afford 3 (0.76 g, 90%) as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.8 (br s, 1H), 7.58 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.50 (d, *J* = 1.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 4.84 (m, 2H), 4.67 (m, 2H), 4.39–4.22 (m, 4H).

Step c) Preparation of compound 4

A mixture of 3 (0.76 g, 3.09 mmol), thionyl chloride (8 mL) and DMF (1 drop) was heated at reflux for 4 h. The mixture was then cooled to room temperature and concentrated. The residue was dissolved in toluene and again concentrated to afford 4 (0.82 g, 100%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.85 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 4.89 (m, 2H), 4.75 (m, 2H), 4.43–4.26 (m, 4H); IR (ATR) 1734, 1582, 1513, 1417 cm⁻¹.

25 **Step d) Preparation of compound 6**

A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (3.25 mL, 3.25 mmol) was added to a stirred suspension of (3-bromo-4-fluorobenzyl) triphenylphosphonium bromide (1.72 g, 3.25 mmol) in tetrahydrofuran (6 mL). The mixture was stirred for 25 min at room temperature, then cooled to -40 °C, treated with a solution of 4 (0.82 g, 3.10 mmol) in tetrahydrofuran (3 mL) and stirred for an additional 2 h while slowly warming to room temperature. The reaction was then treated with water (5 mL) and sodium periodate (0.69 g, 3.25 mmol), then heated at 50 °C for 19 h. After this time the mixture was cooled to room temperature and

diluted with ethyl acetate (25 mL). The organic layer was separated and washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (silica, 1:3 ethyl acetate/hexanes) afforded **6** (0.27 g, 20%) as a pale yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.22 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.92 (m, 1H), 7.63 (d, *J* = 2.0 Hz), 7.51 (dd, *J* = 8.4, 2.9 Hz, 1H), 7.23 (m, 1H), 7.96 (d, *J* = 8.5 Hz, 1H) 4.85 (m, 2H), 4.76 (m, 2H), 4.39–4.31 (m, 4H).

Step e) Preparation of compound 7

A mixture of **6** (0.26 g, 0.603 mmol) and 1-methylguanidine hydrochloride (0.30 g, 2.71 mmol) in dioxane (8 mL) and ethanol (5.3 mL) was stirred at room temperature for 5 min. A solution of sodium carbonate (0.29 g, 2.71 mmol) in water (2.3 mL) was then added and the mixture immersed into an 85 °C oil bath and stirred for 30 min. The reaction mixture was cooled to room temperature, concentrated and the residue partitioned between methylene chloride (50 mL) and water (20 mL). The organic layer was separated, washed with water (20 mL), brine (20 mL), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (silica, 95:5:0.5 methylene chloride/methanol/concentrated ammonium hydroxide) afforded **7** (0.154 g, 53%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.68 (m, 1H), 7.33 (m, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 4.80 (m, 2H), 4.66 (m, 2H), 4.28 (m, 2H), 4.18 (m, 2H); ESI MS *m/z* 486 [C₂₀H₁₉BrF₃N₃O₃ + H]⁺.

Step f) Preparation of 2-amino-5-[3,4-bis-(2-fluoro-ethoxy)-phenyl]-5-[4-fluoro-3-(2-fluoro-pyridin-3-yl)-phenyl]-3-methyl-3,5-dihydro-imidazol-4-one

A mixture of **7** (0.140 g, 0.288 mmol), 2-fluoropyridine-3-boronic acid (0.061 g, 0.430 mmol), sodium carbonate (0.092 g, 0.860 mmol), bis(triphenylphosphino)palladium (II)chloride (0.010 g, 0.014 mmol) and triphenylphosphine (0.008 g, 0.028 mmol) in 1:1 toluene/ethanol (8 mL) was degassed and heated at 110 °C for 1.5 h. The mixture was cooled to room temperature, concentrated and purified by flash chromatography (silica, 97:3:0.25 methylene chloride/methanol/concentrated ammonium hydroxide) to afford **8** (0.055 g, 39%) as a white solid, mp 85–95 °C; ¹H NMR (300 MHz, CD₃OD) δ 8.23 (m, 1H), 7.93 (m, 1H), 7.51–7.38 (m, 3H), 7.21 (t, *J* = 9.0 Hz, 1H), 6.98 (m, 3H), 4.78 (m, 2H), 4.68 (m, 2H), 4.62–4.58 (m, 4H), 3.11 (s, 3H); IR (ATR) 1733, 1686, 1502, 1260 cm⁻¹;

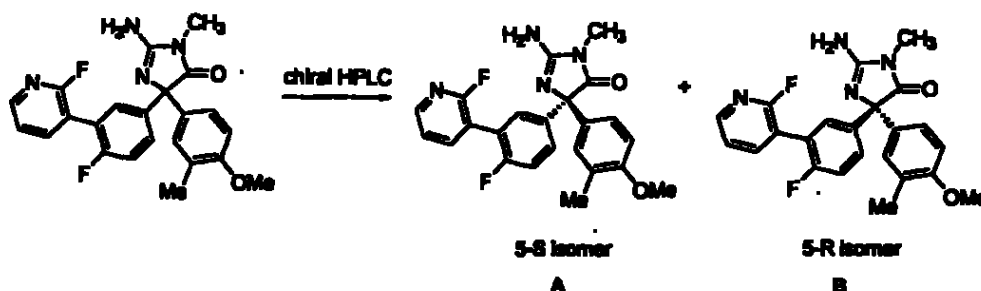
ESI MS m/z 503 [$C_{25}H_{24}F_4N_4O_3 + H$]⁺. Anal. Calcd for $C_{25}H_{24}F_4N_4O_3 \cdot 0.25H_2O$: C, 59.28; H, 4.45; N, 10.73. Found: C, 59.23; H, 4.47; N, 11.05.

5

EXAMPLE 105

Preparation of (5S)-2-Amino-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]

10

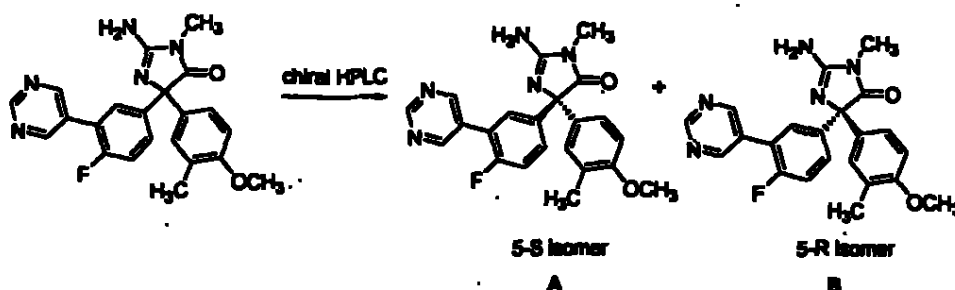


The racemate 2-amino-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by HPLC using Chiralcel OJ, 2 x 25 cm, mobile phase 15% EtOH/DEA in hexane and a flow rate of 21 mL/min to give the title S isomer (A), ¹H NMR (DMSO-d₆, 300 MHz) δ 2.0 (s, 3H), 2.95 (s, 3H), 3.7 (s, 3H), 6.6 (b, 2H), 6.8 (d, 1H), 7.3 (m, 3H), 7.5 (m, 3H), 8.0 (m, 1H), 8.3 (m, 1H); MS m/e (M)⁺ 423; [α]₂₅ = +76.4 (C = 1% in MeOH); mp 103-105 °C and the title R isomer (B), ¹H NMR (DMSO-d₆, 300 MHz) δ 2.0 (s, 3H), 2.95 (s, 3H), 3.7 (s, 3H), 6.6 (b, 2H), 6.8 (d, 1H), 7.3 (m, 3H), 7.5 (m, 3H), 8.0 (m, 1H), 8.3 (m, 1H); MS m/e (M)⁺ 423; [α]₂₅ = -40.8 (C = 1% in MeOH); mp 103-105 °C.

25

EXAMPLE 106

Preparation of (5S)-2-Amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]



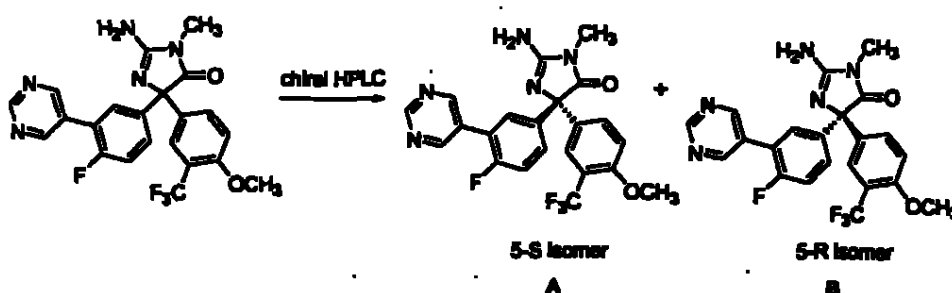
The racemate 2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by HPLC using Chiralcel OD, 2 x 25 cm, mobile phase can using mobile phase MeOH (30% with 0.1 % DEA) in CO₂ (100 bar) and a flow rate of 50 mL/min to give the title S isomer (A), ¹H NMR (400 MHz, DMSO-d₆) δ 2.04 (s, 3H), 2.93 (s, 3H), 3.69 (s, 3H), 6.61 (bs, 2H), 6.81 (m, 1H), 7.22 (m, 1H), 7.27 (m, 1H), 7.29 (m, 1H), 7.60 (m, 1H), 7.61 (m, 1H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e (M+H)⁺ 406; mp 115° C; [α]_D²⁵ = 48 (C = 1% in MeOH); and the title R isomer (B), ¹H NMR (400 MHz, DMSO-d₆) δ 2.04 (s, 3H), 2.93 (s, 3H), 3.69 (s, 3H), 6.60 (bs, 2H), 6.81 (m, 1H), 7.22 (m, 1H), 7.27 (m, 1H), 7.29 (m, 1H), 7.60 (m, 1H), 7.61 (m, 1H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e (M+H)⁺ 406; mp 115 °C; [α]_D²⁵ = -39.2 (C = 1% in MeOH).

15

EXAMPLE 107

Preparation of (5S)-2-Amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-(4-methoxy-3-(trifluoromethyl)phenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-(4-methoxy-3-(trifluoromethyl)phenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]

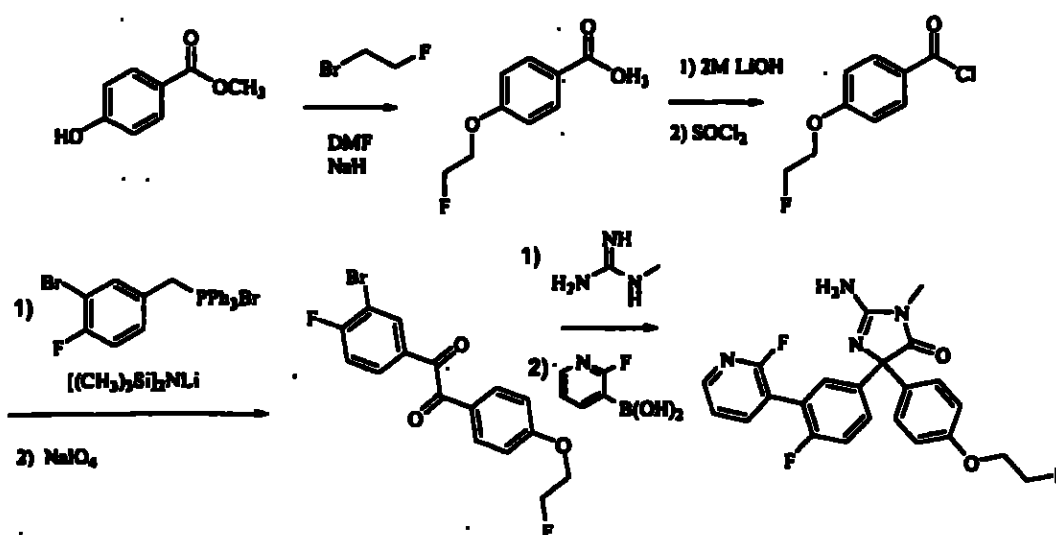
20



A racemic mixture of 2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-[4-methoxy-3-(trifluoromethyl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by HPLC using Chiralcel OD, 2 x 25 cm, mobile phase cm, mobile phase
 5 EtOH/Hexane (15/85) and a flow rate of 20 mL/min to give the title S isomer (A), ¹H NMR (400 MHz, DMSO-d₆) δ 2.94 (s, 3H), 3.81 (s, 3H), 6.76 (bs, 2H), 7.19 (m, 1H), 7.32 (m, 1H), 7.32 (m, 1H), 7.50 (m, 1H), 7.70 (m, 2H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e (M+H)⁺ 460.1; mp 100°C; [α]₂₅ = 1.6 (C = 1% in MeOH); and the title R isomer (B), ¹H NMR (400 MHz, DMSO-d₆) δ 2.94 (s, 3H), 3.81 (s, 3H), 6.76 (bs, 2H), 6.82
 10 (m, 1H), 7.22 (m, 1H), 7.32 (m, 1H), 7.50 (m, 1H), 7.59 (m, 1H), 7.70 (m, 1H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e (M-H)⁻ 458; mp 100°C; [α]₂₅ = -1.8 (C = 1% in MeOH).

EXAMPLE 108

15 Preparation of 2-Amino-5-[4-(2-fluoroethoxy)phenyl]-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one



Step a) Preparation of Methyl 4-(2-fluoroethoxy)benzoate

20 Under nitrogen atmosphere to a cold (5 °C) solution of 4-hydroxy-benzoic acid methyl ester (7 g, 46 mmol) in DMF (30 ml) was added NaH (60 %; 2.2 g) portion wise over 20 minutes. After the addition was completed, the ice bath was removed and the resulting white suspension was heated up to room temperature and stirred

for 3 hours. A prepared solution of 1-Bromo-2-fluoro-ethane (6.42 g, 50.56 mmol) in DMF (20 mL) was added and the new mixture was stirred at 50 °C for 18 hours. After cooling to room temperature the mixture was poured into a mixture of ice and 1 N HCl (1:1) and extracted with ethyl acetate. The organic extracts were washed with
5 brine, dried over MgSO₄. Evaporation and purification by flash chromatography (hexane/ethyl acetate 9/1) gave a white solid (7.75 g, 85 % yield); ¹H NMR (400 MHz, CDCl₃) δ 3.86 (s, 3H), 4.20 (m, 1H), 4.21 (m, 1H), 4.27 (m, 1H), 4.28 (m, 1H), 6.93 (d, 2H), 7.98 (d, 2H); MS m/e (M+H)⁺ 198; mp 77 °C.

Step b) Preparation of 4-(2-Fluoroethoxy)benzoic acid

10 To a solution of methyl 4-(2-fluoroethoxy)benzoate (7.7 g, 38.85 mmol) in dioxane (100 mL) was added LiOH (2M, 39 mL). The reaction mixture was stirred at room temperature for 18 hours, and then concentrated in vacuo. The residue was dissolved in H₂O (30 mL) and extracted with ether. Under cooling the aqueous was acidified with HCl (6N) and extracted with CHCl₃. The organic extracts were dried
15 over MgSO₄. Evaporation and recrystallization from ethyl acetate and methylene chloride gave the title compound as a white solid (5 g, 71 % yield); ¹H NMR (400 MHz, DMSO-d₆) δ 4.28 (m, 1H), 4.35 (m, 1H), 4.68 (m, 1H), 4.80 (m, 1H), 7.04 (d, 2H), 7.89 (d, 2H); MS m/e (M-H)⁻ 183.1; mp 203 °C.

Step c) Preparation of 1-(3-bromo-4-fluorophenyl)-2-[4-(2-fluoroethoxy)-phenyl]ethane-1,2-dione

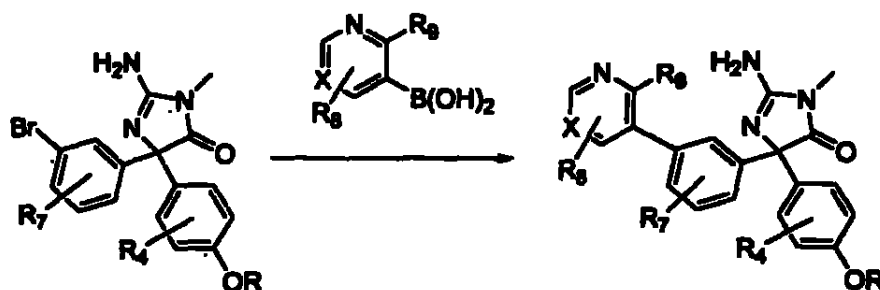
20 A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (20 mL, 20 mmol) was added at room temperature to a stirred suspension of (3-bromo-4-fluorobenzyl)triphenylphosphonium bromide (10.6 g, 20 mmol) in tetrahydrofuran (40 mL). The mixture was stirred for 40 minutes, then cooled to -20 °C and treated with
25 4-(2-fluoroethoxy)benzoyl chloride (4.1 g, 20 mmol) in tetrahydrofuran (40 mL) and stirred for an additional 2 hours while slowly warming to room temperature. The mixture was treated with water (20 mL) and sodium periodate (4.3 g, 20 mmol) then stirred at 50 °C for 18 hours. After cooling to room temperature the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over
30 MgSO₄. Evaporation and purification by flash chromatography (hexane/ethyl acetate 9/1) gave a yellow solid (3 g, 41 % yield); ¹H NMR (400 MHz, CDCl₃) δ 4.25 (m, 1H), 4.32 (m, 1H), 4.70 (m, 1H), 4.82 (m, 1H), 7.01 (d, 2H), 7.23 (m, 1H), 7.94 (m, 3H), 8.22 (m, 1H); MS m/e (M+CH₃COO)⁻ 427; mp 107 °C.

Step d) Preparation of 2-Amino-5-[4-(2-fluoroethoxy)phenyl]-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one

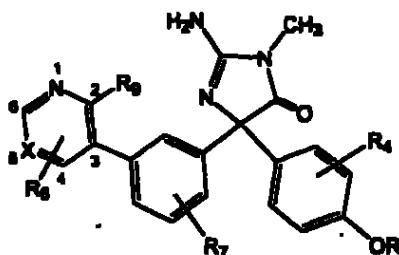
Using essentially the same procedure described in Examples 39 and 40 and employing methylaminoguanidine and 2-fluoropyridine-3-boronic acid, respectively, the title product was obtained as a white solid, mp 135 °C, ¹H NMR (400 MHz, DMSO-d₆) δ 2.93(s, 3H), 4.09 (m, 1H), 4.11 (m, 1H), 4.59 (m, 1H), 4.61 (m, 1H), 6.84, (bs, 2H), 6.86 (m, 2H), 7.30 (m, 3H), 7.44 (m, 1H), 7.52 (m, 2H), 7.95 (m, 1H), 8.26 (m, 1H); MS m/e (M-H)⁺ 439.2.

EXAMPLES 109-124

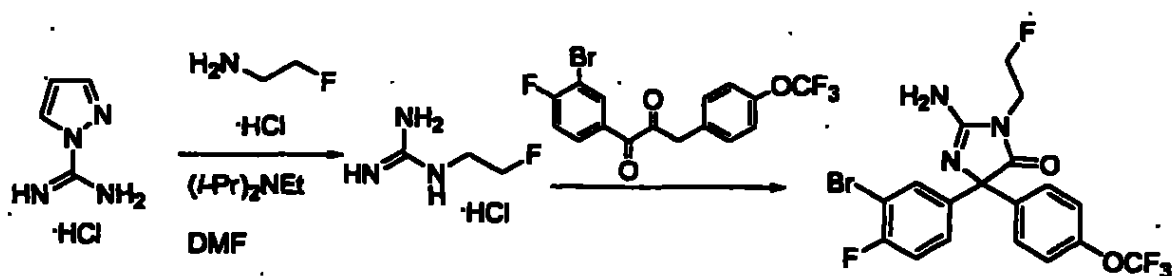
Preparation of 2-Amino-5-alkoxyphenyl-5-(3-heteroaryl)phenyl-3-methyl-3,5-dihydro-4H-imidazol-4-one Compounds



Using essentially the same procedure described in Example 108 and employing the appropriate boronic acid and 5-(3-bromophenyl)hydantoin substrate, the compounds shown on Table III were obtained and identified by NMR and mass spectral analyses.

Table III

Ex. No	R ₄	R	R ₇	R ₈	R ₉	X	mp °C
109	H	CH ₂ CH ₂ F	4-F	H	H	N	123
110	H	CH ₂ CH ₂ F	H	H	H	CF	—
111	H	CH ₂ CH ₂ F	H	6-F	H	CH	100
112	3-CH ₃	CH ₂ CH ₂ F	4-F	H	F	CH	105-108
113	3-CH ₃	CH ₂ CH ₂ F	4-F	H	H	N	108-110
114	3-CH ₃	CH ₂ C ₆ H ₅	H	H	H	N	107-109
115	3-CH ₃	H	H	H	H	N	168-170
116	3-CH ₃	CH ₂ CH ₂ F	H	H	H	N	108-110
117	3-CH ₃	CH ₂ CN	H	H	H	N	220-222
118	3-CH ₃	i-propyl	H	H	H	N	101-103
119	3-CH ₃	CH ₂ CO ₂ C ₂ H ₅	H	H	H	N	105-107
120	3-CH ₃	C ₂ H ₅	H	H	H	N	108-108
121	3-CH ₃	n-propyl	H	H	H	N	102-104
122	3-CH ₃	i-butyl	H	H	H	N	103-105
123	3-CH ₃	CH ₂ CH ₂ cyclohexyl	H	H	H	N	1-7-109
124	3-CH ₃	n-C ₃ H ₇ -OC ₆ H ₅	H	H	H	N	72-74

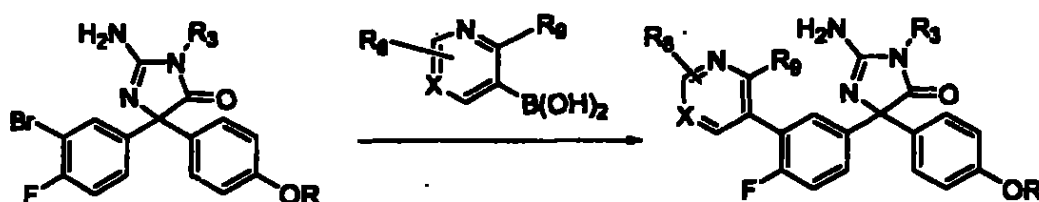
EXAMPLE 125**5 Preparation of 2-Amino-5-(3-bromo-4-fluorophenyl)-3-(2-fluoroethyl)-5-(4-trifluoromethoxy-phenyl)-3,5-dihydro-imidazol-4-one**

To a stirred mixture of 2-fluoroethylamine hydrochloride (1.50 g; 15.1 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (1.77 g; 12.1 mmol) in DMF was added diisopropylethylamine (3.58 g; 27.7 mmol). The mixture was stirred under nitrogen atmosphere for 3 hours. Diethyl ether was added (35 mL) and the mixture was shaken and the oily product was allowed to settle to the bottom of the flask, whereupon the ether was decanted. This was repeated and the clear oil was dried under high vacuum at ambient temperature for 24 hours. The N-(2-fluoroethyl)-guanidine product was used without further purification (1.6 g).

A solution of 1-(3-bromo-4-fluoro-phenyl)-2-(4-trifluoromethoxy-phenyl)-ethane-1,2-dione (0.181 g; 0.46 mmol) and N-(2-fluoroethyl)-guanidine (0.105 g; 0.74 mmol) in a mixture of dioxane, water and ethanol, was treated with solid sodium carbonate heated at 90°C for five hours, and evaporated to dryness. The resultant residue is dissolved in chloroform, washed with water, dried over sodium sulfate, and evaporated to give the title compound as a light-green solid, 116 mg (52% yield), MS (API-ES) 480.3 [M+H]⁺.

EXAMPLES 126-128

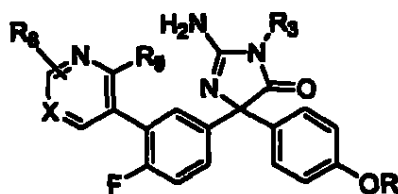
20 Preparation of 2-Amino-3-substituted-5-(3-heteroaryl)phenyl-5-(4-trifluoromethoxy-phenyl)-3,5-dihydro-Imidazol-4-one Compounds



25 Using essentially the same procedure described in Example 108 and employing the appropriate boronic acid and 3-alkyl-2-amino-5-(3-bromophenyl)hydantoin substrate, the compounds shown on Table IV were obtained and identified by NMR and mass spectral analyses.

51

nnn78

Table IV

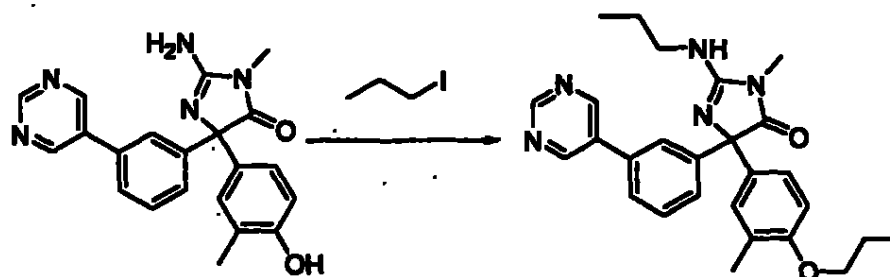
Ex. No	R	R3	R8	R9	X	mp °C
126	CF ₃	CH ₂ CH ₂ F	H	H	N	168-170
127	CF ₃	CH ₂ CH ₂ F	H	F	CH	138-150
128	CHF ₂	C ₂ H ₅	H	H	C-F	

5

EXAMPLE 129

Preparation of 3-Methyl-5-(3-methyl-4-propoxyphenyl)-2-(propylamino)-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one

10

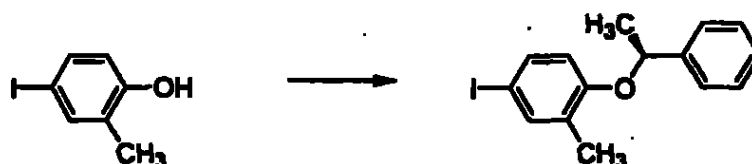


A solution of 2-amino-5-(4-hydroxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one (74.6 mg, 0.2 mmol) in N,N-dimethylformamide was treated with 2-iodopropane (31.2 mg, 0.4 mmol) and Cs₂CO₃ (130 mg, 0.4 mmol) at room temperature, stirred overnight at room temperature and quenched with H₂O. The phases were separated, the aqueous phase was extracted with ethyl acetate. The organic phase was combined with the extracts, washed sequentially with H₂O and brine, dried over MgSO₄ and evaporated to dryness. The resultant residue was purified by flash chromatography with ethyl acetate/ethanol

15

(2M ammonia) (90/10) as eluent to afford the title compound as a white solid, 60 mg (65% yield), mp 64-66 °C; MS (+) ES: 458 (M+H)⁺.

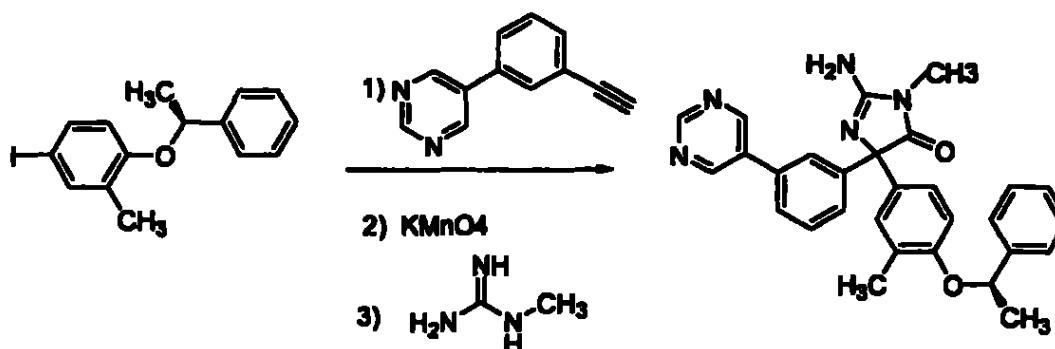
5

EXAMPLE 130**Preparation of 4-iodo-2-methyl-1-[(1*R*)-1-phenylethoxy]benzene**

10

A cooled solution of PPh₃ (262 mg 10 mmol) in THF was treated with diethyl azodicarboxylate (1.74 g, 10 mmol) at 0 °C, stirred for 5 min, allowed to warm-up to room temperature, treated with 4-iodo-2-methylphenol (1.17 g, 5 mmol) and *R*(+)-1-phenylethanol (1.22 g, 10 mmol), stirred for 24 h at room temperature and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, 100% hexane) to afford the title compound as a clear oil 2.5 g (50%). MS (+): EI 338 M⁺.

15

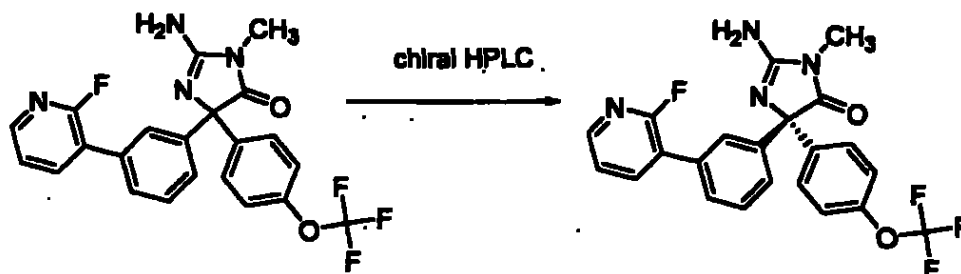
EXAMPLE 131**Preparation of 2-amino-3-methyl-5-[(3-methyl-4-[(1*R*)-1-phenylethoxy]phenyl)-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4*H*-imidazol-4-one]**

A solution of 4-iodo-2-methyl-1-[(1*R*)-1-phenylethoxy]benzene (10 mmol) in triethylamine is treated with tetrakis(triphenylphosphine)Pd (0.69 mmol), copper iodide (0.97 mmol) and a solution of 3-(pyrimidin-5-yl)ethynylbenzene (10 mmol) in acetonitrile at room temperature. The reaction mixture is heated for 1 h at 80°C, cooled and concentrated *in vacuo*. The resultant residue is purified by chromatography to give 5-[3-[(3-methyl-4-[(1*R*)-1-phenylethoxy]phenyl]ethynyl]phenyl]pyrimidine as an oil, MS (+) ES: 391(M+H)⁺. A solution of 5-[3-[(3-methyl-4-[(1*R*)-1-phenylethoxy]phenyl]ethynyl]phenyl]pyrimidine (8.3 mmol) in acetone is treated with a warm (~40°C) solution of NaHCO₃ (4.98 mmol) and MgSO₄ (12.45 mmol) in water (80 mmol) followed by a single portion of solid KMnO₄ (8.3 mmol), stirred for 40 min. at room temperature and extracted with 1:1 ether:hexane. The extracts are combined, dried over MgSO₄ and concentrated to dryness to give 1-[3-methyl-4-[(1*R*)-1-phenylethoxy]phenyl]-2-(3-pyrimidin-5-ylphenyl)ethane-1,2-dione as a foam, MS (+) ES: 423 (M+H)⁺. A solution of 1-[3-methyl-4-[(1*R*)-1-phenylethoxy]phenyl]-2-(3-pyrimidin-5-ylphenyl)ethane-1,2-dione (5.0 mmol) in ethanol is treated with *N*-methylguanidine hydrochloride (5.5 mmol) and an aqueous solution of Na₂CO₃ (10.0 mmol), heated at reflux temperature for 1 h and concentrated *in vacuo*. The resultant residue is purified by chromatography to afford the title product as a white solid, mp 112-114 °C. MS (+) ES: 478 (M+H)⁺.

20

EXAMPLE 132

Preparation of (5*R*)-2-Amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4*H*-imidazol-4-one



25

A racemic mixture of 2-amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4*H*-imidazol-4-one was separated by chiral HPLC using Chiralcel AD, 2x25 cm (column) with mobile phase 9% EtOH in hexanes

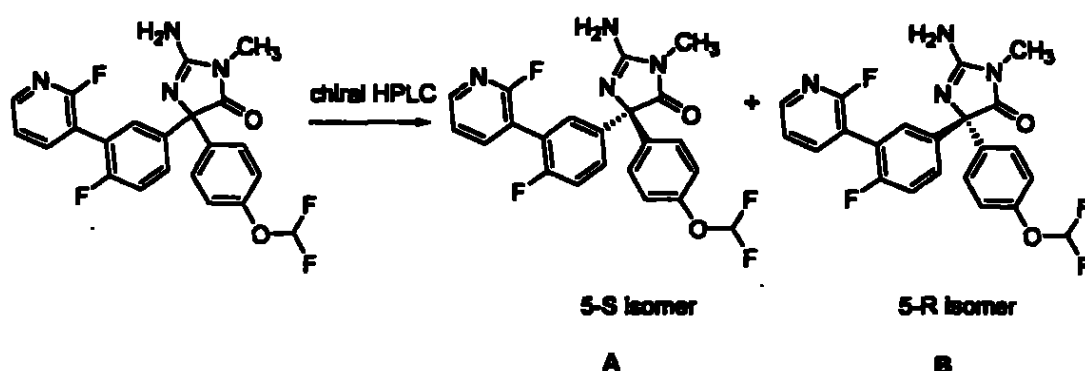
(0.1% diethylamine) to give the title R-isomer. $[\alpha]_{25} = -13.4$ (1% in MeOH); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.95 (s, 3H), 6.65 (brs, 2H), 7.28 (d, 2H), 7.4-7.45 (m, 3H), 7.5 (m, 1H), 7.55 (d, 2H), 7.65 (d, 1H), 7.95-8.0 (m, 1H), 8.2 (m, 1H); MS m/e (M+H) $^+$ 445.

5

EXAMPLE 133

Preparation of (5S)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and
(5R)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]

10



A racemic mixture of 2-amino-5-[4-(difluoromethoxy)phenyl]-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by chiral HPLC: Chiralcel AD, 2x25 cm (column) with mobile phase 9% EtOH in hexanes/TFA to give the the title product A, $[\alpha]_{25} = +11.4$ (1% in MeOH); ^1H NMR (DMSO- d_6 , 300 MHz) δ 3.12 (s, 3H), 7.25 (m, 3H), 7.4-7.5 (m, 4H), 7.5 (m, 2H), 8.0 (m, 1H), 8.6 (m, 1H), 9.5-9.7 (br, 2H); MS m/e (M+H) $^+$ 445 and the title product B, $[\alpha]_{25} = -10.4$ (1% in MeOH); ^1H NMR (DMSO- d_6 , 300 MHz) δ 3.12 (s, 3H), 7.25 (m, 3H), 7.4-7.5 (m, 4H), 7.5 (m, 2H), 8.0 (m, 1H), 8.6 (m, 1H), 9.5-9.7 (br, 2H); MS m/e (M+H) $^+$ 445.

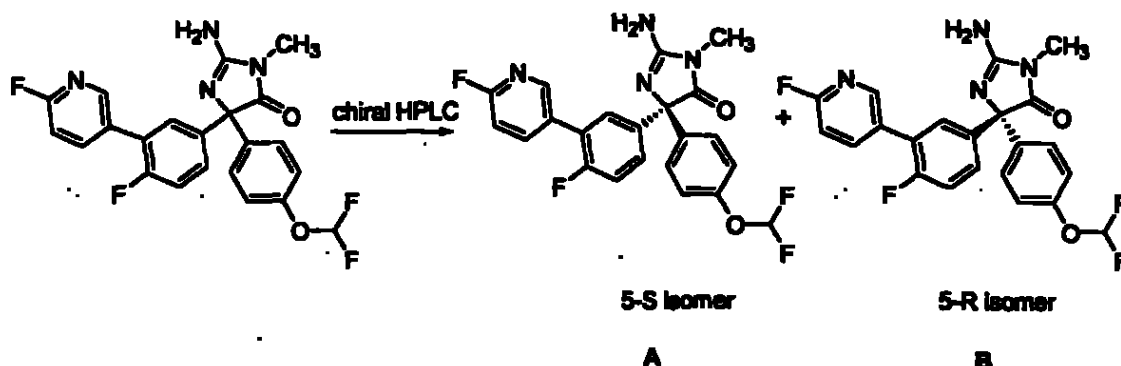
25

53

nnngg

EXAMPLE 134

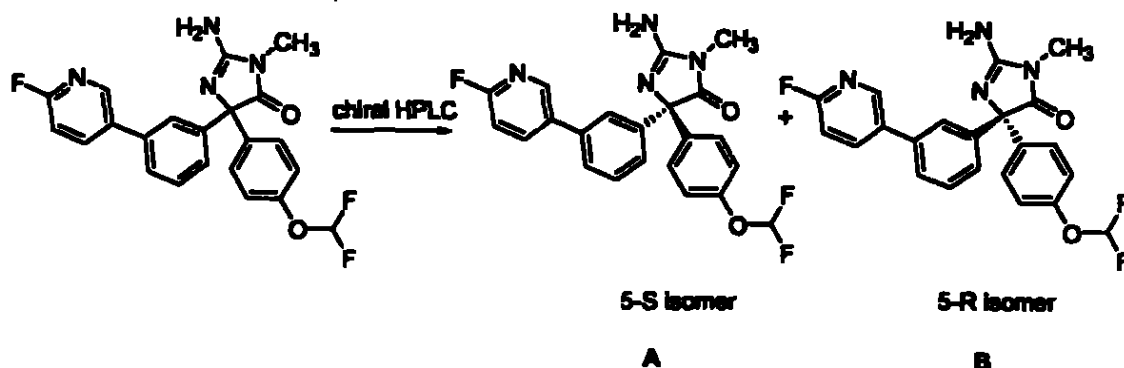
Preparation of (5S)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[4-fluoro-3-(6-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[4-fluoro-3-(6-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]



A racemic mixture of 2-amino-5-[4-(difluoromethoxy)phenyl]-5-[4-fluoro-3-(6-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by chiral HPLC: Chiralcel OJ, 0.46x10 cm (column) with mobile phase 15% EtOH in hexanes to give the title S-isomer (A): $[\alpha]_{25} = +6$ (1% in MeOH); $^1\text{H NMR}$ (DMSO-d_6 , 300 MHz) δ 2.94 (s, 3H), 6.8 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.28 (m, 2H), 7.4-7.5 (m, 3H), 7.6 (dd, 1H), 8.05 (m, 1H), 8.3 (s, 1H); MS m/e ($\text{M}+\text{H}$) $^+$ 445 and the title R-isomer (B): $[\alpha]_{25} = -7.4$ (1% in MeOH); $^1\text{H NMR}$ (DMSO-d_6 , 300 MHz) δ 2.94 (s, 3H), 6.8 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.28 (m, 2H), 7.45 (d, 2H), 7.4-7.5 (m, 1H), 7.6 (dd, 1H), 8.05 (m, 1H), 8.3 (s, 1H); MS m/e ($\text{M}+\text{H}$) $^+$ 445.

