Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 05-32254

54. **TÍTULO** Acetil 2- Hydroxi-1,3-Diaminoalcanos

51. **CLASIFICACIÓN INTERNACIONAL** C07C 285/06 C07C 23 A61K. 31/04 31/40

71. **SOLICITANTE** Elan pharmaceuticals inc y pharmacia &up John Uc

DOMICILIO San francisco-california y Kalamazoo, michigan
Estados unidos de America, Respectivamente

74. **APODERADO** Emilio ferrero cc. 438 clq de wagon.

22. **BOGOTÁ, D. C.,** _____

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
[illegible]

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 10-04-2005

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

Nombre: **ELAN PHARMACEUTICALS, INC y PHARMACIA & UPJOHN LLC**
sociedades constituidas y existente bajo las leyes del estado de Delaware, Estados Unidos de América.
Dirección: 800 Gateway Blvd.,
South San Francisco, California 94080,
Estados Unidos de América,
y
301 Henrietta Street,
Kalamazoo, Michigan 49007,
Estados Unidos de América,
Respectivamente.
Domicilio: San Francisco, California, Estados Unidos de América, y
Kalamazoo, Michigan, Estados Unidos de América, respectivamente.

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____ Número_____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@camyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____ No. 438.019 T.P 31.929

4 INVENTOR (ES) (72)

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Estados Unidos de América.
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3. **James T. BECK**
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Zionsville, Indiana 46077,
Estados Unidos de América.
4. **Robert HUGHES**
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Eureka, Missouri 63025
Estados Unidos de América
5. **John VARGHESE**
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Estados Unidos de América.
6. **Shon R. PULLEY.**
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Noblesville, Indiana 46060,
Estados Unidos de América.
7. **Ruth TERBRINK**
125 Skyview Lane,
Labadie, Missouri 63055,
Estados Unidos de América.

5 PCT (86)

Solicitud Internacional No. PCT/US2003/028503 Fecha: 10 de Septiembre de 2003
Publicación Internacional No. WO 2004/024081 A2 Fecha: 25 de Marzo de 2004

6 Título (54)

ACETIL 2-HYDROXI-1,3 DIAMIN ALCANOS

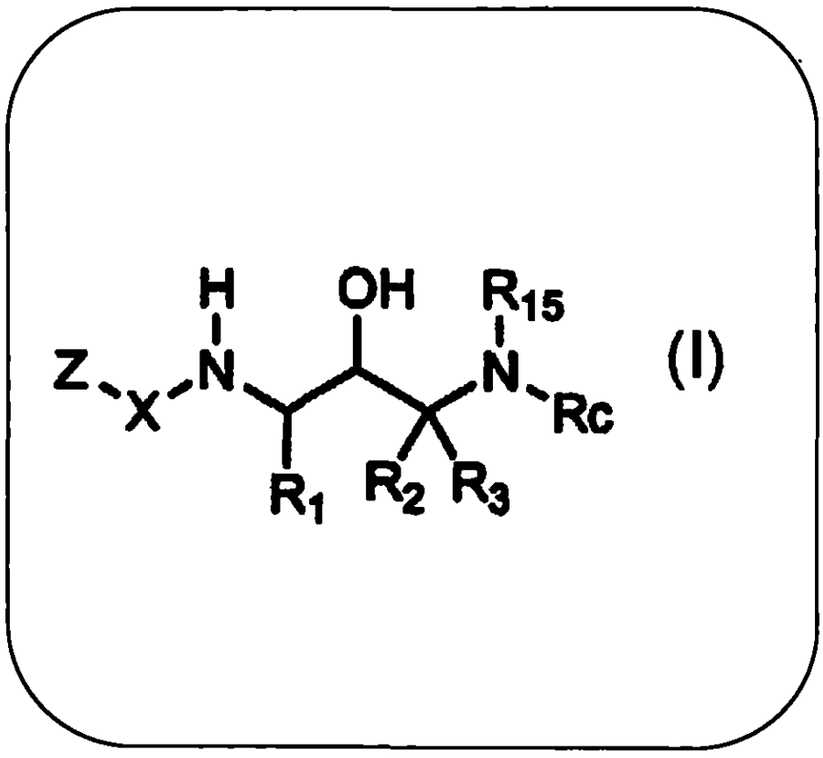
7 **Clasificación Internacional (51)** A61K 31/44 ; A61K31/40

8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	10 de Septiembre de 2002	60/409.453
	US.	5 de Marzo de 2003	60/452.231
	US.	1 de Agosto de 2003	60/491.757

9 **Comprobante de pago No.:** 05 – 19.197 **Fecha:** 14 de Marzo de 2005

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 443.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros



(I)

(12) Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

PRP/MRM.Id-5

CAVELIER
ABOGADOS
EDIFICIO SUKI
CARRERA 4ª Nº 72-35
BOGOTÁ, D. C. - COLOMBIA

4 de

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

15170
6654

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

Elan Pharmaceuticals, Inc.

of/domiciliado (a) en 800 Gateway Blvd.,
South San Francisco, California 94080- U.S.A, hereby ratify the patent application No. 02.117.312 filed by Emilio Ferrero on December 30, 2002, and,

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

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, especially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by, me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this/Dado y firmado hoy 11-3-05

In/en South San Francisco, CA 94080, USA

Signature / Firma

Jean M. Duvall, Executive Vice President & General Counsel

HOTARIA SESTO DEL CIRCULO DE BOGOTA, D.C. CONSTAR QUE LA FIRMA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2005
PABLO MENDEZ DA... NOTARIO ...

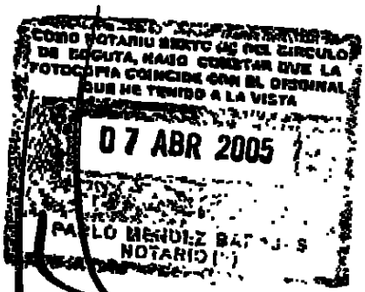
© CAVELIER ABOGADOS
WPPODERE-3 (MINUTA Nº 12.1.1.2.6 USA)

Colombia 5

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY "ELAN PHARMACEUTICALS, INC." IS DULY INCORPORATED UNDER THE LAWS OF THE STATE OF DELAWARE AND IS IN GOOD STANDING AND HAS A LEGAL CORPORATE EXISTENCE SO FAR AS THE RECORDS OF THIS OFFICE SHOW, AS OF THE TWENTY-FIRST DAY OF JANUARY, A.D. 2003.



Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

2104559 8300

030040793

AUTHENTICATION: 2215096

DATE: 01-21-03

6

ALIF RNIA ALL-PURP SE ACKN WLEDGMENT

State of California
County of San Mateo } ss.

On 11/3/03 (Date), before me, Denise Malatesta (Name and Title of Officer (e.g., "Jane Doe, Notary Public")),

personally appeared JEAN M. DUVALL (Name(s) of Signer(s)),

☒ personally known to me
☒ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/~~are~~ subscribed to the within instrument and acknowledged to me that ~~he/she/they~~ executed the same in ~~his/her/their~~ authorized capacity(~~ies~~), and that by ~~his/her/their~~ signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

DENISE MALATESTA
Commission # 1297750
Notary Public - California
San Francisco County
My Comm. Expires Apr 14, 2006

Place Notary Seal Above

Denise Malatesta
Signature of Notary Public

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document
Title or Type of Document: Representation/Power of Attorney

Document Date: 11/3/03 Number of Pages: -1-

Signer(s) Other Than Named Above: ———

Capacity(ies) Claimed by Signer
Signer's Name: _____
☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer is Representing: _____

Firmo hare
COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, NADO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2005
PAOLO ALFREDO BARAJAS
NOTARIO (E)

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2

State of California

SECRETARY OF STATE

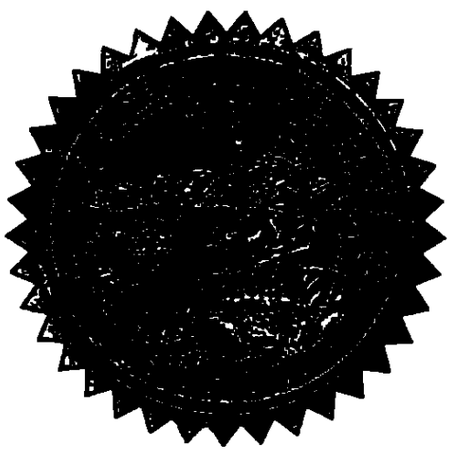
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by DENISE MALATESTA*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of DENISE MALATESTA, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 19th day of November 2003*
7. *by Deputy Secretary of State, State of California*
8. *No. 174254*
9. *Seal/Stamp:*



10. Signature

COMO NOTARIO SETO (10) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HA TENIDO A LA VISTA

07 ABR 2005

ABDO MENDEZ BARAJAS
NOTARIO (S)

KEVIN SHELLEY
Secretary of State

BY _____

OFFICIAL SEAL OF SECRETARY OF STATE

NP-24 A (REV. 1-03)

A 8

TRADUCCIÓN OFICIAL 180/2003 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL **ELAN PHARMACEUTICALS, INC.**, EMPRESA DOMICILIADA EN 800 GATEWAY BLVD., SOUTH SAN FRANCISCO, CALIFORNIA 94080 ESTADOS UNIDOS DE AMÉRICA POR EL PRESENTE RATIFICA LA SOLICITUD DE PATENTE 02.117.312 PRESENTADA POR EMILIO FERRERO EL 30 DE DICIEMBRE DE 2002 Y OTORGA PODER A GERMÁN CAVELIER, TPA 832 GONZALO PERDOMO, TPA 831, EMILIO FERRERO, TPA 31929 Y LUZ CLEMENCIA DE PAEZ TPA 23555. EXPEDIDO Y FIRMADO EN SOUTH SAN FRANCISCO, CA 94080, ESTADOS UNIDOS DE AMÉRICA. FIRMADO: JEAN M. DUVALL, VICEPRESIDENTE EJECUTIVO Y JEFE DE ASUNTOS JURÍDICOS.

DELAWARE, PRIMER ESTADO

YO, HARRIET SMITH WINDSOR, SECRETARIO DE ESTADO PARA EL ESTADO DE DELAWARE, POR EL PRESENTE CERTIFICO QUE " ELAN PHARMACEUTICALS, INC" ESTÁ DEBIDAMENTE CONSTITUIDA DE ACUERDO CON LAS LEYES DEL ESTADO DE DELAWARE Y ES EMPRESA DE BUENA REPUTACIÓN Y CONTINUAMENTE EXISTE LEGALMENTE DE ACUERDO CON LO INDICADO POR LOS REGISTROS EXISTENTES EN ESTA OFICINA, A VEINTIUNO DE ENERO DEL AÑO 2003 DE LA ERA CRISTIANA.

COMO NOTARIO SEXTO (6) DEL CIRCUITO DE BOGOTÁ D.C. DOY CONSTANCIA QUE LA PRESENTE FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2003
PABLO MENDEZ BARAJAS
NOTARIO (E)

FIRMADO: HARRIET SMITH WINDSOR, SECRETARIO DE ESTADO

2104559 8300 - 030040793. AUTENTICACIÓN 2215096. FECHA 21 DE ENERO DE 2003.

RECONOCIMIENTO MULTIPROPÓSITO DE CALIFORNIA

ESTADO DE CALIFORNIA, CONDADO DE LOS ANGELES

El 3 de noviembre del 2003, ante mí, DENISE MALATESTA, compareció personalmente JEAN M DUVALL, conocido personalmente por mi como la persona cuyo nombre está escrito en el documento adjunto y reconoció ante mí que ella firmó el mismo en su calidad autorizada y que mediante su firma en el documento la persona o entidad a cuyo nombre actuaba, firmó el documento.

Atestiguo mediante mi firma y sello oficial

DENISE MALATESTA

Sello: DENISE MALATESTA, Cargo 1297750 notario público, California. Condado de San Francisco. Mi cargo vence el 16 de abril de 2005.

Descripción del documento adjunto: poder y representación. Fecha del documento 3 de noviembre de 2003. Número de páginas 1.

APOSTILLA:

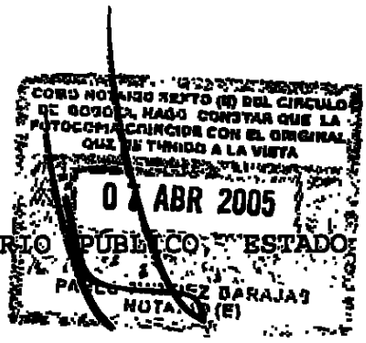
(Convención de La Haya del 5 de octubre de 1961)

1. Estados Unidos de América

   Este documento público

2. ha sido firmado por DENISE MALATESTA

3. quien actúa en su calidad de NOTARIO PÚBLICO, ESTADO DE CALIFORNIA



4. lleva el sello de DENISE MALATESTA, notario público, estado de California

CERTIFICADO

5. en Sacramento, California

6. el 19 de noviembre de 2003

7. por el Secretario suplente del estado de California

8. Número 174254

9. Sello:

GRAN SELLO DEL ESTADO DE CALIFORNIA

10. Firma: KEVIN SHELLEY, secretario de estado.

Por: firma ilegible.

COLO-13562-841-001-5

WPCL002G ID 5096

Bogotá, 2 de diciembre de 2003.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Res 541 Febrero de [illegible]

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

07 ABR 2005

PABLO MENDEZ BARAJAS
NOTARIO (E)

COMO NOTARIO SEXTO DEL CIR...
...HAGO CONSTAR QUE LA
Eduardo Salcedo
Vásquez
...CIDE CON LA FIRMA REGISTRADA POR
EL SELLOS: EN ESTA NOTARIA
SANTAFE DE BOGOTA 03 DIC. 2003

...DE BOGOTA D.C.

...SEXTO (E) DEL CIRCULO
...BOGOTA, HAGO CONSTAR QUE LA
...COPIA COINCIDE CON EL ORIGINAL
...QUE HE TENIDO A LA VISTA
07 ABR 2005
PAD... MENDEZ CARAJAS
NOTARIO (E)

CAVELIER
ABOGADOS

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTA 8, COLOMBIA

WEB SITE: www.cavelier-abogados.com
E-MAIL: cavelier@colomsat.net.co

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

Señora Jefe de la

DIVISION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Poderdante: **ELAN PHARMACEUTICALS, INC.**

Poder conferido el: **11-03-2003**

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado, atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

DESPACHO DEL CORO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2005
NOTARIO

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil y tiene los otros sustitutos faltan en este momento.

Señora Jefe,

GERMAN CAVELIER
T.P.A. No. 832
C.C. No. 2.877.924 de Bogotá

Acepto:

EMILIO FERRERO
T.P.A. N° 31.929
C.C. No. 438.019 de Usaquén

2e-780-2

...RIA SEXTA DE B...

...MIENTO - PRESENTACION PER...

Bogotá ... 26 ENE. 2004

... DEL BOTERO MEDINA

NOTA... EL CIRCULO DE BOGOTA

Compareció ...

quien ... 28777924 ... 38019 ...

y ...

en el ...

que el ... del ... su constan-

cia se firma esta diligencia

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

07 ABR 2005

PABLO MENDEZ BARAJAS
NOTARIO (E)

4 12

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4ª Nº 72-35
BOGOTA, 8 - COLOMBIA

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

14590
5514

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

PHARMACIA & UPJOHN COMPANY LLC

of/domiciliado (a) en 301 Henrietta Street
Kalamazoo, Michigan 49009, U.S.A.