EXAMPLE 135

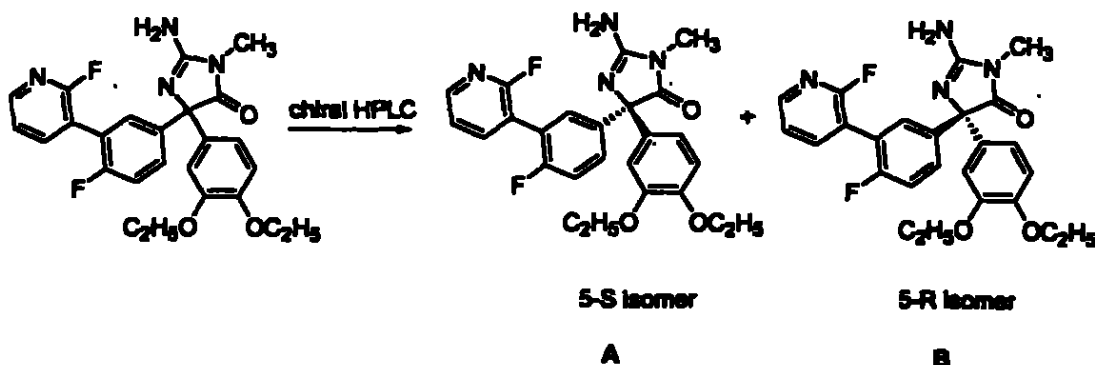
Preparation of (5S)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[3-(6-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[3-(6-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]



A racemic mixture of 2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[3-(6-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by
 5 chiral HPLC: Chiralcel OJ, 0.46x10 cm (column) with mobile phase 15% EtOH in hexanes to give the title S-isomer (A): $[\alpha]_{25} = -7.4$ (1% in MeOH); $^1\text{H NMR}$ (DMSO- d_6 , 300 MHz) δ 2.95 (s, 3H), 6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.25 (dd, 1H), 7.4 (t, 1H), 7.5-7.55 (m, 4H), 7.7 (s, 1H), 8.2 (m, 1H), 8.37 (s, 1H); MS m/e (M+H) $^+$ 427; and the title R-isomer (B): $[\alpha]_{25} = +8.4$ (1% in MeOH); $^1\text{H NMR}$ (DMSO- d_6 , 300 MHz) δ
 10 2.95 (s, 3H), 6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.25 (dd, 1H), 7.4 (t, 1H), 7.5-7.55 (m, 4H), 7.7 (s, 1H), 8.2 (m, 1H), 8.37 (s, 1H); MS m/e (M+H) $^+$ 427.

EXAMPLE 136

15 Preparation of (5S)-2-Amino-5-(3,4-dieethoxyphenyl)-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-(3,4-dieethoxyphenyl)-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]



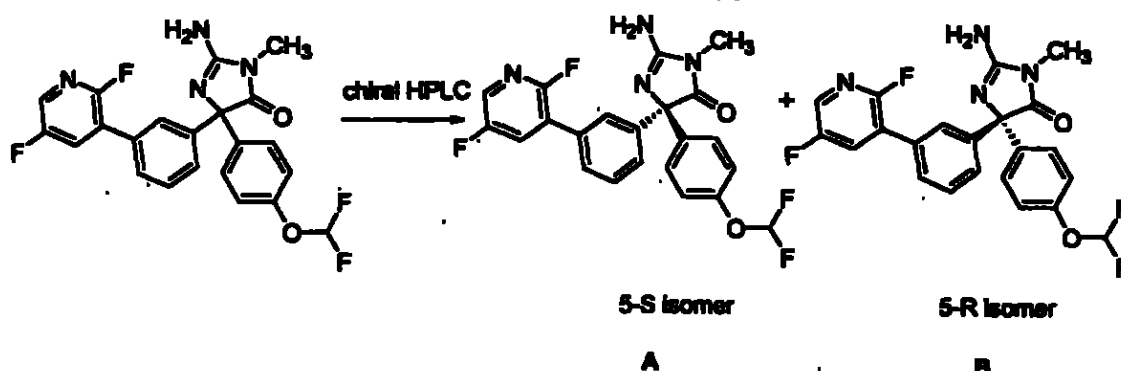
54

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A racemic mixture of 2-amino-5-(3,4-diethoxyphenyl)-5-[4-fluoro-3-(2-fluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated using a WhelkO, 2x25 cm chiral HPLC column and 20% EtOH in heptane with 1% triethylamine, as the eluent to give the title S-isomer (A) as a white solid, $[\alpha]_{25} = -22.2$, 1% in methanol; $^1\text{H NMR}$ (DMSO-d_6 , 300 MHz) δ 1.3 (t, 6H), 2.9 (s, 3H), 3.9 (dxq, 4H), 6.6 (b, 2H), 6.8 (d, 1H) 7.0 (m, 2H), 7.3 (t, 1H), 7.5 (m, 3H), 7.9 (s, 1H), 8.3 (m, 1H); MS m/e (M^+) 467; and the title R-isomer (B) as a white solid, $[\alpha]_{25} = +26.0$, 1% in methanol; $^1\text{H NMR}$ (DMSO-d_6 , 300 MHz) δ 1.3 (t, 6H), 2.9 (s, 3H), 3.9 (dxq, 4H), 6.6 (b, 2H), 6.8 (d, 1H) 7.0 (m, 2H), 7.3 (t, 1H), 7.5 (m, 3H), 7.9 (s, 1H), 8.3 (m, 1H); MS m/e (M^+) 467.

EXAMPLE 137

15 Preparation of (5S)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[3-(2,5-difluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-[4-(difluoromethoxy)phenyl]-5-[3-(2,5-difluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]



20

A racemic mixture of 2-amino-5-[4-(difluoromethoxy)phenyl]-5-[3-(2,5-difluoropyridin-3-yl)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by chiral HPLC: Chiralcel OJ, 2x25 cm (column) with mobile phase 35% EtOH in hexanes/DEA to give the title S-isomer (A): $[\alpha]_{25} = +2.8$ (1% in MeOH); $^1\text{H NMR}$ (DMSO-d_6 , 300 MHz) δ 2.94 (s, 3H), 6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.4-7.5 (m, 5H), 7.7 (s, 1H), 8.0 (m, 1H), 8.2 (m, 1H); MS m/e ($\text{M}+\text{H}^+$) 445; and the title R-isomer (B): $[\alpha]_{25} = +2.8$ (1% in MeOH); $^1\text{H NMR}$ (DMSO-d_6 , 300 MHz) δ 2.94 (s, 3H),

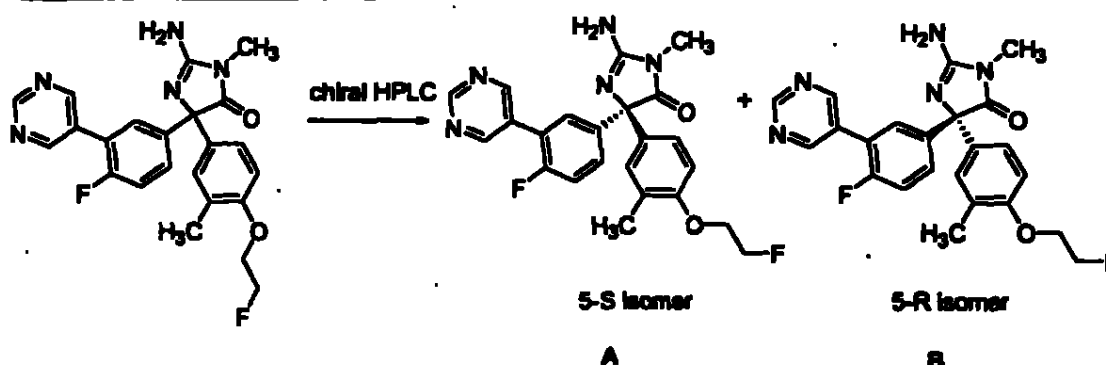
25

6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.4-7.5 (m, 5H), 7.7 (s, 1H), 8.0 (m, 1H), 8.2 (m, 1H); MS m/e (M+H)⁺ 445.

5

EXAMPLE 138

Preparation of (5S)-2-Amino-5-[4-(2-fluoroethoxy)-3-methylphenyl]-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-[4-(2-fluoroethoxy)-3-methylphenyl]-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one [B]



10

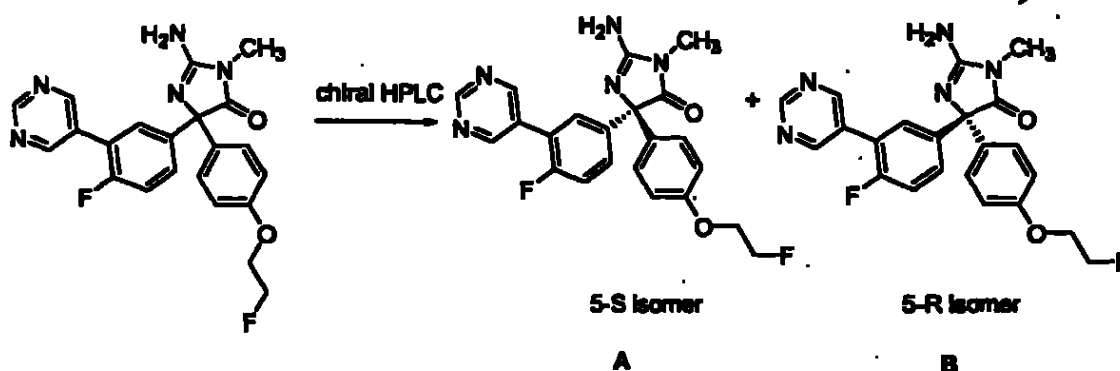
Using essentially the same procedure described in Examples 133-137 and employing a racemic mixture of 2-amino-5-[4-(2-fluoroethoxy)-3-methylphenyl]-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one, the title S-isomer (A) was obtained as a white solid, mp 116-118° C; $[\alpha]_{25} = -31.46$ (1% in DMSO); MS(+)/ES: 438 (M+H)⁺; and the title R-isomer was obtained as a white solid, mp 112-114° C; $[\alpha]_{25} = +35$ (1% in DMSO); MS(+)/ES: 438 (M+H)⁺.

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EXAMPLE 139

Preparation of (5S)-2-Amino-5-[4-(2-fluoroethoxy)phenyl]-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-[4-(2-fluoroethoxy)phenyl]-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]

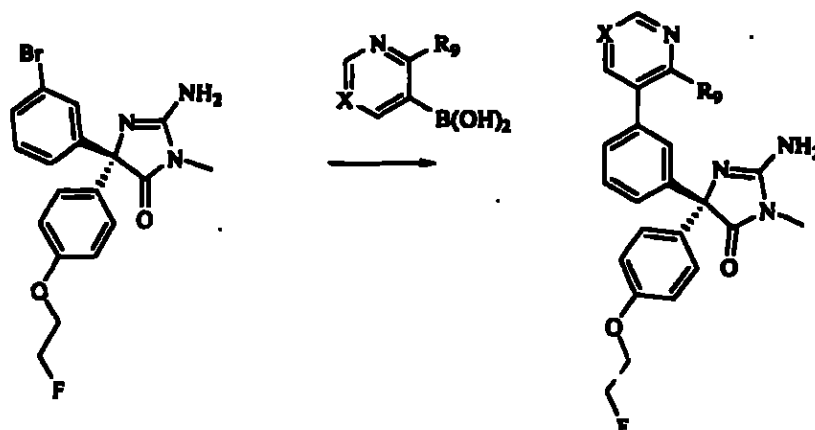


A racemic mixture of 2-amino-5-[4-(2-fluoroethoxy)phenyl]-5-(4-fluoro-3-pyridin-5-ylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by
 5 chiral HPLC: Chiralcel AD, 2 x 25 cm using mobile phase EtOH:Hexane (15:85) and
 a flow rate of 20 mL/min to give the title S-isomer (A) as a white solid, mp 120 °C;
 $[\alpha]_{25} = -35.09$ (0.53% in MeOH); $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 2.97 (s, 3H), 4.14-
 4.15 (m, 1H), 4.20-4.21 (m, 1H), 4.65-4.66 (m, 1H), 4.74-4.75 (m, 1H), 6.67 (bs, 2H),
 6.88-6.89 (d, 2H), 7.34 (m, 1H), 7.35-7.37 (d, 2H), 7.57, (m, 1H), 7.65 (m, 1H), 8.92
 10 (s, 2H), 9.22 (s, 1H); MS m/e (M-H)⁺ 422.1; and the title R-isomer as a white solid, mp
 120 °C; $[\alpha]_{25} = +31.2$ (1% in MeOH); $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 2.97 (s, 3H),
 4.15-4.16 (m, 1H), 4.20-4.21 (m, 1H), 4.65-4.66 (m, 1H), 4.74-4.75 (m, 1H), 6.67 (bs,
 2H), 6.88-6.89 (d, 2H), 7.34 (m, 1H), 7.35-7.37 (d, 2H), 7.55, (m, 1H), 7.65 (m, 1H),
 8.92 (s, 2H), 9.22 (s, 1H); MS m/e (M-H)⁺ 422.1.

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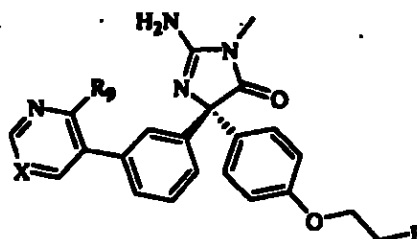
EXAMPLES 140 AND 141

Preparation of (5S)-2-Amino-5-[4-(2-fluoroethoxy)phenyl]-3-methyl-5-(3-heteroarylphenyl)-3,5-dihydro-4H-imidazol-4-one Compounds



Using essentially the same procedure described in Example 40 and employing (5S)-2-amino-5-(3-bromophenyl)-5-[4-(2-fluoroethoxy)phenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one and a suitable heteroarylboronic acid, the compounds shown on Table V were obtained and identified by HNMR and mass spectral analyses.

TABLE V



10

Ex. No	R9	X	$[\alpha]_D^{25}$	mp °C
140	H	N	-18.4 (1% MeOH)	145
141	F	CH	—	106

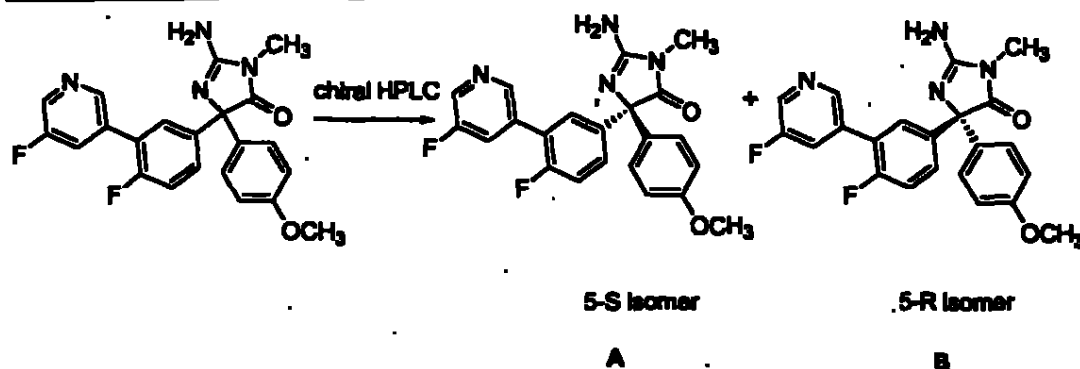
EXAMPLE 142

15 **Preparation of (5S)-2-Amino-5-[4-fluoro-3-(5-fluoropyridin-3-yl)phenyl]-5-[4-methoxyphenyl]-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-**

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nnnn

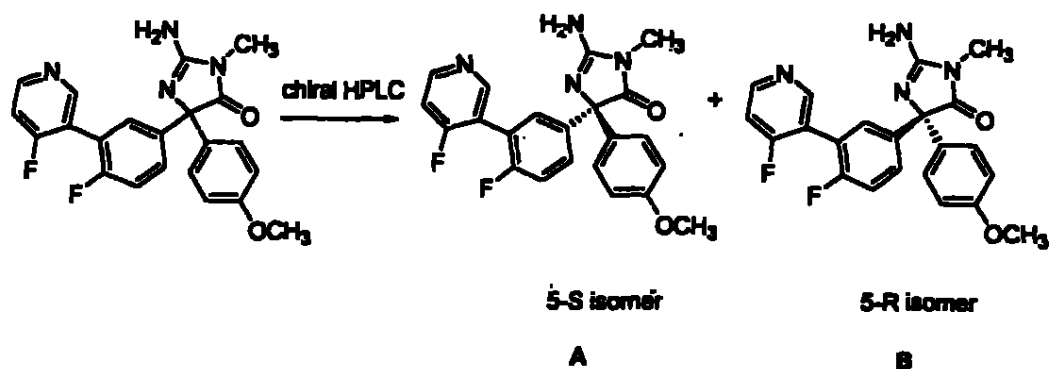
5-[4-fluoro-3-(5-fluoropyridin-3-yl)phenyl]-5-(4-methoxyphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]



A racemic mixture of 2-amino-5-[4-fluoro-3-(5-fluoropyridin-3-yl)phenyl]-5-(4-methoxyphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by chiral HPLC: Chiralcel OJ, 2x25 cm (column) with mobile phase 30% EtOH in hexanes (0.1% diethylamine) to give the title S-isomer (A): $[\alpha]_{25} = -37.6$ (1% in MeOH); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.93 (s, 3H), 3.63 (s, 3H), 6.6 (brs, 2H), 6.8 (d, 2H), 7.22-7.35 (m, 3H), 7.5 (m, 1H), 7.6 (dd, 1H), 7.8 (m, 1H), 8.5 (d, 1H), 8.6 (d, 1H); MS m/e (M+H) $^+$ 409 and the title R-isomer (B): $[\alpha]_{25} = +35.4$ (1% in MeOH); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.93 (s, 3H), 3.63 (s, 3H), 6.6 (brs, 2H), 6.8 (d, 2H), 7.22-7.35 (m, 3H), 7.5 (m, 1H), 7.6 (dd, 1H), 7.8 (m, 1H), 8.5 (d, 1H), 8.6 (d, 1H); MS m/e (M+H) $^+$ 409.

EXAMPLE 143

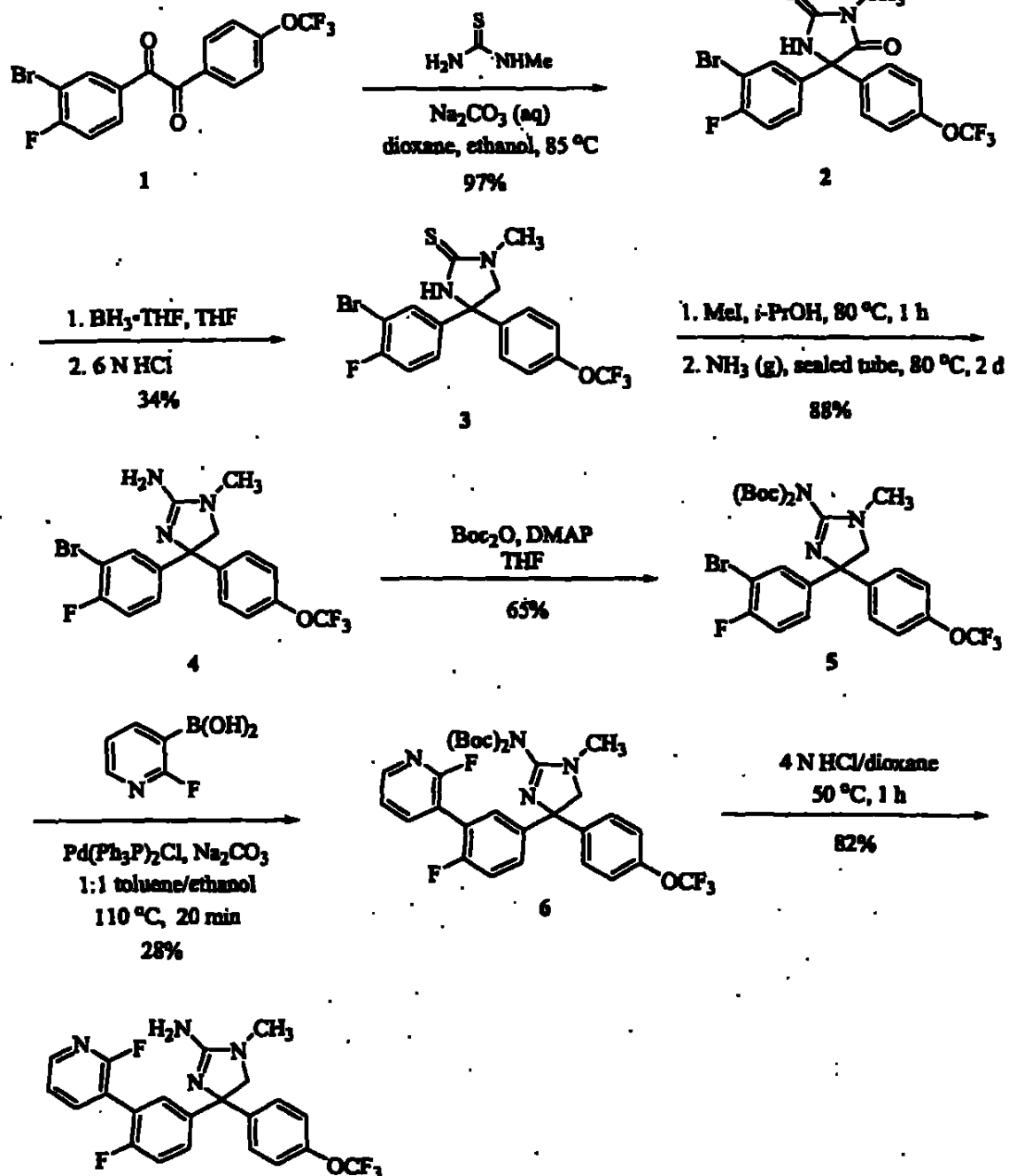
Preparation of (5S)-2-Amino-5-[4-fluoro-3-(4-fluoropyridin-3-yl)phenyl]-5-(4-methoxyphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [A] and (5R)-2-Amino-5-[4-fluoro-3-(4-fluoropyridin-3-yl)phenyl]-5-(4-methoxyphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one [B]



A racemic mixture of 2-amino-5-[4-fluoro-3-(4-fluoropyridin-3-yl)phenyl]-5-(4-methoxyphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one was separated by chiral HPLC: Chiralcel OJ, 0.46x25 cm (column) with mobile phase 80% EtOH in hexanes (0.1% diethylamine) to give the title S-isomer (A): $[\alpha]_{25} = -40$ (1% in MeOH); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.93 (s, 3H), 3.66 (s, 3H), 6.65 (brs, 2H), 6.8 (d, 2H), 7.3 (m, 3H), 7.43 (m, 1H), 7.52 (m, 2H), 8.55 (d, 1H), 8.63 (t, 1H); MS m/e (M+H) $^+$ 409; and title R-isomer (B): $[\alpha]_{25} = +38.8$ (1% in MeOH); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.93 (s, 3H), 3.66 (s, 3H), 6.65 (brs, 2H), 6.8 (d, 2H), 7.3 (m, 3H), 7.43 (m, 1H), 7.52 (m, 2H), 8.55 (d, 1H), 8.63 (t, 1H), MS m/e (M+H) $^+$ 409.

EXAMPLE 144

Preparation of 4-[4-Fluoro-3-(2-fluoropyridin-3-yl)phenyl]-1-methyl-4-(4-trifluoromethoxyphenyl)-4,5-dihydro-1H-imidazol-2-ylamine

**Step a) Preparation of compound 2**

A mixture of 1 (2.00 g, 5.1 mmol) and 1-methyl-2-thiourea (2.07 g, 23.0 mmol) in ethanol (50 mL) and dioxane (50 mL) was stirred at room temperature for 5 min. A solution of sodium carbonate (2.44 g, 23.0 mmol) in water (20 mL) was added and

the reaction was stirred at 85 °C for 15 min. The reaction was then cooled to room temperature, concentrated and diluted with ethyl acetate (100 mL) and brine (20 mL). The organic layer was separated and washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (silica, 1:9
5 ethyl acetate/hexanes) afforded 2 (2.30 g, 97%) as a yellow solid: ¹H NMR (300 MHz, CD₃OD) δ 7.61 (dd, *J* = 6.3, 2.4 Hz, 1H), 7.46–7.27 (m, 6H), 3.27 (s, 3H).

Step b) Preparation of compound 3

A mixture of 2 (2.20 g, 4.75 mmol) and 1.0 M borane tetrahydrofuran complex in tetrahydrofuran (47.5 mL, 47.5 mmol) in tetrahydrofuran (66 mL) was heated at
10 reflux overnight, then treated with 6 N HCl (24 mL, 143 mmol) and heated at 80 °C for 1 h. The reaction was cooled to room temperature, neutralized with sodium bicarbonate solid (12.0 g, 143 mmol) and diluted with ethyl acetate (200 mL). The organic layer was separated and washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (silica, 1:9 to
15 2:8 ethyl acetate/hexanes) afforded 3 (0.73 g, 34%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 8.14 (s, 1H), 7.42 (m, 1H), 7.31–7.05 (m, 6H), 4.18 (s, 2H), 3.19 (s, 3H); ESI MS *m/z* 450 [C₁₇H₁₃BrF₄N₂OS + H]⁺.

Step c) Preparation of compound 4

A mixture of 3 (0.73 g, 1.63 mmol), methyl iodide (0.25 g, 1.79 mmol) in
20 isopropanol (10 mL) was heated at 80 °C for 1 h, concentrated, redissolved in isopropanol (20 mL), cooled to 0 °C and charged with ammonia gas (2.0 g). The reaction vessel was sealed and heated at 80 °C for 48 h. The reaction was cooled to room temperature, concentrated and purified by flash chromatography (100:0:0 to
80:20:0.5 methylene chloride/methanol/concentrated ammonium hydroxide) afforded
25 4 (0.62 g, 88%) as a colorless syrup: ¹H NMR (300 MHz, CD₃OD) δ 7.62 (dd, *J* = 6.3, 2.4 Hz, 1H), 7.61–7.20 (m, 6H), 4.35 (s, 2H), 3.08 (s, 3H); ESI MS *m/z* 432 [C₁₇H₁₄BrF₄N₂O + H]⁺.

Step d) Preparation of compound 5

A mixture of 4 (0.52 g, 1.20 mmol), 4-dimethylaminopyridine (0.77 g, 6.32
30 mmol) and di-*tert*-butyldicarbonate (1.38 g, 6.32 mmol) in tetrahydrofuran (5 mL) was stirred at room temperature for 1 h and concentrated. Purification by flash chromatography (silica, 1:9 to 2:8 ethyl acetate/hexanes) afforded 5 (0.49 g, 65%) as a white solid: ¹H NMR (300 MHz, CD₃OD) δ 7.67 (dd, *J* = 6.6, 2.1 Hz, 1H), 7.44–7.03

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(m, 6H), 4.05 (d, $J = 9.9$ Hz, 1H), 3.86 (d, $J = 9.9$ Hz, 1H), 2.79 (s, 3H), 1.39 (s, 18H); ESI MS m/z 632 [$C_{27}H_{30}BrF_4N_3O_5 + H$] $^+$.

Step e) Preparation of compound 8.

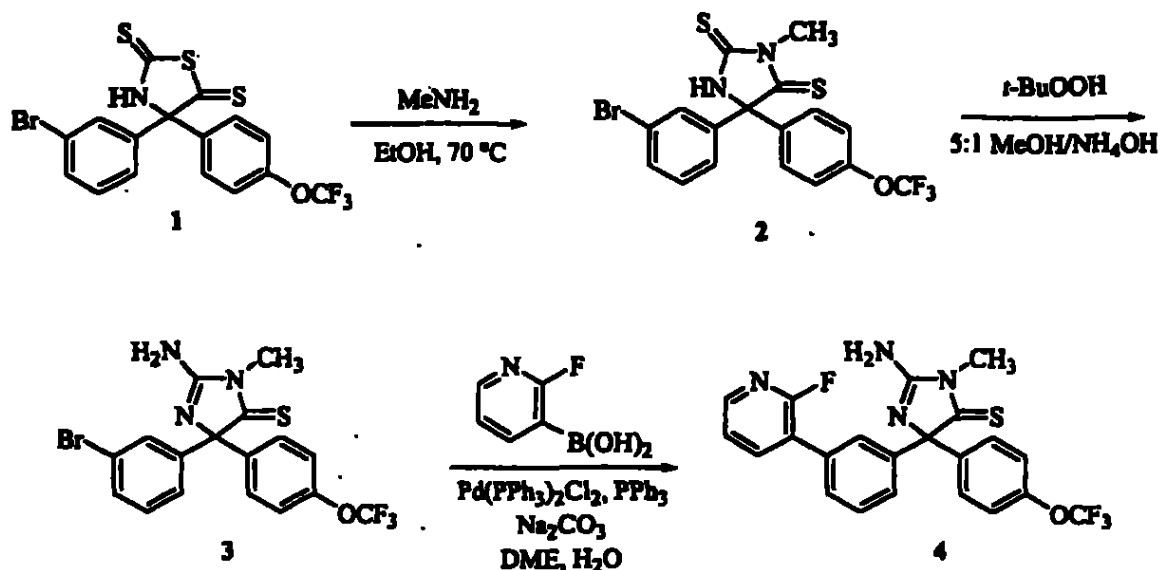
A mixture of 5 (0.19 g, 0.300 mmol), 2-fluoropyridine-3-boronic acid (0.064 g, 0.451 mmol), sodium carbonate (0.096 g, 0.900 mmol), bis(triphenylphosphino)palladium (II) dichloride (0.021 g, 0.030 mmol) and triphenylphosphine (0.016 g, 0.060 mmol) in 1:1 toluene/EtOH (10 mL) was degassed and heated at 110 °C for 20 min. The mixture was cooled to room temperature and concentrated. Purification by flash chromatography (silica, 1:9 to 4:6 ethyl acetate/hexanes) afforded 8 (0.055 g, 28%) as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (m, 1H), 7.82 (m, 1H), 7.48–7.11 (m, 8H), 4.03 (d, $J = 9.5$ Hz, 1H), 3.95 (d, $J = 9.5$ Hz, 1H), 2.78 (s, 3H), 1.31 (s, 18H); ESI MS m/z 649 [$C_{32}H_{33}F_5N_4O_5 + H$] $^+$.

Step f) Preparation of 4-[4-fluoro-3-(2-fluoro-pyridin-3-yl)-phenyl]-1-methyl-4-(4-trifluoromethoxy-phenyl)-4,5-dihydro-1H-imidazol-2-ylamine

A mixture of 8 (0.055 g, 0.085 mmol) and 4 M hydrogen chloride in dioxane (5 mL) was heated at 50 °C for 1 h, cooled to room temperature and concentrated. The reaction mixture was then diluted with chloroform (50 mL) and sodium bicarbonate (10 mL). The organic layer was separated and washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. Purification by preparative HPLC afforded the title product as a white solid, 0.031 g (82% yield), mp 65–70 °C; ^1H NMR (500 MHz, CD_3OD) δ 8.22 (m, 1H), 7.95 (m, 1H), 7.35–7.23 (m, 8H), 4.10 (t, $J = 7.5$ Hz, 2H), 2.93 (t, $J = 7.5$ Hz, 3H); IR (ATR) 3059, 2926, 1670, 1641, 1570, 1503, 1427, 1253, 1201, 1161, 829, 804, 765, 718 cm^{-1} ; ESI MS m/z 449 [$C_{22}H_{17}F_9N_4O + H$] $^+$.

EXAMPLE 145

Preparation of 2-Amino-5-[3-(2-fluoro-pyridin-3-yl)-phenyl]-3-methyl-5-(4-trifluoromethoxy-phenyl)-3,5-dihydro-imidazole-4-thione



Step a) Preparation of Compound 2

A mixture of methylamine hydrochloride (0.210 g, 3.18 mmol), triethylamine (0.320 g, 3.18 mmol) and 1 (0.470 g, 1.06 mmol) in ethanol was stirred at 70 °C for 1h. The solvents were evaporated and the residue partitioned between ethyl acetate and water. The organic layer was separated and washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated to afford 2 (0.460 g, 99%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 7.71 (br s, 1H), 7.58–7.49 (m, 2H), 7.37 (d, J = 8.9 Hz, 2H), 7.30–7.19 (m, 3H), 3.68 (s, 3H).

Step b) Preparation of Compound 3

A mixture of 2 (0.458 g, 1.05 mmol) and *t*-butyl hydroperoxide (1.88 g of a 70% solution in water, 21.0 mmol) in methanol (50 mL) and concentrated aqueous ammonium hydroxide (10 mL) was stirred overnight at room temperature. After this time, 10% aqueous sodium thiosulfate (30 mL) was added; the mixture was concentrated to remove most of the methanol and then the aqueous mixture was diluted with methylene chloride. The organic layer was separated, washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. Purification of the resultant residue by flash chromatography (silica, 95:5 methylene chloride/methanol) afforded 3 (0.250 g, 57%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.88 (t, J = 1.7 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.72–7.65 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H); ESI MS *m/z* 444 [C₁₇H₁₃BrF₃N₃OS + H]⁺.

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Step c) Preparation of 2-amino-5-[3-(2-fluoro-pyridin-3-yl)-phenyl]-3-methyl-5-(4-trifluoromethoxy-phenyl)-3,5-dihydro-imidazole-4-thione

A mixture of **3** (0.16 g, 0.38 mmol), 2-fluoropyridine-3-boronic acid (0.075 g, 0.530 mmol), bis(triphenylphosphino)palladium(II) chloride (0.013 g, 0.019 mmol),
5 triphenylphosphine (0.010 g, 0.038 mmol) and sodium carbonate (0.121 g 1.14 mmol) in 3:1 DME/water (6.0 mL) was heated at 80 °C for 1 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The resultant residue was diluted with ethyl acetate and water. The organic layer was separated and washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. Purification
10 of this residue by flash chromatography (silica, 97:2.5:0.5 methylene chloride/methanol/concentrated ammonium hydroxide) afforded 0.087 g of a pale yellow solid. This material was freeze dried from 1:1 acetonitrile/water (6 mL) to afford the title product as a pale yellow solid, 0.069 g (39% yield), mp 89–99 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.17 (dt, *J* = 4.8, 1.5 Hz, 1H), 7.86–7.79 (m, 1H), 7.65 (br
15 s, 1H), 7.55–7.48 (m, 4H), 7.44–7.38 (m, 1H), 7.27–7.25 (m, 1H), 7.14 (d, *J* = 8.9 Hz, 2H), 3.48 (s, 3H); ESI MS *m/z* 461 [C₂₂H₁₈F₄N₄OS + H]⁺;

EXAMPLE 148

20 Evaluation of the Inhibition of hBACE1, MuBACE1 and hBACE2 by Test Compounds

Assay Conditions: 10 nM human BACE1 (or 10 nM Murine BACE1, 1.5 nM human BACE2) 25 μM substrate (WABC-6, MW 1549.6, from AnaSpec); final buffer
25 conditions: 50 mM Na-Acetate, pH 4.5, 0.05% CHAPS, 25% PBS; temperature: room temperature; reagent information: Na-Acetate: Aldrich, Cat.# 24,124-5 CHAPS: Research Organics, Cat. # 1304C 1X PBS: Mediatech (Cellgro), Cat# 21-031-CV; peptide substrate AbzSEVNLDAEFRDpa: AnaSpec, Peptide Name: WABC-6; determination of stock substrate (AbzSEVNLDAEFRDpa) concentration: a 25 mM
30 stock solution in dimethyl sulfoxide (DMSO) is prepared using the peptide weight and MW and diluted to 25 μM. The concentration is determined by absorbance at 354 nm using an extinction coefficient ϵ of 18172 M⁻¹cm⁻¹. The substrate stock is stored in small aliquots at -80° C. [Substrate Stock] = $ABS^{354\text{ nm}} \cdot 10^9 / 18172$ (in mM)

Determination of Stock Enzyme Concentration: The stock concentration of each enzyme by ABS at 280 nm using ϵ of 64150 M⁻¹cm⁻¹ for hBACE1 and MuBACE1, 62870 M⁻¹cm⁻¹ for hBACE2 in 6 M Guanidinium Hydrochloride (from Research Organics, Cat. # 5134G-2), pH 6.

- 5 (The extinction coefficient $\epsilon^{280\text{nm}}$ for each enzyme was calculated based on known amino acid composition and published extinction coefficients for Trp (5.69 M⁻¹ cm⁻¹) and Tyr (1.28 M⁻¹ cm⁻¹) residues (*Anal. Biochem.* 182, 319-326).

Dilution and mixing steps: total reaction volume: 100 μ L

1. 2X Inhibitor dilutions in buffer A(66.7 mM Na-Acetate, pH 4.5, 0.0667% CHAPS)
- 10 are prepared,
2. 4X enzyme dilution in buffer A(66.7 mM Na-Acetate, pH 4.5, 0.0667% CHAPS)
- are prepared,
3. 100 μ M substrate dilution in 1X PBS is prepared,
4. 50 μ L 2X Inhibitor and 25 μ L 100 μ M substrate are added to each well of 96-well
- 15 plate (from DYNEX Technologies, VWR #: 11311-046), the immediately 25 μ L 4X enzyme are added to the inhibitor and substrate mixer, the fluorescence readings are initiated.

Fluorescence Readings: Readings at λ_{ex} 320 nm and λ_{em} 420 nm are taken every 40-sec for 30 min at room temperature to determine the linear slope for

20 substrate cleavage rate (v_i).

Calculation of % Inhibition: % Inhibition = 100 * (1- v_i / v_0)

(v_i = substrate cleavage rate in the presence of inhibitor,

v_0 = substrate cleavage rate in the absence of inhibitor)

IC₅₀ Determination: % Inhibition = [(B * IC₅₀ⁿ) + (100 * I_0 ⁿ)] / (IC₅₀ⁿ + I_0 ⁿ),

25

Fluorescent Kinetic Assay for human recombinant BACE 2

This assay is used to provide kinetic and selectivity parameters for the analyses of the tested compounds.

Materials and methods: final assay conditions:10 nM human BACE1

- 30 (or 10 nM Murine BACE1, 1.5 nM human BACE2) 25 μ M Substrate (WABC-6, MW 1549.6, from AnaSpec). Final buffer conditions: 50 mM Na-Acetate, pH 4.5, 0.05% CHAPS, 25% PBS. Temperature: room temperature. Reagent Information: Na-Acetate: Aldrich, Cat.# 24,124-5 CHAPS: Research Organics, Cat. # 1304C 1X PBS:

Mediatech (Cellgro), Cat# 21-031-CV Peptide Substrate AbzSEVNLDAEFRDpa:
AnaSpec, Peptide Name: WABC-6

Determination of stock substrate (AbzSEVNLDAEFRDpa) concentration:

A 25 mM stock solution in DMSO is prepared using the peptide weight and MW, and
5 diluted to 25 μ M. The concentration is determined by absorbance at 354 nm using
an extinction coefficient ϵ of 18172 $M^{-1}cm^{-1}$. The substrate stock is stored in small
alliquots at $-80^{\circ}C$. [Substrate Stock] = $ABS^{354nm} \times 10^8 / 18172$ (in mM)

Determination of stock enzyme concentration: The stock concentration of
each enzyme is determined by ABS at 280 nm using ϵ of 64150 $M^{-1}cm^{-1}$ for hBACE1
10 and MuBACE1, 82870 $M^{-1}cm^{-1}$ for hBACE2 in 6 M guanidinium hydrochloride (from
Research Organics, Cat. # 5134G-2), pH 6. (The extinction coefficient ϵ^{280nm} for
each enzyme is calculated based on known amino acid composition and published
extinction coefficients for Trp (5.69 $M^{-1}cm^{-1}$) and Tyr (1.28 $M^{-1}cm^{-1}$) residues (*Anal.*
Biochem. 182, 319-326).)

15 **Dilution and Mixing Steps:** Total Reaction Volume.: 100 μ L

1. 2X inhibitor dilutions in buffer A(66.7 mM Na-Acetate, pH 4.5, 0.0667%
CHAPS) are prepared,
2. 4X enzyme dilution in buffer A(66.7 mM Na-Acetate, pH 4.5, 0.0667%
CHAPS) are prepared,
- 20 3. 100 μ M substrate dilution in 1X PBS, 50 μ L 2X Inhibitor and 25 μ L 100 μ M
substrate are added to each well of 96-well plate (from DYNEX Technologies, VWR
#: 11311-046), then immediately 25 μ L 4X enzyme is added to the inhibitor and
substrate mixer and the fluorescence readings are initiated.

Fluorescence Readings: Readings at λ_{ex} 320 nm, λ_{em} 420 nm are taken
25 every 40-sec for 30 min at room temperature and to determine the linear slope for
substrate cleavage rate (v_i).

Analysis of calculation of % Inhibition: % Inhibition = $100 \times (1 - v_i / v_0)$

v_i = substrate cleavage rate in the presence of inhibitor,

v_0 = substrate cleavage rate in the absence of inhibitor)

30 **IC₅₀ Determination:**

% Inhibition = $((B \times IC_{50}^n) + (100 \times I_0^n)) / (IC_{50}^n + I_0^n)$.

The data obtained are shown on Table VI.