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

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

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

Given and signed this/Dado y firmado hoy
22 December 2004
in/en New York, NY 10017

Signature / Firma
Grover F. Fuller, Jr.,
Assistant Secretary

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2005
PABLO MENDOZ BARAJAS
NOTARIO (E)

© CAVELIER ABOGADOS

13

NEW YORK COUNTY

State of New York
County of New York, ss.:

Nº 414813 Form 1

I, NORMAN GOODMAN, County Clerk and Clerk of the Supreme Court of the State of New York, in and for the County of New York, a Court of Record, having by law a seal,

DO HEREBY CERTIFY pursuant to the Executive Law of the State of New York, that

Sharon Z. Williams

whose name is subscribed to the annexed affidavit, deposition, certificate of acknowledgment or proof, was at the time of taking the same a NOTARY PUBLIC in and for the State of New York duly commissioned, sworn and qualified to act as such; that pursuant to law, a commission or a certificate of his official character, with his autograph signature has been filed in my office; that at the time of taking such proof, acknowledgment or oath, he was duly authorized to take the same; that I am well acquainted with the handwriting of such NOTARY PUBLIC or have compared the signature on the annexed instrument with his autograph signature deposited in my office, and I believe that such signature is genuine.

IN WITNESS WHEREOF, I have hereunto set my hand affixed my official seal this

JAN 14 2005

FEE PAID $3.00

Norman Goodman

County Clerk and Clerk of the Supreme Court, New York County

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

07 ABR 2005

PABLO MENDEZ BARAJAS
NOTARIO (E)

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 22 días del mes de Diciembre de 19 2004

ante mí, Notario Público de l estado de Nueva York

compareció(eron) personalmente

Grover F. Fuller, Jr.

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

Notario Público

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 22 day of December 19 2004

before me, a Notary Public of New York STATE
New York County

personally appeared

Grover F. Fuller, JR.

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

Notary Public Suzan Z. Killian

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy, 22 de Diciembre de 19 2004

compareció(eron) ante mí

Grover F. Fuller, Jr.

a quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía

denominada Pharmacia & Upjohn Company LLC

Certifico:

1. Que he visto los siguientes documentos:*

Certificado de Secretario Asistente

2. Que dichos documentos prueban lo siguiente:

2.1. Que Pharmacia & Upjohn Company, LLC es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de l estado de Delaware

2.2. Que el domicilio de dicha Sociedad/Compañía es 301 Henrietta Street, Kalamazoo, Michigan 49009 Estado Unidos

2.3. Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad/Compañía

2.4. Que el(los) Sr.(Sres.)

Grover F. Fuller, Jr.

está(n) autorizado(s) para otorgar el presente Poder.

Ciudad Nueva York

Estado Nueva York

Hoy 22 Diciembre de 19 2004

Notario Público

* Los documentos deben identificarse con fecha y origen.

NOTARIAL CERTIFICATE (CORPORATION)

On this 22 day of December 19 2004

appeared before me

Grover F. Fuller, Jr.

who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company

named Pharmacia & Upjohn Company LLC

I Certify:

1. That I have seen the following documents:*

Assistant Secretary's Certificate

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL
ABR 2005
PABLO EMILIO DE LA MORA V.

2. That the above documents duly prove the following:

2.1. That Pharmacia & Upjohn Company LLC is a Corporation/Company legally constituted and in existence in accordance with the laws of Delaware

2.2. That the domicile of said Corporation/Company is 301 Henrietta Street Kalamazoo Michigan 49009 USA

2.3. That the purpose of purposes for which the present Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned Corporation/Company.

2.4. That Mr.(Messrs.) Grover F. Fuller, Jr.

is(are) authorized to grant the present Power of Attorney.

City New York

State New York

This 22 day of December 2004

Notary Public

SUZAN Z. KILLIAN
Notary Public, State of New York
No. 01KI6116521
Qualified in New York County
Commission Expires October 4, 2008

* Documents must be identified with date and origin.

15

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

   This public document

2. has been signed by **Norman Goodman**

3. acting in the capacity of **County Clerk**

4. bears the seal/stamp of the county of **New York**

Certified

5. At Albany, New York 6. the 24th day of January 05

7. by Special Deputy Secretary of State, State of New York

8. No. A-132166E

9. Seal/Stamp 10. Signature

Daniel E Shapiro
Special Deputy Secretary of State

CONSUL HONORARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2005
PABLO MENDEZ BARAJAS
NOTARIO (E)

04135595.RSL (REV: 2/8/99)

16

State of Delaware
Secretary of State
Division of Corporations
Delivered 12:48 PM 08/13/2004
FILED 12:48 PM 08/13/2004
SRV 040594300 - 0527510 FILE

CERTIFICATE OF FORMATION

OF

PHARMACIA & UPJOHN COMPANY LLC

This Certificate of Formation of Pharmacia & Upjohn Company LLC is being duly executed and filed by Charles F. Raeburn, as an authorized person, to form a limited liability company under the Delaware Limited Liability Company Act.

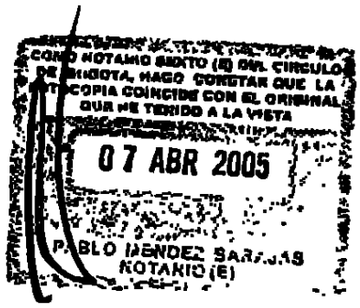
1. The name of the limited liability company is Pharmacia & Upjohn Company LLC.

2. The address of its registered office in the State of Delaware is Corporation Trust Center, 1209 Orange Street, in the City of Wilmington, County of New Castle, Delaware 19801. The name of its registered agent at such address is The Corporation Trust Company.

IN WITNESS WHEREOF, the undersigned has executed this Certificate of Formation of Pharmacia & Upjohn Company LLC as of the date written below.

/s/ Charles F. Raeburn
Name: Charles F. Raeburn
Authorized Person

Dated: August 13, 2004



Delaware

17

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE DO HEREBY CERTIFY THAT THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF FORMATION OF "PHARMACIA & UPJOHN COMPANY LLC" FILED IN THIS OFFICE ON THE THIRTEENTH DAY OF AUGUST, A.D. 2004, AT 12:48 O'CLOCK P.M.

CONO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

07 ABR 2005

PABLO [illegible]
NOTARIO (E)

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

0527510 8100V

AUTHENTICATION: 3544900

040900672

DATE: 12-14-04

18

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. *Country: United States of America*

This public document:

2. *has been signed by Harriet Smith Windsor*

3. *acting in the capacity of Secretary of State of Delaware*

4. *bears the seal/stamp of Office of Secretary of State*

Certified

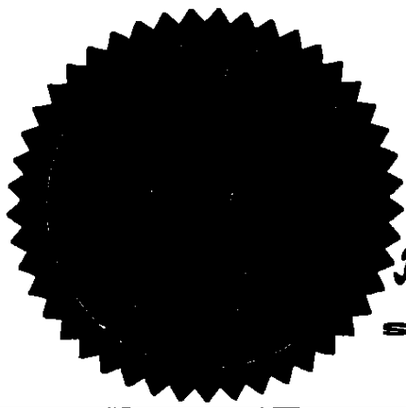
5. *at Dover, Delaware*

6. *the second day of February, A.D. 2005*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0245814*

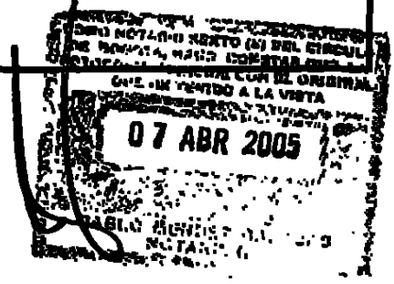
9. *Seal/Stamp:*



10. *Signature:*

Harriet Smith Windsor

Secretary of State



TRADUCCIÓN OFICIAL No. 16.02/05 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia mediante Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

A continuación se traducen las legalizaciones de un documento escrito en inglés y español, por el cual **PHARMACIA & UPHOHN LLC.**, sociedad domiciliada en 301 Henrietta Street, Kalamazoo, Michigan 49009, Estados Unidos de América, otorga poder a **GERMAN CAVELIER, GONZALO PERDOMO, EMILIO FERRERO Y LUZ CLEMENCIA DE PAEZ.**
Dado y firmado el 22 de diciembre de 2004 en New York, N.Y, 10017.
(Firma ilegible), Grover F. Fuller, Jr., Secretario Asistente.

CERTIFICADO NOTARIAL - SOCIEDAD- otorgado en inglés y español referente a la existencia legal de PHARMACIA & UPJOHN COMPANY, LLC.
Dado en la ciudad de New York, Estado de New York, el 22 de diciembre de 2004.
(Sello notarial en tinta), SUZAN Z. KILLIAN, Notario Público, Estado de New York, No. 01K16116521, Calificada en el Condado de New York, Comisión expira el 4 de octubre del 2008.

Estado de New York
Condado de New York) ss No. 414813

Yo, NORMAN GOODMAN, Escribano de Condado y Escribano de la Suprema Corte del Estado de New York, en y para el Condado de New York, una Corte de registro que por ley tiene un sello, POR EL PRESENTE CERTIFICO de acuerdo con la ley ejecutiva del Estado de New York, que SUZAN Z. KILLIAN, cuyo nombre se escribe la declaración juramentada, declaración, certificado de reconocimiento o prueba adjunta, era en el momento de tomarla un NOTARIO PÚBLICO en y para el Estado de New York, debidamente comisionado, juramentado y calificado para actuar como tal; que de acuerdo con la ley, una comisión o certificado de su carácter oficial, con firma autógrafa, ha sido registrada en mi oficina; que estoy familiarizado con la escritura de dicho NOTARIO PÚBLICO o he comparado la firma del instrumento adjunto con su firma autógrafa

COMO NOTARIO SENTO (#) DEL CIRCULO DE NOTARIOS DEL ESTADO DE NEW YORK
FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2005
PABLO [illegible]
NOTARIA

depositada en mi oficina y creo que dicha firma es genuina.

EN FE DE LO CUAL, he firmado e impuesto el sello oficial hoy 14 de enero de 2005.

(Firma facsimilar ilegible), Escribano de Condado y Escribano de la Corte Suprema, Condado de New York. (Sello en tinta del Escribano de Condado).

APOSTILLA

(Convención de La Haye du 5 Octobre 1961)

1. País: **Estados Unidos de América**

Este documento público

2. Ha sido firmado por **Norman Goodman**

3. Actuando en su capacidad de **Escribano de Condado**

4. Lleva el sello/timbre de **New York**

CERTIFICADO

5. En New York, New York.

6. el 24 de enero de 2005

7. Por el Subsecretario de Estado Especial, Estado de New York

8. **No. A-132166E**

9. Sello: EL GRAN SELLO DEL ESTADO DE NEW YORK.

10. Firma (Firma ilegible) Daniel E. Shapiro, Subsecretario de Estado Especial

María E. Martelo.
TRADUCCION No.: 160205
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

CONSTA MEDIANTE SELLO DE ESTE CONSULADO DE BOGOTA, HABER CONSTATADO QUE LA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE SE TUVO A LA VISTA
07 ABR 2005
PABLO BENAVIDES BARAJAS
NOTARIO (E)

ESTADO DE DELAWARE
SECRETARIO DE ESTADO
DIVISIÓN DE SOCIEDADES
Entregado 12:48 PM 08/13/2004
PRESENTADO 12:48 PM 08/13/2004
SRV 040594300 - 0527510 ARCHIVO

CERTIFICADO DE FORMACIÓN

DE

PHARMACIA & UPJOHN LLC

Este certificado de formación de Pharmacia & Upjohn Company LLC está siendo debidamente ejecutado por Charles F. Raeburn como

MINISTERIO DE
RELACIONES EXTERIORES

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB 17 P 12:04

327789
Hana Haritdo
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

JEFE DE LEGALIZACIONES
BOGOTA D.C.

07 ABR 2005

PADILLA VELEZ BARAJAS
NOTARIO (E)

personal autorizada para formar una compañía de responsabilidad limitada bajo la Ley de Sociedades de Responsabilidad Limitada de Delaware.

1. El nombre de la sociedad es Pharmacia & Upjohn Company LLC.

2. La dirección de la oficina registrada en el Estado de Delaware es Corporation Trust Center, 1209 Orange Street, en la Ciudad de Wilmington, Condado de New Castle, Delaware 19801. El nombre de su agente registrado en dicha dirección es The Corporation Trust Company

EN FE DE LO CUAL, el suscrito firma este Certificado de Formación de Pharmacia & Upjohn Company LLC.

/F/ Charles F. Raeburn

Nombre: Charles F. Raeburn

Funcionario Autorizado

Fecha: 13 de agosto de 2004

Estado de Delaware

El Primer Estado

YO, HARRIET SMITH WINDSOR, SECRETARIO DE ESTADO DEL ESTADO DE DELAWARE, POR EL PRESENTE CERTIFICO QUE LA ADJUNTA ES UNA COPIA FIEL Y CORRECTA DEL CERTIFICADO DE FORMACIÓN DE "PHARMACIA & UPJOHN COMPANY LLC" PRESENTADO EN ESTA OFICINA EL DÉCIMO TERCERO DE AGOSTO, A.D. 2004, A LAS 12:48 DE LA TARDE.

(Firma) Harriet Smith Windsor, Secretario de Estado

0527510 8100 (ilegible) *Autenticación: 3544900*

040900672 *Fecha: 12 14-04*

07 ABR 2005

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América

Este documento público

2. Ha sido firmado por Harriet Smith Windsor

3. Actuando en su capacidad de Secretario de Estado del Estado de Delaware

4. Lleva el sello/timbre de la Secretaría de Estado

CERTIFICADO

5. En Dover, Delaware

6. el dos de febrero, A.D. 2005

7. Por el Secretario de Estado, Departamento de Estado de Delaware

8. No. 0245814

9. Sello: (sello dorado) SECRETARÍA DE ESTADO, DELAWARE 1793 - 1855.

10. Firma: (Firma) Harriet Smith Windsor, Secretario de Estado.

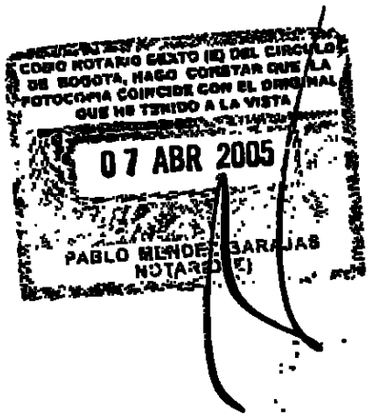
Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

COLO 14592-841-001-1

WPC 14592 ID. 6

FEB 15/05

María E. Martelo.
TRADUCCION No.: 16.0205
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia



COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) QUE
APARECE(N) EN EL PRESENTE DOCUMENTO
COINCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA. 17 FEB 2005

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

JEFE DE TRADUCCIONES

07 ABR 2005

PABLO [illegible]
NOTARIO [illegible]

MINISTERIO DE
RELACIONES EXTERIORES

327790

COTEJA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

CAVELIER
ABOGADOS

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTA 8, COLOMBIA

WEB SITE: www.cavelier-abogados.com
E-MAIL: cavelier@colomsat.net.co

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

23

Señora Jefe de la

DIVISION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Poderdante: **PHARMACIA & UPJOHN COMPANY LLC**

Poder conferido el: 22-12-2004

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado, atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

EL SUSCRITO NOTARIO SESENTA (60) DEL CIRCULO DE BOGOTA, D.C. HACE CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
07 ABR 2005
PABLO MENDEZ BARAJAS
NOTARIO (E)

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil ya que los otros sustitutos faltan en este momento.

Señora Jefe,

GERMAN CAVELIER
T.P.A. No. 832
C.C. No. 2.877.924 de Bogotá

Acepto:

EMILIO FERRERO
T.P.A. N° 31.929
C.C. No. 438.019 de Usaquén

2e-780-2

NOTARIA SEXTA DE BOGO

Y PRESENTACION PERSON

18 FEB 2005

OTERO MEDINA

CULO DE BOGOTA

287924 DE 882

438019 DE 31929

en el presente documento expresó(a) suyo(s) y que el contenido del mismo es cierto. En constancia se firma esta diligencia.