For Table VI**A = 0.01 μ M-0.10 μ M****B = 0.11 μ M-1.00 μ M****C = >1.00 μ M****5****I = >100-fold selectivity****II = 10-100-fold selectivity****III = <10-fold selectivity****10****Table VI**

<u>Ex. No.</u>	<u>IC₅₀ (μM)</u>	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
5	B	III
6	B	III
7	A	II
8	A	II
9	A	II
10	A	II
11	A	II
12	A	II
13	A	II
14	A	II
15	B	II
16	A	III
17	A	III
18	A	II
19	A	III
20	B	III
21	A	II
22	A	III
23	A	II
24	A	II

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Table VI. cont.

<u>Ex. No.</u>	<u>IC₅₀ (μM)</u>	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
25	A	II
26	A	II
27	A	II
28	A	II
29	A	II
30	B	III
31	B	III
32	A	III
36	A	III
37	A	III
38A	C	III
38B	A	II
41	B	II
42	B	II
43	A	II
44	A	II
46	B	II
47	B	II
48	C	II
49	B	I
50	A	II
51	A	III
52	B	II
53	B	III
54	A	I
55	A	II
56	A	I

Table VI, Cont.

Ex. No.	IC₅₀ (μM)	
	BACE1	BACE1/BACE2
57	A	II
58	A	II
59	A	II
60	A	II
61	A	II
62	A	II
63	A	I
64	C	III
65	B	II
66	A	II
67	A	III
68	B	III
69	A	III
70	A	II
71	A	III
72	B	II
73	B	II
74	A	II
75	B	II
77	A	I
78	A	II
79	A	II
80	A	III
81	A	II
82	A	II
83	A	II
84	B	I

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~~000008~~Table VI. cont.

<u>Ex. No.</u>	<u>IC₅₀ (μM)</u>	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
86	A	I
88	A	II
89	A	II
90	A	II
91	A	II
92	A	II
93	A	II
94	B	II
95	A	II
96	A	II
97	A	II
99	A	III
100	B	III
101A	C	III
101B	A	I
102A	B	III
102B	A	II
103A	C	III
103B	A	II
104	A	II
105A	B	III
105B	A	II
106A	C	III
106B	A	I
107A	A	I
107B	C	III
108	A	II

Table VI. cont.

<u>Ex. No.</u>	<u>IC₅₀ (μM)</u>	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
109	A	II
110	A	II
111	B	III
112	A	II
113	A	I
114	A	II
115	A	II
116	A	II
117	A	II
118	A	I
119	B	II
120	A	I
121	A	II
122	A	II
123	B	II
124	A	II
126	B	I
127	B	I
128	B	II
131	A	II
132	C	III
133A	B	III
133B	A	II
134A	B	III
134B	A	II
135A	C	III
135B	A	II

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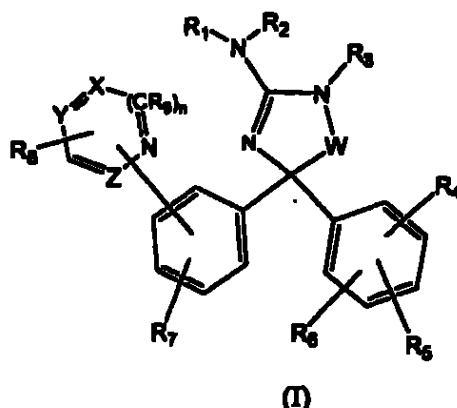
Table VI, cont.

<u>Ex. No.</u>	<u>IC₅₀ (μM)</u>	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
136A	A	II
137A	C	III
137B	A	II
138A	A	I
138B	C	III
139A	A	I
139B	B	III
140	A	I
141	A	II
142A	C	III
142B	A	II
143A	C	III
143B	A	II
144	B	I
145	A	II

Results and Discussion:

- 5 As can be seen from the data shown on Table VI hereinabove, the compounds of the invention are potent and selective inhibitors of BACE1.

1. A compound of formula I



-76-

6A

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R_{12} , R_{13} , R_{16} , R_{20} and R_{21} are each independently H or a C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl or aryl group each optionally substituted; and

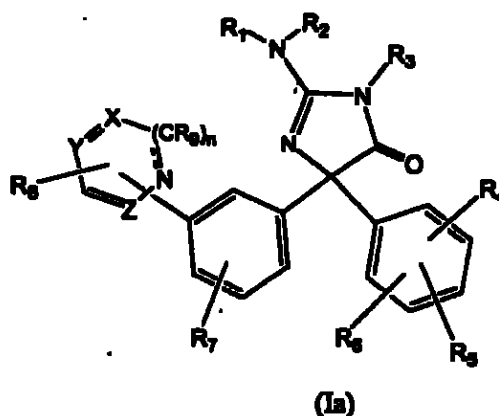
R_{14} , R_{15} , R_{17} and R_{18} are each independently H or C_1 - C_4 alkyl; or
 5 a tautomer thereof, a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein W is CO.

10 3. The compound according to claim 1 or 2, wherein R_1 and R_2 are H and R_3 is C_1 - C_4 alkyl.

4. The compound according to claim 1, 2 or 3, wherein n is 1.

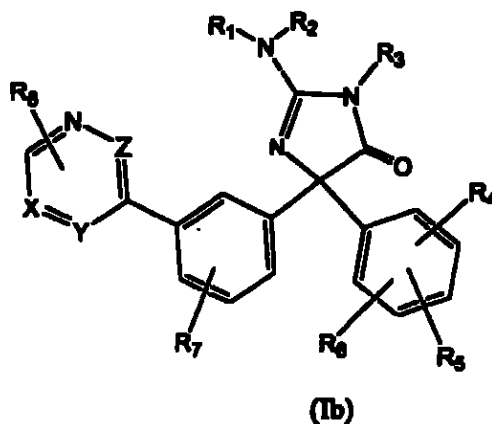
15 5. The compound according to any one of claims 1, 2, 3 and 4 wherein Formula has the structure Ia



20

6. The compound according to claim wherein formula I has the structure

Ib



7. The compound according to claim 6 wherein R_3 is methyl.
- 5 8. The compound according to claim 7 wherein Y is CR_{11} and R_1 and R_2 are H.
9. The compound according to claim 1 selected from the group
- 10 consisting of:
- 2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one;
- (5S)-2-amino-5-[3-(2-fluoropyridin-3-yl)phenyl]-5-(4-methoxy-3-methylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one;
- 15 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- (5S)-2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- (5R)-2-amino-5-(4-fluoro-3-pyrimidin-5-ylphenyl)-3-methyl-5-[4-
- 20 (trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one;
- 4-[2-amino-4-(4-methoxy-3-methylphenyl)-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-4-yl]-2-pyridin-3-ylbenzonitrile;
- 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(4-methyl-3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;

- 2-amino-5-[4-methoxy-3-(trifluoromethyl)phenyl]-3-methyl-5-(3-pyridin-3-ylphenyl)-
3,5-dihydro-4H-imidazol-4-one;
- 2-amino-3-ethyl-5-(4-methoxy-3-methylphenyl)-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-
4H-imidazol-4-one;
- 5 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrazin-2-ylphenyl)-3,5-
dihydro-4H-imidazol-4-one;
- 2-amino-3-methyl-5-(3-pyrimidin-2-ylphenyl)-5-[4-(trifluoromethoxy)phenyl]-3,5-
dihydro-4H-imidazol-4-one;
- 2-amino-5-(4-hydroxy-3-methylphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-
4H-imidazol-4-one;
- 10 2-amino-5-[4-methoxy-3-(trifluoromethyl)phenyl]-3-methyl-5-(3-pyrazin-2-ylphenyl)-
3,5-dihydro-4H-imidazol-4-one;
- (5*R*)-2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyrimidin-5-ylphenyl)-3,5-
dihydro-4H-imidazol-4-one;
- 15 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-
4H-imidazol-4-one;
- 2-amino-5-(3,4-diethoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-
imidazol-4-one;
- 2-amino-5-(3,4-dimethoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-
imidazol-4-one;
- 20 2-amino-5-(3-cyclopentyl-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-
dihydro-4H-imidazol-4-one;
- 2-amino-5-(4-methoxy-3-propoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-
dihydro-4H-imidazol-4-one;
- 25 2-amino-5-(3-butoxy-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-
4H-imidazol-4-one;
- 2-amino-5-(3-isopropoxy-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-
dihydro-4H-imidazol-4-one;
- 2-amino-5-(1,3-benzodioxol-5-yl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-
imidazol-4-one;
- 30 2-amino-5-(2,3-dihydro-1-benzofuran-5-yl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-
dihydro-4H-imidazol-4-one;

- 2-amino-5-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 5 5-[2-amino-1-methyl-5-oxo-4-(3-pyridin-3-ylphenyl)-4,5-dihydro-1H-imidazol-4-yl]-2-methoxybenzotrile;
- 2-amino-5-(3-fluoro-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 10 2-amino-5-(3-chloro-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-3-methyl-5-(3-pyridin-3-ylphenyl)-5-(3,4,5-trimethoxyphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(4-methoxy-3-methylphenyl)-3-methyl-5-(3-pyridin-4-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 15 2-amino-5-(3-ethoxy-4-methoxyphenyl)-3-methyl-5-(3-pyridin-3-ylphenyl)-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-3-methyl-5-(3-pyridin-3-ylphenyl)-5-[4-(trifluoromethoxy)phenyl]-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-3-methyl-5-(3-pyridin-3-ylphenyl)-5-[(4-trifluoromethoxy-3-trifluoromethyl)phenyl]-3,5-dihydro-4H-imidazol-4-one;
- 20 2-amino-5-(3,4-dieethoxyphenyl)-5-(4-fluoro-3-pyridin-3-ylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one;
- 2-amino-5-(3-chloro-4-trifluoromethoxyphenyl)-5-(4-fluoro-3-pyridin-3-ylphenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one;
- 25 a tautomer thereof; a stereoisomer thereof; and
a pharmaceutically acceptable salt thereof.

10. A method for the treatment, prevention or amelioration of a disease or disorder characterized by elevated β -amyloid deposits or β -amyloid levels in a patient which comprises providing said patient with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 9.
- 30

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11. The method according to claim 10 wherein said disease or disorder is selected from the group consisting of Alzheimer's disease; mild cognitive impairment; Down's syndrome; hereditary cerebral hemorrhage with amyloidosis of the Dutch type; cerebral amyloid angiopathy; and degenerative dementia.

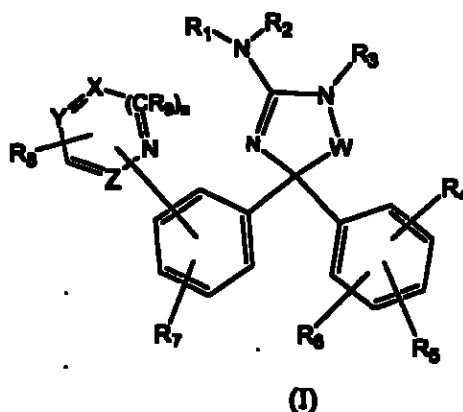
5

12. The method according to claim 11 wherein said disease is Alzheimer's disease.

13. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound as claimed in any one of claims 1 to 9.

10

14. A process for the preparation of a compound of formula I



15

wherein W is CO, CS or CH₂;

X is N, NO or CR₁₀;

Y is N, NO or CR₁₁;

Z is N, NO or CR₁₂ with the proviso that no more than two of X, Y or Z may be N or NO;

20

R₁ and R₂ are each independently H, COR₂₀, CO₂R₂₁ or an optionally substituted C₁-C₄alkyl group;

R₃ is H, OR₁₂ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl or aryl(C₁-C₆)alkyl group each optionally substituted;

25

R₄ and R₅ are each independently H, halogen, NO₂, CN, OR₁₃, NR₁₄R₁₅ or a C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl or

C_3 - C_6 cycloalkyl group each optionally substituted or when attached to adjacent carbon atoms R_4 and R_5 may be taken together with the atoms to which they are attached to form an optionally substituted 5- to 7-membered ring optionally containing one or two heteroatoms selected from O, N or S;

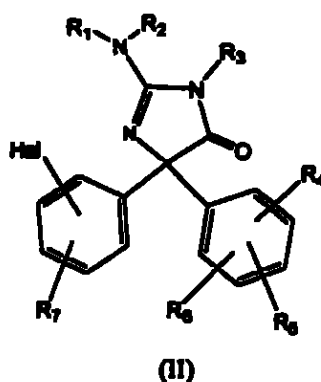
R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{18} are each independently H, halogen, NO_2 , CN, OR_{16} , $NR_{17}R_{18}$ or a C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_6 cycloalkyl group each optionally substituted; n is 0 or 1;

$\equiv$ is a single bond when n is 0 or a double bond when n is 1;

R_{12} , R_{13} , R_{19} , R_{20} and R_{21} are each independently H or a C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or aryl group each optionally substituted; and

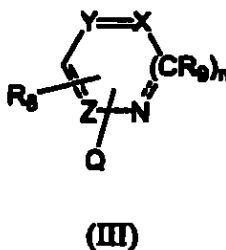
R_{14} , R_{15} , R_{17} and R_{18} are each independently H or C_1 - C_4 alkyl

which process comprises reacting a compound of formula II



wherein Hal is Cl or Br and R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are as described for formula

I hereinabove with a compound of formula III



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wherein Q is $B(OH)_2$, $Sn(nBu)_3$ or $Sn(CH_3)_3$ and X, Y, Z, R_6 , R_9 and n are as described for formula I hereinabove in the presence of a palladium catalyst optionally in the presence of a solvent.

15. Use of a compound as claimed in any one of claims 1 to 9 for the
5 manufacture of a medicament for the treatment, prevention or amelioration of a disease or disorder characterized by elevated β -amyloid deposits or β -amyloid levels in a patient.

DERIVADOS DE AMINO-5,5-DIFENILIMIDAZOLONA PARALA INHIBICIÓN DE β -SECRETASAANTECEDENTES DE LA INVENCION

La enfermedad de Alzheimer (AD), una enfermedad degenerativa progresiva del cerebro principalmente asociada con la edad, es un problema de salud serio. Clínicamente, la AD se caracteriza por la pérdida de la memoria, cognición, razonamiento, juicio, y orientación. También afectadas, en la medida en que progresa la enfermedad, están las capacidades motoras, sensorial, y lingüística hasta que ocurre el daño global de las múltiples funciones cognitivas. Estas pérdidas cognitivas tienen lugar gradualmente, pero típicamente conducen a un daño severo y a la eventual muerte en 4-12 años. Los pacientes con AD despliegan los característicos depósitos de β -amiloide en el cerebro y en los vasos sanguíneos cerebrales (angiopatía β -amiloide) así como también los enmarañamientos neurofibrilares. Las placas amiloidogénicas y la angiopatía amiloide vascular también caracterizan los cerebros de los pacientes con Trisomía 21 (Síndrome de Down), Hemorragia Cerebral Hereditaria con Amiloidosis del tipo Holandés (HCHWA-D), y otros trastornos neurodegenerativos. Los enmarañamientos neurofibrilares también ocurren en otros trastornos que inducen demencia.

La familia de las proteínas conocida como β -amiloide se cree que es la causa de la patología y la posterior declinación cognitiva en la enfermedad de Alzheimer. El procesamiento proteolítico de la proteína precursora amiloide (APP) genera el

péptido amiloide β (A-beta); específicamente, el A-beta es producido mediante el clivaje del APP en el terminal N mediante β -secretasa y en el terminal C mediante una o más γ -secretasas. La actividad de la enzima aspartilo proteasa, o de la enzima β -secretasa (BACE), se correlaciona directamente con la generación del péptido A-beta proveniente del APP (Sinha, et al, Nature, 1999, 402, 537-540). Los crecientes estudios indican que la inhibición de la enzima β -secretasa, inhibe la producción del péptido A-beta. La inhibición de la β -secretasa y la consecuente disminución del péptido A-beta pueden conducir a la reducción de los depósitos β -amiloide en el cerebro y en los niveles β -amiloide en los vasos sanguíneos cerebrales y a un tratamiento efectivo de una enfermedad o trastorno originado de esta forma.

Por lo tanto, es un objeto de esta invención suministrar compuestos que son inhibidores de la β -secretasa y son útiles como agentes terapéuticos en el tratamiento, prevención o mejoramiento de una enfermedad o trastorno caracterizado por los elevados depósitos de β -amiloide o niveles de β -amiloide en un paciente.

Es otro objeto de esta invención suministrar métodos terapéuticos y composiciones farmacéuticas útiles para el tratamiento, prevención o mejoramiento de una enfermedad o trastorno caracterizado por los elevados depósitos de β -amiloide o niveles de β -amiloide en un paciente.

R₄ y R₅ son cada uno independientemente H, halógeno, NO₂, CN, OR₁₃, NR₁₄R₁₅ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆ o cicloalquilo C₃-C₈ cada uno opcionalmente sustituido o cuando se unen a átomos de carbono adyacente R₄ y R₅ pueden ser tomados juntos con los átomos a los cuales ellos están unidos para formar un anillo de 5 a 7 miembros opcionalmente sustituido que contiene opcionalmente uno o dos heteroátomos seleccionados de O, N o S;

R₆, R₇, R₈, R₉, R₁₀, R₁₁ y R₁₉ son cada uno independientemente H, halógeno, NO₂, CN, OR₁₆, NR₁₇R₁₈ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆ o cicloalquilo C₃-C₈ cada uno opcionalmente sustituido;

n es 0 o 1;

----- es un enlace simple cuando n es 0 o un doble enlace cuando n es 1;

R₁₂, R₁₃, R₁₆, R₂₀ y R₂₁ son cada uno independientemente H o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₈ o arilo cada uno opcionalmente sustituido; y

R₁₄, R₁₅, R₁₇ y R₁₈ son cada uno independientemente H o alquilo C₁-C₄, o

Un tautómero de éstos, un estereoisómero de éstos o una sal farmacéuticamente aceptable de éstos.

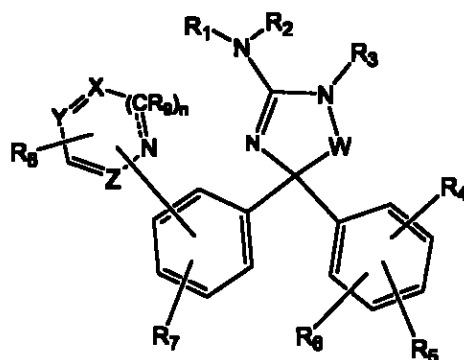
La presente invención también suministra métodos terapéuticos y composiciones farmacéuticas útiles para el tratamiento, prevención o mejoramiento de una enfermedad o trastornos caracterizados por depósitos crecientes de β -amiloide o por niveles crecientes de β -amiloide en el paciente.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La enfermedad de Alzheimer (AD) es una enfermedad degenerativa mayor del cerebro que presenta clínicamente pérdida progresiva de la memoria, cognición, razonamiento, juicio y estabilidad emocional y gradualmente conduce a un profundo deterioro mental y la muerte. La causa exacta del AD es desconocida, pero la evidencia creciente indica que el péptido beta amiloide (A-beta) juega un papel central en la patogénesis de la enfermedad. (D. B. Schenk; R. E. Rydel et al, Journal of Medicinal Chemistry, 1995, 21,4141 y D. J. Selkoe, Physiology Review, 2001, 81,741). Los pacientes con AD exhiben marcadores neuropatológicos característicos tales como placas neuríticas (y en angiopatía β -amiloide, los depósitos en los vasos sanguíneos cerebrales) así como también los enmarañamientos neurofibrilares detectados en el cerebro en la autopsia. El A-beta es el componente mayor de las placas neuríticas en los cerebros AD. Además, los depósitos β -amiloide y la angiopatía β -amiloide vascular también caracteriza individuos con Síndrome de Down, Hemorragia Cerebral Hereditaria con Amiloidosis del tipo Holandés y otros trastornos neurodegenerativos y que inducen demencia. La sobre expresión de la proteína precursora amiloide (APP), altera

el clivaje del APP al A-beta o una disminución en el espacio de A-beta de un cerebro de paciente puede incrementar los niveles de formas solubles o fibrilares de A-beta en el cerebro. La enzima de clivaje APP de sitio β , BACE1, también denominada memapsin-2 o Asp-2, se identificó en 1999 (R. Vassar, B. D. Bennett, et al, Nature, 1999, 402, 537). El BACE1 es una proteasa aspártica unida a membrana con todas las propiedades funcionales conocidas y las características de la β -secretasa. Paralelo al BACE1, una segunda aspartilo proteasa homóloga denominada BACE2 se encontró que tiene actividad de β -secretasa *in vitro*. Los inhibidores no relacionados con sustrato, no péptido, de bajo peso molecular del BACE1 o la β -secretasa son seriamente vistas ambas como una ayuda en el estudio de la enzima β -secretasa y como agentes terapéuticos potenciales.

Sorprendentemente, se ha encontrado que los compuestos amino-5,5-difenilimidazolona,-imidazotona y -imidazol de fórmula I demuestran la inhibición de β -secretasa y la inhibición selectiva de BACE1. Ventajosamente, dichos compuestos se pueden utilizar como agentes terapéuticos efectivos para el tratamiento, prevención o mejoramiento de una enfermedad o trastornos caracterizados por depósitos de β -amiloide o niveles de β -amiloide elevados en un paciente. De acuerdo con esto, la presente invención suministra un compuesto de fórmula I



(I)

En donde W es CO, CS o CH₂;

X es N, NO o CR₁₀;

Y es N, NO o CR₁₁;

Z es N, NO o CR₁₉ con la condición de que no más de dos de X,
Y o Z puedan ser N o NO;

R₁ y R₂ son cada uno independientemente H, COR₂₀, CO₂R₂₁ o un
grupo alquilo C₁-C₄ opcionalmente sustituido;

R₃ es H, OR₁₂ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆,
alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₈,
o arilo (C₁-C₆) alquilo cada uno opcionalmente
sustituido;

R₄ y R₅ son cada uno independientemente H, halógeno, NO₂, CN,
OR₁₃, NR₁₄R₁₅ o un grupo alquilo C₁-C₆, haloalquilo C₁-
C₆, alquenilo C₂-C₆, alquinilo C₂-C₆ o cicloalquilo
C₃-C₈ cada uno opcionalmente sustituido o cuando se
unen a átomos de carbono adyacente R₄ y R₅ pueden ser
tomados juntos con los átomos a los cuales ellos
están unidos para formar un anillo de 5 a 7 miembros
opcionalmente sustituido que contiene opcionalmente
uno o dos heteroátomos seleccionados de O, N o S;

$R_6, R_7, R_8, R_9, R_{10}, R_{11}$ y R_{19} son cada uno independientemente H, halógeno, NO_2 , CN, OR_{16} , $NR_{17}R_{18}$ o un grupo alquilo C_1-C_6 , haloalquilo C_1-C_6 , alqueno C_2-C_6 , alquino C_2-C_6 o cicloalquilo C_3-C_8 cada uno opcionalmente sustituido;

n es 0 o 1;

----- es un enlace simple cuando n es 0 o un doble enlace cuando n es 1;

$R_{12}, R_{13}, R_{16}, R_{20}$ y R_{21} son cada uno independientemente H o un grupo alquilo C_1-C_6 , haloalquilo C_1-C_6 , alqueno C_2-C_6 , alquino C_2-C_6 , cicloalquilo C_3-C_8 o arilo cada uno opcionalmente sustituido; y

R_{14}, R_{15}, R_{17} y R_{18} son cada uno independientemente H o alquilo C_1-C_4 , o

Un tautómero de éstos, un estereoisómero de éstos o una sal farmacéuticamente aceptable de éstos.

X es N, NO o CR_{10} ; preferiblemente N o CR_{10} . Y es N, NO o CR_{11} ; preferiblemente CR_{11} . Z es N, NO o CR_{19} ; preferiblemente CR_{19} . El símbolo n es 0 o 1, preferiblemente 1. $R_6, R_7, R_8, R_9, R_{10}, R_{11}$ y R_{19} son cada uno independientemente H, halógeno, NO_2 , CN, OR_{16} , $NR_{17}R_{18}$ o un grupo alquilo C_1-C_6 , haloalquilo C_1-C_6 , alqueno C_2-C_6 , alquino C_2-C_6 , o cicloalquilo C_3-C_8 , cada uno opcionalmente sustituido; preferiblemente H, halógeno, alquilo C_1-C_4 o alcoxi C_1-C_4 . El anillo que contiene X, Y y Z sustituye el grupo fenilo, preferiblemente en la posición 3 de éste. El

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miembro del anillo que contiene X, Y y Z que esta ligado al grupo fenilo es preferiblemente el átomo de carbono ligado a Y y Z.

R_1 y R_2 son cada uno independientemente H, COR_{20} , CO_2R_{21} o un grupo alquilo C_1-C_4 opcionalmente sustituido; preferiblemente H o un grupo alquilo C_1-C_4 opcionalmente sustituido; más preferiblemente H, un grupo alquilo C_1-C_4 o un grupo haloalquilo C_1-C_4 ; ventajosamente H.

W es preferiblemente CO.

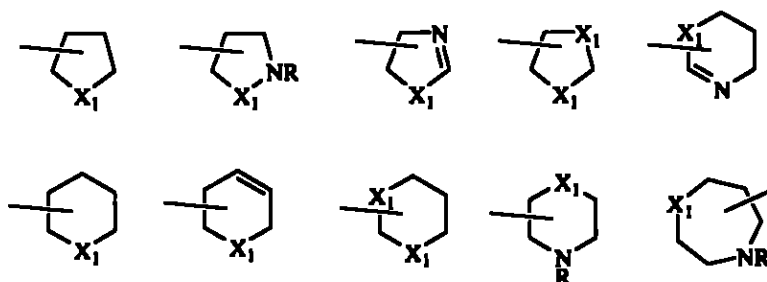
R_4 y R_5 son cada uno independientemente H, halógeno, NO_2 , CN, OR_{13} , $NR_{14}R_{15}$ o un grupo alquilo C_1-C_6 , haloalquilo C_1-C_6 , alqueno C_2-C_6 , alquino C_2-C_6 , o cicloalquilo C_3-C_6 , cada uno opcionalmente sustituido o cuando esta unido a átomos de carbono adyacentes R_4 y R_5 pueden ser tomados junto con los átomos a los cuales ellos están unidos para formar un anillo de 5 a 7 miembros opcionalmente sustituido que contiene uno o dos heteroátomos seleccionados de O, N o S. Preferiblemente R_4 y R_5 son cada uno independientemente H, halógeno, CN, OR_{13} o un grupo alquilo C_1-C_6 , haloalquilo C_1-C_6 , o cicloalquilo C_3-C_6 , cada uno opcionalmente sustituido o, cuando están unidos a átomos de carbono adyacentes, R_5 y R_6 pueden ser tomados juntos con dichos átomos de carbono adyacente para formar un anillo de 5 a 7 miembros opcionalmente sustituido que contiene opcionalmente uno o dos heteroátomos seleccionados de O, N o S, el anillo contiene preferiblemente dos átomos de oxígeno como heteroátomos. Más preferiblemente R_4 y R_5 son cada uno independientemente H, halógeno, CN, OR_{13} , o un grupo alquilo C_1-C_6 , haloalquilo C_1-C_6 , o cicloalquilo C_3-C_6 , o, cuando

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están unidos a los átomos de carbono adyacentes, R_4 y R_5 pueden ser tomados juntos con dichos átomos de carbono adyacentes para formar un anillo de 5 a 7 miembros que contiene opcionalmente uno o dos heteroátomos seleccionados de O, N o S, siendo el anillo opcionalmente sustituido por 1, 2 o 3 átomos de halógeno. Ventajosamente, al menos uno de R_4 y R_5 es OR_{13} o R_4 y R_5 cuando se toman juntos representan un radical divalente que es un radical metilenodioxi o etilenodioxi opcionalmente sustituido por uno o más átomos de halógeno. R_{13} es H o un grupo alquilo C_1-C_6 , haloalquilo C_1-C_6 , alqueno C_2-C_6 , alquino C_2-C_6 , cicloalquilo C_3-C_8 o arilo cada uno opcionalmente sustituido; preferiblemente alquilo C_1-C_6 sustituido por 0, 1, 2, o 3 sustituyentes independientemente seleccionados de átomos de halógeno, grupos nitro, ciano, tiocianato, cianato, hidroxilo, alquilo, haloalquilo, alcoxi, haloalcoxi, amino, alquilamino, dialquilamino, formilo, alcóxicarbonilo, carboxilo, alcóxicarbonilo, alcanoilo, alcanoiloxi, alquiltio, alquilsulfinilo, alquilsulfonilo, carbamoilo, alquilamido, fenilo, fenoxi, bencilo, benciloxi, heterociclilo y cicloalquilo.

Como se utiliza en la especificación y reivindicaciones, el término halógeno designa F, Cl, Br o I y el término cicloheteroalquilo designa un sistema de anillo cicloalquilo de cinco a siete miembros que contiene 1 o 2 heteroátomos, que pueden ser iguales o diferentes, seleccionados de N, O o S y que contiene opcionalmente un doble enlace. Ejemplos de sistemas de anillos cicloheteroalquilo incluidos en el término como se designó aquí son los siguientes anillos en donde X_1 es NR, O o S;

y R es H o un sustituyente opcional como se describe a continuación:



De manera similar, como se utiliza en la especificación y reivindicaciones, el término heteroarilo designa un sistema de anillo aromático de cinco a diez miembros que contiene 1, 2 o 3 heteroátomos, que pueden ser iguales o diferentes, seleccionados de N, O o S. Tales sistemas de anillo heteroarilo incluyen pirrolilo, azolilo, oxazolilo, tiazolilo, imidazolilo, furilo, tienilo, quinolinilo, isoquinolinilo, indolilo, benzotienilo, benzofuranilo, benzisoxazolilo o similares. El término arilo designa un sistema de anillo aromático carbocíclico tal como fenilo, naftilo, antracenilo o similar. El término aril(C₁-C₄)alquilo designa un grupo arilo como se definió anteriormente unido a un grupo alquilo C₁-C₄ que puede ser recto o ramificado. Dichos grupos aril(C₁-C₄)alquilo incluye bencilo, fenetilo, naftilmetilo, o similares. El término haloalquilo como se utiliza aquí designa un grupo C_nH_{2n+1} que tiene de uno a 2n+1 átomos de halógeno que pueden ser iguales o diferentes y el término haloalcoxi como se utiliza aquí designa un grupo OC_nH_{2n+1} que tiene de uno a 2n+1 átomos de halógeno que pueden ser iguales o diferentes. Preferiblemente el término haloalquilo designa CF₃ y el término haloalcoxi designa OCF₃.

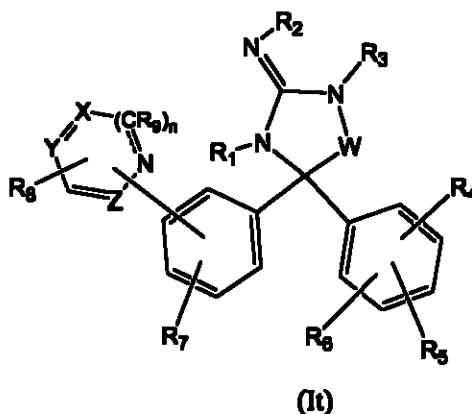
En la especificación y reivindicaciones, cuando los términos alquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₆, cicloheteroalquilo, arilo, aril(C₁-C₄)alquilo o heteroarilo son designados como siendo opcionalmente sustituidos, los grupos sustituidos que están opcionalmente presentes pueden ser uno o más de aquellos empleados de costumbre en el desarrollo de compuestos farmacéuticos o la modificación de tales compuestos para influenciar su estructura/actividad, persistencia, absorción, estabilidad u otra propiedad benéfica. Ejemplos específicos de tales sustituyentes incluyen átomos de halógeno, grupos nitro, ciano, tiocianato, cianato, hidroxilo, alquilo, haloalquilo, alcoxi, haloalcoxi, amino, alquilamino, dialquilamino, formilo, alcoxicarbonilo, carboxilo, alcanilo, alquiltio, alquilsulfinilo, alquilsulfonilo, carbamoilo, alquilamido, fenilo, fenoxi, bencilo, benciloxi, heterociclilo o cicloalquilo, preferiblemente átomos de halógeno o grupos alquilo inferior o alcoxi inferior. Típicamente, 0-3 sustituyentes pueden estar presentes. Cuando cualquiera de los sustituyentes precedente representa o contiene un grupo sustituyente alquilo, este puede ser lineal o ramificado y puede contener hasta 12, preferiblemente hasta 6, más preferiblemente hasta 4 átomos de carbono.

Las sales farmacéuticamente aceptables pueden ser cualquier sal de adición de ácido formada por un compuesto de fórmula I y un ácido farmacéuticamente aceptable tal como ácido fosfórico, sulfúrico, clorhídrico, bromhídrico, cítrico, maleico, malónico,

mandélico, succínico, fumárico, acético, láctico, nítrico, sulfónico, p-tolueno sulfónico, metanosulfónico o similares.

Los compuestos de la invención incluyen amidas, ésteres, carbamatos u otras formas de pro-droga convencionales, que en general, son derivados funcionales de los compuestos de la invención y que son fácilmente convertidas en la porción activa inventiva *in vivo*. Correspondientemente, el método de la invención abarca el tratamiento de varias condiciones descritas anteriormente con un compuesto de fórmula I o con un compuesto que no esta específicamente descrito pero el cual, luego de administración, se convierte a un compuesto de fórmula I *in vivo*. También se incluyen metabolitos de los compuestos de la presente invención definidos como especies activas producidas luego de la introducción de estos compuestos en un sistema biológico.

Los compuestos de la invención pueden existir como uno o más tautómeros. Un experto en la técnica reconocerá que los compuestos de fórmula I pueden existir como el tautómero It como se muestra adelante.

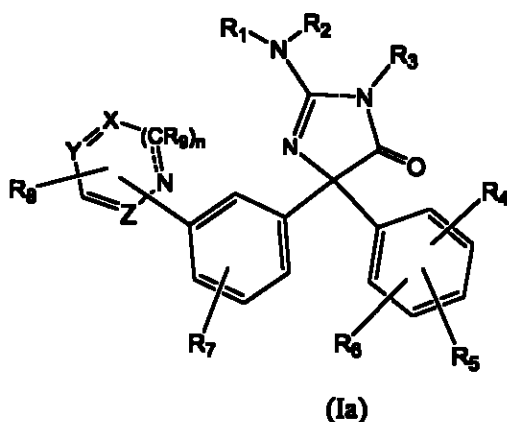


Los tautómeros a menudo existen en equilibrio uno con el otro. Como estos tautómeros se interconvierten bajo condiciones ambientales y fisiológicas, ellos suministran los mismos efectos biológicos útiles. La presente invención incluye mezclas de tales tautómeros así como también los tautómeros individuales de la Fórmula I y Fórmula It.

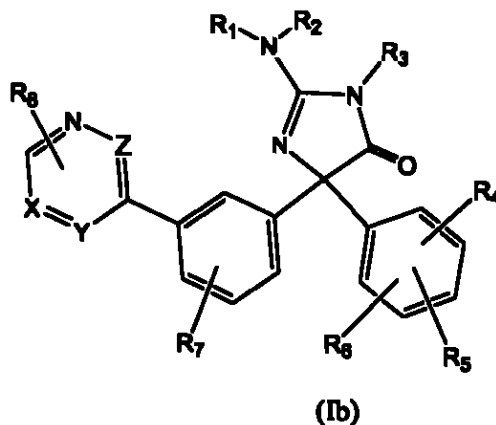
Los compuestos de la invención pueden contener uno o más átomos de carbono asimétrico o uno o más centros asimétricos (quirales) y pueden dar origen así a isómeros y diaestereómeros ópticos. Así, la invención incluye tales isómeros ópticos y diaestereómeros; así como también estéreoisómeros enantioméricamente puros racémicos y resueltos; así como también otras mezclas de los estereoisómeros R y S. Un experto en la técnica apreciará que un estereoisómero puede ser más activo o puede exhibir efectos benéficos cuando se enriquece con relación a otro u otros estereoisómeros o cuando se separan del otro u otros estereoisómeros. Adicionalmente, el experto sabe como separar, enriquecer o preparar selectivamente dichos estereoisómeros. De acuerdo con esto, la presente invención comprende compuestos de Fórmula I, los estereoisómeros de éstos, los tautómeros de éstos y las sales farmacéuticamente aceptables de éstos. Los compuestos de la invención pueden estar presentes como una mezcla de estereoisómeros, estereoisómeros individuales, o como una forma ópticamente activa o enantioméricamente pura.

Los compuestos preferidos de la invención son aquellos compuestos de fórmula I en donde W es CO. Otro grupo de compuestos preferidos de la invención son aquellos compuestos de

fórmula I en donde R_1 y R_2 son H y R_3 es alquilo C_1-C_4 . También preferidos son aquellos compuestos de fórmula I en donde n es 1. Un grupo adicional de los compuestos preferidos de la invención son aquellos compuestos de formula I en donde el anillo heteroarilo de 5 miembros o 6 miembros que contiene nitrógeno esta unido al anillo de fenilo en la posición 3 del anillo de fenilo; este grupo preferido de compuestos de fórmula I se designa en la especificación y reivindicaciones como fórmula Ia. El compuesto de fórmula Ia se muestra adelante.



Los compuestos más preferidos de la invención son aquellos compuestos de fórmula Ia en donde el anillo de heteroarilo que contiene nitrógeno es un anillo de 6 miembros y esta unido al anillo de fenilo en la posición 3 de dicho anillo heteroarilo; este grupo más preferido de compuestos de fórmula I se designa en la especificación y reivindicaciones como fórmula Ib. La fórmula Ib se muestra adelante.



Otro grupo de compuestos más preferidos de la invención son aquellos compuestos de fórmula Ib en donde R_3 es metilo. Un grupo adicional de compuestos más preferidos de la invención son aquellos compuestos de fórmula Ib en donde Y es CR_{11} ; R_1 y R_2 son H; y R_3 es metilo.

Ejemplos de compuestos preferidos de fórmula I incluyen:

2-amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

(5S)-2-amino-5-[3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

(5S)-2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

(5R)-2-amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona;

4-[2-amino-4-(4-metoxi-3-metilfenil)-1-metil-5-oxo-4,5-dihidro-1H-imidazol-4-il]-2-piridin-3-ilbenzonitrilo;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(4-metil-3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-[4-metoxi-3-(trifluorometil)fenil]-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-etil-5-(4-metoxi-3-metilfenil)-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirazin-2-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-pirimidin-2-ilfenil)-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-hidroxi-3-metilfenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-[4-metoxi-3-(trifluorometil)fenil]-3-metil-5-(3-pirazin-2-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

(5R)-2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3,4-dietoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3,4-dimetoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-ciclopentil-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-propoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-butoxi-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-isopropoxi-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(1,3-benzodioxol-5-il)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(2,3-dihidro-1-benzofurano-5-il)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-[3-(ciclopentiloxi)-4-metoxifenil]-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

5-[2-amino-1-metil-5-oxo-4-(3-piridin-3-ilfenil)-4,5-dihidro-1H-imidazol-4-il]-2-metoxibezonitrilo;

2-amino-5-(3-fluoro-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(2,3-dihidro-1,4-benzodioxin-6-il)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-cloro-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-piridin-3-ilfenil)-5-(3,4,5-trimetoxifenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-piridin-4-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-etoxi-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-piridin-3-ilfenil)-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-piridin-3-ilfenil)-5-[4-(trifluorometoxi-3-trifluorometil)fenil]-3,5-dihidro-4H-imidazol-4-ona;

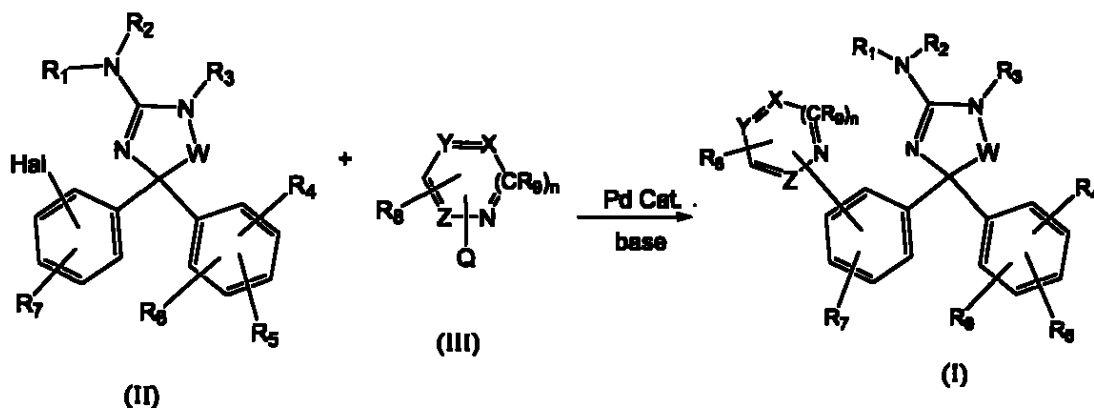
2-amino-5-(3,4-dietoxifenil)-5-(4-fluoro-3-piridin-3-ilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-cloro-4-trifluorometoxifenil)-5-(4-fluoro-3-piridin-3-ilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

Un tautómero de éstos; un estéreo isómero de éstos; una sal farmacéuticamente aceptable de éstos.