COPIA NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

07 ABR 2005

PABLO MENDEZ BARRERA
NOTARIO (E)

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 March 2004 (25.03.2004)

PCT

(10) International Publication Number
WO 2004/024081 A2

(51) International Patent Classification⁷: A61K

(21) International Application Number:
PCT/US2003/028503

(22) International Filing Date:
10 September 2003 (10.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/409,453	10 September 2002 (10.09.2002)	US
60/452,231	5 March 2003 (05.03.2003)	US
60/491,757	1 August 2003 (01.08.2003)	US

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(72) Inventors; and

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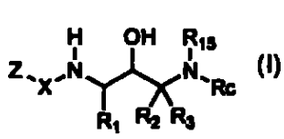
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(54) Title: ACETYL 2-HYDROXY-1,3 DIAMINOALKANES



(I)

(57) Abstract: Disclosed are compounds of the formula: (I) where variables Z, X, R_{15}, R_2, R_3, and R_c are defined herein. Compounds disclosed herein are inhibitors of the beta-secretase enzyme and are therefore useful in the treatment of Alzheimer's disease and other diseases characterized by deposition of A beta peptide in a mammal.

ACETYL 2-HYDROXY-1, 3-DIAMINOALKANES

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to acetyl 2-hydroxy-1,3-diaminoalkanes and to such compounds that are useful in the treatment of Alzheimer's disease and related diseases. More specifically, it relates to such compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce amyloid beta peptide (A beta), a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

Background of the Invention

Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgment, and orientation. As the disease progresses, motor, sensory, and linguistic abilities are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

Alzheimer's disease is characterized by two major pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment know as A beta. Individuals with AD exhibit characteristic beta-amyloid deposits in the brain (beta amyloid plaques) and in cerebral blood vessels (beta amyloid angiopathy) as well as neurofibrillary tangles. Neurofibrillary tangles occur not only in Alzheimer's disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged

humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurodegenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition of A beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin. See, for example, Sinha et al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A beta) plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example,

Selkoe, 1991, *Neuron* 6:487. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. See, for example, Seubert et al., 1992, *Nature* 359:325-327.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. *In vivo* processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

BACE1 knockout mice fail to produce A beta, and present a normal phenotype. When crossed with transgenic mice that over express APP, the progeny show reduced amounts of A beta in brain extracts as compared with control animals (Luo et al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A beta in the brain provides a therapeutic method for the treatment of AD and other beta amyloid disorders.

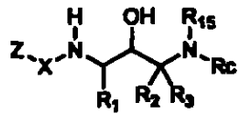
At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are effective inhibitors of A beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

SUMMARY OF THE INVENTION

The invention encompasses the compounds of formula (I) shown below, pharmaceutical compositions containing the compounds and methods employing such compounds or compositions in the treatment of Alzheimer's disease and more specifically compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce A-beta peptide, a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

In a broad aspect, the invention provides compounds of formula I



(I)

and pharmaceutically acceptable salts thereof, wherein

Z is hydrogen, or

Z is $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_1\text{-}C_6$ alkyl$)$-, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkenyl$)$-, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkynyl$)$- or $(C_3\text{-}C_7$ cycloalkyl$)$-, wherein each of said groups is optionally substituted with 1, 2, or 3 R_g groups, wherein 1 or 2 methylene groups within said $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_1\text{-}C_6$ alkyl$)$-, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkenyl$)$-, $(C_3\text{-}C_7$ cycloalkyl$)_{0\text{-}1}(C_2\text{-}C_6$ alkynyl$)$-. or $(C_3\text{-}C_7$ cycloalkyl$)$- groups are optionally replaced with -(C=O)-;

R_g at each occurrence is independently halogen (in one aspect, F or Cl), -OH, -SH, -CN, $-CF_3$, $-OCF_3$, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_7$ cycloalkyl, $C_3\text{-}C_7$ cycloalkoxy or $-NR_{100}R_{101}$;

R_{100} and R_{101} at each occurrence are independently H, $C_1\text{-}C_6$ alkyl, phenyl, $CO(C_1\text{-}C_6$ alkyl$)$ or $SO_2C_1\text{-}C_6$ alkyl;

X is -(C=O)- or $-(SO_2)$-;

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, -CF_3, -OCF_3, -C_{3-7} cycloalkyl, -C_1-C_4 alkoxy, amino, mono- or dialkylamino, aryl, heteroaryl, and heterocycloalkyl, wherein each aryl group is optionally substituted with 1, 2 or 3 R_{50} groups; each heteroaryl is optionally substituted with 1 or 2 R_{50} groups; and each heterocycloalkyl group is optionally substituted with 1 or 2 groups that are independently R_{50} or =O;

R_{50} is selected from halogen, OH, SH, CN, -CO-(C_1-C_4 alkyl), -NR_7R_8, -$S(O)_{0-2}$-(C_1-C_4 alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl; wherein

the alkyl, alkenyl, alkynyl, alkoxy and cycloalkyl groups are optionally substituted with 1 or 2 substituents independently selected from C_1-C_4 alkyl, halogen, OH, -NR_5R_6, CN, C_1-C_4 haloalkoxy, NR_7R_8, and C_1-C_4 alkoxy; wherein

R_5 and R_6 are independently H or C_1-C_6 alkyl; or

R_5 and R_6 and the nitrogen to which they are attached form a 5 or 6 membered heterocycloalkyl ring;

R_7 and R_8 are independently selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, -NH_2, and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl;

R_2 and R_3 are independently selected from H; F; -C_1-C_6 alkyl optionally substituted with -F, -OH, -C≡N, -CF_3, C_1-C_3 alkoxy, or -NR_5R_6; -$(CH_2)_{0-2}$-R_{17}; -$(CH_2)_{0-2}$-R_{18}; -C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl and alkynyl groups are optionally substituted with 1 or 2 groups that are independently -F, -OH, -C≡N, -CF_3 or C_1-C_3 alkoxy; -$(CH_2)_{0-2}$-C_3-C_7 cycloalkyl, which is optionally substituted with 1

or 2 groups that are independently -F, -OH, -C≡N, $-CF_3$, C_1-C_3 alkoxy and $-NR_5R_6$;

R_{17} at each occurrence is an aryl group (preferably selected from phenyl, 1-naphthyl, 2-naphthyl , indanyl, indenyl, dihydronaphthyl and tetralinyl,) wherein said aryl group is optionally substituted with one or two groups that are independently -C_1-C_3 alkyl; -C_1-C_4 alkoxy; CF_3; -C_2-C_6 alkenyl or -C_2-C_6 alkynyl each of which is optionally substituted with one substituent selected from F, OH, C_1-C_3 alkoxy; halogen; OH; -C≡N; -C_3-C_7 cycloalkyl; -CO-(C_1-C_4 alkyl); or -SO_2-(C_1-C_4 alkyl);

R_{18} is a heteroaryl group (preferably selected from pyridinyl, pyrimidinyl, quinolinyl, indolyl, pryidazinyl, pyrazinyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrrolyl, oxadiazolyl or thiadiazolyl,) wherein said heteroaryl groups are optionally substituted with one or two groups that are independently -C_1-C_6 alkyl optionally substituted with one substituent selected from OH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$;

R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, halo C_1-C_6 alkyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, and NH_2, and $-R_{26}$-R_{27}; wherein

R_{26} is selected from a bond, -C(O)-, $-SO_2$-, $-CO_2$-, $-C(O)NR_5$-, and $-NR_5C(O)$-,

R_{27} is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl C_1-C_6 alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, haloalkyl, hydroxyalkyl, $-NR_5R_6$, or $-C(O)NR_5R_6$; or

R_2, R_3 and the carbon to which they are attached form a C_3-C_7 carbocycle, wherein 1, 2, or 3 carbon atoms are optionally replaced by groups that are independently selected from -O-, -S-, -SO_2-, -C(O)-, or -NR_7-;

R_C is selected from -$(CH_2)_{0-3}$-(C_3-C_8) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from -R_{205}; and -CO_2-(C_1-C_8 alkyl); -$(CR_{245}R_{250})_{0-4}$-aryl; -$(CR_{245}R_{250})_{0-4}$-heteroaryl; -$(CR_{245}R_{250})_{0-4}$-heterocycloalkyl; -$(CR_{245}R_{250})_{0-4}$-aryl-heteroaryl; -$(CR_{245}R_{250})_{0-4}$-aryl-heterocycloalkyl; -$(CR_{245}R_{250})_{0-4}$-aryl-aryl; -$(CR_{245}R_{250})_{0-4}$-heteroaryl-aryl; -$(CR_{245}R_{250})_{0-4}$-heteroaryl-heterocycloalkyl; -$(CR_{245}R_{250})_{0-4}$-heteroaryl-heteroaryl; -CHR_{245}-CHR_{250}-aryl; -$(CR_{245}R_{250})_{0-4}$-heterocycloalkyl-heteroaryl; -$(CR_{245}R_{250})_{0-4}$-heterocycloalkyl-heterocycloalkyl; -$(CR_{245}R_{250})_{0-4}$-heterocycloalkyl-aryl; a monocyclic or bicyclic ring of 5, 6, 7 8, 9, or 10 carbons fused to 1 or 2 aryl (preferably phenyl), heteroaryl (preferably pyridyl, imidazolyl, thienyl, thiazolyl, or pyrimidyl), or heterocycloalkyl (preferably piperidinyl or piperazinyl) groups;

wherein 1, 2 or 3 carbons of the monocyclic or bicyclic ring are optionally replaced with -NH-, -$N(CO)_{0-1}R_{215}$-, -$N(CO)_{0-1}R_{220}$-, -O-, or -$S(=O)_{0-2}$-, and wherein the monocyclic or bicyclic ring is optionally substituted with 1, 2 or 3 groups that are independently -R_{205}, -R_{245}, -R_{250} or =O;

and -C_2-C_6 alkenyl optionally substituted with 1, 2, or 3 R_{205} groups;

wherein each aryl or heteroaryl group attached directly or indirectly to the -$(CR_{245}R_{250})_{0-4}$ group is optionally substituted with 1, 2, 3 or 4 R_{200} groups;

wherein each heterocycloalkyl attached directly or indirectly to the -$(CR_{245}R_{250})_{0-4}$ group is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{200} at each occurrence is independently selected from -C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; -OH; -NO_2; -halogen; -C≡N; -$(CH_2)_{0-4}$-CO-$NR_{220}R_{225}$; -$(CH_2)_{0-4}$-CO-(C_1-C_8 alkyl); -$(CH_2)_{0-4}$-CO-(C_2-C_8 alkenyl); -$(CH_2)_{0-4}$-CO-(C_2-C_8 alkynyl); -$(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl); -$(CH_2)_{0-4}$-$(CO)_{0-1}$-aryl (preferably phenyl); -$(CH_2)_{0-4}$-$(CO)_{0-1}$-heteroaryl (preferably pyridyl, pyrimidyl, furanyl, imidazolyl, thienyl, oxazolyl, thiazolyl, or pyrazinyl); -$(CH_2)_{0-4}$-$(CO)_{0-1}$-heterocycloalkyl (preferably imidazolidinyl, piperazinyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl); -$(CH_2)_{0-4}$-CO_2R_{215}; -$(CH_2)_{0-4}$-SO_2-$NR_{220}R_{225}$; -$(CH_2)_{0-4}$-S(O)$_{0-2}$-(C_1-C_8 alkyl); -$(CH_2)_{0-4}$-S(O)$_{0-2}$-(C_3-C_7 cycloalkyl); -$(CH_2)_{0-4}$-N(H or R_{215})-CO_2R_{215}; -$(CH_2)_{0-4}$-N(H or R_{215})-SO_2-R_{220}; -$(CH_2)_{0-4}$-N(H or R_{215})-CO-$N(R_{215})_2$; -$(CH_2)_{0-4}$-N(-H or R_{215})-CO-R_{220}; -$(CH_2)_{0-4}$-$NR_{220}R_{225}$; -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alkyl); -$(CH_2)_{0-4}$-O-(R_{215}); -$(CH_2)_{0-4}$-S-(R_{215}); -$(CH_2)_{0-4}$-O-(C_1-C_6 alkyl optionally substituted with 1, 2, 3, or 5 -F); -C_2-C_6 alkenyl optionally substituted with 1 or 2 R_{205} groups; -C_2-C_6 alkynyl optionally substituted with 1 or 2 R_{205} groups; adamantly, and -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl;

each aryl and heteroaryl group included within R_{200} is optionally substituted with 1, 2, or 3 groups that are independently -R_{205}, -R_{210} or -C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210};

each heterocycloalkyl group included within R_{200} is optionally substituted with 1, 2, or 3 groups that are independently R_{210};

R_{205} at each occurrence is independently selected from -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_1-C_6 haloalkoxy, -$(CH_2)_{0-3}$(C_3-C_7 cycloalkyl), -halogen, -$(CH_2)_{0-6}$-OH, -O-phenyl,

OH, SH, $-(CH_2)_{0-6}-C\equiv N$, $-(CH_2)_{0-6}-C(=O)NR_{235}R_{240}$, $-CF_3$, $-C_1-C_6$ alkoxy, C_1-C_6 alkoxycarbonyl, and $-NR_{235}R_{240}$;

R_{210} at each occurrence is independently selected from $-C_1-C_6$ alkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-C_2-C_6$ alkenyl optionally substituted with 1, 2, or 3 R_{205} groups; C_1-C_6 alkanoyl; $-SO_2-(C_1-C_6$ alkyl); $-C_2-C_6$ alkynyl optionally substituted with 1, 2, or 3 R_{205} groups; -halogen; $-C_1-C_6$ alkoxy; $-C_1-C_6$ haloalkoxy; $-NR_{220}R_{225}$; -OH; $-C\equiv N$; $-C_3-C_7$ cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-CO-(C_1-C_4$ alkyl); $-SO_2-NR_{235}R_{240}$; $-CO-NR_{235}R_{240}$; $-SO_2-(C_1-C_4$ alkyl); and =O;

R_{215} at each occurrence is independently selected from $-C_1-C_6$ alkyl, $-(CH_2)_{0-2}-$(aryl), $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_7$ cycloalkyl, $-(CH_2)_{0-2}-$(heteroaryl), and $-(CH_2)_{0-2}-$(heterocycloalkyl); wherein the aryl group included within R_{215} is optionally substituted with 1, 2, or 3 groups that are independently $-R_{205}$ or $-R_{210}$; wherein the heterocycloalkyl and heteroaryl groups included within R_{215} are optionally substituted with 1, 2, or 3 R_{210};

R_{220} and R_{225} at each occurrence are independently H, $-C_1-C_6$ alkyl, -CHO, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, -amino C_1-C_6 alkyl, $-SO_2-C_1-C_6$ alkyl, C_1-C_6 alkanoyl optionally substituted with up to three halogens, $-C(O)NH_2$, $-C(O)NH(C_1-C_6$ alkyl), $-C(O)N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl), -halo C_1-C_6 alkyl, $-(CH_2)_{0-2}-(C_3-C_7$ cycloalkyl), $-(C_1-C_6$ alkyl)$-O-(C_1-C_3$ alkyl), $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, -aryl (preferably phenyl), -heteroaryl, or -heterocycloalkyl; wherein the aryl, heteroaryl and heterocycloalkyl groups

included within R_{220} and R_{225} is optionally substituted with 1, 2, or 3 R_{270} groups,

R_{270} at each occurrence is independently -R_{205}, -C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; -C_2-C_6 alkenyl optionally substituted with 1, 2, or 3 R_{205} groups; -C_2-C_6 alkynyl optionally substituted with 1, 2, or 3 R_{205} groups; -phenyl; -halogen; -C_1-C_6 alkoxy; -C_1-C_6 haloalkoxy; -$NR_{235}R_{240}$; -OH; -C≡N; -C_3-C_7 cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; -CO-(C_1-C_4 alkyl); -SO_2-$NR_{235}R_{240}$; -CO-$NR_{235}R_{240}$; -SO_2-(C_1-C_4 alkyl); and =O;

R_{235} and R_{240} at each occurrence are independently -H, -C_1-C_6 alkyl, C_2-C_6 alkanoyl, -SO_2-(C_1-C_6 alkyl), or -phenyl;

R_{245} and R_{250} at each occurrence are independently selected from H, -$(CH_2)_{0-4}CO_2C_1$-C_4 alkyl, -$(CH_2)_{0-4}C(=O)C_1$-C_4 alkyl, -C_1-C_4 alkyl, -C_1-C_4 hydroxyalkyl, -C_1-C_4 alkoxy, -C_1-C_4 haloalkoxy, -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -$(CH_2)_{0-4}$ aryl, -$(CH_2)_{0-4}$ heteroaryl, and -$(CH_2)_{0-4}$ heterocycloalkyl, or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle or bicycle of 3, 4, 5, 6, 7 or 8 carbon atoms, where 1, 2, or 3 carbon atoms are optionally replaced by 1, 2, or 3 groups that are independently -O-, -S-, -SO_2-, -C(O)-, -NR_{220}-, or -$NR_{220}R_{220}$- wherein both R_{220} groups are alkyl; and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH-C(O)C_1-C_5 alkyl, -NH-SO_2-(C_1-C_6 alkyl), or halogen;

wherein the aryl, heteroaryl or heterocycloalkyl groups included within R_{245} and R_{250} are optionally substituted with 1, 2, or 3 groups that are independenly halogen, C_{1-6} alkyl, CN or OH.