Ventajosamente, la presente invención suministra un proceso para la preparación de un compuesto de fórmula I que comprende hacer reaccionar un compuesto de fórmula II en donde Hal es Cl o Br con un compuesto de fórmula III en donde Q es $B(OH)_2$, $Sn(Bu)_3$ o $Sn(CH_3)_3$ en la presencia de catalizador de paladio y una base inorgánica opcionalmente en la presencia de un solvente. El proceso se muestra en el diagrama de flujo I, en donde Hal y Q son como se definió anteriormente.

Diagrama de Flujo I

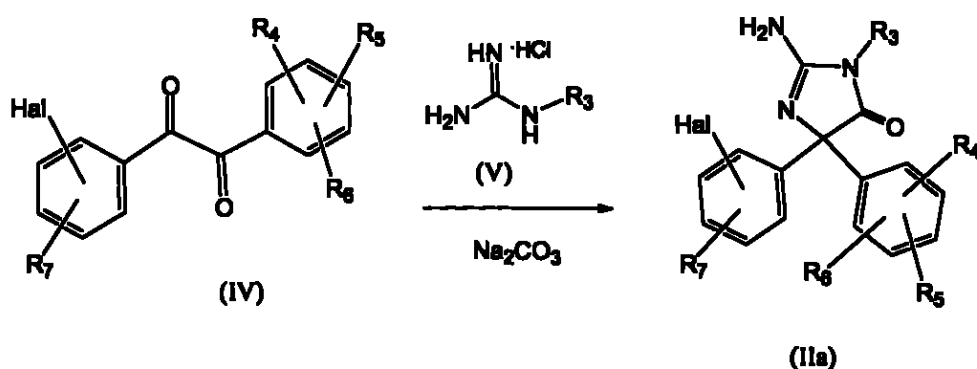


Los catalizadores de paladio adecuados para uso en el proceso de la invención incluye catalizadores Pd(0) o Pd(II) tal como diclorobis(tri-o-tolilfosfina) paladio(II), Pd(OCOCH₃)₂/tri-o-tolilfosfina, tetrakis(trifenilfosfina)paladio(0), tris(dibencilidenoacetona)dipaladio(0)trifenilfosfina, o similares.

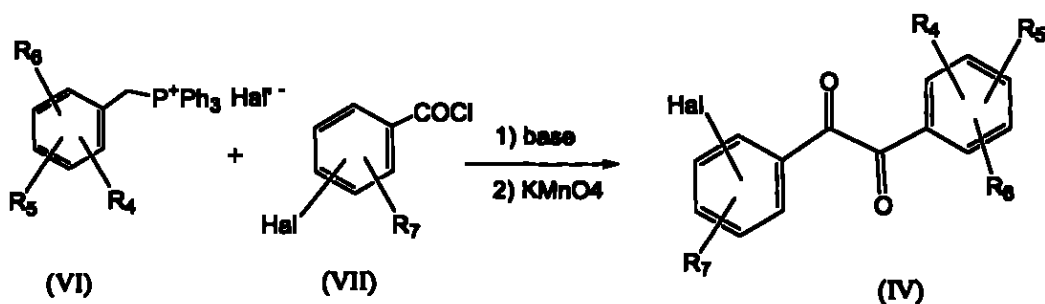
Las bases inorgánicas adecuadas para uso en el proceso de la invención incluyen hidróxidos Na o K, carbonatos o bicarbonatos, preferiblemente Na₂CO₃ o K₂CO₃.

Los solventes adecuados para uso en el proceso de la invención incluye solventes orgánicos polares o no polares tales como tolueno, dietoxi etiléter, dioxano, etilenglicol dimetiléter o cualquier solvente orgánico no reactivo que es capaz de solubilizar los compuestos de fórmula II o fórmula III.

Los compuestos de fórmula II se pueden preparar utilizando métodos sintéticos convencionales y, si se requiere, técnicas de separación o aislamiento estándar. Por ejemplo, los compuestos de fórmula II en donde W es CO y R₁ y R₂ son H(IIa), se pueden preparar al hacer reaccionar una dicetona de fórmula IV con guanidina sustituida de fórmula V en la presencia de una base tal como Na₂CO₃ para dar el compuesto deseado de fórmula IIa. La reacción se muestra en el diagrama de flujo II en donde Hal es Cl o Br.

Diagrama de Flujo II

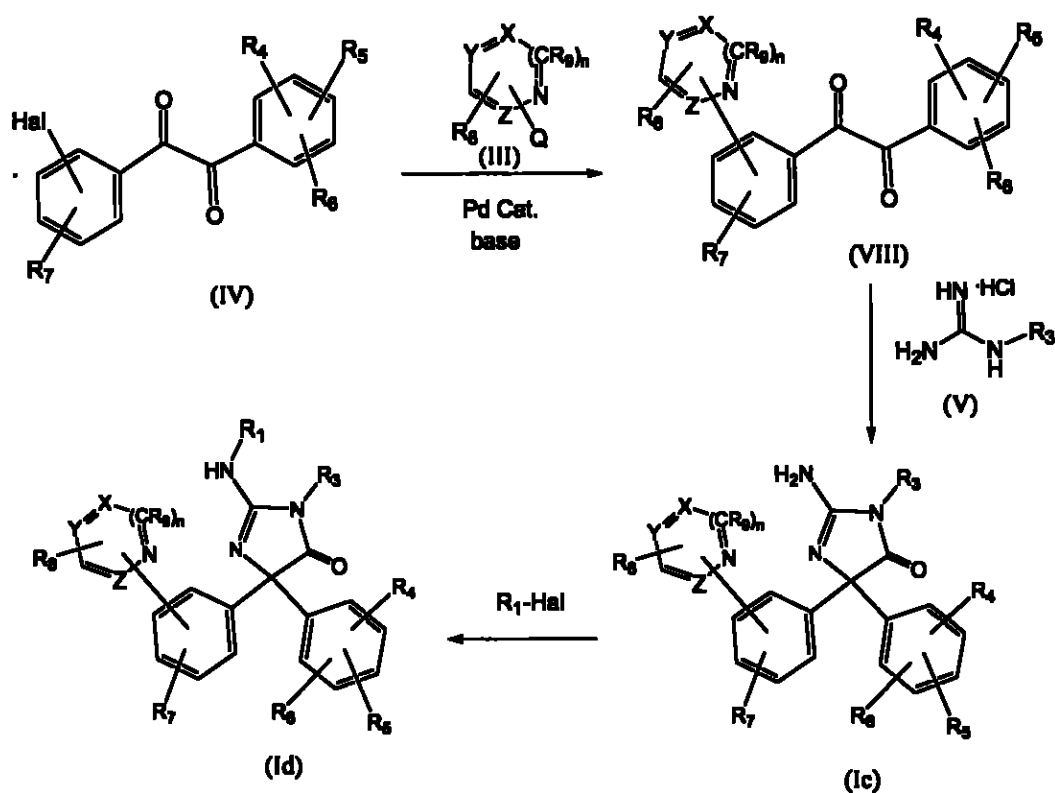
Los compuestos de fórmula IV se pueden preparar al hacer reaccionar una sal de trifenilfosfonio de fórmula VI con un benzoil cloruro de fórmula VII en la presencia de una base tal como Na_2CO_3 para formar la trifenilfosfinailuro correspondiente y oxidar dicho iluro con KMnO_4 en la presencia de MgSO_4 para dar la dicetona deseada de fórmula IV. La reacción se muestra en el diagrama de flujo III en donde Hal y Hal' son cada uno independientemente Cl o Br y Ph representa un grupo fenilo

Diagrama de Flujo III

Alternativamente, los compuestos de fórmula I en donde W es CO y R_1 y R_2 son H (Ic) se pueden preparar al hacer reaccionar una dicetona de fórmula IV con un compuesto de fórmula III en la presencia de un catalizador de paladio y una base inorgánica para

dar la dicetona de fórmula VIII y hacer reaccionar dicha dicetona de fórmula VIII con una guanidina sustituida de fórmula V (como se muestra en el diagrama de flujo II anterior) para dar el compuesto deseado de fórmula Ic. Los compuestos de fórmula I en donde R_1 es diferente de H (Id) se pueden preparar utilizando técnicas de alquilación estándar tal como hacer reaccionar el compuesto de fórmula Ic con un haluro de alquilo, R_1 -Hal, para dar el compuesto de fórmula I en donde R_1 es diferente de H y R_2 es H (Id). La reacción se muestra en el diagrama de flujo IV en donde Q es $B(OH)_2$, $Sn(Bu)_3$ o $Sn(CH_3)_3$ y Hal es Cl o Br.

Diagrama de Flujo IV



Los compuestos de fórmula I en donde W es CO y R_1 y R_2 son diferentes de H se pueden preparar al hacer reaccionar dicho compuesto de fórmula Id con un segundo haluro de alquilo, R_2 -Hal,

para dar el compuesto deseado de fórmula I en donde R_1 y R_2 son diferentes de H.

Ventajosamente, los compuestos de la invención son útiles para el tratamiento, prevención o mejoramiento de una enfermedad o trastorno caracterizado por los depósitos β -amiloide o niveles β -amiloide elevados en un paciente, que incluye enfermedad de Alzheimer, Síndrome de Down, Hemorragia Cerebral Hereditaria con Amiloidosis del tipo Holandés u otros trastornos neurodegenerativos o que inducen demencia. De acuerdo con esto, la presente invención suministra un método para el tratamiento, prevención o mejoramiento de una enfermedad o trastorno caracterizado por los depósitos β -amiloide o niveles β -amiloide elevados en un paciente, que comprende suministrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de fórmula I como se describió anteriormente. El compuesto se puede suministrar mediante administración oral o parenteral o de cualquier manera común conocida por ser una administración efectiva de un agente terapéutico a un paciente necesitado de ello.

El término "suministrar" como se utiliza aquí con respecto a suministrar un compuesto o sustancia abarcada por la invención, designa directamente administrar tal compuesto o sustancia, o administrar una pro-droga, derivado o análogo que forma una cantidad equivalente del compuesto o sustancia dentro del cuerpo.

Como se describe aquí, una cantidad terapéutica o profilácticamente útil de un compuesto de la invención es aquella

cantidad de un compuesto que alivia los síntomas de la enfermedad, por ejemplo, AD, o que previene la arremetida de los síntomas, o la arremetida de síntomas más severos. Las cantidades útiles de un compuesto pueden variar dependiendo de la formulación y la ruta de suministro. Por ejemplo, cantidades mayores se pueden suministrar oralmente que cuando el compuesto se formula para inyección o inhalación, con el fin de suministrar una cantidad biológicamente equivalente de la droga. Adecuadamente, una dosis individual (es decir, por unidad) de un compuesto de la invención esta en el rango desde aproximadamente 1 $\mu\text{g/kg}$ a aproximadamente 10g/kg. Deseablemente, estas cantidades se suministran sobre una base diaria. Sin embargo, la dosis a ser utilizada en el tratamiento o prevención de un déficit cognitivo específico u otra condición puede ser determinada subjetivamente por el médico que la atiende. Las variables involucradas incluyen el déficit cognitivo específico y el tamaño, edad y patrón de respuesta del paciente. Por ejemplo, con base en el perfil de actividad y la potencia de los compuestos de esta invención, una dosis de partida de aproximadamente 375 a 500 mg por día con incremento gradual en la dosis diaria a aproximadamente 1000 mg por día puede suministrar el nivel de dosis deseado en el humano.

En la práctica actual, los compuestos de la invención se suministran al administrar el compuesto o un precursor de éste en una forma sólida o líquida, puro o en combinación con uno o más vehículos convencionales farmacéuticos o excipientes. De acuerdo con esto, la presente invención suministra una composición farmacéutica que comprende un vehículo farmacéuticamente

aceptable y una cantidad efectiva de un compuesto de fórmula I como se describió anteriormente.

Los vehículos sólidos adecuados para uso en la composición de la invención incluyen una o más sustancias que también pueden actuar como agentes saborizantes, lubricantes solubilizadores, agentes de suspensión, llenadores, deslizantes, ayudas de compresión, ligadores, agentes desintegrantes de tableta o materiales encapsulantes. En los polvos, el vehículo puede ser un sólido finamente dividido el cual esta en mezcla con un compuesto de fórmula I finamente dividido. En las tabletas, el compuesto de fórmula I se puede mezclar con un vehículo que tiene las propiedades de compresión necesarias en proporciones adecuadas y compactado en la forma y tamaño deseado. Dichos polvos y tabletas pueden contener hasta 99% en peso del compuesto de fórmula I. Los vehículos sólidos adecuados para uso en la composición de la invención incluyen fosfato de calcio, estearato de magnesio, talco, azúcares, lactosa, dextrina, almidón, gelatina, celulosa, metilcelulosa, carboximetilcelulosa de sodio, polivinilpirrolidina, ceras de fusión baja y resinas intercambiadoras de iones.

Cualquier vehículo líquido farmacéuticamente aceptable adecuado para preparar soluciones, suspensiones, emulsiones, melazas y elixires se puede emplear en la composición de la invención. Los compuestos de fórmula I se pueden disolver o suspender en un vehículo líquido farmacéuticamente aceptable tal como agua, un solvente orgánico, o un aceite o grasa farmacéuticamente aceptable, o una mezcla de éstos. Dicha

composición líquida puede contener otros aditivos farmacéuticamente adecuados tales como solubilizadores, emulsificadores, amortiguadores, preservativos, endulzantes, agentes saborizantes, agentes de suspensión, agentes espesantes, agentes colorantes, reguladores de la viscosidad, estabilizadores, osmo-reguladores, o similares. Ejemplos de vehículos líquidos adecuados para administración oral y parenteral incluyen agua (que contiene particularmente aditivos como anteriormente, por ejemplo, derivados de celulosa, preferiblemente solución de carboximetilcelulosa de sodio), alcoholes (que incluye alcoholes monohídricos y alcoholes polihídricos, por ejemplo, glicoles) o sus derivados, o aceites (por ejemplo, aceite de coco fraccionado y aceite de araquís). Para la administración parenteral el vehículo también puede ser un éster aceitoso tal como etil oleato o isopropil miristato.

Las composiciones de la invención que son soluciones o suspensiones estériles son adecuadas para inyección intramuscular, intraperitoneal o subcutánea. Las soluciones estériles también se pueden administrar intravenosamente. Las composiciones de la invención adecuadas para administración oral pueden estar en cualquier forma de composición líquida o sólida.

Alternativamente, el uso de dispositivos de suministro sostenido puede ser deseable, con el fin de evitar la necesidad para el paciente de tomar medicamentos de manera diaria. "Suministro sostenido" se define como retrasar la liberación de un agente activo, es decir, un compuesto de la invención, hasta después de la ubicación en el ambiente de suministro, seguido por

una liberación sostenida del agente en un tiempo posterior. Aquellos expertos en la técnica conocen dispositivos de suministro sostenido adecuados. Ejemplos de dispositivos de suministro sostenido adecuados, por ejemplo, hidrogeles (ver, por ejemplo, Patentes US No. 5,266,325; 4,959,217; y 5,292,515), una bomba osmótica, tal como la descrita por Alza (Patentes US No. 4,295,987 y 5,273,752) o Merck (Patente Europea No. 314,206), entre otras; materiales de membrana hidrófoba, tales como etilenometacrilato (EMA) y etilenovinilacetato (EVA); sistemas de polímero bioreabsorbibles (ver, por ejemplo, Solicitud de Patente Internacional No. WO 98/44964, Bioxid y Cellomeda; Patentes US No. 5,756,127 y 5,854,388); otros dispositivos de implante bioreabsorbibles se han descrito por ser compuestos de, por ejemplo, poliésteres, polianhídridos, o copolímeros de ácido láctico/ácido glicólico (ver, por ejemplo, Patente US No. 5,817,343 (Alkermes Inc)). Para uso en tales dispositivos de suministro sostenido, los compuestos de la invención se pueden formular como se describe aquí.

En otro aspecto, la invención suministra un kit farmacéutico para suministro de un producto. Adecuadamente, el kit contiene empaque o un recipiente con el compuesto formulado para la ruta de suministro deseada. Por ejemplo, si el kit se designa para administración mediante inhalación, éste puede contener una suspensión que contiene un compuesto de la invención formulado para suministro por aerosol o rociado de una dosis predeterminada por inhalación. Adecuadamente, el kit contiene instrucciones sobre la dosificación y un inserto con relación al agente activo. Opcionalmente, el kit puede además contener instrucciones para

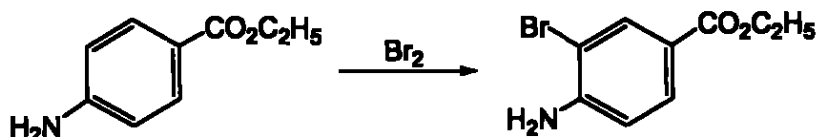
monitorear los niveles circulantes de producto y los materiales para desarrollar tales ensayos que incluyen, por ejemplo, reactivos, placas de pozo, recipientes, marcadores o etiquetas, y similares. Tales kits son fácilmente empacados de una manera adecuada para el tratamiento de una indicación deseada. Por ejemplo, el kit puede contener también instrucciones para uso en la bomba de rociado u otro dispositivo de suministro.

Otros componentes adecuados tales como los kits serán fácilmente evidentes para un experto en la técnica, tomando en consideración la indicación deseada y la ruta de suministro. Las dosis pueden ser repetidas diariamente, semanalmente o mensualmente, durante un periodo predeterminado de tiempo o según se prescriba.

Para un más claro entendimiento, y con el fin de ilustrar la invención más claramente, ejemplos específicos de éstas se establecen a continuación. Los siguientes ejemplos son simplemente ilustrativos y no deben ser entendidos como limitantes del alcance y principios subyacentes de la invención de ninguna manera. De hecho, varias modificaciones de la invención, además de aquellas mostradas y descritas aquí, serán evidentes para aquellos expertos en la técnica de los ejemplos establecidos a continuación para la descripción anterior. Tales modificaciones también pretenden caer dentro del alcance de las reivindicaciones finales.

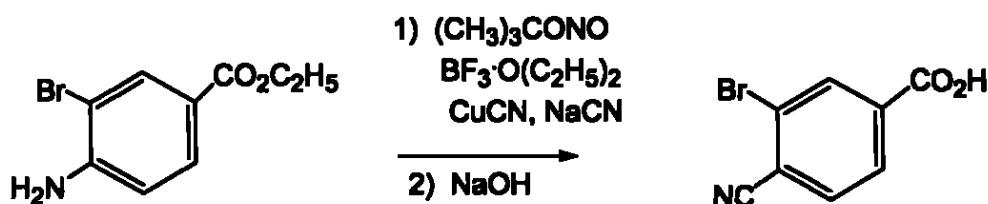
A menos que se anote otra cosa, todas las partes son partes en peso. Los términos HRMN y HPLC designan resonancia magnética

nuclear de protón y cromatografía líquida de alto desempeño, respectivamente. Los términos EtOAc y THF designan acetato de etilo y tetrahidrofurano, respectivamente. En las estructuras, el término Ph designa un grupo fenilo.

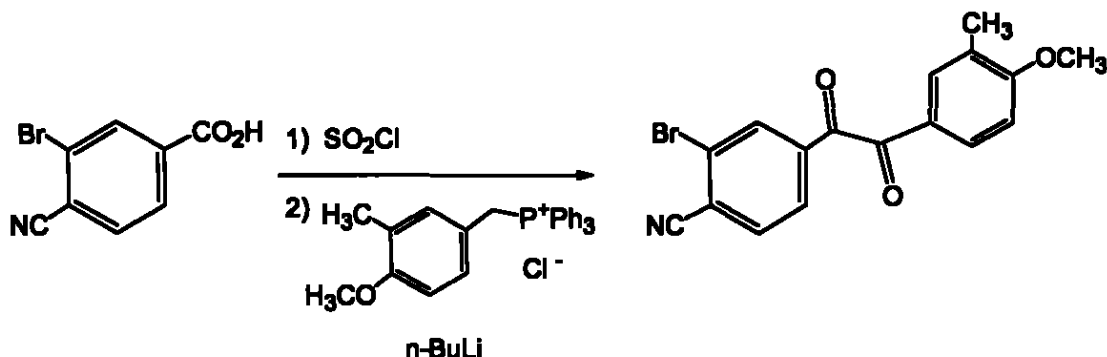
EJEMPLO 1Preparación de Etil 4-amino-3-bromobenzoato

Se agrega gota a gota a una solución de bromuro (7.0 mL, 137.3 mmol) en diclorometano a una solución fría (-10°C) de etil 4-aminobenzoato (22.0 g, 133.3 mmol) en diclorometano. La mezcla de reacción se le permite llegar a temperatura ambiente, agitada durante 18 horas y diluida con agua. La fase orgánica se separa, se lava dos veces con agua salina, se seca sobre MgSO₄ y se concentra in vacuo. El residuo resultante se purifica mediante cromatografía flash (SiO₂, 8/1 hexano/EtOAc como eluyente) para lograr el compuesto del título como un sólido blanco, 28.6 g (88% rendimiento), identificado por HRMN y análisis espectral de masa. MS m/e 242 (M-H)⁺; ¹H RMN (400 MHz, DMSO-d₆) δ 1.28 (t, J=7.01 Hz, 3 H), 4.22 (q, J=7.16 Hz, 2 H), 6.18 (brs, 2 H), 6.81 (d, J=7.91 Hz, 1H), 7.65 (dd, J=8.54, 1.98 Hz 1 H), 7.89 (d, J=1.83 Hz, 1H).

EJEMPLO 2Preparación de Ácido 3- Bromo-4-cianobenzoico



Una solución de etil 4-amino-3-bromobenzoato (23.5 g, 96.3 mmol) en cloruro de metileno a -10°C se trata gota a gota con terc-butyl nitrito (14.0 mL, 118.4 mmol), seguido mediante trifluoruro dietil eterato de boro (18.4 mL, 164.5 mmol). La mezcla de reacción se le permite llegar a temperatura ambiente, agitada durante 4 h, diluida con etiléter y filtrada. La torta de filtro se seca, se dispersa en tolueno, se enfría a 0°C , se trata con una solución de cianuro de cobre (I) (11.5 g, 129.2 mmol) y cianuro de sodio (15.8 g, 323.1 mmol) en agua, agitada a 0°C durante 30 min., calentada a 60°C , agitada durante 1h, enfriada a temperatura ambiente y diluida con EtOAc y agua. La fase orgánica se separa, se seca sobre MgSO_4 y se concentra in vacuo. El residuo resultante se cristaliza de etiléter/hexanos para dar el etil éster del compuesto del título como un sólido blanco apagado, 18.6 g (76% de rendimiento). Una solución de este éster (8.5 g, 33.6 mmol) en THF se trata con una solución de NaOH (30 mL, 2.5 N) y etanol, agitado durante 20 h, acidificado con HCl 2N y extraído con etiléter. Los extractos de éter se combinan, se secan sobre MgSO_4 y se concentran in vacuo. El residuo resultante se cristaliza de etiléter/hexanos para lograr el compuesto del título como una sólido beige, 6.81 g (90% de rendimiento), identificado mediante HRMN y análisis espectral de masa. MS m/e 223 $(\text{M}-\text{H})^+$; ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ 8.05 (dd, $J=9.76, 1.37$ Hz 1 H), 8.09 (d, $J=8.08$ Hz, 1H), 8.29 (d, $J=1.37$ Hz, 1H).

EJEMPLO 3Preparación de 2-Bromo-4-[(4-metoxi-3-metilfenil) (oxo)acetil]benzonitrilo

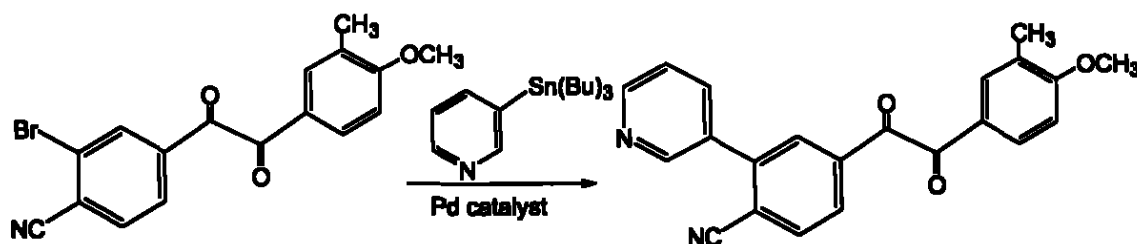
Una suspensión de ácido 3-bromo-4-cianobenzoico (1.65 g, 7.28 mmol) en cloruro de tionilo (10 mL) se trata con 3 gotas de N,N-dimetilformamida, calentada a temperatura de reflujo durante 1 h y concentrada *in vacuo*. Este residuo de cloruro ácido se re-evapora 3X con tolueno para remover cualquier cloruro de tionilo restante. Una mezcla de 3-metil-4-metoxibencil trifenilfosfonio (6.3 g, 14.55 mmol) en tolueno a 0°C se trata gota a gota con n-butililitio (6.1 mL, 2.5 M en hexanos), se le permitió llegar a temperatura ambiente, agitado durante 2 h, enfriado a 0°C, tratado gota a gota con una solución del cloruro ácido anterior obtenido en tolueno, se le permitió llegar a temperatura ambiente, agitado durante 2h, apagado con agua y concentrado *in vacuo*. El residuo resultante se dispersó en acetona y agua, se trato con MgSO_4 (7.5 g, 62.5 mmol) y KMnO_4 (2.18 g, 13.8 mmol), se agitó vigorosamente a 45°C durante 18 h y se filtró. El filtrado se diluyó con EtOAc, se lavó secuencialmente con agua y solución salina, se secó sobre MgSO_4 y se evaporó hasta secado.

Este residuo se purificó mediante cromatografía flash (SiO_2 , 2/1 hexanos/EtOAc como eluyente) para lograr el compuesto del título como un sólido amarillo, 1.8 g (69% de rendimiento), identificado mediante HRMN y análisis espectral de masa.

MS m/e 357 ($\text{M}+\text{H}$)⁺; ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ 2.21 (s, 3H), 3.93 (s, 3H), 7.15 (d, $J=8.54$ Hz, 1H), 7.81 (d, $J=1.38$ Hz 1H), 7.85 (dd, $J=8.54$, 2.14 Hz, 1H), 8.03 (dd, $J=8.08$, 1.52 Hz 1 H), 8.18 (d, $J=8.08$ Hz, 1H), 8.30 (d, $J=1.38$ Hz, 1H).

EJEMPLO 4

Preparación de 4-[(4-Metoxi-3-metilfenil)(oxo)acetil]-2-piridin-3-ilbenzonitrilo

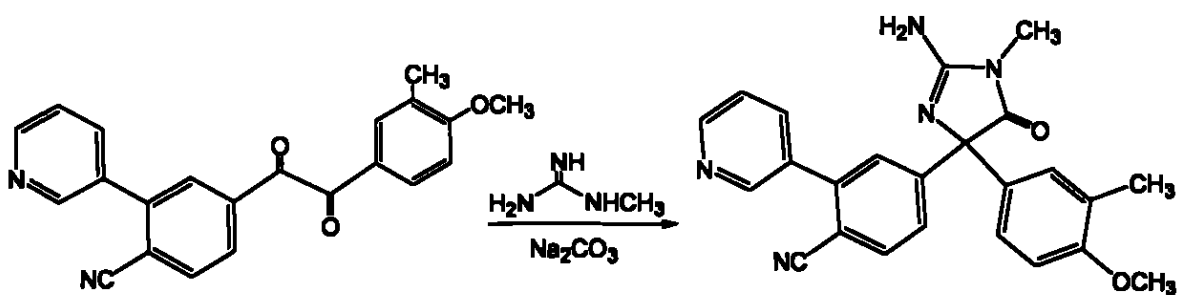


Una mezcla de 2-bromo-4-[(4-metoxi-3-metilfenil)(oxo)acetil]benzonitrilo (200mg, 0.56 mmol) y 3-(tributylestanil)piridina (268 mg, 0.73 mmol) en 1,2-dietoxietano se trata con diclorobis (tri-o-tolilfosfina)paladio(II) (39.6 mg, 0.05 mmol), calentado a 145°C, agitado durante 30 min., y filtrado para remover el catalizador. El filtrado se evapora hasta seco. El residuo resultante se purifica mediante cromatografía flash (SiO_2 , 2/1 hexanos/EtOAc como eluyente) y la cristalización de etiléter/hexanos para lograr el compuesto del título como un sólido amarillo, 181 mg (91% de rendimiento),

identificado mediante HRMN y análisis espectral de masa. MS m/e 357 (M+H)⁺; ¹H RMN (400 MHz, DMSO-d₆) δ 2.21 (s, 3H), 3.93 (s, 3H), 7.18 (d, J=8.69 Hz, 1H), 7.61 (m, 1H), 7.82 (d, J=8.54 1H), 7.84 (dd, J=8.54, 1.99 Hz, 1H), 8.07 (dd, J=7.76, 1.67 Hz, 1H), 8.12 (m, J=1.38 Hz, 2H), 8.25 (d, J=8.08 Hz, 1H), 8.74 (m, 1H), 8.85 (d, 1.68 Hz, 1H).

EJEMPLO 5

Preparación de 4-[2-amino-4-(4-metoxi-3-metilfenil)-1-metil-5-oxo-4,5-dihidro-1H-imidazol-4-il]-2-piridin-3-il benzonitrilo

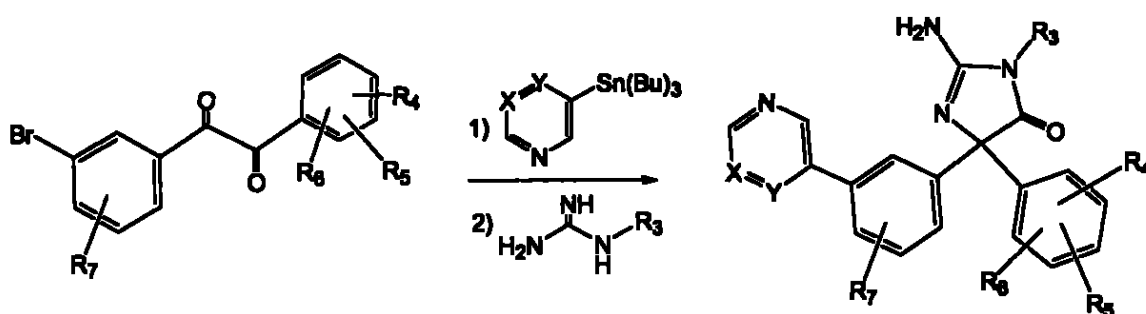


Una mezcla de 4-[(4-metoxi-3-metilfenil)(oxo)acetil]-2-piridin-3-ilbenzonitrilo (160 mg, 0.45 mmol) y clorhidrato de 1-metilguanidina (222 mg, 2.02 mmol) en dioxano y alcohol etílico se trata con NaCO₃ (214 mg, 2.02 mmol) en agua, se agitó a 85°C durante 3h y se concentra in vacuo. El residuo resultante se particiona entre cloroformo y agua. Las fases se separan y la fase orgánica se seca sobre MgSO₄ y se concentra in vacuo. Este residuo se purifica mediante cromatografía flash (SiO₂, 15/1 EtOAc/metanol como eluyente) y la cristalización de CHCl₃/hexanos para dar el compuesto del título como un sólido blanco, 138 mg (75% de rendimiento), identificado mediante HRMN y análisis

espectral de masa. MS m/e 412 (M+H)⁺; ¹H RMN (400 MHz, DMSO-d₆) δ 2.09 (s, 3H), 2.98 (s, 3H), 3.74 (s, 3H), 6.74 (brs, 2H), 6.86 (d, J=8.69 Hz, 1H), 7.22 (s, 1H), 7.26 (d, J=8.54 Hz, 1H), 7.58 (m, 1H), 7.69 (s, 1H), 7.70 (s, 1H), 7.9-8.0 (m, 2H), 8.7 (m, 2H).

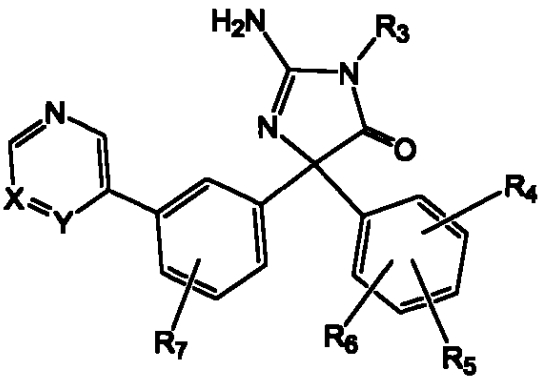
EJEMPLOS 6-33

Preparación de Derivados de Amino -5,5-difenilimidazolona



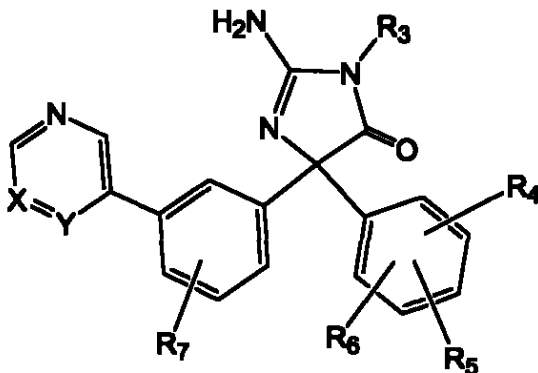
Utilizando esencialmente los mismos procedimientos descritos en los Ejemplos 4 y 5 anteriores y empleando el sustrato de diona apropiado, el intermedio de tributilestanil-piridina o pirimidina y el reactivo de guanidina deseado, los compuestos mostrados en la Tabla I se obtiene e identifican mediante HRMN y análisis espectral de masa.

Tabla I



Ej. No	R ₃	R ₄	R ₅	R ₆	R ₇	X	Y	pt °C
6	CH ₃	3-CH ₃	4-OCH ₃	H	4-CH ₃	CH	CH	—
7	CH ₃	3-CF ₃	4-OCH ₃	H	H	CH	CH	—
8	C ₂ H ₅	3-CH ₃	4-OCH ₃	H	H	CH	CH	—
9	CH ₃	3-CH ₃	4-OCH ₃	H	H	CH	N	—
10	CH ₃	3-CH ₃	4-OH	H	H	CH	CH	—
11	CH ₃	3-CF ₃	4-OCH ₃	H	H	CH	N	—
12	CH ₃	3-CH ₃	4-OCH ₃	H	H	N	CH	126

Tabla I Continuación

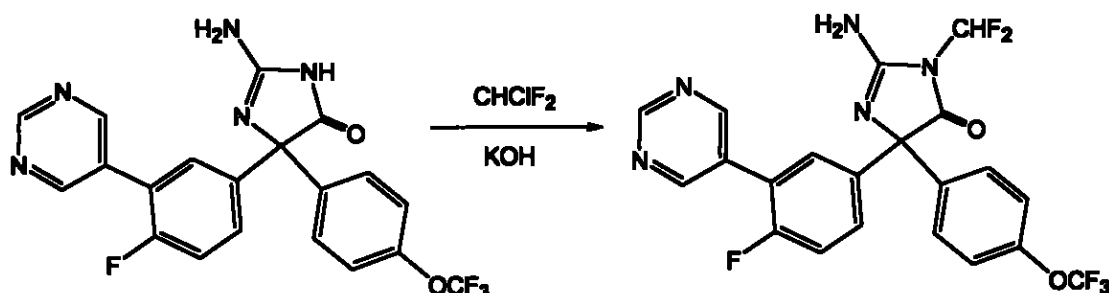


Ej. No	R ₃	R ₄	R ₆	R ₉	R ₇	X	Y	pf °C
13	CH ₃	3-CH ₃	4-OCH ₃	H	H	CH	CH	117-120
14	CH ₃	3-OCH ₃	4-OCH ₃	H	H	CH	CH	108-111
15	CH ₃	3-ciclopentil	4-OCH ₃	H	H	CH	CH	105-110
16	CH ₃	3-OC ₃ H ₇	4-OCH ₃	H	H	CH	CH	103-106
17	CH ₃	3-OC ₄ H ₉	4-OCH ₃	H	H	CH	CH	97-100
18	CH ₃	3-OCH(CH ₃) ₂	4-OCH ₃	H	H	CH	CH	108-109
19	CH ₃	3-Ociclopentil	4-OCH ₃	H	H	CH	CH	117-120
20	CH ₃	3-CN	4-OCH ₃	H	H	CH	CH	140-143
21	CH ₃	3-F	4-OCH ₃	H	H	CH	CH	111-114
22	CH ₃	3-Cl	4-OCH ₃	H	H	CH	CH	112-116
23	CH ₃	3-OCH ₃	4-OCH ₃	5-OCH ₃	H	CH	CH	104-107

24	CH ₃	3-OC ₂ H ₅	4-OCH ₃	H	H	CH	CH	125
25	CH ₃	3-OCF ₃	H	H	H	CH	CH	198
26	CH ₃	3-CF ₃	4-OCF ₃	H	H	CH	CH	98
27	CH ₃	3-OC ₂ H ₅	4-OC ₂ H ₅	H	4-F	CH	CH	99-100
28	CH ₃	3-Cl	4-OCF ₃	H	4-F	CH	CH	99-102
29	CH ₃	3-OC ₂ H ₅	3-OC ₂ H ₅	H	H	CH	CH	95-99
30	CH ₃	3-O-CH ₂ -O-4		H	H	CH	CH	104-106
31	CH ₃	3-CH ₂ -CH ₂ -O-4		H	H	CH	CH	122-128
32	CH ₃	3-O-CH ₂ -CH ₂ -O-4-		H	H	CH	CH	157-160
33	H	H	4-OCF ₃	H	4-F	N	CH	—

EJEMPLO 34

Preparación de 2-Amino-3-difluorometil-5-[4-fluoro-3-pirimidin-5-il) fenil]-5-[4-trifluorometoxi) fenil]-3,5-dihidro-4H-imidazol-4-ona

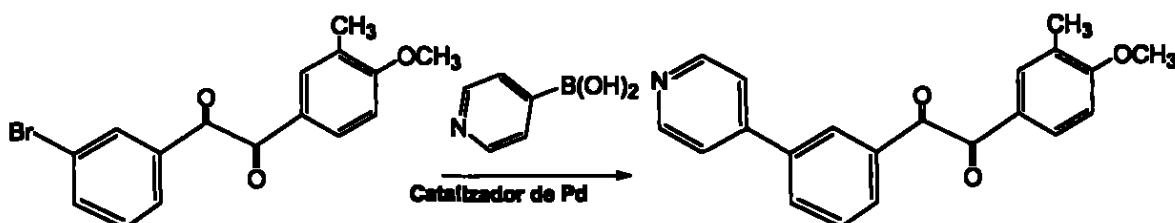


Una solución de 2-amino-5-[4-fluoro-3-(pirimidin-5-il) fenil]-5-[4-(trifluorometoxi) fenil]-3,5-dihidro-4H-imidazol-4-ona (0.398 g, 0.92 mmol) en dimetilformamida se trata con KOH (0.057 g, 1.01 mmol), se enfrió a -45°C, y se burbujea con clorodifluorometano (1.40 g, 17.6 mmol). El recipiente de reacción se sella y se calienta a 70°C durante 18h. La reacción se enfría a temperatura ambiente, se apaga mediante adición cuidadosa de agua, se extrae con acetato de etilo, se diluye con solución salina y se extrae de nuevo con acetato de etilo. Los extractos combinados se lavan con solución salina, se secan sobre

sulfato de sodio y se concentran. El residuo resultante se purifica dos veces mediante cromatografía flash (sílice, 95:5:0.5 a 90:10:0.5 cloruro de metileno/metanol/hidróxido de amonio concentrado y 100:0 a 98:2 cloruro de metileno/metanol como eluyentes) para lograr el compuesto del título como un sólido blanco, 0.064 g (14% de rendimiento), pf 82-94°C, identificado mediante HRMN, infrarrojo y análisis espectral de masa. ^1H RMN (500 MHz, CDCl_3) δ 9.21 (s, 1H), 8.89 (s, 2H), 7.64-7.60 (m, 2H), 7.54 (d, $J=8.8$ Hz, 2H), 7.23-7.18 (m, 3H), 6.95 (t, $J=58$ Hz, 1H), 4.92 (br s, 2H); IR (ATR) 3497, 3309, 3149, 1761, 1678, 1497, 1449, 1416, 1252, 1212, 1162 cm^{-1} ; ESI MS m/z 482 $[\text{C}_{21}\text{H}_{13}\text{F}_6\text{N}_5\text{O}_2+\text{H}]^+$;

EJEMPLO 35

Preparación de 1-(4-Metoxi-3-metilfenil)-2-(3-piridin-4-ilfenil)etano-1,2-diona

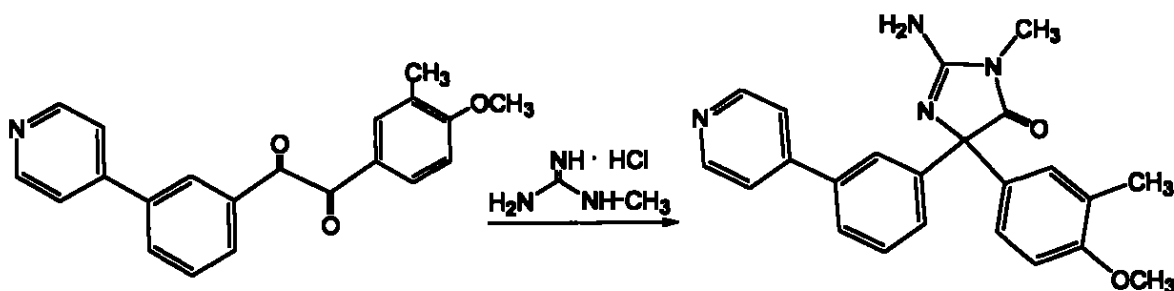


Una solución de 1-(3-bromo-fenil)-2-(4-metoxi-3-metilfenil)etano-1,2-diona (0.25 g, 0.75 mmol) en dioxano se trata secuencialmente con tri-*o*-tolilfosfina (57 mg, 0.187 mmol), acetato de paladio (II) (21 mg, 0.093 mmol), ácido piridino-4-borónico (139 mg, 1.125 mmol) y H_2O , agitado a 100°C durante 4h, enfriado a temperatura ambiente y filtrado. El filtrado se evapora in vacuo. El residuo resultante se purificó mediante

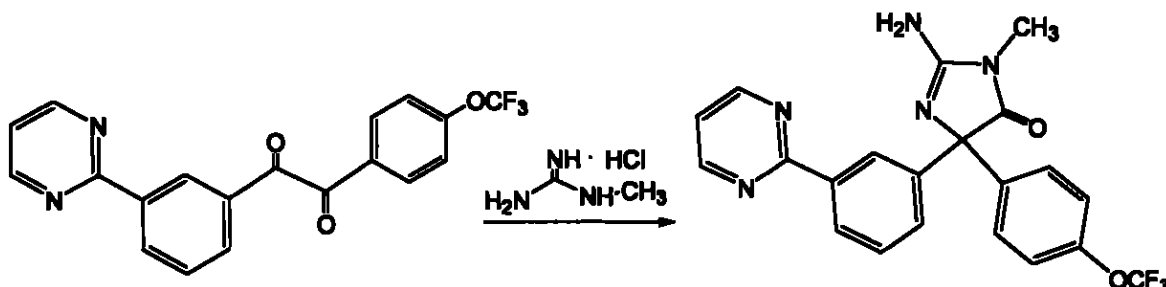
cromatografía flash sobre gel de sílice (hexanos/EtOAc 3/7 como eluyente), para lograr el compuesto del título como un sólido amarillo, 0.145 g (58% de rendimiento), identificado mediante HRMN y análisis espectral de masa. MS m/e (M+H)⁺ 332; ¹H RMN (400 MHz, CDCl₃) δ 2.28 (s, 3H) 3.95 (s, 3H) 6.94 (d, 1H) 7.68 (m, 3H) 7.84 (m, 2H) 7.88 (m, 1H) 8.08 (m, 1H) 8.30 (m, 1H) 8.75 (m, 2H).