The invention also provides methods for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising administration of a therapeutically effective amount of a compound or salt of formula I, to a patient in need thereof.

Preferably, the patient is a human.

More preferably, the disease is Alzheimer's disease.

More preferably, the disease is dementia.

The invention also provides pharmaceutical compositions comprising a compound or salt of formula I and at least one pharmaceutically acceptable carrier, solvent, adjuvant or diluent.

The invention also provides the use of a compound or salt according to formula I for the manufacture of a medicament.

The invention also provides the use of a compound or salt of formula I for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

The invention also provides compounds, pharmaceutical compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A-beta peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A-beta peptide.

The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD, and for treating frontotemporal dementias with parkinsonism (FTDP).

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention is readily demonstrated, for example, using one or more of the assays described herein or known in the art.

Unless the substituents for a particular formula are expressly defined for that formula, they are understood to carry the definitions set forth in connection with the preceding formula to which the particular formula makes reference.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

The invention also provides the use of compounds and pharmaceutically acceptable salts of formula I for the manufacture of a medicament for use in: treating a subject who has, or in preventing a subject from developing Alzheimer's disease (AD); preventing or delaying the onset of Alzheimer's disease; treating subjects with mild cognitive impairment (MCI); preventing or delaying the onset of Alzheimer's disease in subjects who would progress from MCI to AD; treating Down's syndrome; treating subjects who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type; treating cerebral amyloid angiopathy and preventing its potential consequences; treating other degenerative dementias; treating dementia associated with Parkinson's disease, progressive supranuclear palsy, or cortical basal degeneration; treating diffuse Lewy body type AD; and treating frontotemporal dementias with parkinsonism (FTDP).

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the invention provides compounds of formula I. In accordance with compounds of formula I and other applicable formulas below, when Z is (C_3-C_7 cycloalkyl)$_{0-1}$(C_1-C_6 alkyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkenyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkynyl)- or (C_3-C_7 cycloalkyl)-, 1 or 2 methylene groups within said (C_3-C_7 cycloalkyl)$_{0-1}$(C_1-C_6 alkyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkenyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkynyl)- or (C_3-C_7 cycloalkyl)- groups are optionally replaced with -(C=O)-. This optionally substitution may be alpha to X, e.g., α,β-diketo compounds are contemplated by the invention Further such carbonyl substitution contemplates compounds, for example, in which a methylene group is replaced in the cyclic portion the cycloalkyl group (to form a cyclic ketone moiety) and/or in which a methylene group is replaced in the alkyl, alkenyl or alkynyl portion of such groups.

Preferred compounds of formula I include those wherein Z is (C_3-C_7 cycloalkyl)$_{0-1}$(C_1-C_6 alkyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkenyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkynyl)- or (C_3-C_7 cycloalkyl)-, wherein each of said groups is optionally substituted with 1, 2, or 3 R_z groups;

R_z at each occurrence is independently halogen, -OH, -CN, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy, or $-NR_{100}R_{101}$;

R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1$-C_6 alkyl) or SO_2C_1-C_6 alkyl.

In another preferred embodiment, the invention encompasses compounds of formula I wherein Z is as defined above and X is -(C=O)-. In an alternative embodiment, X is -(C=O)-, and Z is H. In another preferred embodiment, X is -(C=O)-, and Z is C_1-C_4 alkyl, more preferably C_1-C_3 alkyl, even more preferably methyl.

Preferred compounds of formula I further include those wherein R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, $-CF_3$, $-OCF_3$, $-C_{3-7}$ cycloalkyl, $-C_1$-C_4 alkoxy, amino and aryl, wherein the aryl (preferably phenyl) group is optionally substituted with 1 or 2 R_{50} groups;

R_{50} is selected from halogen, OH, $-CO-(C_1$-C_4 alkyl), $-NR_7R_8$, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl; wherein the alkyl, alkoxy and cycloalkyl groups are optionally substituted with 1 or 2 substituents independently selected from C_1-C_4 alkyl, halogen, OH, $-NR_5R_6$, NR_7R_8, and C_1-C_4 alkoxy;

R_5 and R_6 at are independently H or C_1-C_6 alkyl; or

R_5 and R_6 and the nitrogen to which they are attached form a 5 or 6 membered heterocycloalkyl ring; and

R_7 and R_8 are independently selected from -H; $-C_1$-C_4 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, $-NH_2$,

and halogen; -C_3-C_6 cycloalkyl; and -(C_2-C_4 alkyl)-O-(C_1-C_4 alkyl).

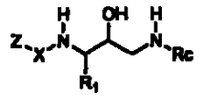
Preferred compounds of formula I also include those wherein

R_1 is -CH_2-phenyl where the phenyl ring is optionally substituted with 1 or 2 groups independently selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy and hydroxy. More preferably, R_1 is benzyl, 3-fluorobenzyl or 3,5-difluorobenzyl.

Preferred compounds of formula I include those wherein R_2 and R_3 are independently -H or -C_1-C_6 alkyl.

Equally preferred compounds of formula I include those wherein R_{15} is H.

In another aspect, the invention provides compounds of the formula II:



(II)

and pharmaceutically acceptable salts thereof, wherein

Z is hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl, where each of said groups is optionally substituted with 1 or 2 R_E groups, wherein 1 or 2 methylene groups within said -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl groups are optionally replaced with -(C=O)-;

R_E at each occurrence is independently halogen, -OH, -CN, -CF_3, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy or -$NR_{100}R_{101}$;

R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, CO(C_1-C_6 alkyl) or SO_2C_1-C_6 alkyl;

X is -C(=O)-;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cycloalkyl, -C_1-C_4 alkoxy, amino, mono-dialkylamino, aryl, heteroaryl or heterocycloalkyl,

wherein the aryl group is optionally substituted with 1 or 2 R_{50} groups;

R_{50} is halogen, OH, CN, -CO-(C_1-C_4 alkyl), $-NR_7R_8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, and C_3-C_8 cycloalkyl;

R_7 and R_8 are selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups selected from -OH, $-NH_2$ and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl;

R_C is selected from $-(CR_{245}R_{250})_{0-4}$-aryl; $-(CR_{245}R_{250})_{0-4}$-heteroaryl; $-(CR_{245}R_{250})_{0-4}$-heterocycloalkyl; where the aryl and heteroaryl groups attached to the $-(CR_{245}R_{250})_{0-4}$- group are optionally substituted with 1, 2, 3 or 4 R_{200} groups; where the heterocycloalkyl group attached to the $-(CR_{245}R_{250})_{0-4}$- group is optionally substituted with 1, 2, 3, or 4 R_{210} groups; and

R_{245} R_{250}, R_{200}, and R_{210} are as defined above.

In another aspect, the invention provides compounds wherein

R_C is $-(CR_{245}R_{250})_{0-4}$-heterocycloalkyl (preferably piperidinyl, piperazinyl, pyrrolidinyl, 2-oxo-tetrahydroquinolinyl, 2-oxo-dihydro-1H-indolyl, or imidazolidinyl); where the heterocycloalkyl group attached to the $-(CR_{245}R_{250})_{0-4}$- group is optionally substituted with 1, 2, 3, or 4 R_{210} groups.

In a further preferred embodiment for compounds of formula II, Z is -C_1-C_6 alkyl;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 aryl groups, which are optionally substituted with 1 or 2 R_{50} groups,

each R_{50} is independently halogen, OH, CN, $-NR_7R_8$ or C_1-C_6 alkyl,

R_7 and R_8 are independently -H; -C_1-C_4 alkyl optionally substituted with 1 or 2 groups

independently selected from -OH, $-NH_2$, and halogen; or $-C_3-C_6$ cycloalkyl; and

R_C is $-(CR_{245}R_{250})_{0-4}$-aryl or $-(CR_{245}R_{250})_{0-4}$-heteroaryl (preferably the heteroaryl is pyridyl, pyrimidyl, quinolinyl, isoquinolinyl, more preferably pyridyl), where the aryl and heteroaryl groups are optionally substituted with 1 or 2 R_{200} groups, where R_{200} is as defined above.

Still more preferred compounds of formula II, include those wherein

R_1 is C_1-C_{10} alkyl substituted with one aryl group, where the aryl (preferably phenyl or naphthyl, still more preferably phenyl) group is optionally substituted with 1 or 2 R_{50} groups;

R_C is $-(CR_{245}R_{250})_{1-4}$-aryl or $-(CR_{245}R_{250})_{1-4}$-heteroaryl,

R_{245} and R_{250} are independently selected from H, $-(CH_2)_{0-4}CO_2C_1-C_4$ alkyl, $-(CH_2)_{0-4}CO_2H$, $-C_1-C_4$ alkyl, $-(C_1-C_4$ alkyl)OH, or

R_{245}, R_{250} and the carbon to which they are attached form a monocycle or bicycle of 3, 4, 5, 6, 7 or 8 carbon atoms, where 1 or 2 carbon atoms are optionally replaced by -O-, -S-, $-SO_2-$, or $-NR_{220}-$, where R_{220} is as defined above; and

wherein the aryl and heteroaryl groups attached to the $-(CR_{245}R_{250})_{1-4}-$ groups are optionally substituted with 1 or 2 R_{200} groups.

In another preferred embodiment of compounds of formula II,

R_1 is C_1-C_{10} alkyl substituted with one aryl group (preferably phenyl or naphthyl), which is optionally substituted with 1 or 2 R_{50} groups,

R_{50} is independently halogen, OH, or C_1-C_6 alkyl;

R_C is $-(CR_{245}R_{250})$-aryl or $-(CR_{245}R_{250})$-heteroaryl, wherein the aryl and heteroaryl groups attached to the $-(CR_{245}R_{250})_{1-4}-$ groups are optionally substituted with 1 or 2 substitutents selected from -Cl, -Br, -I, $-C_1-C_3$ alkyl, $-(C_1-C_3$ alkyl)OH, -CN, -C≡CH, $-C\equiv C-CH_2-OH$, $-CF_3$, -thienyl

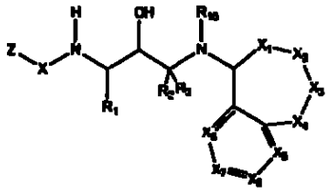
optionally substituted with a -C(=O)H group, -phenyl optionally substituted with 1 or 2 C_1-C_3 alkyl groups, -(C_1-C_3 alkyl)OH group or -CO(C_1-C_3 alkyl) group, -isoxazolyl optionally substituted with a C_1-C_4 alkyl group, or -(C_1-C_2 alkyl)oxazolyl where the oxazole ring is optionally substituted with -C_1-C_2 alkyl group;

R_{245} and R_{250} at each occurance are independently -H, -C_1-C_3 alkyl, -(C_1-C_3 alkyl)CO_2H, -(C_1-C_3 alkyl)CO_2(C_1-C_3 alkyl), or -(C_1-C_3 alkyl)OH, or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle or bicycle of 3, 4, 5, 6, 7 or 8 carbon atoms, where 1 or 2 carbon atoms is optionally replaced by -O-, -S-, -SO_2-, or -NR_{220}-, and

R_{220} is as defined above.

In another aspect, the invention provides compounds of the formula III:



(III)

and pharmaceutically acceptable salts thereof; where

Z, X, R_1, R_2, R_3 and R_{15} are as definded above;

X_1 is CH_2, CHR_{200}, $C(R_{200})_2$, or -(C=O)-;

X_2, and X_3 are independently CH_2, CHR_{200}, $C(R_{200})_2$, O, C=O, S, SO_2, NH, or NR_7;

X_4 is a bond, CH_2, CHR_{200}, $C(R_{200})_2$ O, C=O, S, SO_2, NH, or NR_7;

provided that when X_1 is -(C=O)-, X_2 is CH_2, CHR_{200}, $C(R_{200})_2$, O, NH or NR_7 and the X_3 group attached to X_2 is CH_2, CHR_{200}, $C(R_{200})_2$, or SO_2 when X_2 is NH or NR_7 and X_4 is CH_2, CHR_{200}, or $C(R_{200})_2$ or a bond; or

-X_2-X_3- is -(C=O)O-, -O(C=O)-, -(C=O)NH-, -NH(C=O)- , -(C=O)NR_7-, or -NR_7(C=O)-, with the proviso that X_1 is not

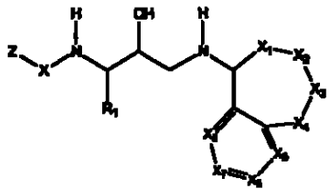
-(C=O)- and with the proviso that X_4 is CH_2, CHR_{200}, or $C(R_{200})_2$ or a bond; or

$-X_3-X_4-$ is -(C=O)O-, -O(C=O)-, -(C=O)NH-, -NH(C=O)-, -(C=O)NR_7-, or -NR_7(C=O)-, with the proviso that X_2 is CH_2, CHR_{200}, or $C(R_{200})_2$; or

$-X_2-X_3-X_4-$ is -(C=O)NH-SO_2- or -SO_2-NH(C=O)-, -(C=O)NR_7-SO_2- or -SO_2-NR_7(C=O)-, with the proviso that X_1 is not -(C=O)-; and

X_5, X_6, X_7 and X_8 are CH or CR_{200}, where 1 or 2 of X_5, X_6, X_7 and X_8 is optionally replaced with N, and where R_{200} and R_7 are as defined above.

In a preferred embodiment of compounds of formula III, the invention further provides compounds of the formula IV:



(IV)

wherein

Z is hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl, where each is optionally substituted with 1 or 2 R_Z groups, and wherein 1 or 2 methylene groups within said -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl groups are optionally replaced with -(C=O)-;

R_Z at each occurrence is independently halogen, -OH, -CN, -CF_3, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy or -$NR_{100}R_{101}$;

R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1$-C_6 alkyl) or SO_2C_1-C_6 alkyl;

X is -C(=O)-;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cycloalkyl, -C_1-C_4 alkoxy, amino, mono-

dialkylamino, aryl optionally substituted with 1 or 2 R_{50} groups, heteroaryl or heterocycloalkyl;

R_{50} is halogen, OH, CN, -CO-(C_1-C_4 alkyl), -NR_7R_8, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl; and

R_7 and R_8 are selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups selected from -OH, -NH_2 and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl.