EJEMPLO 36

Preparación de 2-Amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-piridin-4-ilfenil)-3,5-dihidro-4H-imidazol-4-ona

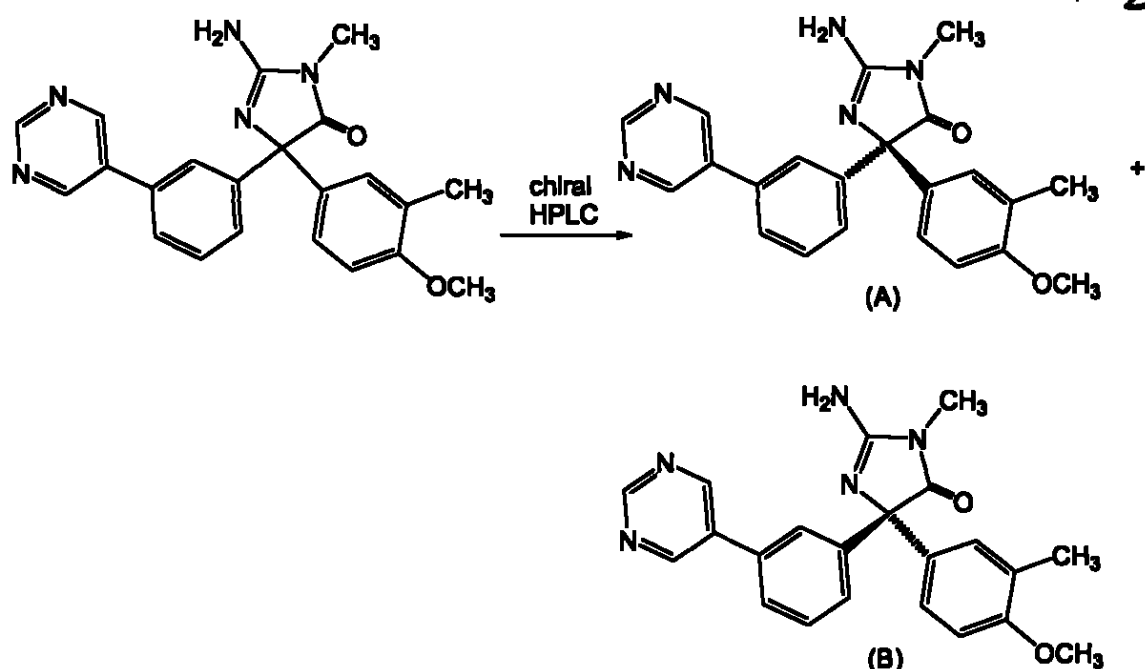


Utilizando esencialmente el mismo procedimiento descrito en el Ejemplo 5 anterior, y empleando 1-(4-metoxi-3-metilfenil)-2-(3-piridin-4-ilfenil)etano-1,2-diona y clorhidrato de 1-metilguanidina como reactivos, se obtiene el compuesto del título como un sólido blanco, 0.15 g (90% de rendimiento), pf 175°C, identificado mediante HRMN y análisis espectral de masa. MS m/e (M)⁺ 387; ¹H RMN (400 MHz, DMSO-d₆) δ 2.05 (s, 3H) 3.00 (s, 3H) 3.75 (s, 3H) 6.60 (bs, 2H) 6.82 (d, 1H) 7.20 (m, 1H) 7.25 (m, 1H) 7.40 (m, 1H) 7.50 (m, 3H) 7.62 (m, 1H) 7.8 (m, 1H) 8.6 (m, 2H).

EJEMPLO 37Preparación de 2-Amino-3-metil-5-(3-piridin-4-ilfenil)-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona

Utilizando esencialmente el mismo procedimiento descrito en el Ejemplo 36 anterior, y empleando 1-(3-pirimidin-2-ilfenil)-2-[4-(trifluorometoxi)fenil]etano-1,2-diona y clorhidrato de metilguanidina como reactivos, se obtiene el compuesto del título como un sólido blanco, identificado mediante HRMN y análisis espectral de masa. MS m/e 428 (M+H)⁺; ¹H RMN (400 MHz, DMSO-d₆) δ 3.01 (s, 1H), 6.79 (brs, 2H), 7.33-7.49 (m, 2H), 7.58-7.66 (m, 3H), 8.27 (m, 2H), 7.59 (d, J=7.77 Hz, 1H), 7.98 (d, J=7.47 Hz, 1H), 8.26 (s, 1H), 8.61 (t, J=1.67 Hz, 1H), 8.90 (d, J=4.88 Hz, 2H).

EJEMPLO 38Preparación de (5R)-2-Amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona (A) y (5S)-2-Amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona (B)



2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona racémico se redisolvió utilizando técnica HPLC quiral sobre un Chiralcel AD, 2x25 cm y utilizando como fase móvil 50% de IPA/DEA en 7200/DRA con una proporción de flujo de 10mL/min. El isómero R, compuesto A del título, se obtiene, después de cristalización de cloroformo/hexano como un sólido blanco, 98% ee; identificado mediante HRMN y análisis espectral de masa. MS m/e 388 (M+H)⁺; ¹H RMN (400 MHz, DMSO-d₆) δ 2.07 (s, 3H), 2.97 (s, 3H), 3.72 (s, 3H), 6.63 (brs, 2H), 6.85 (d, J=8.39 Hz, 1H), 7.21 (s, 1H), 7.25 (dd, J=7.88, 1.01, 1H), 7.46 (t, J=7.55 Hz, 1H), 7.52 (d, J=7.89 Hz, 1H), 7.63 (dd, J=7.54, 0.84 Hz, 1H), 7.75 (s, 1H), 8.99 (s, 2H), 9.18 (s, 1H).

$[\alpha]_D^{25} = +40.2$ (c = 1% en CH₃OH)

El isómero S, el compuesto B del título, se obtiene, después de cristalización de cloroformo/hexano como un sólido blanco, 95% ee; identificado mediante HRMN y análisis espectral de masa. MS

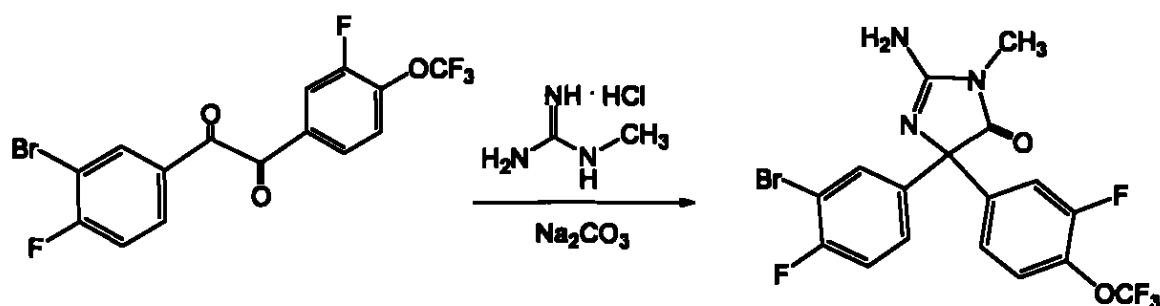
m/e 388 (M+H)⁺; ¹H RMN (400 MHz, DMSO-d₆) δ 2.07 (s, 3H), 2.97 (s, 3H), 3.72 (s, 3H), 6.63 (brs, 2H), 6.85 (d, J=8.39 Hz, 1H), 7.21 (s, 1H), 7.25 (dd, J=7.88, 1.01, 1H), 7.46 (t, J=7.55 Hz, 1H), 7.52 (d, J=7.89 Hz, 1H), 7.63 (dd, J=7.54, 0.84 Hz, 1H), 7.75 (s, 1H), 8.99 (s, 2H), 9.18 (s, 1H).

[α]_D²⁵ = -79.6 (c = 0.67% en CH₃OH)

La configuración absoluta de cada uno de los compuestos A y B del título se determinó mediante cristalografía de rayos x.

EJEMPLO 39

Preparación de 2-Amino-5-(3-bromo-4-fluorofenil)-5-[3-fluoro-4-(trifluorometoxi)fenil]-3-metil-3,5-dihidroimidazol-4-ona

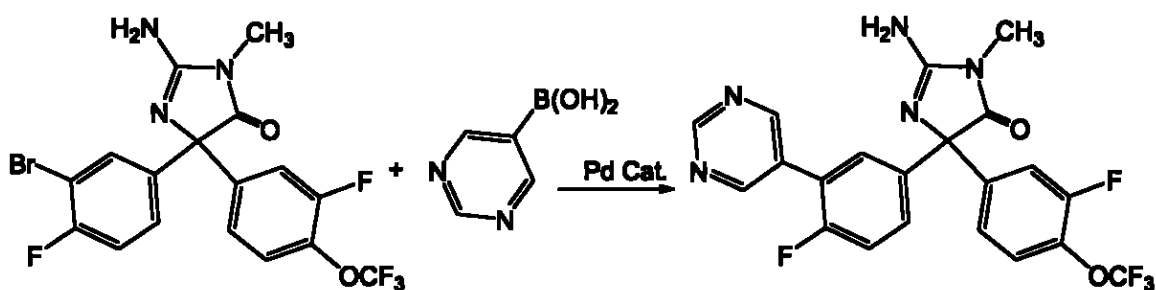


Una mezcla de 1-(3-bromo-4-fluorofenil)-2-[3-fluoro-4-(trifluorometoxi)-fenil]etano-1,2-diona (0.594 g, 1.45 mmol) y clorhidrato de 1-metilguanidina (0.716g, 6.53 mmol) en dioxano y etanol se agita a temperatura ambiente durante 5 min., se trata con una solución de carbonato de sodio (0.692 g, 6.53 mmol) en agua (5 mL), se calentó a 85°C con agitación durante 45 min., se enfrió a temperatura ambiente, y se concentró in vacuo. El residuo resultante se particiona entre cloruro de metileno y

agua. La fase orgánica se separa, se lava secuencialmente con agua y solución salina, se seca sobre sulfato de sodio y se concentra *in vacuo*. Este residuo se purifica mediante cromatografía flash (sílice, 95:5:0.5 cloruro de metileno/metanol/hidróxido de amonio concentrado como eluyente) para lograr un aceite viscoso. Este aceite se disuelve en una cantidad mínima de cloruro de metileno, se trata con hexanos y luego se concentra para lograr el producto del título como un sólido blanco apagado, 0.30 g (45% de rendimiento), identificado mediante HRMN y análisis espectral de masa. ^1H RMN (500 MHz, CD_3OD) δ 7.64 (dd, $J=6.6, 2.2$ Hz, 1H), 7.43-7.37 (m, 2H), 7.33 (dd, $J=11.5, 2.1$ Hz, 1H), 7.30 (m, 1H), 7.18 (t, $J=8.6$ Hz, 1H), 3.11 (s, 3H), ESI MS m/z 464 [$\text{C}_{17}\text{H}_{11}\text{BrF}_5\text{N}_3\text{O}_2 + \text{H}$] $^+$.

EJEMPLO 40

Preparación de 2-Amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-[3-fluoro-4-(trifluorometoxi)fenil]-3-metil-3,5-dihidro-imidazol-4-ona

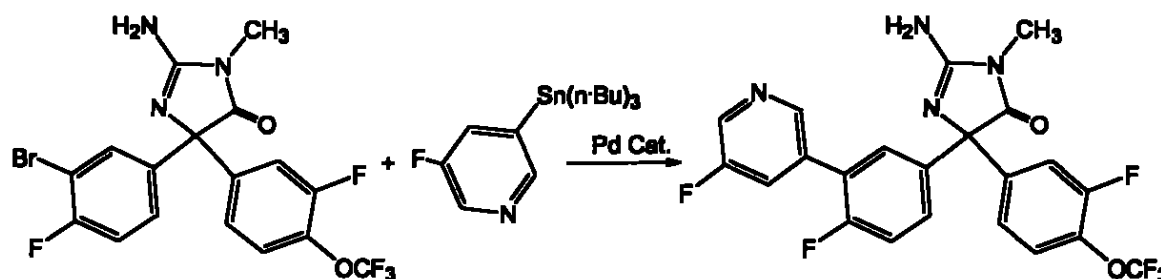


Una mezcla de etilenglicol dimetiléter, tris(dibencilidenoacetona)-dipaladio (0) (0.015 g, 16.5 μmol) y trifenilfosfina (0.008 g, 32.0 μmol) se agita bajo nitrógeno

durante 5 min., se trata con 2-amino-5-(3-bromo-4-fluorofenil)-5-[3-fluoro-4-(trifluorometoxi)fenil]-3-metil-3,5-dihidroimidazol-4-ona (0.154 g, 0.33 mmol), ácido 5-pirimidino borónico (0.046 g, 0.37 mmol), carbonato de sodio (0.105 g, 0.99 mmol) y agua, calentada a temperatura de reflujo durante 1.25 h, enfriada a temperatura ambiente y concentrada in vacuo. El residuo resultante se purifica mediante cromatografía flash (sílice, 95:5:0.5 cloruro de metileno/metanol/hidróxido de amonio concentrado como eluyente) para lograr un aceite viscoso. Este aceite se suspende en una mezcla de cloruro de metileno/hexanos y se concentra para lograr el compuesto del título como un sólido blanco apagado, 0.045 g (29% de rendimiento), pf 102-110°C, identificado mediante HRMN y análisis espectral de masa. ^1H RMN (500 MHz, CD_3OD) δ 9.15 (s, 1H), 8.95 (s, 2H), 7.62-7.56 (m, 2H), 7.39-7.27 (m, 4H), 3.12 (s, 3H); IR 3353, 3061, 2956, 1732, 1668, 1498, 1470, 1416, 1251, 1216, 1170 cm^{-1} ; ESI MS m/z 464 $[\text{C}_{21}\text{H}_{14}\text{F}_5\text{N}_5\text{O}_2 + \text{H}]^+$; HPLC (Método 2) 95.0% (AUC) $t_R = 13.78$ min.

EJEMPLO 41

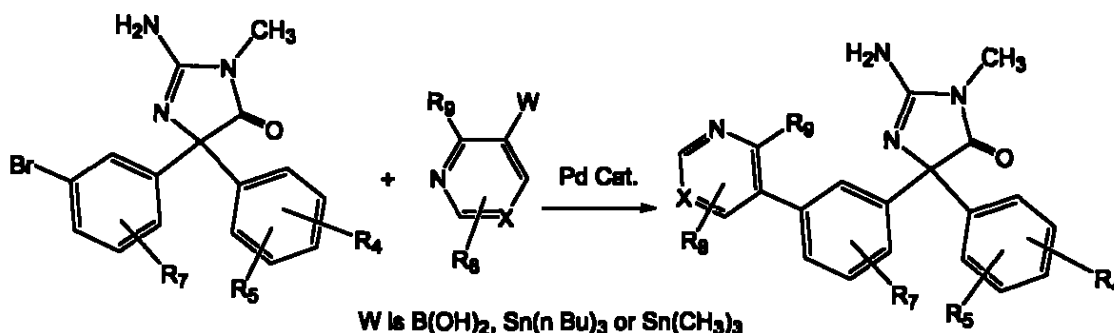
Preparación de 2-Amino-5-[4-fluoro-3-(5-fluoropiridin-3-il)fenil]-5-[3-fluoro-4-(trifluorometoxi)fenil]-3-metil-3,5-dihidro-imidazol-4-ona



Una mezcla de 2-amino-5-(3-bromo-4-fluorofenil)-5-[3-fluoro-4-(trifluorometoxi)fenil]-3-metil-3,5-dihidroimidazol-4-ona (0.17 g, 0.366 mmol), 5-fluoropiridin-3-il-tri(n-butil)estanoato (0.212 g, 0.55 mmol) y cloruro de bis(trifenilfosfino)paladio(II) (0.013 g, 0.018 mmol) en dimetilformamida se desgasifica, se calienta a 150°C durante 1 h, se enfría a temperatura ambiente y se diluye con acetato de etilo y 2% de cloruro de litio acuoso. La fase orgánica se separa, se lava con cloruro de litio acuoso 2%, se seca sobre sulfato de sodio y se concentra in vacuo. La purificación del residuo resultante mediante cromatografía flash (sílice, 97:3:0.25 cloruro de metileno/metanol/hidróxido de amonio concentrado como eluyente) logra el compuesto del título como un sólido blanco, 0.130 g (74% de rendimiento), pf 91-97°C, identificado mediante HRMN y análisis espectral de masa. ^1H RMN (300 MHz, CD_3OD) 8.55 (m, 1H), 8.49 (d, $J=3.0$ Hz, 1H), 7.83 (d, $J=9.6$ Hz, 1H), 7.60-7.21 (m, 6H), 3.13 (s, 3H); IR (ATR) 3352, 3070, 1732, 1669, 1598, 2502, 1479, 1421, 1252, 1217, 1171, 883, 817, 794, 703 cm^{-1} ; ESI MS m/z 481

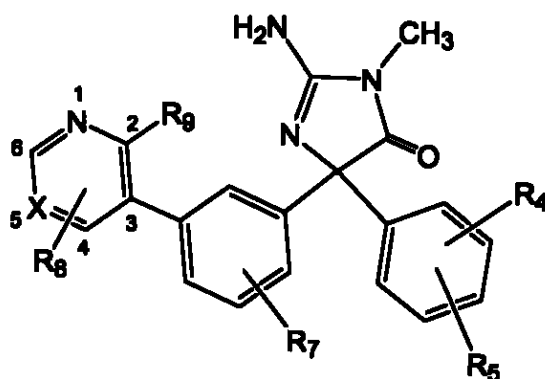
EJEMPLOS 42-99

Preparación de Derivados de 2-Amino-5,5-difenilimidazolona

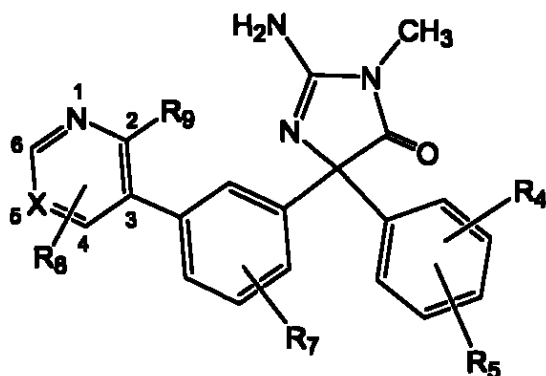


Utilizando esencialmente los mismos procedimientos descritos anteriormente para los ejemplos 40 y 41 y empleando el sustrato de 2-amino-5-(3-bromofenil)-5-(fenil sustituido)imidazolona apropiado y el reactivo de piridinilo o pirimidinilo, los compuestos mostrados en la Tabla II se obtuvieron e identificaron mediante HRMN y análisis espectral de masa.

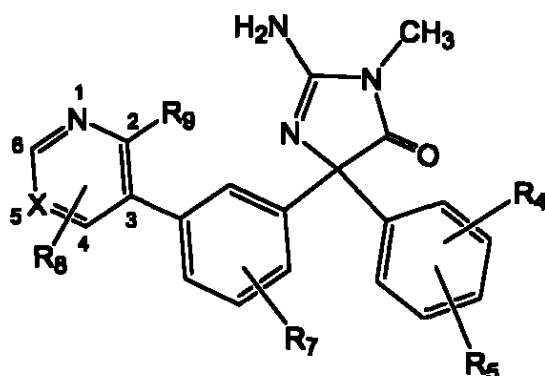
Tabla II



Ej.No	R ₄	R ₅	R ₇	R ₈	R ₉	X	pf °C
42	3-F	4-OCF ₃	4-F	H	H	C-Cl	201-203
43	3-F	4-OCF ₃	4-F	F	H	CH	75-80
44	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	H	N	100-105
46	H	4-OCF ₃	4-F	H	H	C-Cl	241-243
47	H	4-OCF ₃	4-F	H	H	C-F	216-218
48	H	4-OCF ₃	2-F	H	H	N	130-135
49	H	4-OCF ₃	4-Cl	H	H	N	124-129
50	H	4-OCF ₃	4-F	H	H	CH	134

Tabla II, continuación

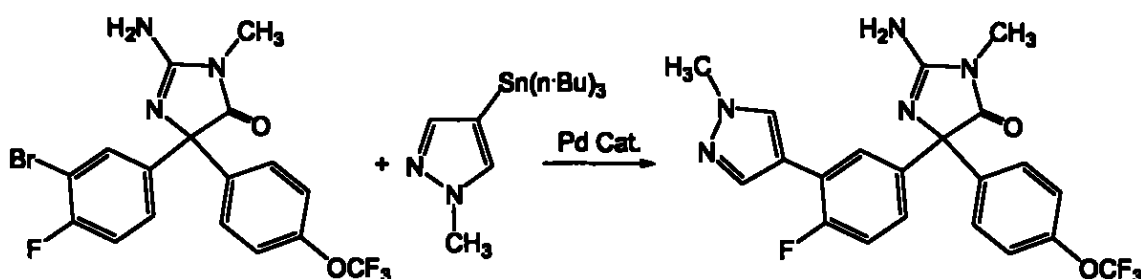
Ej.No	R ₄	R ₅	R ₇	R ₈	R ₉	X	Pt °C
51	H	4-OCF ₃	H	H	H	C-OCH ₃	212
52	H	4-OCF ₃	H	OCH ₃	H	CH	98
53	H	4-OCF ₃	3-F	H	H	N	226
54	3-CH ₃	4-OCH ₃	4-F	H	H	N	116
55	3-CH ₃	4-OCH ₃	4-F	F	H	CH	113
56	3-CF ₃	4-OCH ₃	4-F	H	H	N	115
57	3-CF ₃	4-OCH ₃	4-F	H	6-F	CH	135
58	3-CF ₃	4-OCH ₃	4-F	F	H	CH	118
59	3-CH ₃	4-OCH ₃	H	F	H	CH	125
60	H	4-OCH ₃	4-F	H	H	C-F	—
61	3-CH ₃	4-OCH ₃	4-F	H	H	C-F	—
62	H	4-OCH ₃	4-F	F	H	CH	—
63	H	4-OCH ₃	4-F	H	H	N	—
64	H	4-OCF ₃	H	H	6-OCH ₃	CH	—
65	H	4-OCF ₃	H	H	6-F	CH	—
66	H	4-OCF ₃	H	F	H	CH	—
67	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	H	C-OCH ₃	—
68	3-OC ₂ H ₅	4-OC ₂ H ₅	H	OCH ₃	H	CH	—
69	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	6-F	CH	—
70	3-OC ₂ H ₅	4-OC ₂ H ₅	H	F	H	CH	—
71	H	4-OCF ₃	4-F	H	H	C-OCH ₃	—
72	H	4-OCF ₃	4-F	OCH ₃	H	CH	—
73	H	4-OCF ₃	4-F	H	6-F	CH	—
74	H	4-OCF ₃	4-F	F	H	CH	—
75	3-CH ₃	4-OCH ₃	H	OCH ₃	H	CH	—

TABLA II. Continuación

Ej.No.	R4	R5	R7	R9	R8	X	pf °C
77	H	4-OCF ₃	4-F	H	H	N	—
78	3-F	4-OCF ₃	4-F	H	4-F	CH	93-96
79	3-C ₂ H ₅	3-C ₂ H ₅	4-F	F	H	CH	95-100
80	H	4-OCH ₃	4-F	H	H	C-Cl	—
81	3-OC ₂ H ₅	4-OC ₂ H ₅	H	H	4-F	CH	—
82	H	4-OCF ₃	H	H	4-F	CH	—
83	H	4-OCH ₃	4-F	H	4-F	CH	—
84	H	4-OCF ₃	6-F	H	H	CH	—
85	H	4-OCF ₃	2-F	H	H	CH	239
86	3-OC ₂ H ₅	4-OC ₂ H ₅	4-F	H	H	N	95-98
87	H	4-OCHF ₂	4-F	H	H	C-F	—
88	H	4-OCHF ₂	4-F	H	6-F	CH	—
89	H	4-OCHF ₂	H	F	H	CH	—
90	H	4-OCHF ₂	H	H	6-F	CH	—
91	H	4-OCHF ₂	H	F	H	C-F	—
92	H	4-OCHF ₂	4-F	F	H	C-F	—
93	H	4-SCF ₃	4-F	F	H	CH	95
94	H	4-SCF ₃	4-F	H	H	N	183
95	H	4-OCHF ₂	4-F	H	H	CH	104-106
96	H	4-OCHF ₂	4-F	F	H	CH	108-110
97	H	4-OCHF ₂	4-F	H	H	N	103-105
99	3-OC ₂ H ₅	4-OC ₂ H ₅	4-F	H	H	CH	93-95

EJEMPLO 100

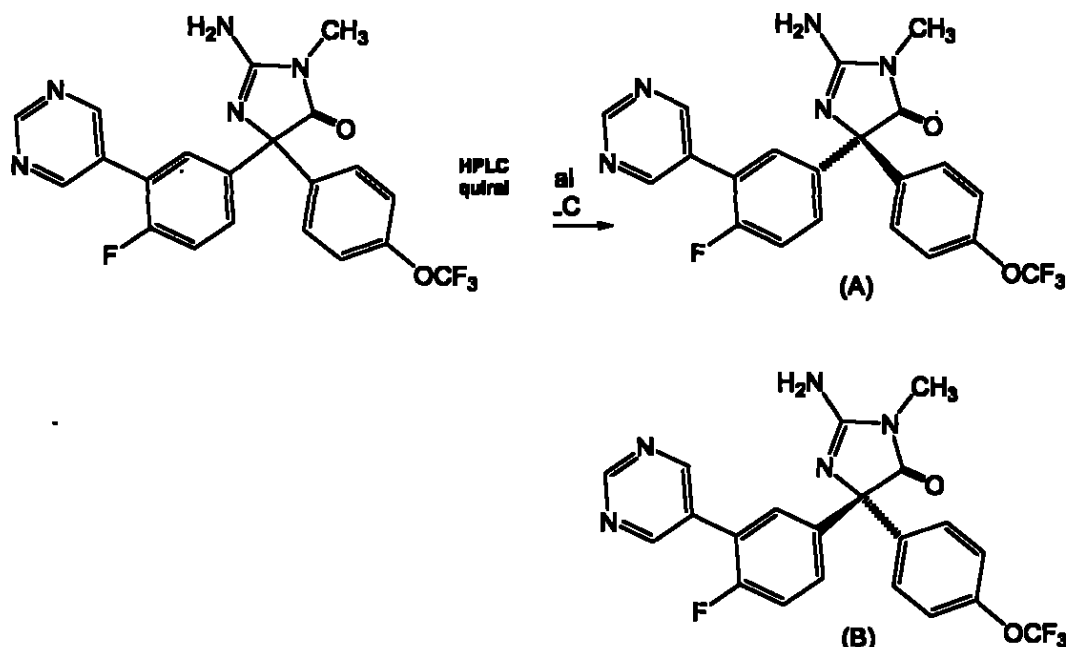
Preparación de 2-Amino-5-[4-fluoro-3-(1-metil-1H-pirazol-4-il)fenil]3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona



Utilizando esencialmente el mismo procedimiento descrito en el Ejemplo 41 anterior y empleando 2-amino-5-(3-bromo-4-fluorofenil)-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona y 1-metil-4-(tributilestanil)-1H-pirazol como reactivos, se obtiene el producto del título como un sólido blanco, identificado mediante HRMN y análisis espectral de masa. ^1H RMN (300 MHz, DMSO-d_6) δ 2.95 (s, 3H), 3.92 (s, 3H), 6.7 (brs, 2H), 7.15 (t, 1H), 7.28 (m, 3H), 7.5 (m, 2H), 7.65 (m, 2H), 8.0 (d, 1H) MS m/e $(\text{M}+\text{H})^+$ 448

EJEMPLO 101

Preparación de (5S)-2-Amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona (A) y (5R)-2-Amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona (B)

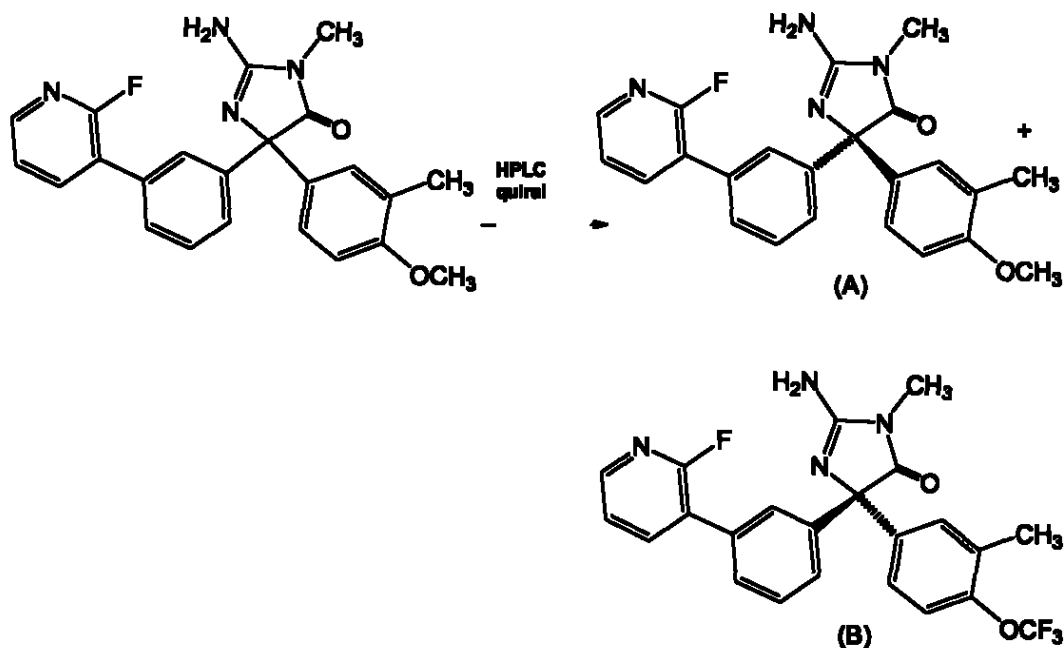


2-amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona racémico se resolvió utilizando técnica de HPLC quiral sobre Chiralcel AD, 2x25 cm y utilizando EtOH de fase móvil con una proporción de flujo de 11 mL/min. Se obtiene el isómero S, del compuesto A del título, después de cristalización de cloroformo/hexanos, como un sólido blanco, 98.8% ee; identificado mediante HRMN y análisis espectral de masa. ^1H RMN (300 MHz, DMSO-d_6) δ 2.95 (s, 3H), 3.95 (m, 4H), 6.72 (brs, 2H), 7.25 (d, 2H), 7.32 (t, 1H), 7.55-7.6 (m, 3H), 7.65 (dd, 1H), 8.9 (s, 2H), 9.2 (s, 1H) MS m/e $(\text{M}+\text{H})^+$ 446

El isómero R, del compuesto B del título, se obtiene después de cristalización de cloroformo/hexanos, como un sólido blanco, 98.4% ee; identificado mediante HRMN y análisis espectral de masa. ^1H RMN (300 MHz, DMSO-d_6) δ 2.95 (s, 3H), 3.95 (m, 4H), 6.72 (brs, 2H), 7.25 (d, 2H), 7.32 (t, 1H), 7.55-7.6 (m, 3H), 7.65 (dd, 1H), 8.9 (s, 2H), 9.2 (s, 1H) MS m/e $(\text{M}+\text{H})^+$ 446

EJEMPLO 102

Preparación de (5R)-2-Amino-5-[3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona (A)
y (5S)-2-Amino-5-[3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona (B)



2-amino-5-[3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona racémico se resolvió utilizando técnica de HPLC quiral sobre Chiralcel AD, 2x25 cm y utilizando como fase móvil EtOH/DEA 9% en hexano/DEA con proporción de flujo de 25 mL/min. El isómero R, del compuesto A del título, se obtiene, después de cristalización de cloroformo/hexanos, como un sólido blanco, 100% ee; identificado mediante HRMN y análisis espectral de masa. ^1H RMN (300 MHz, DMSO-d_6) δ 2.05 (s, 3H), 2.96 (s, 3H), 3.67 (s, 3H), 6.62 (brs,

2H), 6.6 (d, 1H), 7.25-7.35 (m, 2H), 7.35-7.5 (m, 2H), 7.65 (m, 1H), 7.95 (m, 2H), 8.4 (dd, 1H)

MS m/e (M+H)⁺ 405 $[\alpha]_D^{25} = +22$ (c = 1% en CH₃OH)

El isómero S, del compuesto B del título, se obtiene después de cristalización de cloroformo/hexanos, como un sólido blanco, 98% ee; identificado mediante HRMN y análisis espectral de masa.

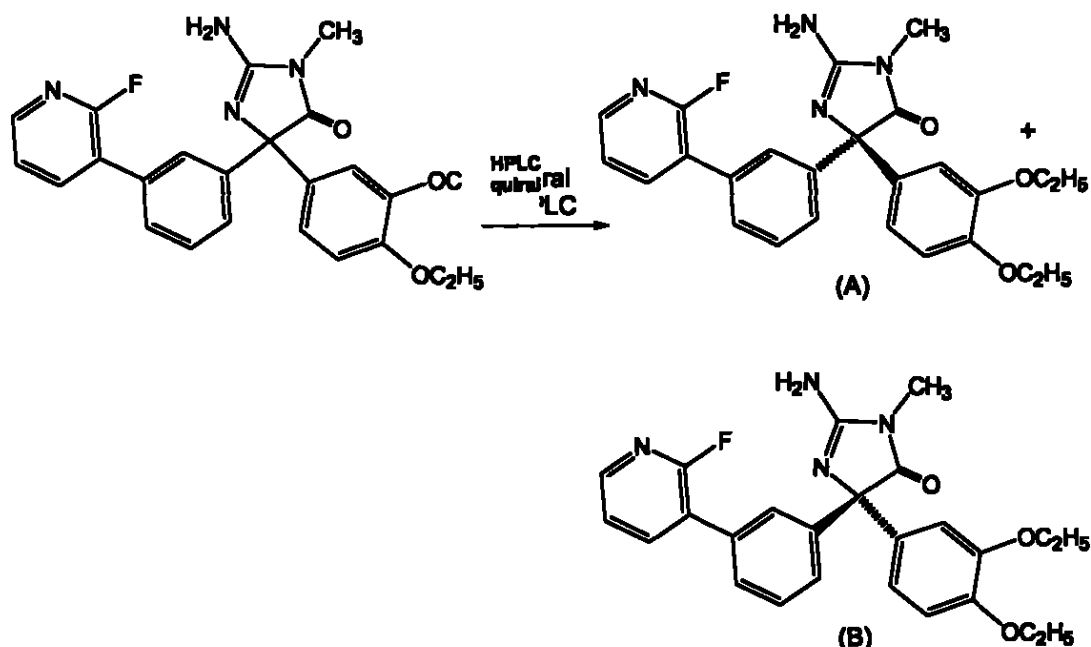
¹H RMN (300 MHz, DMSO-d₆)

δ 2.05 (s, 3H), 2.96 (s, 3H), 3.67 (s, 3H), 6.62 (brs, 2H), 6.6 (d, 1H), 7.25-7.35 (m, 2H), 7.35-7.5 (m, 2H), 7.65 (m, 1H), 7.95 (m, 2H), 8.4 (dd, 1H)

MS m/e (M+H)⁺ 405 $[\alpha]_D^{25} = -9.5$ (c = 0.4% en CH₃OH)

EJEMPLO 103

Preparación de (5R)-2-Amino-5-(3,4-dietoxifenil)-5-[3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona (A) y (5S)-2-Amino-5-(3,4-dietoxifenil)-5-[3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona (B)



2-amino-5-(3,4-dietoxifenil)-5-[3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona racémico se resolvió utilizando técnica de HPLC quiral sobre un Chiralcel AD, columna de 0.46 x 25 cm y utilizando como fase móvil 25% de EtOH en hexano/DEA. El isómero R, del compuesto A del título, se obtiene e identifica mediante HRMN y análisis espectral de masa.

^1H RMN (DMSO-d_6 , 300 MHz) δ 1.22 (m, 6H), 2.95 (s, 3H), 3.95 (m, 4H), 6.6 (brs, 2H), 6.85 (d, 1H), 7.0 (m, 2H), 7.37-7.45 (m, 3H), 7.48 (d, 1H), 7.63 (s, 1H), 7.96 (m, 1H), 8.2 (d, 1H) MS m/e $(\text{M}+\text{H})^+$ 449

$[\alpha]_{\text{D}}^{25} = +7.4$ (c = 1% en CH_3OH)

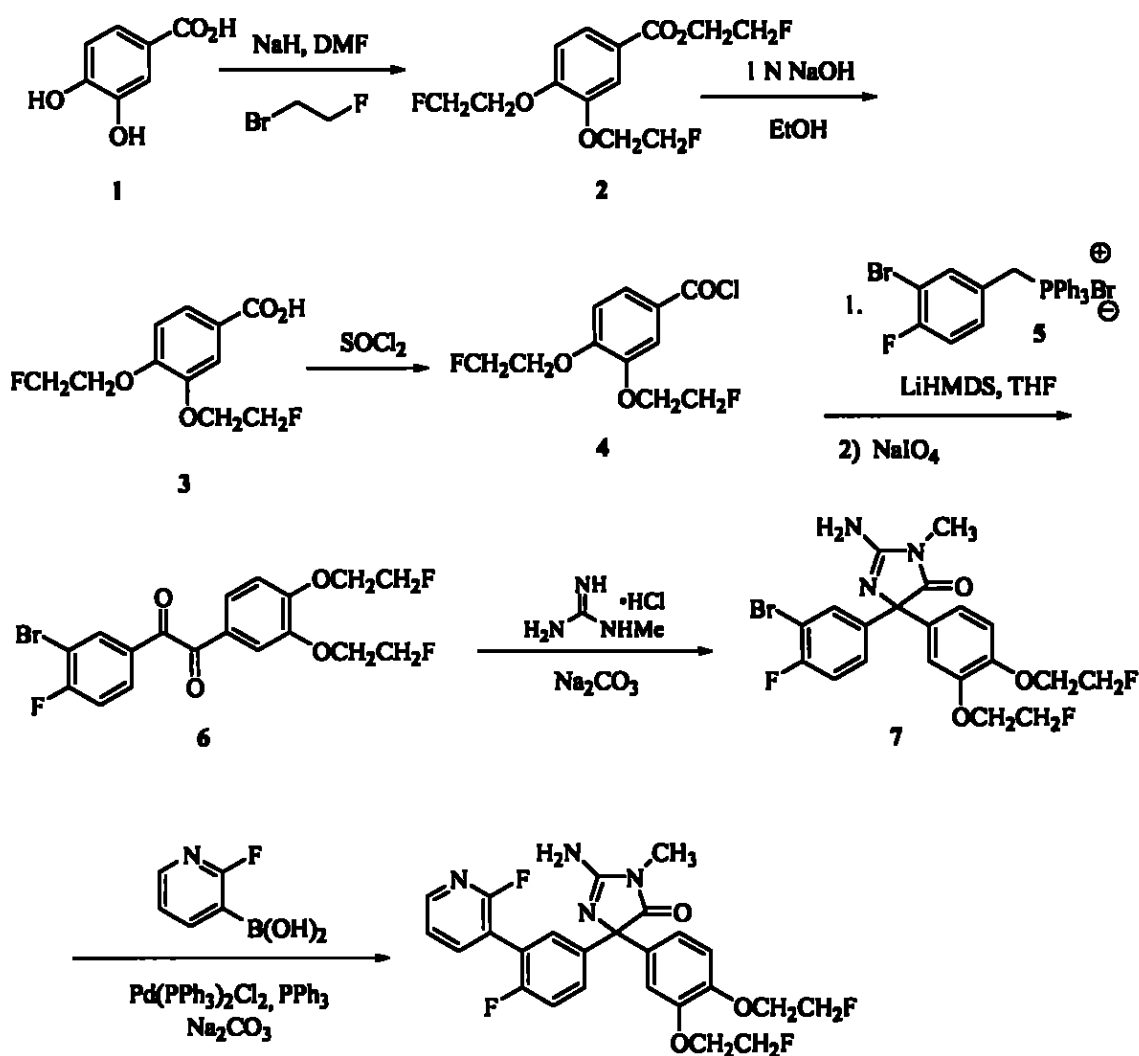
El isómero S, del compuesto B del título, se obtiene e identifica mediante HRMN y análisis espectral de masa. ^1H RMN (DMSO-d_6 , 300 MHz) δ 1.22 (m, 6H), 2.95 (s, 3H), 3.95 (m, 4H), 6.6 (brs, 2H), 6.85 (d, 1H), 7.0 (m, 2H), 7.37-7.45 (m, 3H), 7.48 (d, 1H), 7.63 (s, 1H), 7.96 (m, 1H), 8.2 (d, 1H)

MS m/e (M+H)⁺ 449

$$[\alpha]_D^{25} = -9.8 \quad (c = 1\% \text{ en } \text{CH}_3\text{OH})$$

EJEMPLO 104

Preparación de 2-Amino-5-[3,4-bis-(2-fluoro-etoxi)fenil]-5-[4-fluoro-3-(2-fluoro-piridin-3-il)-fenil]-3-metil-3,5-dihidroimidazol-4-ona



Etapas a) Preparación del compuesto 2

Hidruro de sodio (1.82 g de una dispersión al 60% en aceite, 45.5 mmol) se lava con hexanos, se suspende en DMF (5 mL) y se

trata gota a gota con una solución de **1** (2.0 g, 13.0 mmol) en DMF (15 mL) durante un período de 10 min a temperatura ambiente. Después de agitar durante 1.5 h adicionales a temperatura ambiente, la mezcla se trata con una solución de 1-bromo-2-fluoroetano en DMF (15 mL) y la mezcla se agitó a temperatura ambiente durante 18h, luego se calentó a 60°C durante 4 h. adicional. La mezcla se enfrió a temperatura ambiente y se diluye con acetato de etilo (100 mL) y agua (100 mL). La capa orgánica se separa y se lava con NaOH 1 N (100 mL), cloruro de litio acuoso 5% (2 x 100mL), solución salina (100 mL), se seca sobre sulfato de magnesio, se filtra y se concentra. La purificación mediante cromatografía flash (sílice, 1:3 acetato de etilo/hexanos) produce **2** (1.00 g, 26%) como un sólido blanco: ^1H RMN (300 MHz, CDCl_3) δ 7.74 (dd, $J=8.4$, 2.0 Hz, 1H), 7.63 (d, $J=2.0$ Hz, 1H), 6.94 (d, $J=8.5$ Hz, 1H), 4.84 (m, 2H), 4.75 (m, 3H), 4.67 (m, 1H), 4.58 (m, 1H), 4.52 (m, 1H), 4.36 (m, 2H), 4.30 (m, 2H); ESI MS m/z 293 [$\text{C}_{13}\text{H}_{15}\text{F}_3\text{O}_4 + \text{H}$] $^+$.

Etapas b) Preparación del compuesto 3

Una mezcla de **2** (1.00 g, 3.42 mmol) en etanol (10 mL) y NaOH 1 N (10 mL) se calienta a 75°C durante 1 h. La mezcla se enfría a temperatura ambiente, se concentra, se diluye con agua (10 mL) y se acidifica con HCl 6 N. Los sólidos que formaron fueron recolectados mediante filtración y secado para lograr **3** (0.76 g, 90%) como un sólido blanco: ^1H RMN (300 MHz, $\text{DMSO}-d_6$) δ 12.8 (brs, 1H), 7.58 (dd, $J=8.4$, 1.5 Hz, 1H), 7.50 (d, $J=1.5$ Hz, 1H), 7.11 (d, $J=8.5$ Hz, 1H), 4.84 (m, 2H), 4.67 (m, 2H), 4.39-4.22 (m, 4H).

Etapas c) Preparación del compuesto 4

Una mezcla de 3 (0.76 g, 3.09 mmol), cloruro de tionilo (8 mL) y DMF (1 gota) se calienta a reflujo durante 4 h. La mezcla se enfría luego a temperatura ambiente y se concentra. El residuo se disuelve en tolueno y de nuevo se concentra para lograr 4 (0.82 g, 100%) como un sólido blanco: ^1H RMN (300 MHz, CDCl_3) δ 7.85 (dd, $J=8.4$, 1.8 Hz, 1H), 7.62 (d, $J=2.1$ Hz, 1H), 6.98 (d, $J=8.7$ Hz, 1H), 4.89 (m, 2H), 4.75 (m, 2H), 4.43-4.26 (m, 4H); IR (ATR) 1734, 1582, 1513, 1417 cm^{-1} .

Etapas d) Preparación del compuesto 6

Una solución 1.0 M de bis(trimetilsilil)amida de litio en tetrahidrofurano (3.25 mL, 3.25 mmol) se agrega a una suspensión agitada de bromuro de (3-bromo-4-fluorobencil) trifenilfosfonio (1.72 g, 3.25 mmol) en tetrahidrofurano (6 mL). La mezcla se agita durante 25 min a temperatura ambiente, luego se enfría a -40°C , se trata con una solución de 4 (0.82 g, 3.10 mmol) en tetrahidrofurano (3 mL) y se agita durante 2 h adicionales aunque calentando lentamente a temperatura ambiente. La reacción luego se trata con agua (5 mL) y periodato de sodio (0.69 g, 3.25 mmol), luego se calienta a 50°C durante 19 h. Después de este tiempo la mezcla se enfría a temperatura ambiente y se diluye con acetato de etilo (25 mL). La capa orgánica se separa y se lava con agua (10 mL) y solución salina (10 mL), se seca sobre sulfato de magnesio, se filtra y se concentra. Purificación mediante cromatografía flash (sílice, 1:3 acetato de etilo/hexanos)

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produce 6 (0.27 g, 20%) como un sólido amarillo pálido: ^1H RMN (300 MHz, CDCl_3) δ 8.22 (dd, $J=6.5$, 2.1 Hz, 1H), 7.92 (m, 1H), 7.63 (d, $J=2.0$ Hz), 7.51 (dd, $J=8.4$, 2.9 Hz, 1H), 7.23 (m, 1H), 7.96 (d, $J=8.5$ Hz, 1H), 4.85 (m, 2H), 4.76 (m, 2H), 4.39-4.31 (m, 4H).

Etapas e) Preparación del compuesto 7

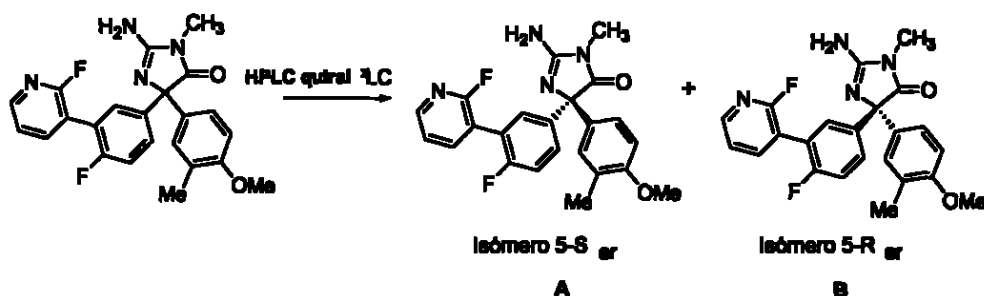
Una mezcla de 6 (0.26 g, 0.603 mmol) y clorhidrato de 1-metilguanidina (0.30 g, 2.71 mmol) en dioxano (8 mL) y etanol (5.3 mL) se agita a temperatura ambiente durante 5 min. Luego se agrega una solución de carbonato de sodio (0.29 g, 2.71 mmol) en agua (2.3 mL) y la mezcla se sumerge en un baño de aceite a 85°C y se agita durante 30 min. La mezcla de reacción se enfría a temperatura ambiente, se concentra y el residuo se particiona entre cloruro de metileno (50 mL) y agua (20 mL). La capa orgánica se separa, se lava con agua (20 mL), solución salina (20 mL), se seca sobre sulfato de magnesio, se filtra y se concentra. Purificación mediante cromatografía flash (sílice, 95:5:0.5 cloruro de metileno/metanol/hidróxido de amonio concentrado) produce 7 (0.154 g, 53%) como un sólido blanco: ^1H RMN (300 MHz, CDCl_3) δ 7.68 (m, 1H), 7.33 (m, 1H), 7.07 (m, 3H), 6.89 (m, 1H), 4.80 (m, 2H), 4.66 (m, 2H), 4.28 (m, 2H), 4.18 (m, 2H); ESI MS m/z 486 $[\text{C}_{20}\text{H}_{19}\text{BrF}_3\text{N}_3\text{O}_3 + \text{H}]^+$.

Etapas f) Preparación de 2-amino-5-[3,4-bis-(2-fluoro-etoxi)-fenil]-5-[4-fluoro-3-(2-fluoro-piridin-3-il)-fenil]-3-metil-3,5-dihidro-imidazol-4-ona

Una mezcla de 7 (0.140 g, 0.288 mmol), ácido 2-fluoropiridina-3-borónico (0.061 g, 0.430 mmol), carbonato de sodio (0.092 g, 0.860 mmol), cloruro de bis(trifenilfosfino)paladio (II) (0.010 g, 0.014 mmol) y trifenilfosfina (0.008 g, 0.028 mmol) en 1:1 tolueno/etanol (8 mL) se desgasifica y se calienta a 110°C durante 1.5 h. La mezcla se enfría a temperatura ambiente, se concentra y se purifica mediante cromatografía flash (sílice, 97:3:0.25 cloruro de metileno/metanol/hidróxido de amonio concentrado) para lograr 8 (0.055 g, 39%) como un sólido blanco, pf 85-95°C; ^1H RMN (300 MHz, CD_3OD) δ 8.23 (m, 1H), 7.93 (m, 1H), 7.51-7.38 (m, 3H), 7.21 (t, $J=9.0$ Hz, 1H), 6.98 (m, 3H), 4.78 (m, 2H), 4.68 (m, 2H), 4.62-4.58 (m, 4H), 3.11 (s, 3H); IR (ATR) 1733, 1666, 1502, 1260 cm^{-1} ; ESI MS m/z 503 [$\text{C}_{25}\text{H}_{24}\text{F}_4\text{N}_4\text{O}_3 + \text{H}$] $^+$. Anal. Calculado para $\text{C}_{25}\text{H}_{24}\text{F}_4\text{N}_4\text{O}_3 \cdot 0.25\text{H}_2\text{O}$: C, 59.28; H, 4.45; N, 10.73. Encontrado: C, 59.23; H, 4.47; N, 11.05.

EJEMPLO 105

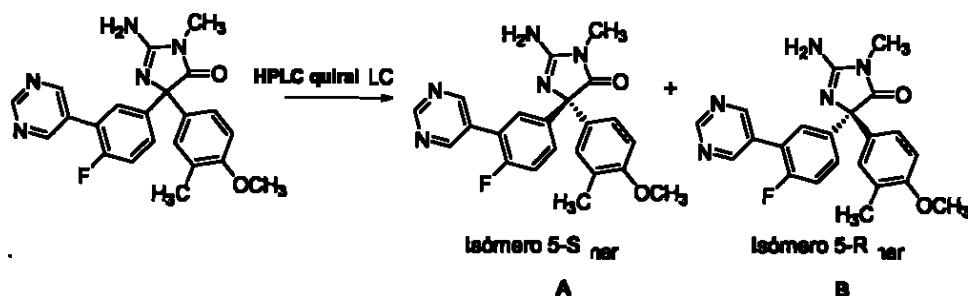
Preparación de (5S)-2-Amino-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



El racemato 2-amino-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa mediante HPLC utilizando Chiralcel OJ, 2x25 cm, fase móvil 15% EtOH/DEA en hexano y proporción de flujo de 21 mL/min para dar el isómero S del título (A), ^1H RMN (DMSO-d_6 , 300 MHz) δ 2.0 (s, 3H), 2.95 (s, 3H), 3.7 (s, 3H), 6.6 (b, 2H), 6.8 (d, 1H), 7.3 (m, 3H), 7.5 (m, 3H), 8.0 (m, 1H), 8.3 (m, 1H); MS m/e (M^+) 423; $[\alpha]_{25} = +76.4$ (C = 1% en MeOH); pf 103- 105°C y el isómero R del título (B), ^1H RMN (DMSO-d_6 , 300 MHz) δ 2.0 (s, 3H), 2.95 (s, 3H), 3.7 (s, 3H), 6.6 (b, 2H), 6.8 (d, 1H), 7.3 (m, 3H), 7.5 (m, 3H), 8.0 (m, 1H), 8.3 (m, 1H); MS m/e (M^+) 423; $[\alpha]_{25} = -40.8$ (C = 1% en MeOH); pf 103- 105°C.

EJEMPLO 106

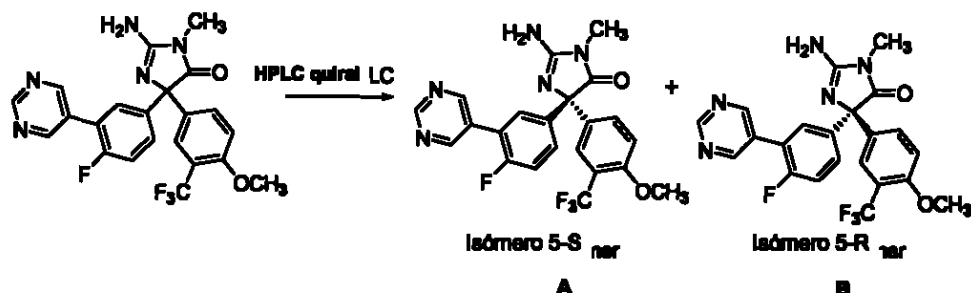
Preparación de (5S)-2-Amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [A]
y (5R)-2-Amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



El racemato 2-amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa mediante HPLC utilizando Chiralcel OD, 2 x 25 cm, fase móvil cm utilizando MeOH de fase móvil (30% con 0.1% DEA) en CO₂ (100 bar) y una proporción de flujo de 50 mL/min para dar el isómero S del título (A), ¹H RMN (400 MHz, DMSO-d₆) δ 2.04 (s, 3H), 2.93 (s, 3H), 3.69 (s, 3H), 6.61 (bs, 2H), 6.81 (m, 1H), 7.22 (m, 1H), 7.27 (m, 1H), 7.29 (m, 1H), 7.60 (m, 1H), 7.61 (m, 1H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e (M+H)⁺ 406; pf 115°C; [α]₂₅ = 48 (C = 1% en MeOH); y el isómero R del título (B), ¹H RMN (400 MHz, DMSO-d₆) δ 2.04 (s, 3H), 2.93 (s, 3H), 3.69 (s, 3H), 6.60 (bs, 2H), 6.81 (m, 1H), 7.22 (m, 1H), 7.27 (m, 1H), 7.29 (m, 1H), 7.60 (m, 1H), 7.61 (m, 1H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e (M+H)⁺ 406; pf 115°C; [α]₂₅ = -39.2 (C = 1% en MeOH).

EJEMPLO 107

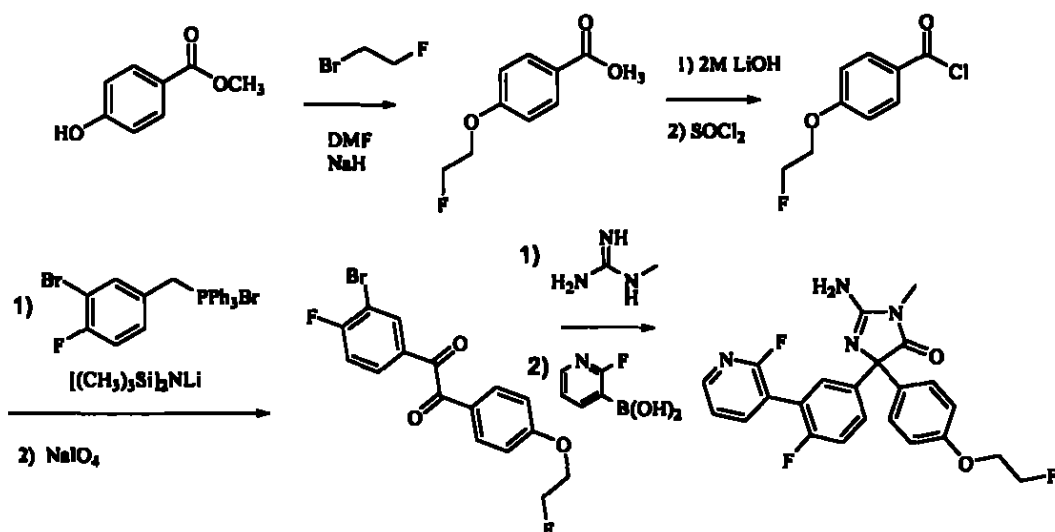
Preparación de (5S)-2-Amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-[4-metoxi-3-(trifluorometil)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-[4-metoxi-3-(trifluorometil)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



Una mezcla racémica de 2-amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-[4-metoxi-3-(trifluorometil)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC utilizando Chiralcel OD, 2 x 25 cm, fase móvil cm, fase móvil EtOH/Hexano (15/85) y un índice de flujo de 20 mL/min para dar el isómero S del título (A), ^1H RMN (400 MHz, DMSO- d_6) δ 2.94 (s, 3H), 3.81 (s, 3H), 6.76 (bs, 2H), 7.19 (m, 1H), 7.32 (m, 1H), 7.32 (m, 1H), 7.50 (m, 1H), 7.70 (m, 2H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e ($M+H$) $^+$ 460.1; pf 100° C; $[\alpha]_{25} = 1.6$ (C = 1% en MeOH); y el isómero R del título (B), ^1H RMN (400 MHz, DMSO- d_6) δ 2.94 (s, 3H), 3.81 (s, 3H), 6.76 (bs, 2H), 6.82 (m, 1H), 7.22 (m, 1H), 7.32 (m, 1H), 7.50 (m, 1H), 7.59 (m, 1H), 7.70 (m, 1H), 8.89 (d, 2H), 9.18 (d, 1H); MS m/e ($M-H$) $^-$ 458; pf 100° C; $[\alpha]_{25} = -1.8$ (C = 1% en MeOH).

EJEMPLO 108

Preparación de 2-Amino-5-[4-(2-fluoroetoxi)fenil]-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona



Etapa a) Preparación de Metil 4-(2-fluoroetoxi)benzoato

Bajo atmósfera de nitrógeno a una solución fría (5° C) de éster de metilo de ácido 4-hidroxi-benzoico (7 g, 46 mmol) en DMF (30 ml) se agrega NaH (60 %; 2.2 g) en forma de porción durante 20 minutos. Después la adición se completa, se remueve el baño de hielo y la suspensión resultante blanca se calienta hasta temperatura ambiente y se agita durante 3 horas. Una solución preparada de 1-Bromo-2-fluoro-etano (6.42 g, 50.56 mmol) en DMF (20 mL) se agrega y la nueva mezcla se agita a 50° C durante 18 horas. Luego de enfriar a temperatura ambiente la mezcla se vierte en una mezcla de hielo y HCl 1 N (1:1) y se extrae con acetato de etilo. Los extractos orgánicos se lavan con solución salina, se secan sobre MgSO₄. La evaporación y purificación mediante cromatografía flash (Hexano/acetato de etilo 9/1) da un sólido blanco (7.75. 85 % de rendimiento); ¹H RMN (400 MHz, CDCl₃) δ 3.86 (s, 3H), 4.20 (m, 1H), 4.21 (m, 1H), 4.27 (m, 1H), 4.28 (m, 1H), 6.93 (d, 2H), 7.98 (d, 2H); MS m/e (M+H)⁺ 198; pf 77° C.

Etapla b) Preparación de ácido 4-(2-Fluoroetoxi)benzoico

A una solución de 4-(2-fluoroetoxi)benzoato de metilo (7.7 g, 38.85 mmol) en dioxano (100 mL) se agrega LiOH (2M, 39 mL). La mezcla de reacción se agita a temperatura ambiente durante 18 horas, y luego se concentra en vacío. El residuo se disuelve en H₂O (30 ml) y se extrae con éter. El acuoso se acidifica bajo frío con HCl (6N) y se extrae con CHCl₃. Se secan los extractos orgánicos sobre MgSO₄. Evaporación y recristalización de acetato de etilo y cloruro de metileno da el compuesto del título como un sólido blanco (5 g, 71 % de rendimiento); ¹H RMN (400 MHz, DMSO-d₆) δ 4.28 (m, 1H), 4.35 (m, 1H,) 4.68 (m, 1H), 4.80 (m, 1H), 7.04 (d, 2H), 7.89 (d, 2H); MS m/e (M-H)⁻ 183.1; pf 203° C.

Etapla c) Preparación de 1-(3-bromo-4-fluorofenil)-2-[4-(2-fluoroetoxi)-fenil]etano-1,2-diona

Se agrega una solución 1.0 M de litio bis(trimetilsilil)amida en tetrahidrofurano (20 mL, 20 mmol a temperatura ambiente a una suspensión agitada de bromuro de (3-bromo-4-fluoro-bencil)trifenilfosfonio (10.6 g, 20 mmol) en tetrahidrofurano (40 mL). La mezcla se agita durante 40 minutos, luego se enfría a -20° C y se trata con cloruro de 4-(2-fluoroetoxi)benzoilo (4.1 g, 20 mmol) en tetrahidrofurano (40 mL) y se agita adicionalmente durante 2 horas mientras se calienta lentamente a temperatura ambiente.

Se trata la mezcla con agua (20 mL) y periodato de sodio (4.3 g, 20 mmol) entonces se agita a 50° C durante 18 horas. Luego

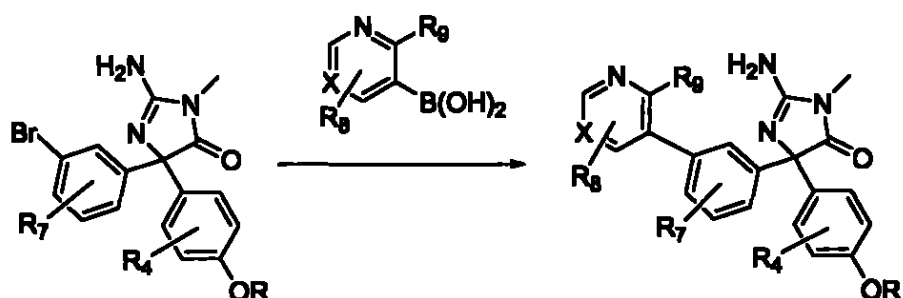
de enfriar a temperatura ambiente la mezcla se extrae con acetato de etilo. Los extractos orgánicos se lavan con solución salina, se secan sobre MgSO_4 . La evaporación y purificación mediante cromatografía flash (Hexano/acetato de etilo 9/1) da un sólido amarillo (3 g, 41 % de rendimiento); ^1H RMN (400 MHz, CDCl_3) δ 4.25 (m, 1H), 4.32 (m, 1H), 4.70 (m, 1H), 4.82 (m, 1H), 7.01 (d, 2H), 7.23 (m, 1H), 7.94 (m, 3H), 8.22 (m, 1H); MS m/e $(\text{M}+\text{CH}_3\text{COO})^-$ 427; pf 107° C.

Etapas d) Preparación de 2-Amino-5-[4-(2-fluoroetoxi)fenil]-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona

Utilizando esencialmente el mismo procedimiento descrito en los Ejemplos 39 y 40 y empleando metilaminoguanidina y ácido 2-fluoropiridina-3-borónico, respectivamente, se obtiene el producto del título como un sólido blanco, pf 135° C, ^1H RMN (400 MHz, $\text{DMSO}-d_6$) δ 2.93 (s, 3H), 4.09 (m, 1H), 4.11 (m, 1H), 4.59 (m, 1H), 4.61 (m, 1H), 6.84 (bs, 2H), 6.86 (m, 2H), 7.30 (m, 3H), 7.44 (m, 1H), 7.52 (m, 2H), 7.95 (m, 1H), 8.26 (m, 1H); MS m/e $(\text{M}-\text{H})^-$ 439.2;.

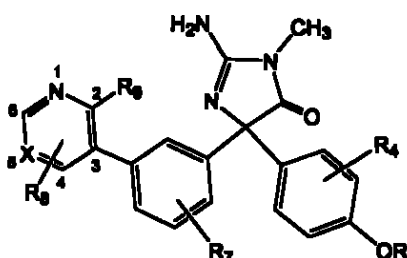
EJEMPLOS 109-124

Preparación de compuestos de 2-Amino-5-alcoxifenil-5-(3-heteroaril)fenil-3-metil-3,5-dihidro-4H-imidazol-4-ona



Utilizando esencialmente el mismo procedimiento descrito en el ejemplo 108 y empleando el ácido borónico apropiado y sustrato de 5-(3-bromofenil)hidantoina, los compuestos que se muestran en la Tabla III se obtienen e identifican por RMN y análisis espectral de masa.

Tabla III

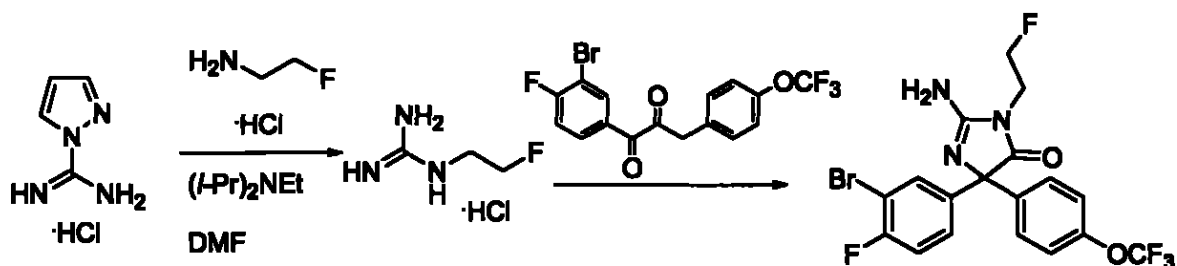


Ej.							Pf
No	R ₄	R	R ₇	R ₈	R ₉	X	°C
109	H	CH ₂ CH ₂ F	4-F	H	H	N	123
110	H	CH ₂ CH ₂ F	H	H	H	CF	--
111	H	CH ₂ CH ₂ F	H	6-F	H	CH	100
112	3-CH ₃	CH ₂ CH ₂ F	4-F	H	F	CH	105-106
113	3-CH ₃	CH ₂ CH ₂ F	4-F	H	H	N	108-110
114	3-CH ₃	CH ₂ C ₆ H ₅	H	H	H	N	107-109
115	3-CH ₃	H	H	H	H	N	168-170
116	3-CH ₃	CH ₂ CH ₂ F	H	H	H	N	108-110
117	3-CH ₃	CH ₂ CN	H	H	H	N	220-222
118	3-CH ₃	i-propilo	H	H	H	N	101-103
119	3-CH ₃	CH ₂ CO ₂ C ₂ H ₅	H	H	H	N	105-107

120	3-CH ₃	C ₂ H ₅	H	H	H	N	106-108
121	3-CH ₃	n-propilo	H	H	H	N	102-104
122	3-CH ₃	i-butilo	H	H	H	N	103-105
123	3-CH ₃	CH ₂ CH ₂ cicloh exilo	H	H	H	N	1-7-109
124	3-CH ₃	n-C ₃ H ₇ -OC ₆ H ₅	H	H	H	N	72-74

EJEMPLO 125

Preparación de 2-Amino-5-(3-bromo-4-fluorofenil)-3-(2-fluoroetil)-5-(4-trifluorometoxi-fenil)-3,5-dihidro-imidazol-4-ona

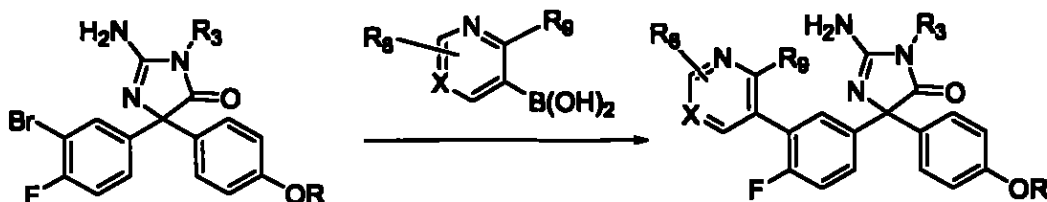


A una mezcla agitada de clorhidrato de 2-fluoroetilamina (1.50 g; 15.1 mmol) y clorhidrato 1H-pirazol-1-carboxamidina (1.77 g; 12.1 mmol) en DMF se agrega diisopropiletilamina (3.58 g; 27.7 mmol). Se agita la mezcla bajo atmósfera de nitrógeno durante 3 horas. Se agrega éter de dietilo (35 mL) y se sacude la mezcla y se le permite al producto aceitoso asentarse en el fondo del frasco, con lo cual se decanta el éter. Esto se repite y el aceite claro se seca bajo alto vacío a temperatura ambiente durante 24 horas. Se utiliza el producto N-(2-fluoroetil)-guanidina (1.6 g) sin purificación adicional.

Una solución de 1-(3-bromo-4-fluoro-fenil)-2-(4-trifluorometoxi-fenil)-etano-1,2-diona (0.181 g; 0.46 mmol) y N-(2-fluoroetil)-guanidina (0.105 g; 0.74 mmol) en una mezcla de dioxano, agua y etanol, se trata con carbonato de sodio sólido caliente a 90° C durante cinco horas, y se evapora hasta secado. El residuo resultante se disuelve en cloroformo, se lava con agua, se seca sobre sulfato de sodio, y se evapora para dar el compuesto del título como un sólido verde claro, 116 mg (52% de rendimiento), MS (API-ES) 480.3 [M+H]⁺.

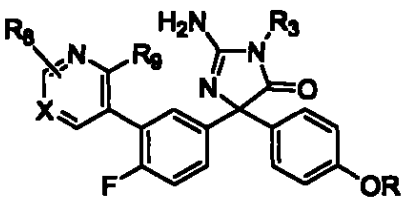
EJEMPLOS 126-128

Preparación de compuestos 2-Amino-3-sustituido-5-(3-heteroaril)fenil-5-(4-trifluorometoxi-fenil)-3,5-dihidro-imidazol-4-ona



Utilizando esencialmente el mismo procedimiento descrito en el ejemplo 108 y empleando el ácido borónico apropiado y 3-alkyl-2-amino-5-(3-bromofenil)hidantoina, los compuestos que se muestran en la Tabla IV se obtienen e identifican por RMN y análisis espectral de masa.

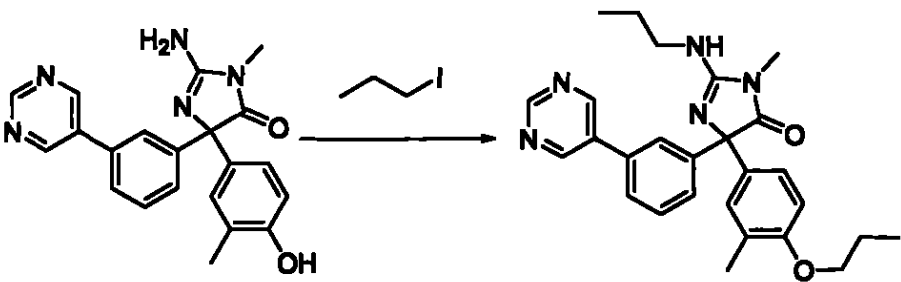
Tabla IV



Ej.						Pf
No	R	R3	R8	R9	X	°C
126	CF ₃	CH ₂ CH ₂ F	H	H	N	166-170
127	CF ₃	CH ₂ CH ₂ F	H	F	CH	138-150
128	CHF ₂	C ₂ H ₅	H	H	C-F	

EJEMPLO 129

Preparación de 3-Metil-5-(3-metil-4-propoxifenil)-2-(propiloamino)-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona

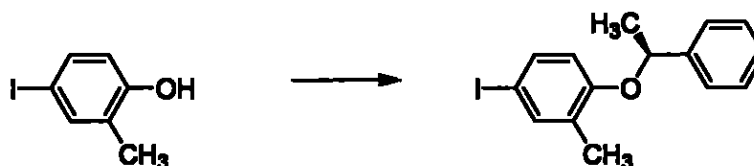


Una solución de 2-amino-5-(4-hidroxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona (74.6 mg, 0.2 mmol) en N,N-dimetilformamida se trata con 2-yodopropano (31.2 mg, 0.4 mmol) y Cs₂CO₃ (130 mg, 0.4 mmol) a temperatura ambiente, se agita durante la noche a temperatura ambiente y se apaga con H₂O. Las fases se separan, la fase acuosa se extrae con acetato de etilo. La fase orgánica se combina con los extractos,

se lava secuencialmente con H₂O y solución salina, se seca sobre MgSO₄ y se evapora hasta secado. El residuo resultante se purifica por cromatografía flash con acetato de etilo/etanol (amoníaco 2M) (90/10) como eluyente para producir el compuesto del título como un sólido blanco, 60 mg (65% de rendimiento), pf 64-66° C; MS (+) ES: 458 (M+H)⁺.

EJEMPLO 130

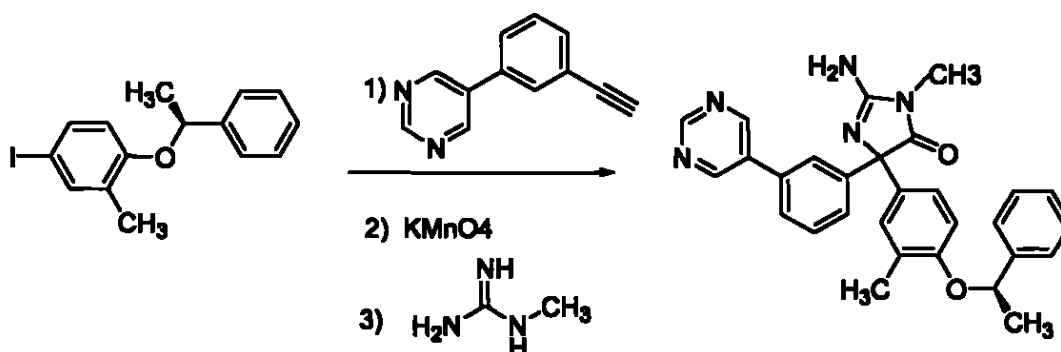
Preparación de 4-yodo-2-metil-1-[(1R)-1-feniletoksi]benceno



Se trata una solución fría de PPh₃ (262 mg 10 mmol) en THF con azodicarboxilato de dietilo (1.74 g, 10 mmol) a 0° C, se agita durante 5 min, se le permite calentarse hasta temperatura ambiente, se trata con 4-yodo-2-metilfenol (1.17 g, 5 mmol) y R(+)-1-feniletanol (1.22 g, 10 mmol), se agita durante 24 h a temperatura ambiente y se concentra en vacío. El residuo resultante se purifica por cromatografía flash (gel de sílice, 100% de Hexano) para producir el compuesto del título como un aceite claro 2.5 g (50%). MS (+): EI 338 M⁺.