In other preferred compounds of formula IV,

Z is -C_1-C_6 alkyl;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 aryl (preferably phenyl or naphthyl) groups, which are optionally substituted with 1 or 2 R_{50} groups,

R_{50} is independently halogen, OH, CN, -NR_7R_8 or C_1-C_6 alkyl, R_7 and R_8 are independently H; -C_1-C_4 alkyl optionally substituted with 1 or 2 groups independently selected from -OH, -NH_2, and halogen; or -C_3-C_6 cycloalkyl; and

X_1, X_2 or X_3 are CH_2 or CHR_{200}, where one of X_2 or X_3 is optionally replaced with O, C=O, SO_2, NH, NR_7,

X_4 is a bond; and

X_5, X_6, X_7 and X_8 are CH or CR_{200}, where one of X_5, X_6, X_7 or X_8 is optionally replaced with N, and

R_{200} is as defined above.

In yet another preferred aspect of the invention for compounds of formula VI, R_1 is C_1-C_{10} alkyl substituted with one aryl group, where the aryl group is optionally substituted with 1 or 2 R_{50} groups;

X_1, X_2 and X_3 are CH_2, CHR_{200}, or $C(R_{200})_2$, where one of X_2 or X_3 is optionally replaced with O, NH or NR_7, and where X_4 is a bond; and

X_5, X_6, X_7 and X_8 are CH or CR_{200}, where one of X_5, X_6, X_7 or X_8 is optionally replaced with N, where R_{50}, R_{200} and R_7 are as defined above.

In a futher preferred embodiment of compound of formula IV,

R_1 is C_1-C_{10} alkyl substituted with one aryl group (preferably phenyl or naphthyl, more preferably phenyl), where the aryl group is optionally substituted with 1 or 2 R_{50} groups,

R_{50} is independently halogen,. OH, or C_1-C_6 alkyl;

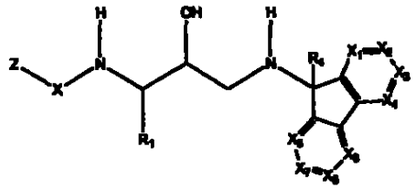
X_1, X_2 and X_3 are CH_2 or CHR_{200}, where one of X_2 or X_3 is optionally replaced with O, NH or NR_7;

X_4 is a bond;

X_5, X_6, X_7 and X_8 are CH or CR_{200}, where one of X_5, X_6, X_7 and X_8 is optionally replaced with N; and

R_{200} is -C_{1-4} alkyl, -halogen; -O-C_{1-3} alkyl; -pyrrolyl or -$(CH_2)_{1-3}$-$N(R_7)_2$, where R_7 is as defined above.

In another aspect, the invention provides compounds of V:



(V)

and a pharmaceutically acceptable salt thereof, wherein

Z is hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl, where each of said groups is optionally substituted with 1 or 2 R_z groups, wherein 1 or 2 methylene groups within said -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl groups are optionally replaced with -(C=O)-;

R_z at each occurrence is independently halogen, -OH, -CN, -CF_3, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy or -$NR_{100}R_{101}$;

R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1$-C_6 alkyl) or SO_2C_1-C_6 alkyl;

X is -C(=O)-;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, -CN, -CF_3,

$-OCF_3$, $-C_3-C_7$ cycloalkyl, $-C_1-C_4$ alkoxy, amino, mono-dialkylamino, aryl optionally substituted with 1 or 2 R_{50} groups, heteroaryl or heterocycloalkyl;

R_{50} is halogen, OH, CN, $-CO-(C_1-C_4$ alkyl), $-NR_7R_8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl;

R_7 and R_8 are selected from H; $-C_1-C_4$ alkyl optionally substituted with 1, 2, or 3 groups selected from -OH, $-NH_2$ and halogen; $-C_3-C_6$ cycloalkyl; $-(C_1-C_4$ alkyl)$-O-(C_1-C_4$ alkyl); $-C_2-C_4$ alkenyl; and $-C_2-C_4$ alkynyl;

X_1-X_8 are indepdendently CH or CR_{200}, where 1, 2, 3 or 4 of X_1-X_8 are optionally replaced with N (more preferably, 1, 2, or 3 are replaced with N);

where R_{200} is as definded above.

In another preferred embodiment for compounds of forumula V,

Z is $-C_1-C_6$ alkyl;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 aryl groups, where each aryl group is optionally substituted with 1 or 2 R_{50} groups,

R_{50} is independently halogen, OH, CN, $-NR_7R_8$ or C_1-C_6 alkyl,

R_7 and R_8 are independently H; $-C_1-C_4$ alkyl optionally substituted with 1 or 2 groups independently selected from -OH, $-NH_2$, and halogen; or $-C_3-C_6$ cycloalkyl; and

X_1-X_8 are CH or CR_{200}, where one or two of X_1-X_8 is optionally replaced with N, and R_{50} and R_{200} are as defined above.

In another preferred embodiment for compounds of forumula V,

R_1 is C_1-C_{10} alkyl substituted with one aryl group, where the aryl group (preferably phenyl) is optionally substituted with 1 or 2 R_{50} groups,

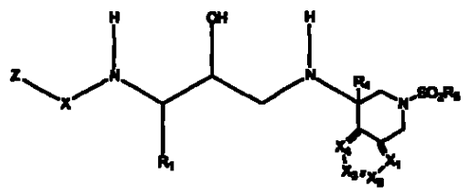
R_{50} is independently selected from halogen, OH, or C_1-C_6 alkyl;

X_1 - X_8 are CH or CR_{200}, where one of X_1-X_8 is optionally replaced with N.

In another preferred embodiment for compounds of forumula V,

R_{200} is -C_1-C_5 alkyl, -C_2-C_5 alkenyl, -C_3-C_6 cycloalkyl, halogen, $-CF_3$, -O-C_1-C_3 alkyl, -(C_1-C_3 alkyl)-O-(C_1-C_3 alkyl), pyrrolyl, or $-(CH_2)_{1-3}-N(R_7)_2$.

In a further aspect, the invention provides compounds of the formula VI:



(VI)

and a pharmaceutically acceptable salt thereof, wherein

Z is hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl, where each of said groups is optionally substituted with 1 or 2 R_z groups, wherein 1 or 2 methylene groups within said -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_3-C_6 alkynyl or -C_3-C_7 cycloalkyl groups are optionally replaced with -(C=O)-;

R_z at each occurrence is independently halogen, -OH, -CN, $-CF_3$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy or $-NR_{100}R_{101}$;

R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1$-C_6 alkyl) or SO_2C_1-C_6 alkyl;

X is -C(=O)-;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, -CN, $-CF_3$, $-OCF_3$, -C_3-C_7 cycloalkyl, -C_1-C_4 alkoxy, amino, mono-dialkylamino, aryl, heteroaryl and heterocycloalkyl, wherein the aryl, heterocycloalkyl and heteroaryl groups are optionally substituted with 1 or 2 R_{50} groups, wherein the heterocycloalkyl group is optionally further substituted with =O;

R_{50} is halogen, OH, CN, -CO-(C_1-C_4 alkyl), -NR_7R_8, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl;

R_7 and R_8 are selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups selected from -OH, -NH_2 and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl;

R_4 is H or -C_1-C_4 alkyl;

R_5 is -C_1-C_4 alkyl;

X_1 - X_4 are indepdendently CH or CR_{200}, where 1 or 2 of X_1 - X_4 are optionally replaced with N; and where

R_{200} is as definded above.

In a preferred embodiment for compounds of formula VI,

Z is -C_1-C_6 alkyl;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 aryl groups, where each aryl group is optionally substituted with 1 or 2 R_{50} groups,

each R_{50} is independently halogen, OH, CN, -NR_7R_8 or C_1-C_6 alkyl,

R_7 and R_8 are independently H; -C_1-C_4 alkyl optionally substituted with 1 or 2 groups independently selected from -OH, -NH_2, and halogen; or -C_3-C_6 cycloalkyl; and

X_1 - X_4 are CH or CR_{200}, where one or two of X_1 - X_4 is optionally replaced with N,

R_{200} is as defined above.

In a further preferred embodiment for compounds of formula VI,

R_1 is C_1-C_{10} alkyl substituted with one aryl group (preferably phenyl), where the aryl group is optionally substituted with 1 or 2 R_{50} groups,

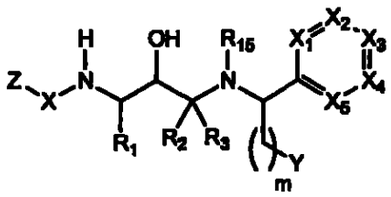
R_{50} is independently selected from halogen, OH, or C_1-C_6 alkyl;

X_1-X_4 are CH or CR_{200}, where one of X_1 - X_4 is optionally replaced with N, and where R_{50} and R_{200} are as defined above.

In yet another preferred embodiment for compounds of formula VI,

R_{200} is $-C_1-C_5$ alkyl, $-C_1-C_5$ alkenyl, $-C_3-C_6$ cycloalkyl, halogen, $-CF_3$, $-O-C_1-C_3$ alkyl, $-(C_1-C_3$ alkyl$)-O-(C_1-C_3$ alkyl), pyrrolyl, or $-(CH_2)_{1-3}-N(R_7)_2$.

In another aspect, the invention provides compounds of the formula VII:



(VII)

and pharmaceutically acceptable salts thereof, wherein
Z, X, R_1, R_2 and R_3 are as defined above;
m is 0 or an integer of 1-6;
Y is H, CN, OH, C_1-C_6 alkoxy, CO_2H, CO_2R_{215}, NH_2, aryl or heteroaryl; and
X_1-X_5 are indepdendently CH or CR_{200}, where 1, or 2 of X_1-X_5 are optionally replaced with N, and
R_{200} is as definded as above.

In a preferred embodiment of compounds of formula VII, R_2, R_3 and R_{15} are H;
Z is hydrogen, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl or $-C_3-C_7$ cycloalkyl, where each of said groups is optionally substituted with 1 or 2 R_z groups, wherein 1 or 2 methylene groups within said $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl or $-C_3-C_7$ cycloalkyl groups are optionally replaced with $-(C=O)-$;
R_z at each occurrence is independently halogen, -OH, -CN, $-CF_3$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy or $-NR_{100}R_{101}$;
R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1-C_6$ alkyl) or $SO_2C_1-C_6$ alkyl;
X is $-C(=O)-$;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cycloalkyl, -C_1-C_4 alkoxy, amino, mono- dialkylamino, aryl, heteroaryl or heterocycloalkyl, wherein the aryl, heterocycloalkyl and heteroaryl groups are optionally substituted with 1 or 2 R_{50} groups, and wherein the heterocycloalkyl group is optionally further substituted with =O;

R_{50} is halogen, OH, CN, -CO-(C_1-C_4 alkyl), -NR_7R_8, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl;

R_7 and R_8 are independently H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups selected from -OH, -NH_2 and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; or -C_2-C_4 alkynyl;

Y is as defined above;

X_1-X_5 are indepdendently CH or CR_{200}, where 1 or 2 of X_1-X_5 are optionally replaced with N; and

R_{200} is as definded above.

In yet another preferred embodiment for compounds of forumula VII,

Z is -C_1-C_6 alkyl;

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 aryl groups, where each aryl group is optionally substituted with 1 or 2 R_{50} groups,

R_{50} is independently halogen, OH, CN, -NR_7R_8 or C_1-C_6 alkyl, R_7 and R_8 are independently -H; -C_1-C_4 alkyl optionally substituted with 1 or 2 groups independently selected from -OH, -NH_2, and halogen; or -C_3-C_6 cycloalkyl;

X_1-X_5 are CH or CR_{200}, where one or two of X_1-X_5 is optionally replaced with N.

More preferably for compounds of formula VII,

R_1 is C_1-C_{10} alkyl substituted with one aryl group, where the aryl group is optionally substituted with 1 or 2 R_{50}

groups, where R_{50} is independently selected from halogen, OH, or C_1-C_6 alkyl;

wherein X_1 - X_5 are CH or CR_{200}, where one of X_1 - X_5 is optionally replaced with N,

where R_{50} and R_{200} are as definded above.

In yet another preferred embodiment for compounds of formula VII,

R_{200} is -C_1-C_5 alkyl, -C_1-C_5 alkenyl, -C_3-C_6 cycloalkyl, halogen, -CF_3, -O-C_1-C_3 alkyl, -(C_1-C_3 alkyl)-O-(C_1-C_3 alkyl), pyrrolyl, or -$(CH_2)_{1-3}$-$N(R_7)_2$, where R_7 is as defined above.

In another aspect, the invention provides compounds of formula II, i.e., compounds of formula II-a, wherein

R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, -CF_3, -OCF_3, -C_{3-7} cycloalkyl, -C_1-C_4 alkoxy, amino and aryl, wherein the aryl group is optionally substituted with 1 or 2 R_{50} groups;

wherein

R_{50} is selected from halogen, OH, -CO-(C_1-C_4 alkyl), -NR_7R_8, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl; and

R_7 and R_8 are independently -H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, -NH_2, and halogen; -C_3-C_6 cycloalkyl; or -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl).

Preferred compounds of formula II-a, include those of formula II-b, i.e., compounds wherein

R_C is $(CR_{245}R_{250})_1$-aryl, where the aryl is optionally substituted with 1, 2, or 3 R_{200} groups; and

R_{245} is H and R_{250} is H or C_1-C_6 alkyl; or

R_{245} and R_{250} are independently C_1-C_3 alkyl (preferably both are methyl); or

$CR_{245}R_{250}$ represents a C_3-C_7 cycloalkyl group.

Preferred compounds of formula II-b, include those of formula II-c, i.e., compounds wherein

the $(CR_{245}R_{250})_1$-aryl is $(CR_{245}R_{250})_1$-phenyl where the phenyl is optionally substituted with 1, 2, or 3 R_{200} groups.

Preferred compounds of formula II-c, include those of formula II-d, i.e., compounds wherein the phenyl in $(CR_{245}R_{250})_1$-phenyl is substituted with 1-3 independently selected R_{200} groups, or

1 or 2 independently selected R_{200} groups, and

1 heteroaryl group optionally substituted with 1 R_{200} group or 1 phenyl group optionally substituted with 1 R_{200} group.

Other preferred comounds include those wherein the phenyl is substituted with a heterocycloalkyl group, which is optionally substituted with 1 or 2 R_{200} groups and/or =O.

Preferred compounds of formula II-d, include those of formula II-e, i.e., compounds wherein R_{245} is hydrogen and R_{250} is C_1-C_3 alkyl.

Preferred compounds of formula II-d, include those of formula II-f, i.e., compounds wherein R_{245} and R_{250} are both hydrogen.

Preferred compounds of formula II-f, include those of formula II-g, i.e., compounds wherein the phenyl in $(CR_{245}R_{250})_1$-phenyl is substituted with 1 R_{200} group, and 1 heteroaryl group optionally substituted with 1 R_{200} group or

1 R_{200} group, and 1 phenyl group optionally substituted with 1 R_{200} group; or

1 R_{200} group, and 1 heterocycloalkyl, which is optionally substituted with one R_{200} or =O.

Preferred compounds of formula II-g, include those of formula II-h, i.e., compounds wherein

R_{200} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6)alkyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, heterocycloalkyl, heteroaryl, halogen, hydroxy, cyano, or $-NR_{220}R_{225}$, where R_{220} and R_{225} are independently hydrogen or alkyl.

Preferred compounds of formulas II-g and II-h, include those of formula II-i, i.e., compounds wherein

R_1 is benzyl where the phenyl portion is optionally substituted with 1 or 2 groups independently selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, -O-allyl, and hydroxy.

Preferred compounds of formula II-i, include those of formula II-j, i.e., compounds wherein

Z is hydrogen or C_1-C_3 alkyl.

Preferred compounds of formula II-i, include those of formula II-k, i.e., compounds wherein

the phenyl in $(CR_{245}R_{250})_1$-phenyl is substituted with

1 R_{200} group, and 1 heteroaryl group, wherein

the heteroaryl is a 5-6 membered heteroaromatic ring containing 0 or 1-3 nitrogen atoms and 0 or 1 oxygen atoms provided that the ring contains at least one nitrogen or oxygen atom, and where the ring is optionally substituted with one or two groups which are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy, halogen, cyano, nitro, trifluoromethyl, amino, mono(C_1-C_6)alkylamino, or di(C_1-C_6)alkylamino.

Other preferred compounds include those of formula II-i, i.e., compounds of formula II-K-1, wherein

the phenyl in $(CR_{245}R_{250})_1$-phenyl is substituted with1 R_{200} group, and 1 heterocycloalkyl group, which is piperazinyl, piperidinyl or pyrrolidinyl and where the ring is optionally substituted with one or two groups which are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy, halogen, cyano, nitro, trifluoromethyl, -SO_2-(C_1-C_4 alkyl), -C_1-C_6 alkanoyl, amino, mono(C_1-C_6)alkylamino, or di(C_1-C_6)alkylamino.

Preferred compounds of formula II-k include those of formula II-l, i.e., compounds wherein

the heteroaryl is pyridinyl, pyrimidinyl, imidazolyl, pyrazolyl, furanyl, thiazolyl, or oxazolyl, each of which is optionally substituted with one or two groups which are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy(C_1-

C_6)alkyl, hydroxy, halogen, cyano, nitro, trifluoromethyl, amino, mono(C_1-C_6)alkylamino, or di(C_1-C_6)alkylamino.

Preferred compounds of formula II-l include those of formula II-m, i.e., compounds wherein R_{200} is C_1-C_6 alkyl, or C_2-C_6 alkenyl.

Preferred compounds of formula II-d include those of formula II-n, i.e., compounds wherein $CR_{245}R_{250}$ represents a C_3-C_7 cycloalkyl group.

Preferred compounds of formula II-n include those of formula II-o, i.e., compounds wherein $CR_{245}R_{250}$ represents a C_5-C_7 cycloalkyl group.

Preferred compounds of formula II-n, include those of formula II-p, i.e., compounds wherein $CR_{245}R_{250}$ represents a C_3-C_6 cycloalkyl group.

Preferred compounds of formula II-p include those of formula II-q, i.e., compounds wherein $CR_{245}R_{250}$ represents a C_6 cycloalkyl.

Preferred compounds of formula II-q include those of formula II-r, i.e., compounds wherein the phenyl in $(CR_{245}R_{250})_1$-phenyl is substituted with

1 R_{200} group; or

1 R_{200} group and one heteroaryl group optionally substituted with one R_{200} group or

1 R_{200} group and one phenyl group optionally substituted with one R_{200} group.

Preferred compounds of formula II-r include those of formula II-s, i.e., compounds wherein
the phenyl in $(CR_{245}R_{250})_1$-phenyl is substituted with 1 R_{200} group.

Preferred compounds of formula II-s, include those of formula II-t, i.e., compounds wherein
R_{200} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, hydroxy(C_1-C_6)alkyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, halogen, hydroxy, cyano, or $-NR_{220}R_{225}$, where
R_{220} and R_{225} are independently hydrogen or alkyl.

Preferred compounds of formula II-t, include those of formula II-u, i.e., compounds wherein

R_1 is benzyl where the phenyl portion of the benzyl group is optionally substituted with 1 or 2 groups independently selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, -O-allyl, and hydroxy.

Preferred compounds of formula II-u, include those of formula II-v, i.e., compounds wherein Z is H or C_1-C_3 alkyl.

Preferred compounds of formula II-v, include those of formula II-w, i.e., compounds wherein

R_{200} is C_1-C_6 alkyl or C_2-C_6 alkenyl.

Preferred compounds of formula II-w, include those of formula II-x, i.e., compounds wherein

Z is C_1-C_2 alkyl and

R_1 is benzyl, 3-fluorobenzyl or 3,5-difluorobenzyl.

Preferred compounds of formula II-m, include those of formula II-y, i.e., compounds wherein

Z is C_1-C_2 alkyl optionally substituted with one halogen (which is preferably F or Cl) and R_1 is benzyl, 3-fluorobenzyl or 3,5-difluorobenzyl.

Preferred compounds of formula II-w, include those of formula II-z, i.e., compounds wherein R_{200} is C_3-C_5 alkyl.

Preferred compounds of formula II-m, include those of formula II-aa, i.e., compounds wherein R_{200} is C_3-C_5 alkyl.

In another aspect, the invention provides compounds of formula II-bb, i.e., compounds of formulas II to II-aa, wherein

R_2 is H, methyl, or hydroxymethyl and R_3 is H.

Other preferred compounds of formula II include those of formula II-cc, wherein R_c is a monocyclic or bicyclic ring of 5, 6, 7 8, 9, or 10 carbons fused to 1 aryl (preferably phenyl), heteroaryl (preferably pyridyl, imidazolyl, thienyl, or pyrimidyl), or heterocycloalkyl (preferably piperidinyl or piperazinyl) groups;

wherein 1, 2 or 3 carbons of the monocyclic or bicyclic ring are optionally replaced with -NH-, $-N(CO)_{0-1}R_{215}-$, $-N(CO)_{0-}$

$_1R_{220}$-, -O-, or -S(=O)$_{0-2}$-, and wherein the monocyclic or bicyclic ring is optionally substituted with 1, 2 or 3 groups that are independently -R_{205}, -R_{245}, -R_{250} or =O. More preferably, R_c is as defined above and R_1 is C_1-C_{10} alkyl substituted with one aryl group (preferably phenyl), where the aryl group is optionally substituted with 1 or 2 R_{50} groups. More preferably, Z is also -CH_2-halogen or -CH_3.

Other preferred compounds of formula II include those of formula II-dd, wherein Rc is -CHR_{245}-CHR_{250}-phenyl; wherein the phenyl is optionally substituted with 1, 2, 3 or 4 R_{200} groups; and

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle or bicycle of 5, 6, 7 or 8 carbon atoms, where 1, or 2 carbon atoms are optionally replaced by 1 or 2 groups that are independently -O-, -S-, -SO_2-, -C(O)-, or -NR_{220}-, and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH-C(O)C_1-C_5 alkyl, -NH-SO_2-(C_1-C_6 alkyl), or halogen; and

R_1 is C_1-C_{10} alkyl substituted with one aryl group (preferably phenyl), where the aryl group is optionally substituted with 1 or 2 R_{50} groups. More preferably, Z is also -CH_2-halogen or -CH_3.

Preferred compounds of formula II-cc include those of formula II-dd, i.e. compounds of formula II-cc, wherein

R_{245} and R_{250} are taken together with the carbons to which they are attached to form a monocycle or bicycle of 5, 6, 7 or 8 carbon atoms, and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH-C(O)C_1-C_5 alkyl, -NH-SO_2-(C_1-C_6 alkyl), or halogen.

Preferred compounds of formula II-dd include those of formula II-ee, i.e. compounds of formula II-dd, wherein

R_{245} and R_{250} are taken together with the carbons to which they are attached to form a monocycle or bicycle of 5, or 6, carbon atoms, and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$(C_1$-C_6 alkyl), -NH-C(O)C_1-C_6 alkyl, -NH-SO_2-(C_1-C_6 alkyl), or halogen.

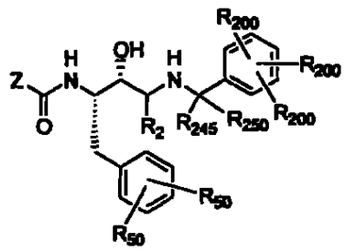
Preferred compounds of formula II include those of formula II-ff, i.e. compounds of formula II wherein

R_c is -($CR_{245}R_{250}$)-heteroaryl (preferred heteroaryl groups include thienyl, pyridyl, pyrimidyl, quinolinyl, oxazolyl, and thiazolyl), wherein the heteroaryl group attached to the -$(CR_{245}R_{250})_{1-4}$- group is optionally substituted with 1 or 2 substitutents selected from -Cl, -Br, -I, -C_1-C_6 alkyl, -(C_1-C_3 alkyl)OH, -CN, -C=CH, -C≡C-CH_2-OH, -CF_3, or -phenyl optionally substituted with 1 or 2 C_1-C_3 alkyl groups, -(C_1-C_3 alkyl)OH group or -CO(C_1-C_3 alkyl) group, wherein

R_{245} and R_{250} at each occurance are independently -H, -C_1-C_3 alkyl, -(C_1-C_3 alkyl)CO_2H, or -(C_1-C_3 alkyl)OH, (in one aspect R_{245} is H; in another aspect, R_{245} and R_{250} are H; in another aspect, R_{245} and R_{250} are both methyl) or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle or bicycle of 3, 4, 5, 6, 7 or 8 carbon atoms (preferably 6 carbon atoms), where 1 or 2 carbon atoms is optionally replaced by -O-, -C(O)-, -S-, -SO_2-, or -NR_{220}-, and R_{220} is as defined above.

In another aspect, the invention provides compounds of the formula VIII:



(VIII)

and pharmaceutically acceptable salts thereof, wherein

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle or bicycle of 3, 4, 5, 6, 7, or 8 carbon atoms, where 1, 2, or 3 CH_2 groups are optionally replaced by 1, 2, or 3 groups that are independently -O-, -S-, $-SO_2-$, -C(O)-, or $-NR_{220}-$; and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, =O, hydroxyl and halogen;

Z, R_2, R_{50}, R_{200}, and R_{220} are as defined for formula I.

Preferred compounds of formula VIII include compounds of formula VIII-a, i.e., compounds of formula VIII, wherein at least one of the R_{50} groups is a halogen.

Preferred compounds of formula VIII-a, include compounds of formula VIII-b, i.e., compounds wherein Z is $-CH_2$-halogen (preferably the halogen is F or Cl) or CH_3.

Preferred compounds of formula VIII-b include compounds of formula VIII-c, i.e., compounds of formula VIII-b, wherein at least one R_{50} group is halogen. More preferably, the other R_{50} group is H, OH or -O-allyl.

In another aspect, both R_{50} groups are halogen and more preferably, F or Cl. Still more preferably, both R_{50} groups are F. Still more preferably, the R_{50} groups are "meta" relative to each other, i.e., 1-3 to each other.

Preferred compounds of formula VIII, VIII-a, VIII-b and VIII-c include compounds of formula VIII-d, wherein

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle of 3, 4, 5, 6, or 7

carbon atoms (preferably 4, 5, or 6 carbon atoms, more preferably, 5 or 6 carbon atoms), wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl, =O, and halogen. More preferably, the ring is optionally substituted with 1, 2, or 3 groups. Still more preferably, if the ring is substituted, one of the groups is =O.

Preferred compounds of formula VIII, VIII-a, VIII-b and VIII-c include compounds of formula VIII-e, wherein

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a bicycle of 5, 6, 7, or 8 carbon atoms, where 1, carbon atom is optionally replaced by a group selected from -O-, -S-, $-SO_2-$, -C(O)-, and $-NR_{220}-$; and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl and halogen. Preferably the bicycle is bicyclo[3.1.0]hexyl, 6-aza-bicyclo[3.1.0]hexane wherein the nitrogen is optionally substituted with $-C(O)CH_3$ or CH_3, octahydro-cyclopenta[c]pyrrolyl, 5-oxo-octahydro-pentalenyl, or 5-hydroxy-octahydro-pentalenyl, each of which is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl and halogen.

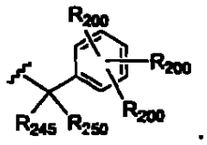
Preferred compounds of formulas VIII-c, VIII-d and VIII-e include compounds wherein one R_{200} is imidazolyl, thiazolyl, oxazolyl, tetrazolyl, thienyl, furanyl, benzyl, piperidinonyl, or pyridyl, wherein each is optionally substituted with halogen, or C_1-C_4 alkyl. Also preferred are compounds wherein a second R_{200} is C_1-C_6 alkyl (preferably C_2-C_6 alkyl, more preferably tert-butyl, neopentyl or isopropyl.)

Preferred compounds of formula VIII, VIII-a, VIII-b and VIII-c, and include compounds of formula VIII-f, i.e., compounds wherein

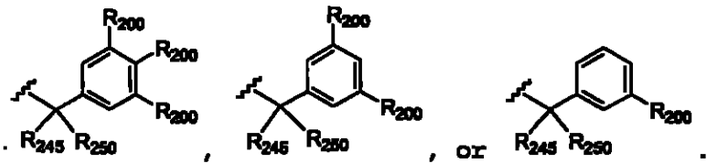
R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle of 3, 4, 5, 6, or 7 carbon atoms, where at least 1, but up to 3 carbon atoms are replaced by groups that are independently -O-, -S-, -SO_2-, -C(O)-, or -NR_{220}- (in one aspect, preferably -O-); and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl and halogen. Preferably the monocycle is tetrahydropyranyl, 2-oxo-tetrahydropyrimidinonyl, piperidinyl, 2-oxo(1,3)oxazinonyl, or cyclohexanonyl. Preferably, R_{220} is H, -C_1-C_6 alkyl, -CHO, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, -amino C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, C_1-C_6 alkanoyl optionally substituted with up to three halogens, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -halo C_1-C_6 alkyl, or -$(CH_2)_{0-2}$-(C_3-C_7 cycloalkyl). More preferably, R_{220} is H, -C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, -SO_2-C_1-C_6 alkyl, -C(O)CF_3, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), or -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl).

Preferred compounds of formulas VIII-d and VIII-e include compounds of formula VIII-g, i.e., compounds wherein at least one R_{200} is C_1-C_6 alkyl. More preferably, R_{200} is C_2-C_6 alkyl. Still more preferably it is C_3-C_6 alkyl.

Preferred compounds of formula VIIIa-VIIIg include compounds of formula VIII-h, i.e., compounds wherein R_c is of the formula:



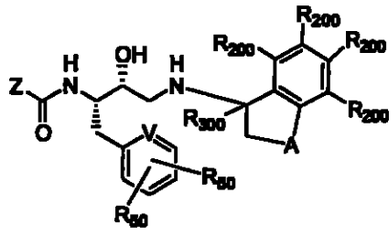
More preferably, R_c is of the formula:



In another aspect, the invention provides compounds of formulas VIII-VIII-h, wherein R_2 is H.

In another aspect, the invention provides compounds of formulas VIII-VIII-h, wherein R_2 is C_1-C_4 alkyl or hydroxy C_1-C_4 alkyl.

In another aspect, the invention provides compounds of formula IX:



(IX)

wherein

A is $-CH_2-CR_{100}R_{101}-$, $-CH_2-S-$, $-CH_2-S(O)-$, $-CH_2-S(O)_2-$, $-CH_2-NR_{100}-$, $-CH_2-C(O)-$, $-CH_2-O-$, $-O-CR_{100}R_{101}-$, $-SO_2-NR_{100}$, or $-C(O)-O-$;

R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1$-C_6 alkyl) or SO_2C_1-C_6 alkyl;

V is CH, CR_{50}, or N;

R_{300} is H or C_1-C_4 alkyl (preferably the alkyl is methyl); and

Z, R_{50} and R_{200} are as defined for formula I.

Preferred compounds of formula IX include compounds of formula IX-a, i.e., compounds of formula IX, wherein at least one of the R_{50} groups is a halogen. In another aspect, the other R_{50} group is H, OH, or -O-allyl. Preferred compounds of formula IX-a, include compounds of formula IX-b, i.e., compounds wherein Z is $-CH_2$-halogen (where the halogen is preferably F or Cl) or CH_3. Preferred compounds of formula IX-b include compounds of formula IX-c, i.e., compounds of

formula IX-b, wherein both R_{50} groups are halogen and more preferably, F or Cl. Still more preferably, both R_{50} groups are F. In other preferred compounds, at least one R_{50} is OH or -O-benzyl. More preferably, a second R_{50} is present and it is a halogen (preferably F or Cl.)

Preferred compounds of formula IX, IX-a, IX-b, and IX-c, include those of formula IX-d, i.e., compounds wherein at least one R_{200} is C_1-C_6 alkyl. In one aspect, R_{200} is C_3-C_6 alkyl, preferably neopentyl, tert-butyl or isopropyl. In another aspect, R_{200} is C_1-C_4 alkyl.