EJEMPLO 131

Preparación de 2-amino-3-metil-5-{3-metil-4-[(1R)-1-feniletoksi]fenil}-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona

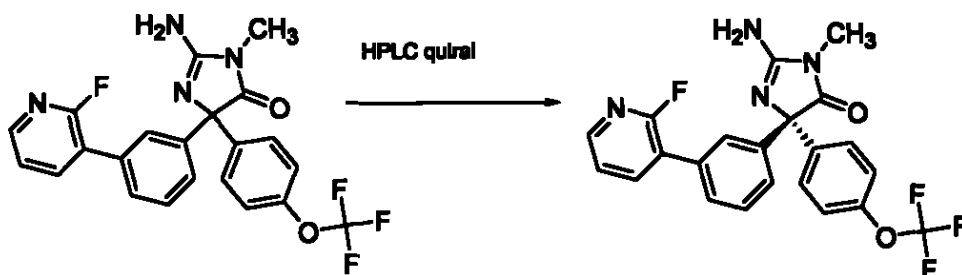


Una solución de 4-yodo-2-metil-1-[(1R)-1-feniletoksi]benceno (10 mmol) en trietilamina se trata con tetrakis(trifenilfosfina)Pd (0.69 mmol), yoduro de cobre (0.97 mmol) y una solución de 3-(pirimidin-5-il)etnilbenceno (10 mmol) en acetonitrilo a temperatura ambiente. La mezcla de reacción se calienta durante 1h a 80° C, se enfría y se concentra en vacío. El residuo resultante se purifica por cromatografía para dar 5-[3-({3-metil-4-[(1R)-1-fenil]etinil}fenil]pirimidina como un aceite, MS (+) ES: 391(M+H)⁺. Una solución de 5-[3-({3-metil-4-[(1R)-1-fenil]etinil}fenil]pirimidina (8.3 mmol) en acetona se trata con una solución caliente (~40°C) de NaHCO₃ (4.98 mmol) y MgSO₄ (12.45 mmol) en agua (80 mmol) seguido por una sola porción de KMnO₄ sólido (8.3 mmol), se agita durante 40 min. a temperatura ambiente y se extrae con 1:1 éter:Hexano. Los extractos se combinan, se secan sobre MgSO₄ y se concentran hasta

secado para dar 1-{3-metil-4-[(1R)-1-feniletoksi]fenil}-2-(3-pirimidin-5-ilfenil)etano-1,2-diona como una espuma, MS (+) ES: 423 (M+H)⁺. Una solución de 1-{3-metil-4-[(1R)-1-feniletoksi]fenil}-2-(3-pirimidin-5-ilfenil)etano-1,2-diona (5.0 mmol) en etanol se trata con clorhidrato de N-metilguanidina (5.5 mmol) y una solución acuosa de Na₂CO₃ (10.0 mmol), se calienta a temperatura de reflujo durante 1 h y se concentra en vacío. El residuo resultante se purifica por cromatografía para producir el producto del título como un sólido blanco, pf 112-114° C. MS (+) ES: 478 (M+H)⁺.

EJEMPLO 132

Preparación de (5R)-2-Amino-5-[3-(2-fluoropiridin-3-il)fenil]-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona



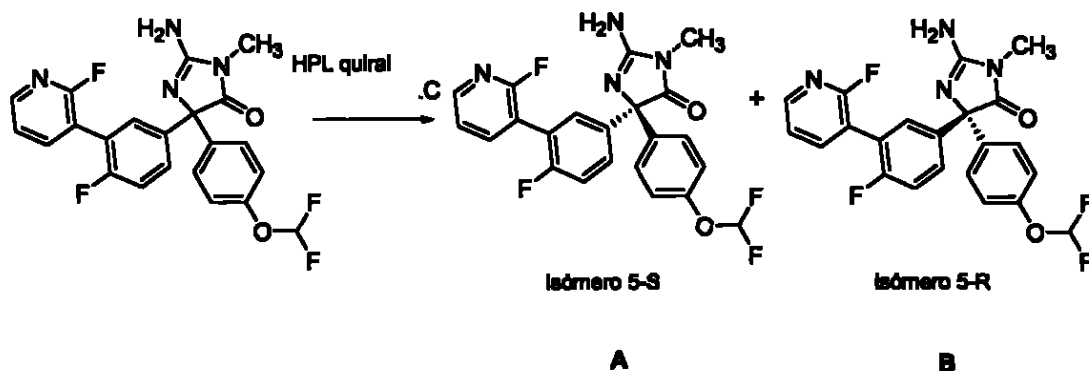
Una mezcla racémica de 2-amino-5-[3-(2-fluoropiridin-3-il)fenil]-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral utilizando Chiralcel AD, 2x25 cm (columna) con fase móvil 9% EtOH en Hexanos (0.1% dietilamina) para dar el isómero R del título: $[\alpha]_{25} = -13.4$ (1% en MeOH); ¹H RMN (DMSO-d₆, 300 MHz) δ 2.95 (s, 3H), 6.65 (brs, 2H),

nn191

7.28 (d, 2H), 7.4-7.45 (m, 3H), 7.5 (m, 1H), 7.55 (d, 2H), 7.65 (d, 1H), 7.95-8.0 (m, 1H), 8.2 (m, 1H); MS m/e (M+H)⁺ 445.

EJEMPLO 133

Preparación de (5S)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



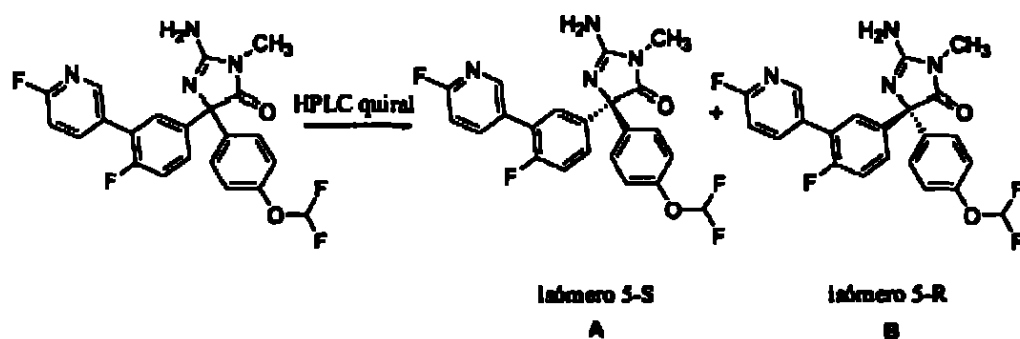
Una mezcla racémica de 2-amino-5-[4-(difluorometoxi)fenil]-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral: Chiralcel AD, 2x25 cm (columna) con fase móvil 9% EtOH en Hexanos/TFA para dar el producto del título A, $[\alpha]_{25} = +11.4$ (1% en MeOH); ¹H RMN (DMSO-d₆, 300 MHz) δ 3.12 (s, 3H), 7.25 (m, 3H), 7.4-7.5 (m, 4H), 7.5 (m, 2H), 8.0 (m, 1H), 8.6 (m, 1H), 9.5-9.7 (br, 2H); MS m/e (M+H)⁺ 445 y

el producto del título B, $[\alpha]_{25} = -10.4$ (1% en MeOH); ¹H RMN (DMSO-d₆, 300 MHz) δ 3.12 (s, 3H), 7.25 (m, 3H), 7.4-7.5 (m, 4H),

7.5 (m, 2H), 8.0 (m, 1H), 8.6 (m, 1H), 9.5-9.7 (br, 2H); MS m/e (M+H)⁺ 445.

EJEMPLO 134

Preparación de (5S)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[4-fluoro-3-(6-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[4-fluoro-3-(6-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



Una mezcla racémica de 2-amino-5-[4-(difluorometoxi)fenil]-5-[4-fluoro-3-(6-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral: Chiralcel OJ, 0.46x10 cm (columna) con fase móvil 15% EtOH en Hexanos para dar el isómero S del título (A): $[\alpha]_{25} = +6$ (1% en MeOH); ¹H RMN (DMSO-d₆, 300 MHz) δ 2.94 (s, 3H), 6.8 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.28 (m, 2H), 7.4-7.5 (m, 3H), 7.6 (dd, 1H), 8.05 (m, 1H), 8.3 (s, 1H); MS m/e (M+H)⁺ 445 y el isómero R del título (B): $[\alpha]_{25} = -7.4$ (1% en MeOH); ¹H RMN (DMSO-d₆, 300 MHz) δ 2.94 (s, 3H), 6.8 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.28 (m, 2H),

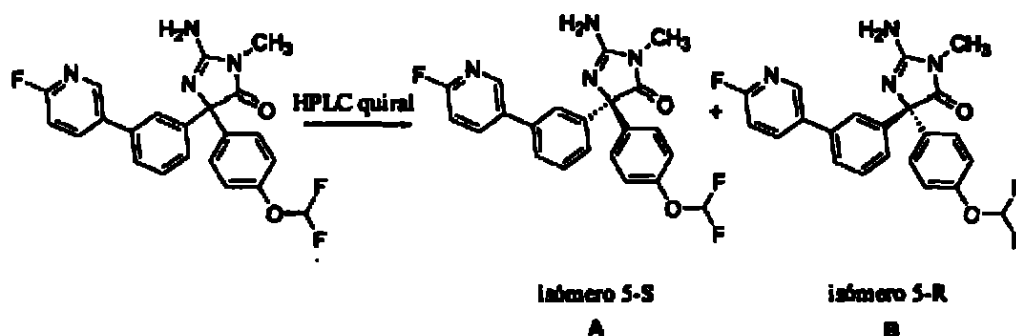
7.45 (d, 2H), 7.4-7.5 (m, 1H), 7.6 (dd, 1H), 8.05 (m, 1H), 8.3 (s, 1H); MS m/e (M+H)⁺ 445.

EJEMPLO 135

Preparación de (5S)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[3-(6-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona

[A] y (5R)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[3-(6-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona

[B]

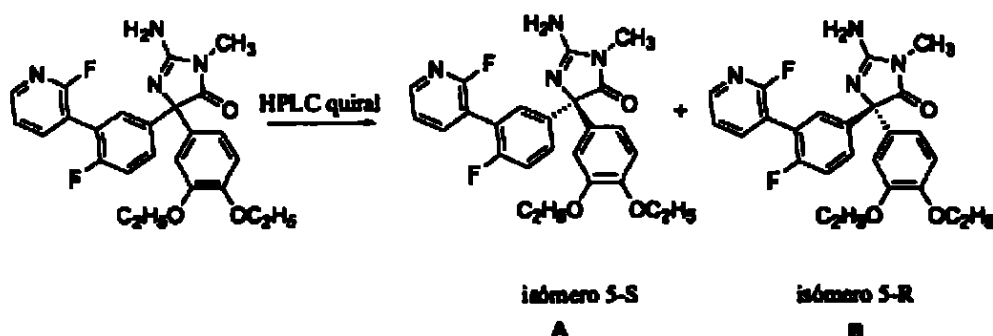


Una mezcla racémica de 2-Amino-5-[4-(difluorometoxi)fenil]-5-[3-(6-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral: Chiralcel OJ, 0.46x10 cm (columna) con fase móvil 15% EtOH en Hexanos para dar el isómero S del título (A): $[\alpha]_{25} = -7.4$ (1% en MeOH); ¹H RMN (DMSO-d₆ 300 MHz) δ 2.95 (s, 3H), 6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.25 (dd, 1H), 7.4 (t, 1H), 7.5-7.55 (m, 4H), 7.7 (s, 1H), 8.2 (m, 1H), 8.37 (s, 1H); MS m/e (M+H)⁺ 427; y el isómero R del título (B): $[\alpha]_{25} = +8.4$ (1% en MeOH); ¹H RMN (DMSO-d₆ 300 MHz) δ 2.95 (s, 3H), 6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.25

(dd, 1H), 7.4 (t, 1H), 7.5-7.55 (m, 4H), 7.7 (s, 1H), 8.2 (m, 1H), 8.37 (s, 1H); MS m/e (M+H)⁺ 427.

EJEMPLO 136

Preparación de (5S)-2-Amino-5-(3,4-dietoxifenil)-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-(3,4-dietoxifenil)-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



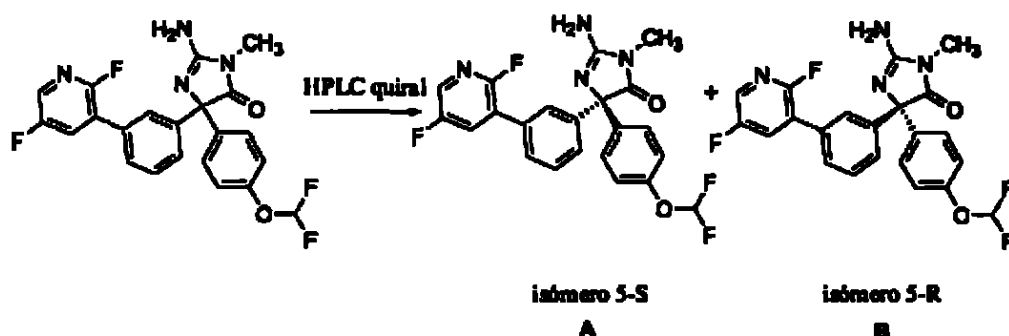
Una mezcla racémica de 2-amino-5-(3,4-dietoxifenil)-5-[4-fluoro-3-(2-fluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa utilizando una columna WhelkO, HPLC quiral 2x25 cm y 20% EtOH en heptano con 1% trietilamina, como el eluyente para dar el isómero S del título (A) como un sólido blanco, $[\alpha]_{25} = -22.2$, 1% en metanol; ¹H RMN (DMSO-d₆, 300 MHz) δ 1.3 (t, 6H), 2.9 (s, 3H), 3.9 (dxq, 4H), 6.6 (b, 2H), 6.8 (d, 1H) 7.0 (m, 2H), 7.3 (t, 1H), 7.5 (m, 3H), 7.9 (s, 1H), 8.3 (m, 1H); MS m/e (M)⁺ 467; y el isómero R del título (B) como un sólido blanco, $[\alpha]_{25} = +26.0$, 1% en metanol; ¹H RMN (DMSO-d₆, 300 MHz) δ 1.3 (t, 6H), 2.9 (s, 3H), 3.9 (dxq, 4H), 6.6 (b, 2H), 6.8 (d, 1H) 7.0 (m, 2H),

nn105 144.

7.3 (t, 1H), 7.5 (m, 3H), 7.9 (s, 1H), 8.3 (m, 1H); MS m/e (M)⁺ 467.

EJEMPLO 137

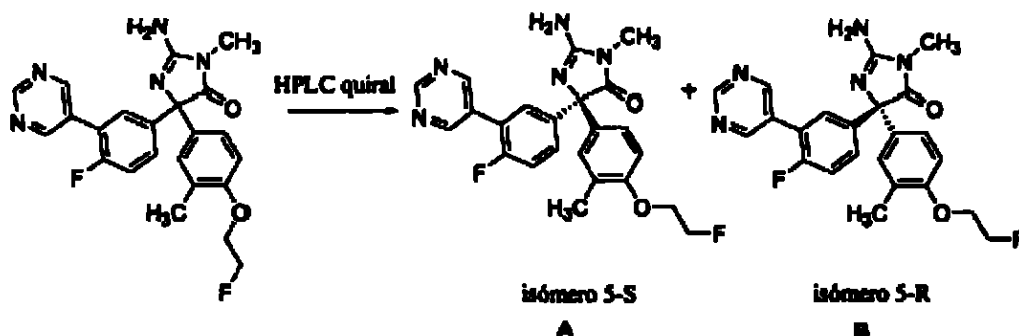
Preparación de (5S)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[3-(2,5-difluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-[4-(difluorometoxi)fenil]-5-[3-(2,5-difluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



Una mezcla racémica de 2-amino-5-[4-(difluorometoxi)fenil]-5-[3-(2,5-difluoropiridin-3-il)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral: Chiralcel OJ, 2x25 cm (columna) con fase móvil 35% EtOH en Hexanos/DEA para dar el isómero S del título (A): $[\alpha]_{25} = +2.8$ (1% en MeOH); ¹H RMN (DMSO-d₆, 300 MHz) δ 2.94 (s, 3H), 6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.4-7.5 (m, 5H), 7.7 (s, 1H), 8.0 (m, 1H), 8.2 (m, 1H); MS m/e (M+H)⁺ 445; y el isómero R del título (B): $[\alpha]_{25} = +2.8$ (1% en MeOH); ¹H RMN (DMSO-d₆, 300 MHz) δ 2.94 (s, 3H), 6.7 (brs, 2H), 7.08 (d, 2H), 7.12 (t, 1H), 7.4-7.5 (m, 5H), 7.7 (s, 1H), 8.0 (m, 1H), 8.2 (m, 1H); MS m/e (M+H)⁺ 445.

EJEMPLO 138

Preparación de (5S)-2-Amino-5-[4-(2-fluoroetoxi)-3-metilfenil]-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona [A]
y (5R)-2-Amino-5-[4-(2-fluoroetoxi)-3-metilfenil]-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona [B]

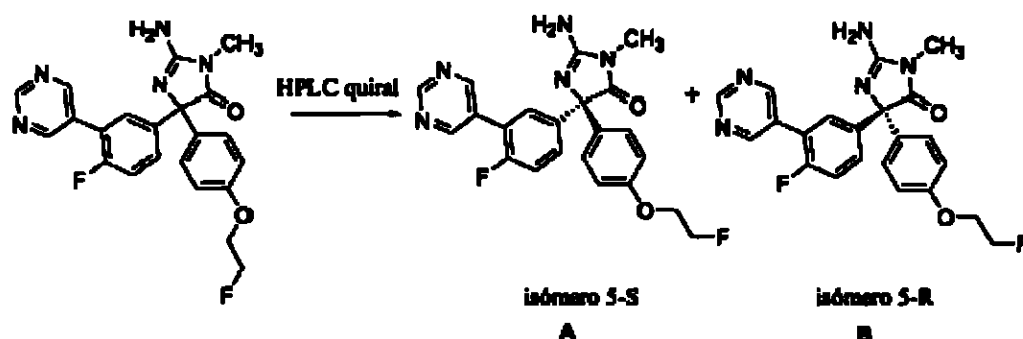


Utilizando esencialmente el mismo procedimiento descrito en los Ejemplos 133-137 y empleando una mezcla racémica de 2-amino-5-[4-(2-fluoroetoxi)-3-metilfenil]-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona, el isómero S del título (A) se obtiene como un sólido blanco, pf 116-118° C; $[\alpha]_{25} = -31.46$ (1% en DMSO); MS(+)ES: 438 (M+H)⁺; y el isómero R del título se obtiene como un sólido blanco, pf 112-114 ° C; $[\alpha]_{25} = +35$ (1% en DMSO); MS(+)ES: 438 (M+H)⁺.

EJEMPLO 139

Preparación de (5S)-2-Amino-5-[4-(2-fluoroetoxi)fenil]-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-

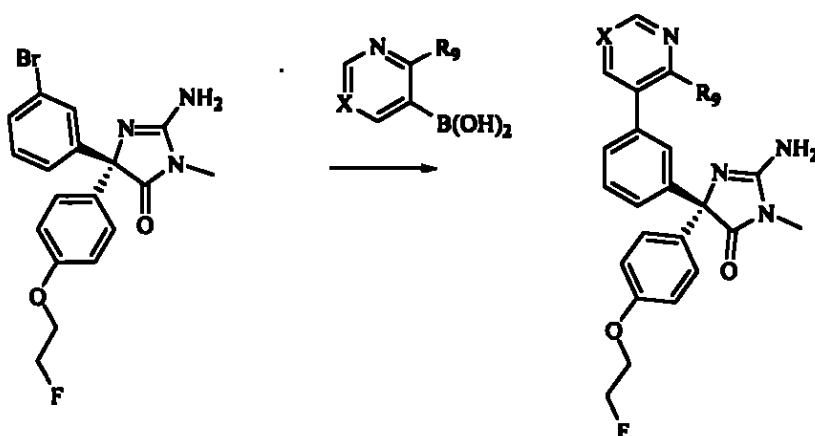
ona [A] y (5R)-2-Amino-5-[4-(2-fluoroetoxi)fenil]-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



Una mezcla racémica de 2-amino-5-[4-(2-fluoroetoxi)fenil]-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral: Chiralcel AD, 2 x 25 cm utilizando fase móvil EtOH:Hexano (15:85) y un índice de flujo de 20 mL/min para dar el isómero S del título (A) como un sólido blanco, pf 120° C; $[\alpha]_{25} = -35.09$ (0.53% en MeOH); ^1H RMN (400 MHz, DMSO- d_6) δ 2.97 (s, 3H), 4.14-4.15 (m, 1H), 4.20-4.21 (m, 1H,) 4.65-4.66 (m, 1H), 4.74-4.75 (m, 1H), 6.67 (bs, 2H), 6.88-6.89 (d, 2H), 7.34 (m, 1H), 7.35-7.37 (d, 2H), 7.57, (m, 1H), 7.65 (m, 1H), 8.92 (s, 2H), 9.22 (s, 1H).; MS m/e (M-H)⁻ 422.1; y el isómero R del título como un sólido blanco, pf 120° C; $[\alpha]_{25} = +31.2$ (1% en MeOH); ^1H RMN (400 MHz, DMSO- d_6) δ 2.97 (s, 3H), 4.15-4.16 (m, 1H,), 4.20-4.21 (m, 1H), 4.65-4.66 (m, 1H), 4.74-4.75 (m, 1H), 6.67 (bs, 2H), 6.88-6.89 (d, 2H), 7.34 (m, 1H), 7.35-7.37 (d, 2H), 7.55, (m, 1H), 7.65 (m, 1H), 8.92 (s, 2H), 9.22 (s, 1H); MS m/e (M-H)⁻ 422.1.

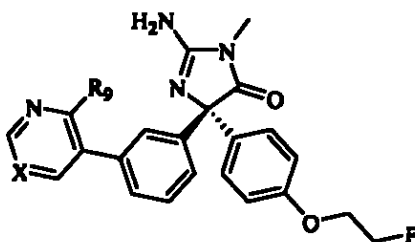
EJEMPLOS 140 Y 141

Preparación de compuestos de (5S)-2-Amino-5-[4-(2-fluoroetoxi)fenil]-3-metil-5-(3-heteroarilfenil)-3,5-dihidro-4H-imidazol-4-ona



Utilizando esencialmente el mismo procedimiento descrito en el ejemplo 40 y empleando (5S)-2-amino-5-(3-bromofenil)-5-[4-(2-fluoroetoxi)fenil]-3-metil-3,5-dihidro-4H-imidazol-4-ona y un ácido heteroarilborónico adecuado, los compuestos que se muestran en la Tabla V se obtienen e identifican por HRMN y análisis espectral de masa.

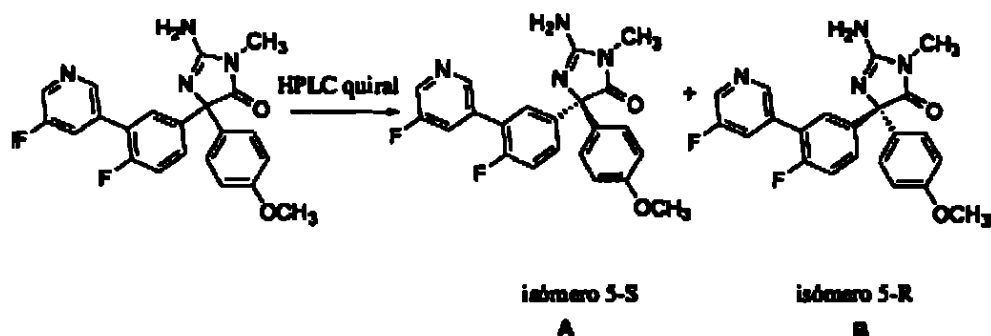
TABLA V



Ej.				pf
No	R ⁹	X	[α] ₂₅	°C
140	H	N	-18.4 (1% MeOH)	145
141	F	CH	--	106

EJEMPLO 142

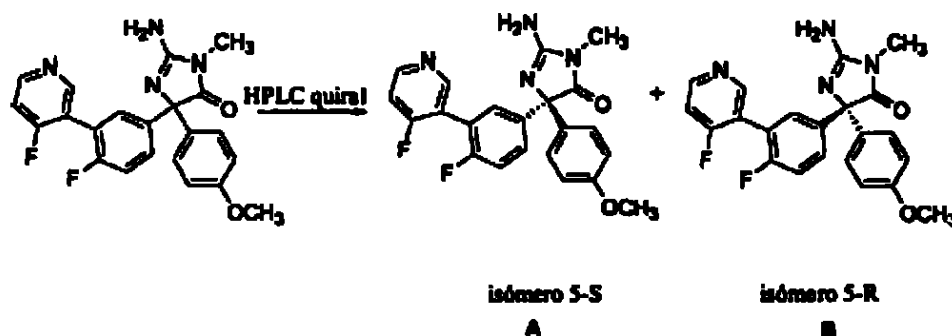
Preparación de (5S)-2-Amino-5-[4-fluoro-3-(5-fluoropiridin-3-il)fenil]-5-(4-metoxifenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-[4-fluoro-3-(5-fluoropiridin-3-il)fenil]-5-(4-metoxifenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



Una mezcla racémica de 2-amino-5-[4-fluoro-3-(5-fluoropiridin-3-il)fenil]-5-(4-metoxifenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral: Chiralcel OJ, 2x25 cm (columna) con fase móvil 30% EtOH en Hexanos (0.1% dietilamina) para dar el isómero S del título (A): $[\alpha]_{25} = -37.6$ (1% en MeOH); ^1H RMN (DMSO- d_6 300 MHz) δ 2.93 (s 3H), 3.63 (s 3H), 6.6 (brs, 2H), 6.8 (d, 2H), 7.22-7.35 (m, 3H), 7.5 (m, 1H), 7.6 (dd, 1H), 7.8 (m, 1H), 8.5 (d, 1H), 8.6 (d, 1H); MS m/e (M+H) $^+$ 409 y el isómero R del título (B): $[\alpha]_{25} = +35.4$ (1% en MeOH); ^1H RMN (DMSO- d_6 300 MHz) δ 2.93 (s 3H), 3.63 (s 3H), 6.6 (brs, 2H), 6.8 (d, 2H), 7.22-7.35 (m, 3H), 7.5 (m, 1H), 7.6 (dd, 1H), 7.8 (m, 1H), 8.5 (d, 1H), 8.6 (d, 1H); MS m/e (M+H) $^+$ 409.

EJEMPLO 143

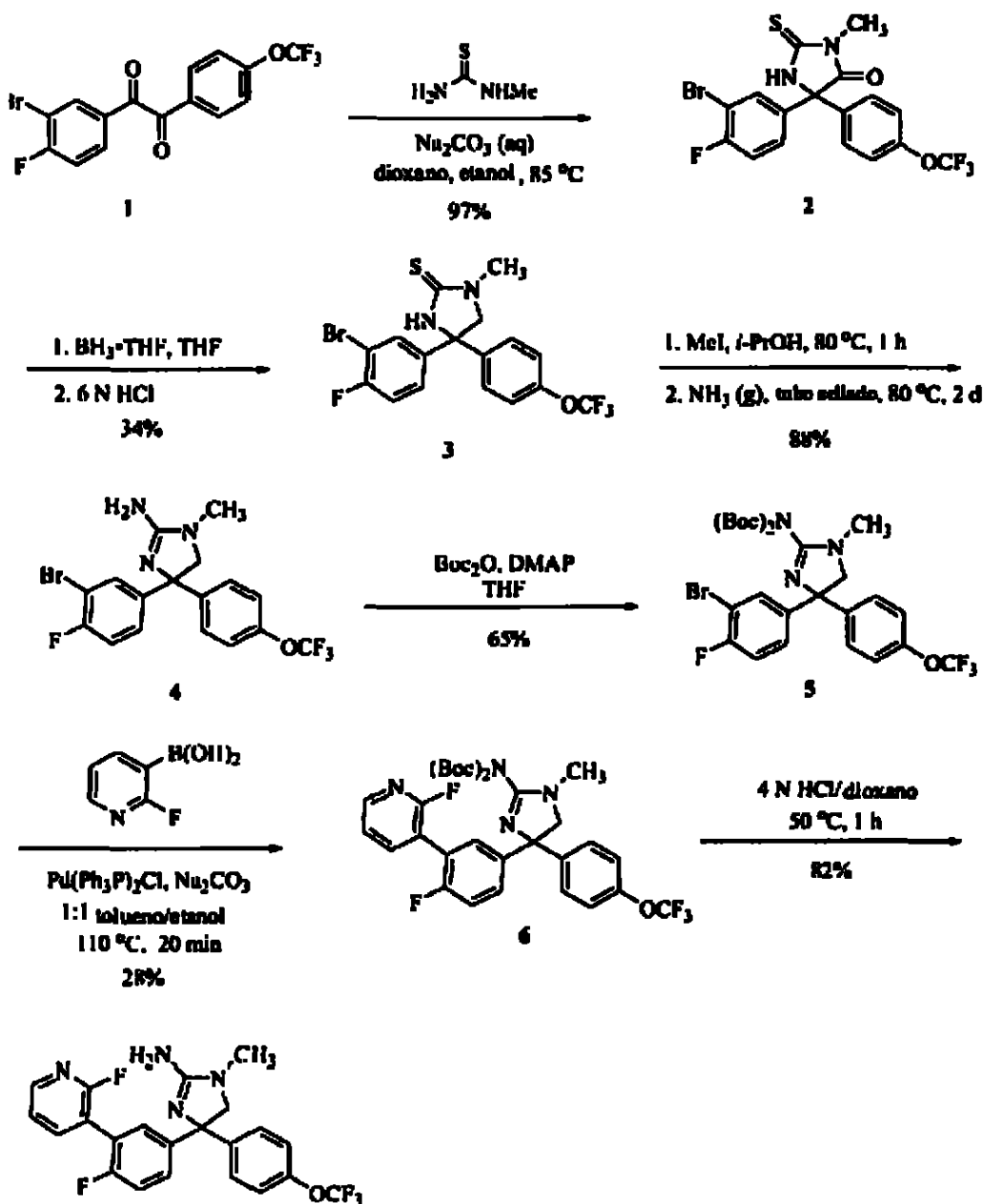
Preparación de (5S)-2-Amino-5-[4-fluoro-3-(4-fluoropiridin-3-il)fenil]-5-(4-metoxifenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [A] y (5R)-2-Amino-5-[4-fluoro-3-(4-fluoropiridin-3-il)fenil]-5-(4-metoxifenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona [B]



Una mezcla racémica de 2-amino-5-[4-fluoro-3-(4-fluoropiridin-3-il)fenil]-5-(4-metoxifenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona se separa por HPLC quiral: Chiralcel OJ, 0.46x25 cm (columna) con fase móvil 80% EtOH en Hexanos (0.1% dietilamina) para dar el isómero S del título (A): $[\alpha]_{25} = -40$ (1% en MeOH); ^1H RMN (DMSO- d_6 , 300 MHz) δ 2.93 (s, 3H), 3.66 (s, 3H), 6.65 (brs, 2H), 6.8 (d, 2H), 7.3 (m, 3H), 7.43 (m, 1H), 7.52 (m, 2H), 8.55 (d, 1H), 8.63 (t, 1H); MS m/e (M+H) $^+$ 409; y el isómero R del título (B): $[\alpha]_{25} = +38.8$ (1% en MeOH); ^1H RMN (DMSO- d_6 , 300 MHz) δ 2.93 (s, 3H), 3.66 (s, 3H), 6.65 (brs, 2H), 6.8 (d, 2H), 7.3 (m, 3H), 7.43 (m, 1H), 7.52 (m, 2H), 8.55 (d, 1H), 8.63 (t, 1H), MS m/e (M+H) $^+$ 409.

EJEMPL 144

Preparación de 4-[4-Fluoro-3-(2-fluoropiridin-3-il)fenil]-1-metil-4-(4-trifluorometoxifenil)-4,5-dihidro-1H-imidazol-2-ilamina



Etapa a) Preparación del compuesto 2

Una mezcla de 1 (2.00 g, 5.1 mmol) y 1-metil-2-tiourea (2.07 g, 23.0 mmol) en etanol (50 mL) y dioxano (50 mL) se agita a temperatura ambiente durante 5 min. Se agrega una solución de carbonato de sodio (2.44 g, 23.0 mmol) en agua (20 mL) y la reacción se agita a 85° C durante 15 min. La reacción luego se enfría a temperatura ambiente, se concentra y se diluye con acetato de etilo (100 mL) y solución salina (20 mL). La capa orgánica se separa y se lava con solución salina (10 mL), se seca sobre sulfato de sodio, se filtra y se concentra. Purificación por cromatografía flash (sílice, 1:9 acetato de etilo/Hexanos) produce 2 (2.30 g, 97%) como un sólido amarillo: ^1H RMN (300 MHz, CD_3OD) δ 7.61 (dd, $J = 6.3, 2.4$ Hz, 1H), 7.46–7.27 (m, 6H), 3.27 (s, 3H).

Etapas b) Preparación del compuesto 3

Una mezcla de 2 (2.20 g, 4.75 mmol) y 1.0 M complejo de tetrahidrofurano borano en tetrahidrofurano (47.5 mL, 47.5 mmol) en tetrahidrofurano (66 mL) se calienta a reflujo durante la noche, entonces se trata con HCl 6 N (24 mL, 143 mmol) y se calienta a 80° C durante 1 h. La reacción se enfría a temperatura ambiente, se neutraliza con bicarbonato de sodio sólido (12.0 g, 143 mmol) y se diluye con acetato de etilo (200 mL). La capa orgánica se separa y se lava con solución salina (20 mL), se seca sobre sulfato de sodio, se filtra y se concentra. Purificación por cromatografía flash (sílice, 1:9 a 2:8 acetato de etilo/Hexanos) produce 3 (0.73 g, 34%) como un aceite incoloro: ^1H RMN (300 MHz, CDCl_3) δ 8.14 (s, 1H), 7.42 (m, 1H), 7.31–7.05

(m, 6H), 4.18 (s, 2H), 3.19 (s, 3H); ESI MS m/z 450 $[C_{17}H_{13}BrF_4N_2OS + H]^+$.

Etapas c) Preparación del compuesto 4

Una mezcla de 3 (0.73 g, 1.63 mmol), yoduro de metilo (0.25 g, 1.79 mmol) en isopropanol (10 mL) se calienta a 80° C durante 1 h, se concentra, se redisuelve en isopropanol (20 mL), se enfría a 0° C y se carga con gas de amoníaco (2.0 g). El vaso de reacción se sella y se calienta a 80° C durante 48 h. La reacción se enfría a temperatura ambiente, se concentra y se purifica por cromatografía flash (100:0:0 a 80:20:0.5 cloruro de metileno/metanol/hidróxido de amonio concentrado) produce 4 (0.62 g, 88%) como un almíbar incoloro: ^1H RMN (300 MHz, CD_3OD) δ 7.62 (dd, J = 6.3, 2.4 Hz, 1H), 7.61–7.20 (m, 6H), 4.35 (s, 2H), 3.08 (s, 3H); ESI MS m/z 432 $[C_{17}H_{14}BrF_4N_3O + H]^+$.

Etapas d) Preparación del compuesto 5

Una mezcla de 4 (0.52 g, 1.20 mmol), 4-dimetilaminopiridina (0.77 g, 6.32 mmol) y di-terc-butilodicarbonato (1.38 g, 6.32 mmol) en tetrahidrofurano (5 mL) se agita a temperatura ambiente durante 1 h y se concentra. Purificación por cromatografía flash (sílice, 1:9 a 2:8 acetato de etilo/Hexanos) produce 5 (0.49 g, 65%) como un sólido blanco: ^1H RMN (300 MHz, CD_3OD) δ 7.67 (dd, J = 6.6, 2.1 Hz, 1H), 7.44–7.03 (m, 6H), 4.05 (d, J = 9.9 Hz, 1H), 3.86 (d, J = 9.9 Hz, 1H), 2.79 (s, 3H), 1.39 (s, 18H); ESI MS m/z 632 $[C_{27}H_{30}BrF_4N_3O_5 + H]^+$.

Etapas e) Preparación del compuesto 6.

Una mezcla de 5 (0.19 g, 0.300 mmol), ácido 2-fluoropiridina-3-borónico (0.064 g, 0.451 mmol), carbonato de sodio (0.096 g, 0.900 mmol), bicloruro de bis(trifenilfosfino)paladio (II) (0.021 g, 0.030 mmol) y trifenilfosfina (0.016 g, 0.060 mmol) en 1:1 tolueno/EtOH (10 mL) se desgasifica y se calienta a 110° C durante 20 min. La mezcla se enfría a temperatura ambiente y se concentra. Purificación por cromatografía flash (sílice, 1:9 a 4:6 acetato de etilo/Hexanos) produce 6 (0.055 g, 28%) como un sólido blanco: ^1H RMN (500 MHz, CDCl_3) δ 8.24 (m, 1H), 7.82 (m, 1H), 7.48-7.11 (m, 8H), 4.03 (d, $J = 9.5$ Hz, 1H), 3.95 (d, $J = 9.5$ Hz, 1H), 2.78 (s, 3H), 1.31 (s, 18H); ESI MS m/z 649 [$\text{C}_{32}\text{H}_{23}\text{F}_5\text{N}_4\text{O}_5 + \text{H}$] $^+$.

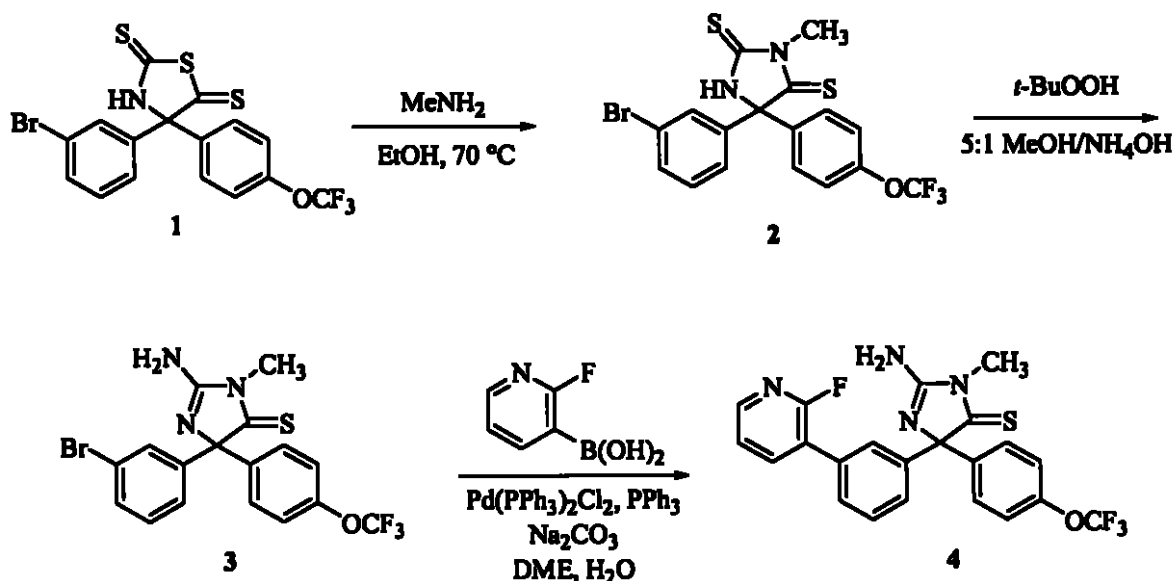
Etapas f) Preparación de 4-[4-fluoro-3-(2-fluoro-piridin-3-il)-fenil]-1-metil-4-(4-trifluorometoxi-fenil)-4,5-dihidro-1H-imidazol-2-ilamina

Una mezcla de 6 (0.055 g, 0.085 mmol) y 4 M cloruro de hidrógeno en dioxano (5 mL) se calienta a 50° C durante 1 h, se enfría a temperatura ambiente y se concentra. La mezcla de reacción entonces se diluye con cloroformo (50 mL) y bicarbonato de sodio (10 mL). La capa orgánica se separa y se lava con solución salina (20 mL), se seca sobre sulfato de sodio, se filtra y se concentra. Purificación por HPLC preparativo da el producto del título como un sólido blanco, 0.031 g (82% de

rendimiento), pf 65-70° C; ^1H RMN (500 MHz, CD_3OD) δ 8.22 (m, 1H), 7.95 (m, 1H), 7.35-7.23 (m, 8H), 4.10 (t, $J = 7.5\text{Hz}$, 2H), 2.93 (t, $J = 7.5\text{ Hz}$, 3H); IR (ATR) 3059, 2926, 1670, 1641, 1570, 1503, 1427, 1253, 1201, 1161, 829, 804, 765, 718 cm^{-1} ; ESI MS m/z 449 $[\text{C}_{22}\text{H}_{17}\text{F}_5\text{N}_4\text{O} + \text{H}]^+$.

EJEMPLO 145

Preparación de 2-Amino-5-[3-(2-fluoro-piridin-3-il)-fenil]-3-metil-5-(4-trifluorometoxi-fenil)-3,5-dihidro-imidazol-4-tiona



Etap a) Preparación del compuesto 2

Una mezcla de clorhidrato de metilamina (0.210 g, 3.18 mmol), trietilamina (0.320 g, 3.18 mmol) y 1 (0.470 g, 1.06 mmol) en etanol se agita a 70° C durante 1h. Los solventes se evaporan y se particiona el residuo entre acetato de etilo y agua. La capa orgánica se separa y se lava con solución salina (30 mL), se secan sobre sulfato de sodio, se filtra y se concentra para

producir 2 (0.460 g, 99%) como un sólido amarillo: ^1H RMN (300 MHz, CDCl_3) δ 7.71 (br s, 1H), 7.58–7.49 (m, 2H), 7.37 (d, J = 8.9 Hz, 2H), 7.30–7.19 (m, 3H), 3.68 (s, 3H).

Etapas b) Preparación del compuesto 3

Una mezcla de 2 (0.458 g, 1.05 mmol) y hidropéroxido de *t*-butilo (1.88 g de una solución en agua 70%, 21.0 mmol) en metanol (50 mL) y se concentra hidróxido de amonio acuoso (10 mL) se agita durante la noche a temperatura ambiente. Después de este tiempo, se agrega 10% de tiosulfato de sodio acuoso (30 mL); la mezcla se concentra para remover la mayoría de metanol y luego la mezcla acuosa se diluye con cloruro de metileno. La capa orgánica se separa, se lava con solución salina (30 mL), se seca sobre sulfato de sodio, se filtra y se concentra. La purificación del residuo resultante por cromatografía flash (sílice, 95:5 cloruro de metileno/metanol) produce 3 (0.250 g, 57%) como un sólido blanco: ^1H RMN (300 MHz, CDCl_3) δ 7.88 (t, J = 1.7 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.72–7.65 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H); ESI MS m/z 444 $[\text{C}_{17}\text{H}_{13}\text{BrF}_3\text{N}_3\text{OS} + \text{H}]^+$.

Etapas c) Preparación de 2-amino-5-[3-(2-fluoro-piridin-3-il)-fenil]-3-metil-5-(4-trifluorometoxi-fenil)-3,5-dihidro-imidazol-4-ona

Una mezcla de 3 (0.16 g, 0.38 mmol), ácido 2-fluoropiridina-3-borónico (0.075 g, 0.530 mmol), cloruro de

bis(trifenilfosfino)paladio (II) (0.013 g, 0.019 ~~mmol~~^{nmol}),
trifenilfosfina (0.010 g, 0.038 mmol) y carbonato de sodio (0.121
g 1.14 mmol) en 3:1 DME/agua (6.0 mL) se calienta a 80° C durante
1 h. La mezcla se enfría a temperatura ambiente y se concentra en
vacío. El residuo resultante se diluye con acetato de etilo y
agua. La capa orgánica se separa y se lava con solución salina
(20 mL), se seca sobre sulfato de sodio, se filtra y se
concentra. La purificación de este residuo por cromatografía
flash (sílice, 97:2.5:0.5 cloruro de metileno/metanol/hidróxido
de amonio concentrado) produce 0.087 g de un sólido amarillo
pálido. Este material se liofiliza de 1:1 acetonitrilo/agua (6
mL) para producir el producto del título como un sólido amarillo
pálido, 0.069 g (39% de rendimiento), pf 89-99° C; ¹H RMN (300
MHz, CDCl₃) δ 8.17 (dt, *J* = 4.8, 1.5 Hz, 1H), 7.86-7.79 (m, 1H),
7.65 (br s, 1H), 7.55-7.48 (m, 4H), 7.44-7.38 (m, 1H), 7.27-7.25
(m, 1H), 7.14 (d, *J* = 8.9 Hz, 2H), 3.48 (s, 3H); ESI MS *m/z* 461
[C₂₂H₁₆F₄N₄OS + H]⁺;

EJEMPLO 146

Evaluación de la Inhibición de hBACE1, MuBACE1 y hBACE2 mediante Compuestos de Ensayo

Condiciones de Ensayo: 10 nM de BACE1 humano (o 10 nM de
BACE1 de Murino, 1.5 nM de BACE2 de humano) 25 μM de sustrato
(WABC-6, MW 1549.6, de AnaSpec); condiciones de amortiguador
final: 50 mM Na-Acetato, pH 4.5, 0.05% de CHAPS, 25% de PBS;
temperatura: temperatura ambiente; información del reactivo :Na-
Acetato: Aldrich, Cat.# 24,124-5 CHAPS: de Research Organics,

Cat. # 1304C 1X PBS: Mediatech (Cellgro), Cat# 21-031-CV; sustrato de péptido AbzSEVNLDAEFRDpa: AnaSpec, Nombre del Péptido: WABC-6; determinación del sustrato madre (AbzSEVNLDAEFRDpa) concentración: a 25 mM de solución madre de sulfóxido de dimetilo (DMSO) se prepara utilizando el peso del péptido y MW y se diluye a 25 μ M. La concentración se determina por absorbancia a 354 nm utilizando un coeficiente de extinción ϵ de 18172 $M^{-1}cm^{-1}$, El sustrato madre se almacena en pequeñas alícuotas a $-80^{\circ}C$. [Sustrato madre] = $ABS^{354\text{ nm}} \cdot 10^6 / 18172$ (en mM)

Determinación de la Concentración de Enzima de Almacenamiento: La concentración de almacenamiento de cada enzima se determina mediante ABS 280 nm utilizando ϵ de 64150 $M^{-1}cm^{-1}$ para hBACE1 y MuBACE1, 62870 $M^{-1}cm^{-1}$ para BACE2 en Clorhidrato de Guanidina 6 M (de Research Organics, Cat. # 5134G-2), pH 6.

(El coeficiente de extinción $\epsilon^{280\text{ nm}}$ para cada enzima se calcula con base en una composición de aminoácido conocida y los coeficientes de extinción publicados para los residuos Trp (5.69 $M^{-1}cm^{-1}$) y Tyr (1.28 $M^{-1}cm^{-1}$) (Anal. Biochem. 182,319-326).

Etapas de dilución y de mezcla: volumen de reacción total: 100 μ L

1. Se preparan disoluciones de inhibidor 2X en amortiguador A (66.7 mM Na-Acetato, pH 4.5, 0.0667% CHAPS),
2. Se preparan dilución de enzima 4X en amortiguador A (66.7 mM Na-Acetato, pH 4.5, 0.0667% CHAPS),

3. Se preparan dilución de sustrato de 100 μM en 1X PBS,
4. Inhibidor 2X 50 μL y sustrato 25 μL 100 μM se agrega a cada pozo de placa de 96 pozos (de DYNEX Technologies, VWR #: 11311-046), se agrega inmediatamente 25 μL de enzima 4X al inhibidor y a la mezcla de sustrato, se inicia las lecturas de fluorescencia.

Lecturas de Fluorescencia: Lecturas a λ_{ex} 320 nm y λ_{em} 420 nm se toman cada una 40 seg durante 30 min a temperatura ambiente y se determina la pendiente lineal para el índice de clivaje del sustrato (v_i).

Cálculo de % Inhibición: % Inhibición = $100 * (1 - v_i/v_o)$

v_i : índice de clivaje de sustrato en la presencia de inhibidor

v_o : índice de clivaje de sustrato en la ausencia del inhibidor

Determinación IC_{50} : % de Inhibición = $((B * \text{IC}_{50}^n) + (100 * I_0^n)) / (\text{IC}_{50}^n + I_0^n)$.

Ensayo Cinético Fluorescente para BACE2 recombinante Humana

Este ensayo se utiliza para suministrar parámetros cinéticos y de selectividad para los análisis de los compuestos ensayados.

Materiales y Métodos: condiciones de ensayo final: 10 nM de BACE1 humano (o 10 nM de BACE1 de Murino, 1.5 nM de BACE2 de humano) 25 μM de sustrato (WABC-6, MW 1549.6, de AnaSpec). Condiciones de amortiguador final: 50 mM de Na-Acetato, pH 4.5,

0.05% de CHAPS, 25% de PBS. Temperatura: temperatura ambiente.
Información del reactivo: Na-Acetato: Aldrich, Cat.# 24,124-5
CHAPS: de Research Organics, Cat. # 1304C 1X PBS: Mediatech
(Cellgro), Cat# 21-031-CV. Sustrato de péptido AbzSEVNLDAEFRDpa:
AnaSpec, Nombre del Péptido: WABC-6.

Determinación del sustrato madre (AbzSEVNLDAEFRDpa)

concentración: A 25 mM de solución madre en DMSO se prepara
utilizando el peso del péptido y MW y se diluye a 25 μ M. La
concentración se determina por absorbancia a 354 nm utilizando un
coeficiente de extinción ϵ de $18172 \text{ M}^{-1}\text{cm}^{-1}$, El sustrato madre se
almacena en pequeñas alícuotas a -80°C . [Sustrato madre] = $\text{ABS}_{354 \text{ nm}} * 10^6 / 18172$ (en mM)

Determinación de la concentración de enzima madre:

La concentración madre de cada enzima se determina mediante ABS 280 nm utilizando ϵ de $64150 \text{ M}^{-1} \text{ cm}^{-1}$ para hBACE1 y MuBACE1, $62870 \text{ M}^{-1} \text{ cm}^{-1}$ para BACE2 en Clorhidrato de Guanidina 6 M (de Research Organics, Cat. # 5134G-2), pH 6. (El coeficiente de extinción $\epsilon^{280 \text{ nm}}$ para cada enzima se calcula con base en una composición de aminoácido conocida y los coeficientes de extinción publicados para los residuos Trp ($5.69 \text{ M}^{-1} \text{ cm}^{-1}$) y Tyr ($1.28 \text{ M}^{-1} \text{ cm}^{-1}$) (Anal. Biochem. 182,319-326).

Etapas de dilución y de mezcla: Volumen de Reacción Total:

100 μ L

1. Se preparan disoluciones de inhibidor 2X en amortiguador A (66.7 mM Na-Acetato, pH 4.5, 0.0667% CHAPS),

2. Se prepara dilución de enzima 4X en amortiguador A (66.7 mM Na-Acetato, pH 4.5, 0.0667% CHAPS),
3. Se prepara dilución de sustrato de 100 μ M en 1X PBS, inhibidor 2X 50 μ L y sustrato 25 μ L 100 μ M se agrega a cada pozo de placa de 96 pozos (de DYNEX Technologies, VWR #: 11311-046), entonces se agrega inmediatamente 25 μ L de enzima 4X al inhibidor y a la mezcla de sustrato y se inicia las lecturas de fluorescencia.

Lecturas de Fluorescencia: Lecturas a λ_{ex} 320 nm y λ_{em} 420 nm se toman cada una 40 seg durante 30 min a temperatura ambiente y se determina la pendiente lineal para el índice de clivaje del sustrato (v_i).

Cálculo de % Inhibición: % Inhibición = $100 * (1 - v_i/v_o)$

v_i : índice de clivaje de sustrato en la presencia de inhibidor

v_o : índice de clivaje de sustrato en la ausencia del inhibidor

Determinación IC_{50} :

$$\% \text{ de Inhibición} = ((B * IC_{50}^n) + (100 * I_0^n)) / (IC_{50}^n + I_0^n).$$

Los datos se muestran en la Tabla VI.

Para la Tabla VI

A = 0.01 μ M-0.10 μ M

B = 0.11 μ M-1.00 μ M

C = >1.00 μ M

I = selectividad >100 veces

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II = selectividad 10-100- veces

III = selectividad <10- veces

Tabla VI

Ej. No.	IC ₅₀ (μM)	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
5	B	III
6	B	III
7	A	II
8	A	II
9	A	II
10	A	II
11	A	II
12	A	II
13	A	II
14	A	II
15	B	II
16	A	III
17	A	III
18	A	II
19	A	III
20	B	III
21	A	II
22	A	III
23	A	II
24	A	II
25	A	II
26	A	II
27	A	II
28	A	II
29	A	II

Tabla VI

Ej. No.	IC ₅₀ (μM)	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
30	B	III
31	B	III
32	A	III
36	A	III
37	A	III
38A	C	III
38B	A	II
41	B	II
42	B	II
43	A	II
44	A	II
46	B	II
47	B	II
48	C	II
49	B	I
50	A	II
51	A	III
52	B	II
53	B	III
54	A	I
55	A	II
56	A	I
57	A	II
58	A	II
59	A	II
60	A	II
61	A	II
62	A	II
63	A	I
64	C	III
65	B	II
66	A	II

Tabla VI

Ej. No.	IC ₅₀ (μM)	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
67	A	III
68	B	III
69	A	III
70	A	II
71	A	III
72	B	II
73	B	II
74	A	II
75	B	II
77	A	I
78	A	II
79	A	II
80	A	III
81	A	II
82	A	II
83	A	II
84	B	I
86	A	I
88	A	II
89	A	II
90	A	II
91	A	II
92	A	II
93	A	II
94	B	II
95	A	II
96	A	II
97	A	II
99	A	III
100	B	III
101A	C	III
101B	A	I

Tabla VI

Ej. No.	IC ₅₀ (μM)	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
102A	B	III
102B	A	II
103A	C	III
103B	A	II
104	A	II
105A	B	III
105B	A	II
106A	C	III
106B	A	I
107A	A	I
107B	C	III
108	A	II
109	A	II
110	A	II
111	B	III
112	A	II
113	A	I
114	A	II
115	A	II
116	A	II
117	A	II
118	A	I
119	B	II
120	A	I
121	A	II
122	A	II
123	B	II
124	A	II
126	B	I
127	B	I
128	B	II
131	A	II

Tabla VI

Ej. No.	IC ₅₀ (μM)	
	<u>BACE1</u>	<u>BACE1/BACE2</u>
132	C	III
133A	B	III
133B	A	II
134A	B	III
134B	A	II
135A	C	III
135B	A	II
136A	A	II
137A	C	III
137B	A	II
138A	A	I
138B	C	III
139A	A	I
139B	B	III
140	A	I
141	A	II
142A	C	III
142B	A	II
143A	C	III
143B	A	II
144	B	I
145	A	II

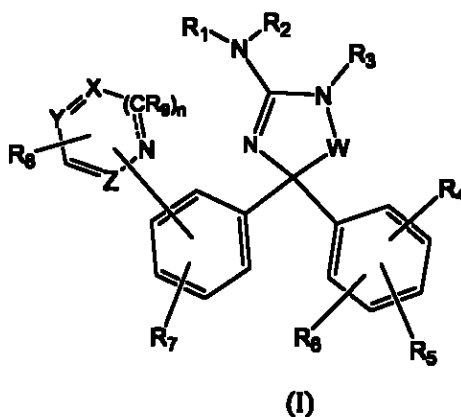
Resultados y Discusión:

Como se puede ver en los datos mostrados en la Tabla VI anterior, los compuestos de la invención son inhibidores selectivos y potentes del BACE1.

REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto de fórmula I



en donde W es CO, CS o CH₂;

X es N, NO o CR₁₀;

Y es N, NO o CR₁₁;

Z es N, NO o CR₁₉ con la condición que no más de dos de X, Y o Z pueden ser N o NO;

R₁ y R₂ son cada uno independientemente H, COR₂₀, CO₂R₂₁ o un grupo alquilo C₁-C₄ opcionalmente sustituido;

R₃ es H, OR₁₂ un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₈ o aril(C₁-C₆)alquilo cada uno opcionalmente sustituido;

R₄ y R₅ son cada uno independientemente H, halógeno, NO₂, CN, OR₁₃, NR₁₄R₁₅ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, o cicloalquilo C₃-C₈ cada uno opcionalmente sustituido o cuando están unidos a los

átomos de carbono adyacentes R_4 y R_5 se pueden tomar juntos con los átomos a los cuales están unidos para formar un anillo de 5 a 7 miembros opcionalmente sustituido que contiene opcionalmente uno o dos heteroátomos seleccionados de O, N o S;

R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} y R_{19} son cada uno independientemente H, halógeno, NO_2 , CN, OR_{16} , $\text{NR}_{17}\text{R}_{18}$ o un grupo alquilo $\text{C}_1\text{-C}_6$, haloalquilo $\text{C}_1\text{-C}_6$, alquenoilo $\text{C}_2\text{-C}_6$, alquinoilo $\text{C}_2\text{-C}_6$ o cicloalquilo $\text{C}_3\text{-C}_8$ cada uno opcionalmente sustituido;

n es 0 o 1;

----- es un enlace único cuando n es 0 o un enlace doble cuando n es 1;

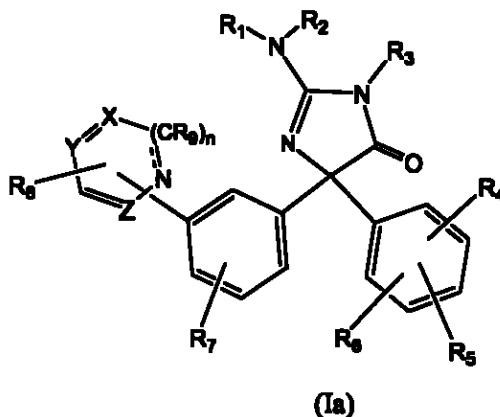
R_{12} , R_{13} , R_{16} , R_{20} y R_{21} son cada uno independientemente H o un grupo alquilo $\text{C}_1\text{-C}_6$, haloalquilo $\text{C}_1\text{-C}_6$, alquenoilo $\text{C}_2\text{-C}_6$, alquinoilo $\text{C}_2\text{-C}_6$, cicloalquilo $\text{C}_3\text{-C}_8$ o arilo cada uno opcionalmente sustituido; y

R_{14} , R_{15} , R_{17} y R_{18} son cada uno independientemente H o alquilo $\text{C}_1\text{-C}_4$; o

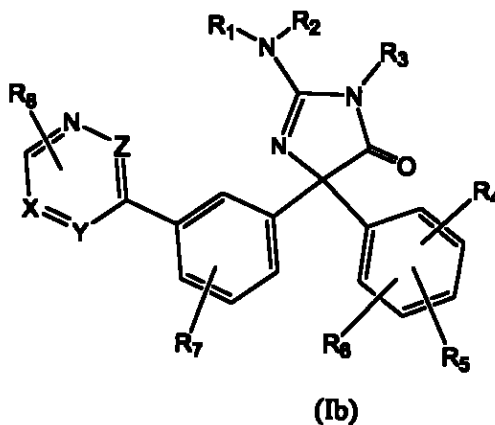
un tautómero de estos, un estereoisómero de estos o una sal farmacéuticamente aceptable de estos.

2. El compuesto de acuerdo con la reivindicación 1 en donde W es CO.

3. El compuesto de acuerdo con la reivindicación 1 o 2, en donde R_1 y R_2 son H y R_3 es alquilo C_1-C_4 .
4. El compuesto de acuerdo con la reivindicación 1, 2 o 3, en donde n es 1.
5. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1, 2, 3 y 4 en donde la Fórmula tiene la estructura Ia



6. El compuesto de acuerdo con la reivindicación en donde fórmula I tiene la estructura Ib



7. El compuesto de acuerdo con la reivindicación 6 en donde R_3 es metilo.

8. El compuesto de acuerdo con la reivindicación 7 en donde Y es CR_{11} y R_1 y R_2 son H.

9. El compuesto de acuerdo con la reivindicación 1 se selecciona del grupo que consiste de:

2-amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

(5S)-2-amino-5-[3-(2-fluoropiridin-3-il)fenil]-5-(4-metoxi-3-metilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

(5S)-2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

(5R)-2-amino-5-(4-fluoro-3-pirimidin-5-ilfenil)-3-metil-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona;

4-[2-amino-4-(4-metoxi-3-metilfenil)-1-metil-5-oxo-4,5-dihidro-1H-imidazol-4-il]-2-piridin-3-ilbenzonitrilo;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(4-metil-3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-[4-metoxi-3-(trifluorometil)fenil]-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-etil-5-(4-metoxi-3-metilfenil)-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirazin-2-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-pirimidin-2-ilfenil)-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-hidroxi-3-metilfenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-[4-metoxi-3-(trifluorometil)fenil]-3-metil-5-(3-pirazin-2-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

(5R)-2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-pirimidin-5-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3,4-dietoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3,4-dimetoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-ciclopentil-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-propoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-butoxi-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-isopropoxi-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(1,3-benzodioxol-5-il)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(2,3-dihidro-1-benzofuran-5-il)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-[3-(ciclopentiloxi)-4-metoxifenil]-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

5-[2-amino-1-metil-5-oxo-4-(3-piridin-3-ilfenil)-4,5-dihidro-1H-imidazol-4-il]-2-metoxibenzonitrilo;

2-amino-5-(3-fluoro-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(2,3-dihidro-1,4-benzodioxin-6-il)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-cloro-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-piridin-3-ilfenil)-5-(3,4,5-trimetoxifenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(4-metoxi-3-metilfenil)-3-metil-5-(3-piridin-4-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3-etoxi-4-metoxifenil)-3-metil-5-(3-piridin-3-ilfenil)-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-piridin-3-ilfenil)-5-[4-(trifluorometoxi)fenil]-3,5-dihidro-4H-imidazol-4-ona;

2-amino-3-metil-5-(3-piridin-3-ilfenil)-5-[(4-trifluorometoxi-3-trifluorometil)fenil]-3,5-dihidro-4H-imidazol-4-ona;

2-amino-5-(3,4-dietoxifenil)-5-(4-fluoro-3-piridin-3-ilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

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2-amino-5-(3-cloro-4-trifluorometoxifenil)-5-(4-fluoro-3-piridin-3-ilfenil)-3-metil-3,5-dihidro-4H-imidazol-4-ona;

un tautómero de estos, un estereoisómero de estos y una sal farmacéuticamente aceptable de estos.

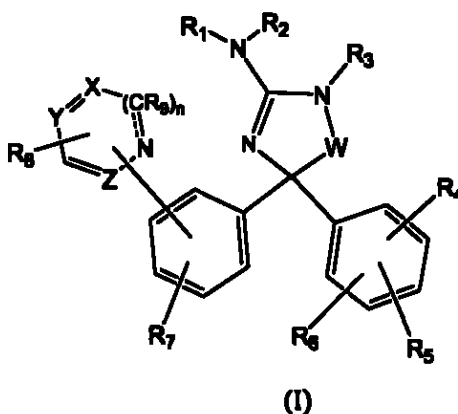
10. Un método para el tratamiento, prevención o mejoramiento de una enfermedad o trastorno caracterizado depósitos β -amiloides o niveles β -amiloides elevados en un paciente que comprende suministrar a dicho paciente con una cantidad terapéuticamente efectiva de un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 9.

11. El método de acuerdo a la reivindicación 10 en donde dicha enfermedad o trastorno se selecciona del grupo que consiste de: enfermedad de Alzheimer, deficiencia cognitiva suave; Síndrome de Down; hemorragia cerebral hereditaria con amiloidosis del tipo Holandés; angiopatía amiloide cerebral; y demencia senil.

12. El método de acuerdo a la reivindicación 11 en donde dicha enfermedad es enfermedad de Alzheimer.

13. Una composición farmacéutica que comprende un portador farmacéuticamente aceptable y una cantidad efectiva de un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 9.

14. Un proceso para la preparación de un compuesto de fórmula I



en donde W es CO, CS o CH₂;

X es N, NO o CR₁₀;

Y es N, NO o CR₁₁;

Z es N, NO o CR₁₉ con la condición que no más de dos de X, Y o Z pueden ser N o NO;

R₁ y R₂ son cada uno independientemente H, COR₂₀, CO₂R₂₁ o un grupo alquilo C₁-C₄ opcionalmente sustituido;

R₃ es H, OR₁₂ un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₆ o aril(C₁-C₆) alquilo cada uno opcionalmente sustituido;

R₄ y R₅ son cada uno independientemente H, halógeno, NO₂, CN, OR₁₃, NR₁₄R₁₅ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, o cicloalquilo C₃-C₆ cada uno opcionalmente sustituido o cuando están unidos a los átomos de carbono adyacentes R₄ y R₅ se pueden tomar juntos con los átomos a los cuales están unidos para formar un

anillo de 5 a 7 miembros opcionalmente sustituido que contiene opcionalmente uno o dos heteroátomos seleccionados de O, N o S;

R₆, R₇, R₈, R₉, R₁₀, R₁₁ y R₁₉ son cada uno independientemente H, halógeno, NO₂, CN, OR₁₆, NR₁₇R₁₈ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆ o cicloalquilo C₃-C₆ cada uno opcionalmente sustituido;

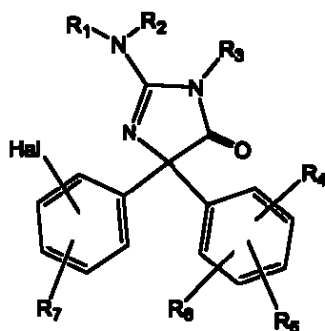
n es 0 o 1;

----- es un enlace único cuando n es 0 o un enlace doble cuando n es 1;

R₁₂, R₁₃, R₁₆, R₂₀ y R₂₁ son cada uno independientemente H o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₆ o arilo cada uno opcionalmente sustituido; y

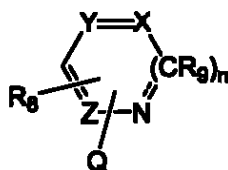
R₁₄, R₁₅, R₁₇ y R₁₈ son cada uno independientemente H o alquilo C₁-C₄

que comprende el proceso de hacer reaccionar un compuesto de fórmula II



(II)

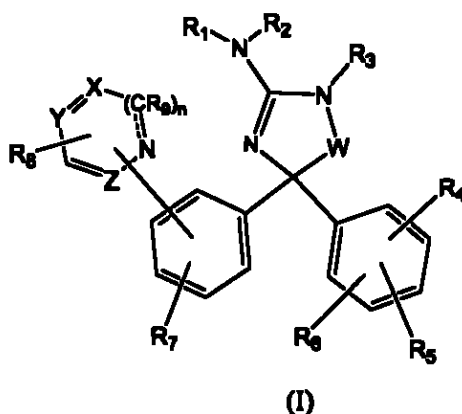
en donde Hal es Cl o Br y R_1 , R_2 , R_3 , R_4 , R_5 , R_6 y R_7 son como se describen para la fórmula I anterior con un compuesto de fórmula III



(III)

en donde Q es $B(OH)_2$, $Sn(n-Bu)_3$ o $Sn(CH_3)_3$ y X, Y, Z, R_8 , R_9 y n son como se describen para la fórmula I anterior en la presencia de un catalizador de paladio opcionalmente en la presencia de un solvente.

15. El uso de un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 9 para la fabricación de un medicamento para el tratamiento, prevención o mejoramiento de una enfermedad o trastorno caracterizado por depósitos β -amiloides o niveles β -amiloides elevados en un paciente.

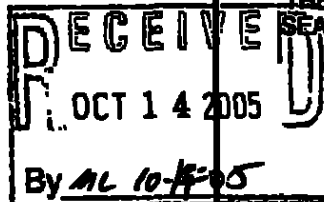


no 178

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
WYETH
Patent Law Department
Attn. Lences, Barbara L.
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

DOCKETED *Art. 5 Amend.*
DUE DATE *12-1-05*
STAT DATE

BY: *ML 10-19-05*
(PCT Rule 42.1)
01-10-06/05

Date of mailing
(day/month/year) 11/10/2005

Applicant's or agent's file reference

791101475

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US2005/020720

International filing date
(day/month/year)

14/06/2005

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 18:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 48):

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 Patentaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax: (+31-70) 340-3016

Authorized officer

Federico Bonomelli

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

CS
rohelss

CC: TAPLOW

CC: PRINCETON

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

When?

Within 2 months from the date of transmittal of the international search report or 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 1-10 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 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.

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).

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

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

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101475	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/020720	International filing date (day/month/year) 14/06/2005	(Earliest) Priority Date (day/month/year) 16/06/2004
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 4 sheets.

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

1. Basis of the report

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

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

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, 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:

AMINO-5, 5-DIPHENYLIMIDAZOLONE DERIVATIVES FOR THE INHIBITION OF BETA-SECRETASE

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

International Application No
PCT/US2005/020720

002/3

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D401/10 C07D403/10 C07D405/14 A61K31/4178 A61P25/28		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/094854 A (ELAN PHARMACEUTICALS, INC; TUNG, JAY S.; GUINN, ASHLEY, C; THORSETT,) 20 November 2003 (2003-11-20) claims 1,5,8; examples 1-6	1-15
E	WO 2005/058311 A (SCHERING CORPORATION; PHARMACOPEIA DRUG DISCOVERY, INC; ZHU, ZHAONING;) 30 June 2005 (2005-06-30) claims 1-4,13,18 compounds 456 (p. 255), 457 (p. 256), 1360 (p. 184), 1373 (p. 187), 1374 (p. 187), 1377 (p. 188), 1378 (p. 188), 1387 (p. 182), 1388 (p. 182) page 301, line 6 - page 309, line 1	1-15
☐ 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 relating 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 "S" document member of the same patent family		
Date of the actual completion of the International search 27 September 2005		Date of mailing of the International search report 11/10/2005
Name and mailing address of the ISA European Patent Office, P.B. 5618 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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/020720
00224

183

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No. **00225**
PCT/US2005/020720

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03094854	A	20-11-2003	AU 2003229024 A1	11-11-2003
WO 2005058311	A	30-06-2005	NONE	

PATENT COOPERATION TREATY

no 228 185

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/US2005/020720

International filing date (day/month/year)
14.06.2005

Priority date (day/month/year)
16.06.2004

International Patent Classification (IPC) or both national classification and IPC
C07D401/10, C07D403/10, C07D405/14, A61K31/4178, A61P25/28

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 66.1 b/s(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.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 apmu d Fax: +49 89 2399 - 4465	Authorized Officer Seymour, L Telephone No. +49 89 2399-6894 
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

nn227 176
International application No.
PCT/US2005/020720

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:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/020720

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 10-12 with respect to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. as above relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | ☐ has not been furnished |
| | ☐ does not comply with the standard |
| the computer readable form | ☐ has not been furnished |
| | ☐ does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

188
PCT/US2005/020720
International application No.
PCT/US2005/020720

**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	1-15
	No: Claims	
Inventive step (IS)	Yes: Claims	1-15
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-8, 13-15
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Claims 10-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

1. Reference is made to the following document:
D1 : WO 03/094854 A
2. The subject-matter of the present claims is new with respect to D1 (Article 33(2) PCT). The compounds of D1 (cf. examples 1,5,6 and claim 1) differ from the present compounds in that the amino substituent is at position 3 of the imidazolone ring and in that the phenyl rings at position 5 are unsubstituted.
3. The problem to be solved by the present invention may be regarded as the provision of further inhibitors of β -amyloid production, which are useful, for example, in the treatment of Alzheimer's disease.

The solution to this problem proposed in the present claims is considered as involving an inventive step (Article 33(3) PCT) since the compounds of D1 are structurally remote from the present compounds. The scope of claim 1 represents a reasonable generalisation of the compounds tested.

4. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 10-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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

nn231 140
International application No.

PCT/US2005/020720

Re Item VI

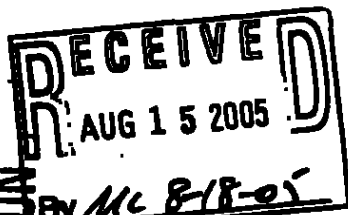
	Application No	Publication date	Filing date	Priority date
D2	WO 2005/058311 A	30.06.2005	13.12.2004	15.12.2003

The subject-matter of present claim 1 overlaps with that of D2. The specific embodiments of D2 as listed in the search report of the prior art fall within the area of overlap. The compounds of D2 are inhibitors of BACE1 (see p. 301 ff., cf. present Table VI) and are useful in the treatment of Alzheimer's disease (cf. claim 18).

Said specific embodiments are not present in the priority document of D2. The validity of the present priority has not been considered because the International Searching Authority does not have in its possession a copy of the priority application.

Re Item VII

1. Claim 14 lacks conciseness (Article 6 PCT), since a reference to claim 1 would render the repetition of the definitions for formula I redundant.
2. In claim 6 the number of the claim which is being referred to has been omitted (Article 6 PCT).



00232/191

CC: PRINCETON

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

From the INTERNATIONAL BUREAU

To:

LENCES, Barbara, L.
Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
ETATS-UNIS D'AMERIQUE

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 04 August 2005 (04.08.2005)	
Applicant's or agent's file reference AM101475	IMPORTANT NOTIFICATION
International application No. PCT/US2005/020720	International filing date (day/month/year) 14 June 2005 (14.06.2005)
International publication date (day/month/year)	Priority date (day/month/year) 16 June 2004 (16.06.2004)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
16 June 2004 (16.06.2004)	60/580,286	US	01 August 2005 (01.08.2005)

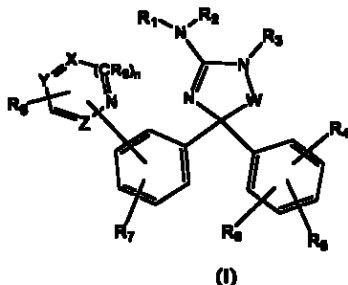
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Alicia OLAIZ Facsimile No. (41-22) 338.71.30 Telephone No. +41 22 338 9288
---	--

CC: TAPLOW

Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT		00235
(21) N° de solicitud: 06-122180		(51) Int Cl: C07D 401/10, 403/10, 405/14; A61K 31/4178; A61P 25/28		
(22) Fecha de solicitud: 04/12/06		(71) Solicitante(s) WYETH		
(30) Prioridad	(31) No. 60/580,286	(32) Fecha 16/06/04	(33) País US	(72) Inventor(es) MALAMAS, Michael Sotirios y otros
				(74) Apoderado: ALVARO CORREA ORDOÑEZ
(85) Fecha límite inicio fase nacional: 16/01/07		(87) Publicación Internacional		
(86) Datos relativos a la presentación de la solicitud PCT		Fecha: 28/01/2006		
Fecha de presentación de la solicitud: 14/06/2005		N° publicación: WO 2006/009853		
No. de solicitud PCT/US2005/020720				
(54) Título: DERIVADOS DE AMINO-5,5-DIFENILIMIDAZOLONA PARA LA INHIBICIÓN DE β-SECRETASA				

Reivindicación(es):

1. Un compuesto de fórmula I



en donde W es CO, CS o CH2;

X es N, NO o CR10;

Y es N, NO o CR11;

Z es N, NO o CR18 con la condición que no más de dos de X, Y o Z pueden ser N o NO;

R1 y R2 son cada uno independientemente H, COR20, CO2R21 o un grupo alquilo C1-C4 opcionalmente sustituido;

R3 es H, OR12 un grupo alquilo C1-C6, haloalquilo C1-C6, alquenoilo C2-C6, alquinilo C2-C6, cicloalquilo C3-C6 o aril(C1-C6)alquilo cada uno opcionalmente sustituido;

R4 y R5 son cada uno independientemente H, halógeno, NO2, CN, OR13, NR14R15 o un grupo alquilo C1-C6, haloalquilo C1-C6, alquenoilo C2-C6, alquinilo C2-C6, o cicloalquilo C3-C6 cada uno opcionalmente sustituido o cuando están unidos a los átomos de carbono adyacentes R4 y R5 se pueden tomar juntos con los átomos a los cuales están unidos para formar un anillo de 5 a 7 miembros opcionalmente sustituido que contiene opcionalmente uno o dos heteroátomos seleccionados de O, N o S;

R6, R7, R8, R9, R10, R11 y R18 son cada uno independientemente H, halógeno, NO2, CN, OR16, NR17R18 o un grupo alquilo C1-C6, haloalquilo C1-C6, alquenoilo C2-C6, alquinilo C2-C6 o cicloalquilo C3-C6 cada uno opcionalmente sustituido;

n es 0 o 1;

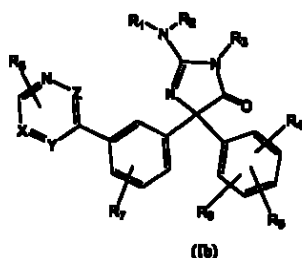
== es un enlace único cuando n es 0 o un enlace doble cuando n es 1;

R12, R13, R16, R20 y R21 son cada uno independientemente H o un grupo alquilo C1-C6, haloalquilo C1-C6, alquenoilo C2-C6, alquinilo C2-C6, cicloalquilo C3-C6 o arilo cada uno opcionalmente sustituido; y

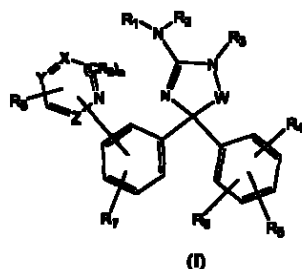
R14, R15, R17 y R18 son cada uno independientemente H o alquilo C1-C4; o

un tautómero de estos, un estereoisómero de estos o una sal farmacéuticamente aceptable de estos.

6. El compuesto de acuerdo con la reivindicación en donde fórmula I tiene la estructura Ib



14. Un proceso para la preparación de un compuesto de fórmula I



en donde W es CO, CS o CH₂;

X es N, NO o CR₁₀;

Y es N, NO o CR₁₁;

Z es N, NO o CR₁₂ con la condición que no más de dos de X, Y o Z pueden ser N o NO;

R₁ y R₂ son cada uno independientemente H, COR₂₃, CO₂R₂₁ o un grupo alquilo C₁-C₄ opcionalmente sustituido;

R₃ es H, OR₁₂ un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₆ o aril(C₁-C₆) alquilo cada uno opcionalmente sustituido;

R₄ y R₅ son cada uno independientemente H, halógeno, NO₂, CN, OR₁₃, NR₁₄R₁₅ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, o cicloalquilo C₃-C₆ cada uno opcionalmente sustituido o cuando están unidos a los átomos de carbono adyacentes R₄ y R₅ se pueden tomar juntos con los átomos a los cuales están unidos para formar un anillo de 5 a 7 miembros opcionalmente sustituido que contiene opcionalmente uno o dos heteroátomos seleccionados de O, N o S;

R₆, R₇, R₈, R₉, R₁₀, R₁₁ y R₁₂ son cada uno independientemente H, halógeno, NO₂, CN, OR₁₆, NR₁₇R₁₈ o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆ o cicloalquilo C₃-C₆ cada uno opcionalmente sustituido;

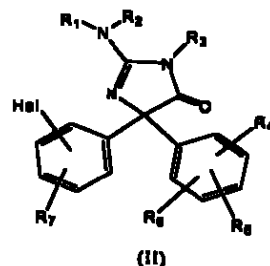
n es 0 o 1;

== es un enlace único cuando n es 0 o un enlace doble cuando n es 1;

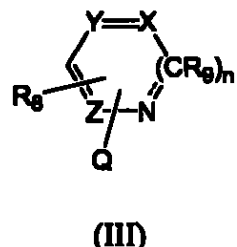
R₁₂, R₁₃, R₁₆, R₂₀ y R₂₁ son cada uno independientemente H o un grupo alquilo C₁-C₆, haloalquilo C₁-C₆, alquenilo C₂-C₆, alquinilo C₂-C₆, cicloalquilo C₃-C₆ o arilo cada uno opcionalmente sustituido; y

R₁₄, R₁₅, R₁₇ y R₁₈ son cada uno independientemente H o alquilo C₁-C₄

que comprende el proceso de hacer reaccionar un compuesto de fórmula II



en donde Hal es Cl o Br y R₁, R₂, R₃, R₄, R₅, R₆ y R₇ son como se describen para la fórmula I anterior con un compuesto de fórmula III



en donde Q es B(OH)₂, Sn(n-Bu)₃ o Sn(CH₃)₃ y X, Y, Z, R₈, R₉ y n son como se describen para la fórmula I anterior en la presencia de un catalizador de paladio opcionalmente en la presencia de un solvente.

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

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 presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☒
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica 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 un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Fdo B

Firma Responsable

Fecha 04-DIC-06

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Bogotá, D.C., Colombia

195

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
WYETH

REFERENCIA	Radicación No.	6 122180
	Solicitud internacional	PCT/US2005/020720
	Fecha inicio fase nacional	16/01/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	886

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

1. Debe aclarar el nombre de los inventores por cuanto difieren en la publicación internacional, con el aportado en el petitorio fase nacional.

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

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

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

El anterior requerimiento fue notificado por fijación en lista de
fecha _____
lrazo _____

26 ENE 2007