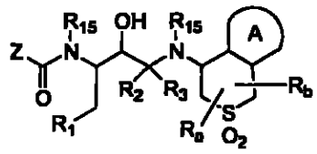
Preferred compounds of formual IX-d include those wherein A is $-CH_2-O-$ or $-CH_2-CH_2-$. Also preferred are compounds wherein A is -C(O)-O-, Also preferred are compounds wherein A is $-CH_2-NR_{100}-$. Also preferred are compounds wherein A is $-CH_2-S-$, $-CH_2-S(O)-$, or $-CH_2-S(O)_2-$.

Preferred compounds of formula IX include compounds wherein one R_{200} is C_1-C_6 alkyl, preferably C_2-C_6 alkyl, more preferably C_3-C_5 alkyl.

Also preferred are compounds wherein a second R_{200} is present and it is imidazolyl, thiazolyl, oxazolyl, tetrazolyl, thienyl, furanyl, benzyl, or pyridyl, wherein each cyclic group is optionally substituted with $-R_{205}$, halogen, and/or C_1-C_4 alkyl. In another aspect, they are substituted with halogen, and/or C_1-C_4 alkyl. Also preferred are compounds wherein a second R_{200} is C_1-C_6 alkyl. Also preferred are compounds wherein R_{100} and R_{101} are independently H or C_1-C_6 alkyl.

In another aspect, preferred compounds of formula IX-d include those wherein R_{300} is methyl. In another aspect, when R_{300} is methyl, A is $-CH_2-O-$ or $-CH_2-CH_2-$.

In one aspect, the invention provides compounds of the formula A-I:



and a pharmaceutically acceptable salt thereof, wherein

the A ring is a heteroaryl group, selected from pyridinyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrrolyl, wherein said heteroaryl groups are optionally substituted with one, two, three, or four R_c and/or R_d groups, wherein

R_c and R_d at each occurrence are independently

C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$; or

OH; NO_2; halogen; CO_2H; C≡N; $-(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$ wherein

R_{21} and R_{22} are the same or different and are selected from H; $-C_1$-C_6 alkyl optionally substituted with one substituent selected from OH and $-NH_2$; $-C_1$-C_6 alkyl optionally substituted with one to three groups that are independently -F, -Cl, -Br, or -I; $-C_3$-C_7 cycloalkyl; $-(C_1$-C_2 alkyl)-(C_3-C_7 cycloalkyl); $-(C_1$-C_6 alkyl)-O-(C_1-C_3 alkyl); $-C_2$-C_6 alkenyl; $-C_2$-C_6 alkynyl; $-C_1$-C_6 alkyl chain with one double bond and one triple bond; R_{17}; and R_{18}; or

$-(CH_2)_{0-4}$-CO-(C_1-C_{12} alkyl); $-(CH_2)_{0-4}$-CO-(C_2-C_{12} alkenyl); $-(CH_2)_{0-4}$-CO-(C_2-C_{12} alkynyl); $-(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl); $-(CH_2)_{0-4}$-CO-R_{17}; $-(CH_2)_{0-4}$-CO-R_{18}; $-(CH_2)_{0-4}$-CO-R_{19}; or $-(CH_2)_{0-4}$-CO-R_{11} wherein

R_{17} at each occurrence is an aryl group selected from phenyl, 1-naphthyl, 2-naphthyl and indanyl, indenyl, dihydronaphthyl, or tetralinyl, wherein said aryl groups are optionally substituted with one, two, three, or four groups that are independently

C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, F, Cl, Br, I, OH, SH, and $-NR_5R_6$, C≡N, CF_3, and C_1-C_3 alkoxy;

or

C_2-C_6 alkenyl or C_2-C_6 alkynyl each of which is optionally substituted with one, two or three substituents selected from F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$;

or

halogen; $-C_1$-C_6 alkoxy optionally substituted with one, two, or three F; $-NR_{21}R_{22}$; OH; C≡N; C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$; or

$-CO-(C_1$-C_4 alkyl); $-SO_2-NR_5R_6$; $-CO-NR_5R_6$; or $-SO_2-(C_1$-C_4 alkyl);

R_{18} at each occurrence is a heteroaryl group selected from pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolcpyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide,

tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide, wherein said heteroaryl group is optionally substituted with one, two, three, or four groups that are independently

C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$; or

C_2-C_6 alkenyl or C_2-C_6 alkynyl each of which is optionally substituted with one, two or three substituents selected from -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_5R_6$; or

halogen; $-C_1$-C_6 alkoxy optionally substituted with one, two, or three -F; $-NR_{21}R_{22}$; -OH; -C≡N; C_3-C_7 cycloalkyl optionally substituted with one, two or three substituents independently selected from F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$; $-CO-(C_1$-C_4 alkyl); $-SO_2-NR_5R_6$; $-CO-NR_5R_6$; or $-SO_2-(C_1$-C_4 alkyl);

R_{19} at each occurrence is independently morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide,

thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, or homothiomorpholinyl S-oxide; wherein said R_{19} group is optionally substituted with one, two, three, or four groups that are independently

C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$;

C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein each is optionally substituted with one, two or three substituents selected from F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$;

halogen; C_1-C_6 alkoxy; C_1-C_6 alkoxy optionally substituted with one, two, or three F; OH; C≡N; $-NR_{21}R_{22}$; C_3-C_7 cycloalkyl optionally substituted with one, two, or three substituents independently selected from F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$; $-CO-(C_1-C_4$ alkyl); $-SO_2-NR_5R_6$; $-CO-NR_5R_6$; $-SO_2-(C_1-C_4$ alkyl); or =O;

R_{11} is selected from morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four groups

that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen;

or

R_c and R_d at each occurrence are independently $-(CH_2)_{0-4}-CO_2R_{20}$; $-(CH_2)_{0-4}-SO_2-NR_{21}R_{22}$; $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl); $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl); $-(CH_2)_{0-4}-N(H$ or $R_{20})-CO-O-R_{20}$; $-(CH_2)_{0-4}-N(H$ or $R_{20})-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-N-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-N(-H$ or $R_{20})-CO-R_{21}$; $-(CH_2)_{0-4}-NR_{21}R_{22}$; $-(CH_2)_{0-4}-R_{11}$; $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl); $-(CH_2)_{0-4}-O-P(O)-(OR_5)_2$; $-(CH_2)_{0-4}-O-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-O-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-O-(R_{20})_2$; $-(CH_2)_{0-4}-O-(R_{20})-CO_2H$; $-(CH_2)_{0-4}-S-(R_{20})$; $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with one, two, three, four, or five halogens); C_3-C_7 cycloalkyl; $-(CH_2)_{0-4}-N(-H$ or $R_{20})-SO_2-R_{21}$; or $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl; wherein

R_{20} is selected from C_1-C_6 alkyl, $-(CH_2)_{0-2}-(R_{17})$, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and $-(CH_2)_{0-2}-(R_{18})$;

or

R_c and R_d at each occurrence are independently C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with C_1-C_3 alkyl, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, or $-NR_5R_6$;

or

the A ring is an aromatic hydrocarbon selected from phenyl, naphthyl, tetralinyl, indanyl, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl, wherein each aromatic hydrocarbon is optionally substituted with one, two, three, or four R_c and/or R_d groups which at each occurrence can be the same or different and are:

C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$;

or

-OH; -NO_2; halogen; -CO_2H; -C≡N; -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alkyl), -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alkenyl), -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alkynyl), -$(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl), -$(CH_2)_{0-4}$-CO-R_{17}; -$(CH_2)_{0-4}$-CO-R_{18}; -$(CH_2)_{0-4}$-CO-R_{19}; -$(CH_2)_{0-4}$-CO-R_{11}; -$(CH_2)_{0-4}$-CO_2R_{20}; -$(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl); -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl), -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl); -$(CH_2)_{0-4}$-N(H or R_{20})-CO_2R_{20}; -$(CH_2)_{0-4}$-N(H or R_{20})-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N(-H or R_{20})-CO-R_{21}; -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-R_{11}; -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alkyl); -$(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; -$(CH_2)_{0-4}$-O-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-$(R_{20})_2$; -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-(C_1-C_6 alkyl optionally substituted with one, two, three, four, or five -F); C_3-C_7 cycloalkyl; -$(CH_2)_{0-4}$-N(-H or R_{20})-SO_2-R_{21}; -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl;

or

C_2-C_6 alkenyl or C_2-C_6 alkynyl each of which is optionally substituted with C_1-C_3 alkyl, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, or -NR_5R_6;

R_a and R_b are independently selected from C_1-C_3 alkyl, F, OH, SH, C≡N, CF_3, C_1-C_6 alkoxy, =O, and -NR_5R_6; or

R_a and R_b and the carbon to which they are attached form a C_3-C_7 spirocycle which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_6 alkoxy, halogen, CF_3, or CN;

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, -CF_3, -C_1-C_4 alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino; or

R_1 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alkoxy, amino, and mono- or dialkylamino; or

R_1 is aryl, heteroaryl, heterocyclyl, aryl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, or heterocycloalkyl C_1-C_6 alkyl, wherein

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

R_1 is G-L-A-E-W-, wherein

W is a bond, absent, -S-, -S(O)-, -SO_2-, -O-, -NH- or -N(C_1-C_4 alkyl);

E is a bond, absent, or C_1-C_3 alkylene;

A is absent, alkyl, aryl or cycloalkyl where each aryl or cycloalkyl is optionally substituted with one, two or three R_{100} groups; heteroaryl optionally substituted with 1 or 2 R_{100} groups; or heterocycloalkyl optionally substituted with 1 or 2 R_{200} groups, wherein

R_{100} at each occurrence is independently selected from NO_2, C≡N, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -N(R)CO(R')R, -CO_2-R_{25}, -NH-CO_2-R_{25}, -O-(C_2-C_6 alkyl)-CO_2H, -NRR', -SR, CH_2OH, -C(O)-(C_1-C_6)alkyl, -C(O)NRR', -SO_2NRR', CO_2H, CF_3, halogen, C_1-C_3 alkoxy, -OCF_3, -NH_2, OH, CN, halogen, and -$(CH_2)_{0-2}$-O-$(CH_2)_{0-2}$-OH;

wherein

R_{25} is selected from C_1-C_6 alkyl, -$(CH_2)_{0-2}$-cycloalkyl, -$(CH_2)_{0-2}$-aryl, where the aryl is optionally substituted with halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkyl, amino, mono(C_1-C_6)alkylamino, or di(C_1-C_6)alkylamino, and hydrogen, and

R and R' at each occurrence are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_{0-2}$-aryl, or -$(CH_2)_{0-2}$-cycloalkyl, where each aryl or cycloalkyl is optionally substituted with halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkyl, amino, mono(C_1-C_6)alkylamino, or di(C_1-C_6)alkylamino;

R_{200} at each occurrence is independently selected from =O, C_1-C_3 alkyl, CF_3, F, Cl, Br, I, C_1-C_3 alkoxy, OCF_3, NH_2, OH, and C≡N;

provided that L is a bond or absent when G is absent,

or

L is -C(O)-, -S(O)-, $-SO_2$-, -O-, $-C(R_{110})(R_{112})O$-, $-OC(R_{110})(R_{112})$-, $-N(R_{110})$-, $-CON(R_{110})$-, $-N(R_{110})CO$-, $-C(R_{110})(R')$-, $-C(OH)R_{110}$-, $-SO_2NR_{110}$-, $-N(R_{110})SO_2$-, $-N(R_{110})CON(R_{112})$-, $N(R_{110})CSN(R_{112})$-, $-OCO_2$-, $-NCO_2$-, or $-OCON(R_{110})$-, wherein

R_{110} and R_{112} are independently hydrogen, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

and

G is absent or C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from $-CO_2H$, $-CO_2$(C_1-C_4 alkyl), C_1-C_6 alkoxy, -OH, -NRR', -C_1-C_6 haloalkyl, -(C_1-C_{10} alkyl)-O-(C_1-C_3 alkyl), -C_2-C_{10} alkenyl, -C_2-C_{10} alkynyl, -C_4-C_{10} alkyl chain with one double bond and one triple bond, aryl optionally substituted with 1, 2, or 3 R_{100}, heteroaryl optionally substituted with 1, 2, or 3 R_{100}, and C_1-C_6 alkyl;

or

G is -$(CH_2)_{0-3}$-(C_3-C_7) cycloalkyl where the cycloalkyl is optionally substituted with one, two or three substituents independently selected from $-CO_2H$, $-CO_2$-(C_1-C_4 alkyl), C_1-C_6 alkoxy, OH, $-NH_2$, -C_1-C_6

48

haloalkyl, -(C_1-C_{10} alkyl)-O-(C_1-C_3 alkyl), -C_2-C_{10} alkenyl with 1 or 2 double bonds, C_2-C_{10} alkynyl with 1 or 2 triple bonds, -C_4-C_{10} alkyl chain with one double bond and one triple bond, aryl optionally substituted with R_{100}, heteroaryl optionally substituted with R_{100}, mono(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl) amino, and C_1-C_6 alkyl,

or

G is -$(CH_2)_{0-4}$-aryl, -$(CH_2)_{0-4}$-heteroaryl, or -$(CH_2)_{0-4}$-heterocycle, wherein the aryl, heteroaryl -$(CH_2)_{0-4}$-heterocycle, groups are optionally substituted with 1, 2, or 3 R_{100}, wherein the heterocycle group is optionally substituted with 1 or 2 R_{200} groups; or

G is -$C(R_{10})(R_{12})$-CO-NH-R_{14} wherein

R_{10} and R_{12} are the same or different and are selected from H, -C_1-C_6 alkyl, -(C_1-C_4 alkyl)-aryl, where the aryl is optionally substituted with 1, 2, or 3 R_{100} groups; -(C_1-C_4 alkyl)-heteroaryl where the heteroaryl is optionally substituted with 1, 2, or 3 R_{100} groups; -(C_1-C_4 alkyl)-heterocycle, where the heterocycle is optionally substituted with 1 or 2 R_{200} groups; heteroaryl optionally substituted with 1, 2, or 3 R_{100} groups; heterocycle optionally substituted with 1 or 2 R_{200} groups; -$(CH_2)_{1-4}$-OH, -$(CH_2)_{1-4}$-Y-$(CH_2)_{1-4}$-aryl where the aryl is optionally substituted with 1, 2, or 3 R_{100} groups; -$(CH_2)_{1-4}$-Y-$(CH_2)_{1-4}$-heteroaryl where the heteroaryl is optionally substituted with 1, 2, or 3 R_{100} groups; -aryl optionally substituted with 1, 2, or 3 R_{100} groups, -heteroaryl optionally substituted with 1, 2, or 3 R_{100} groups, and -heterocycle optionally substituted with 1, 2, or 3 R_{200} groups, wherein

Y is -O-, -S-, -NH-, or -NH(C_1-C_6 alkyl); and

R_{14} is H, -C_1-C_6 alkyl, -aryl optionally substituted with 1, 2, or 3 R_{100} groups, -heteroaryl optionally substituted with 1, 2, or 3 R_{100} groups, -heterocycle optionally

substituted with 1 or 2 R_{200} groups, -(C_1-C_4 alkyl)-aryl, where the aryl is optionally substituted with 1, 2, or 3 R_{100} groups; -(C_1-C_4 alkyl)-heteroaryl where the heteroaryl is optionally substituted with 1, 2, or 3 R_{100} groups; -(C_1-C_4 alkyl)-heterocycle, where the heterocycle is optionally substituted with 1 or 2 R_{200} groups, or $-(CH_2)_{0-2}-O-(CH_2)_{1-2}-OH$;

R_2 and R_3 are independently selected from -H, C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_5R_6$; $-(CH_2)_{0-4}-R_{17}$; $-(CH_2)_{0-4}-R_{18}$; C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein each is optionally substituted with one, two or three substituents selected from -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_5R_6$; $-(CH_2)_{0-4}-C_3$-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_5R_6$; wherein

R_5 and R_6 at each occurrence are independently H or C_1-C_6 alkyl; or

R_5 and R_6 and the nitrogen to which they are attached, at each occurrence form a 5 or 6 membered heterocycloalkyl ring; or

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru seven carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, $-SO_2-$, or $-NR_7-$;

R_{15} at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, halo C_1-C_6 alkyl, C_1-C_6 alkanoyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, alkoxy, NH_2, and $-R_{26}-R_{27}$; and

$-R_{26}-R_{27}$; wherein

R_{26} is selected from a bond, -C(O)-, -SO_2-, -CO_2-, -C(O)NR_5-, and -NR_5C(O)-,

R_{27} is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl C_1-C_6 alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, haloalkyl, hydroxyalkyl, -NR_5R_6, -C(O)NR_5R_6;

Z is selected from H; C_1-C_6 alkoxy; C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently OH, halogen, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, CN, and NR_5R_6; aryl; heteroaryl; arylalkyl; and heteroarylalkyl; and wherein each aryl, heteroaryl, arylalkyl, and heteroarylalkyl group is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, halogen, haloalkyl, and C_1-C_6 alkoxy.

Preferred compounds of formula A-I include those wherein

R_2 and R_3 are independently selected from H; C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents that are independently selected from C_1-C_4 alkyl, halogen, -CF_3, and C_1-C_4 alkoxy; and C_2-C_6 alkenyl or C_2-C_6 alkynyl wherein each is optionally substituted with one, two or three substituents selected from -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -NR_5R_6; or

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru seven carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, -SO_2-, or -NR_7-; wherein

R_7 is selected from H, -C_1-C_8 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, -NH_2, phenyl and halogen; C_3-C_8 cycloalkyl; -(C_1-C_2 alkyl)-(C_3-C_8 cycloalkyl); -(C_1-C_6 alkyl)-O-(C_1-C_4 alkyl); C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; naphthyl; heteroaryl; heterocycloalkyl.

Equally preferred compounds of formula A-I include those wherein

R_{15} at each occurrence is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkanoyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, C_1-C_4 alkoxy, and NH_2; and $-R_{26}-R_{27}$; wherein

R_{26} is selected from a bond, $-C(O)-$, $-SO_2-$, $-CO_2-$, $-C(O)NR_5-$, and $-NR_5C(O)-$; and

R_{27} is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, and benzyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, halo C_1-C_4 alkyl, hydroxyalkyl, $-C(O)NR_5R_6$, or $-NR_5R_6$.

Other equally preferred compounds of formula A-I include those wherein

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, $-CF_3$, $-C_1$-C_4 alkoxy, amino, mono- or dialkylamino, $-N(R)C(O)R'$, $-OC(=O)$-amino and $-OC(=O)$-mono- or dialkylamino; or

R_1 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alkoxy, amino, and mono- or dialkylamino; or

R_1 is aryl, heteroaryl, heterocyclyl, aryl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, or heterocycloalkyl C_1-C_6 alkyl; wherein

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O; and

R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, -CO-(C_1-C_4 alkyl), -CO_2-(C_1-C_4 alkyl), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl; wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, -NR_5R_6, CN, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, NR_7R_8, and C_1-C_4 alkoxy.

Still other equally preferred compounds of formula A-I include those of formula A-I-1, i.e., compounds of formula A-I wherein

R_c and R_d are independently selected from C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and -NR_5R_6; hydroxy; nitro; halogen; -CO_2H; cyano; and -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$; wherein

R_{21} and R_{22} independently represent hydrogen, C_1-C_6 alkyl, hydroxyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, haloalkyl, C_3-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_1-C_6 alkyl chain with one double bond and one triple bond, phenyl, naphthyl, heteroaryl; or

R_c and R_d are independently selected from -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alkyl); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alkenyl); $CH_2)_{0-4}$-CO-(C_2-C_{12})alkynyl; -$(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl); -$(CH_2)_{0-4}$-CO-phenyl; -$(CH_2)_{0-4}$-CO-naphthyl; -$(CH_2)_{0-4}$-CO-heteroaryl; -$(CH_2)_{0-4}$-CO-heterocycloalkyl; -$(CH_2)_{0-4}$-CO_2R_{20}; wherein

R_{20} is selected from C_1-C_6 alkyl, -$(CH_2)_{0-2}$-(phenyl), -$(CH_2)_{0-2}$-(naphthyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and -$(CH_2)_{0-2}$-(heteroaryl), or

R_c and R_d are independently selected from -$(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl); -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl); -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl); -$(CH_2)_{0-4}$-N(H or R_{20})-CO_2R_{20}; -$(CH_2)_{0-4}$-N(H or R_{20})-CO-N(R_{20})$_2$; -$(CH_2)_{0-4}$-N-CS-N(R_{20})$_2$; -$(CH_2)_{0-4}$-N(-H or R_{20})-CO-R_{21}; -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-heterocycloalkyl; -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alkyl); -$(CH_2)_{0-4}$-O-P(O)-(OR_5)$_2$; -$(CH_2)_{0-4}$-O-CO-N(R_{20})$_2$; -$(CH_2)_{0-4}$-O-CS-N(R_{20})$_2$; -$(CH_2)_{0-4}$-O-(R_{20}); -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-halo(C_1-C_6)alkyl; -$(CH_2)_{0-4}$-O-(C_1-C_6)alkyl; C_3-C_8 cycloalkyl; and -$(CH_2)_{0-4}$-N(-H or R_{20})-SO_2-R_{21}; or

R_c and R_d are independently C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with C_1-C_4 alkyl, halogen, hydroxy, SH, cyano, CF_3, C_1-C_4 alkoxy, or NR_5R_6; wherein

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

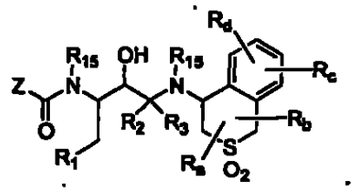
each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, -CO-(C_1-C_4 alkyl), -CO_2-(C_1-C_4 alkyl), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl;

wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, -NR_5R_6, CN, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, NR_7R_8, and C_1-C_6 alkoxy.

Preferred compounds of formula A-I-1 include those of formula A-II:



Preferred compound of formula A-II include those wherein

R_2 and R_3 are independently selected from H; C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents that are independently selected from C_1-C_4 alkyl, halogen, -CF_3, and C_1-C_4 alkoxy; C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein each is optionally substituted with one, two or three substituents selected from -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -NR_5R_6;

R_5 and R_6 at each occurrence are independently H or C_1-C_6 alkyl; or

R_5 and R_6 and the nitrogen to which they are attached, at each occurrence form a 5 or 6 membered heterocycloalkyl ring;

or

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, -SO_2-, or -NR_7-; wherein

R_7 is selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, -NH_2, and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl.

Even more preferred compounds of formula A-II include those wherein

R_{15} at each occurrence is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_6 alkanoyl, benzyl optionally substituted with OCH_3, -C(O)-tertiary butyl, and -CO_2-benzyl.

Still even more preferred compounds of formula A-II include those wherein

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, -CF_3, -C_1-C_4 alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino OC(=O)-mono- and dialkylamino; or

R_1 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alkoxy, amino, and mono- or dialkylamino; or

R_1 is aryl, heteroaryl, heterocyclyl, aryl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, or heterocycloalkyl C_1-C_6 alkyl;

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

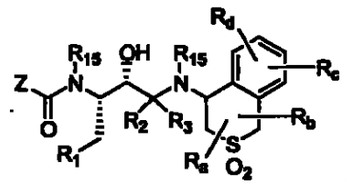
R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, -CO-(C_1-C_4 alkyl), -CO_2-(C_1-C_4 alkyl), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl;

wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, -NR_5R_6, CN, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, NR_7R_8, and C_1-C_4 alkoxy.

Still more preferred compounds of formula A-II include those of formula A-II-1, i.e., compound of formula A-II wherein

R_{50} at each occurrence is independently selected from halogen, OH, SH, $-NR_7R_8$, $-SO_2-(C_1-C_4$ alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl; wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, $-NR_5R_6$, CN, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, NR_7R_8, and C_1-C_4 alkoxy.

Preferred compounds of formula A-II-1 include those of formula A-III:



More preferred compounds of formula A-III include those of formula A-III-1, i.e., compounds of formula A-III wherein

R_1 is phenyl, phenyl C_1-C_6 alkyl, naphthyl, or naphthyl C_1-C_6 alkyl, wherein the phenyl or naphthyl group is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups.

Still more preferred compound of formula A-III-1 include those of formula A-III-2, i.e., compound of formula A-III-1 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, $-SO_2-$, or $-NR_7-$; wherein

R_7 is H, $-C_1-C_8$ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, $-NH_2$, and halogen; $-C_2-C_4$ alkenyl; or $-C_2-C_4$ alkynyl.

Preferred compounds of formula A-III-2 include those of formula A-III-3, i.e., compounds of formula A-III-2 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms.

Equally preferred compound of formula A-III-2 include those of formula A-III-4, i.e., compounds of formula A-III-2 compounds wherein

R_2, R_3 and the carbon to which they are attached form a heterocycloalkyl group containing 2 to 5 carbon atoms and one group selected from -O-, -S-, $-SO_2-$, and $-NR_7-$; wherein

R_7 is H, $-C_1-C_8$ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, $-NH_2$, and halogen; $-C_2-C_4$ alkenyl; or $-C_2-C_4$ alkynyl.

Other equally preferred compounds of formula A-III-1 include those compounds of formula A-III-5, i.e., compounds of formula A-III-1 wherein

R_2 and R_3 are independently selected from H; C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents that are independently selected from C_1-C_4 alkyl, halogen, $-CF_3$, and C_1-C_4 alkoxy; C_2-C_6 alkenyl; and C_2-C_6 alkynyl.

More preferred compound of formulas A-III-3, A-III-4, and A-III-5 include those of formula A-III-6, i.e., compound of formulas A-III-3, A-III-4, and A-III-5 wherein

R_a and R_b are independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CN, OH, hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and $-C_1.C_6$ alkyl-NR_5R_6; or

R_a and R_b are attached to the same carbon and form a C_3-C_7 spirocycle; and

R_{15} at each occurrence is independently H or C_1-C_4 alkyl.

Preferred compound of formula A-III-6 include those of formula A-III-6a, i.e., compounds of formula A-III-6 wherein

R_c and R_d are independently selected from C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$;; hydroxy; halogen; C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein

the alkenyl or alkynyl group is optionally substituted with C_1-C_4 alkyl, halogen, hydroxy, SH, cyano, CF_3, C_1-C_4 alkoxy, or NR_5R_6.

Other preferred compound of formula A-III-6 include those whe

R_c and R_d are $-(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$, $-(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; $-(CH_2)_{0-4}$-SO-(C_1-C_6 alkyl); $-(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl); $-(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl); $-(CH_2)_{0-4}$-N(H or R_{20})-CO-O-R_{20}; $-(CH_2)_{0-4}$-N(H or R_{20})-CO-N(R_{20})$_2$; $-(CH_2)_{0-4}$-N-CS-N(R_{20})$_2$; $-(CH_2)_{0-4}$-N(-H or R_{20})-CO-R_{21}; or $-(CH_2)_{0-4}$-$NR_{21}R_{22}$; wherein

R_{21} and R_{22} independently represent hydrogen, C_1-C_6 alkyl, hydroxyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, haloalkyl, C_3-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, phenyl, naphthyl, or heteroaryl;

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Still other preferred compound of formula A-III-6 include those wherein

R_c and R_d are $-(CH_2)_{0-4}$-CO-(C_1-C_{12} alkyl); $-(CH_2)_{0-4}$-CO-(C_2-C_{12} alkenyl); $CH_2)_{0-4}$-CO-(C_2-C_{12})alkynyl; $-(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl); $-(CH_2)_{0-4}$-CO-phenyl; $-(CH_2)_{0-4}$-CO-naphthyl; $-(CH_2)_{0-4}$-CO-heteroaryl; $-(CH_2)_{0-4}$-CO-heterocycloalkyl; $-(CH_2)_{0-4}$-CO_2R_{20}; where

R_{20} is selected from C_1-C_6 alkyl, $-(CH_2)_{0-2}$-(phenyl), $-(CH_2)_{0-2}$-(naphthyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and $-(CH_2)_{0-2}$-(heteroaryl);

each aryl group and each heteroaryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Yet still other preferred compounds of formula A-III-6 include those wherein

R_c and R_d are $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl); $-(CH_2)_{0-4}-O-P(O)-(OR_5)_2$; $-(CH_2)_{0-4}-O-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-O-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-O-(R_{20})$; $-(CH_2)_{0-4}-O-(R_{20})-CO_2H$; $-(CH_2)_{0-4}-S-(R_{20})$; $-(CH_2)_{0-4}-O$-halo(C_1-C_6)alkyl; $-(CH_2)_{0-4}-O-(C_1-C_6)$alkyl; C_3-C_8 cycloalkyl; or $-(CH_2)_{0-4}-N(-H$ or $R_{20})-SO_2-R_{21}$; wherein

each aryl group and each heteroaryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, $-CO-(C_1-C_4$ alkyl), $-CO_2-(C_1-C_4$ alkyl), $-SO_2-NR_5R_6$, $-NR_7R_8$, $-CO-NR_5R_6$, $-CO-NR_7R_8$, $-SO_2-(C_1-C_4$ alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl; wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, $-NR_5R_6$, CN, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, NR_7R_8, and C_1-C_6 alkoxy.

Other preferred compounds of formula A-III include those of formula A-III-7, i.e., compound of formula A-III wherein

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, $-CF_3$, $-C_1-C_4$ alkoxy, amino, mono- or dialkylamino, $-N(R)C(O)R'$, $-OC(=O)$-amino and $-OC(=O)$-mono- or dialkylamino; or

R_1 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alkoxy, amino, and mono- or dialkylamino.

More preferred compounds of formula A-III-7 include those compounds of formula A-III-8, i.e., compounds of formula A-III-7 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, $-SO_2-$, or $-NR_7-$; wherein

R_7 is selected from H or $-C_1$-C_4 alkyl optionally substituted with 1 group selected from -OH, $-NH_2$, and halogen.

Preferred compounds of formula A-III-8 include those compounds of formula A-III-9, i.e., compounds of formula A-III-8 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms.

Other preferred compounds of formula A-III-8 include those compounds of formula A-III-10, i.e., compounds of formula A-III-8 wherein

R_2, R_3, and the carbon to which they are attached form a heterocycloalkyl group containing 2 to 5 carbon atoms and one group selected from -O-, -S-, $-SO_2-$, and $-NR_7-$; wherein

R_7 is selected from H or $-C_1$-C_4 alkyl optionally substituted with 1 group selected from -OH, $-NH_2$, and halogen.

Still other preferred compounds of formula A-III-8 include those compounds of formula A-III-11, i.e., compounds of formula A-III-8 wherein

R_2 and R_3 are independently selected from H; C_1-C_6 alkyl optionally substituted with 1, or 2 substituents that are

independently selected from C_1-C_4 alkyl, halogen, $-CF_3$, and C_1-C_4 alkoxy; C_2-C_6 alkenyl; and C_2-C_6 alkynyl.

More preferred compound of formulas A-III-9, A-III-10, and A-III-11 include those of formula A-III-12, i.e., compound of formulas A-III-9, A-III-10, and A-III-11 wherein

R_a and R_b are independently selected from C_1-C_3 alkyl, F, OH, C≡N, CF_3, C_1-C_6 alkoxy, and $-NR_5R_6$; and

R_5 at each occurrence is independently H or C_1-C_4 alkyl.

Preferred compounds of formula A-III-12 include those compounds wherein

R_c and R_d are independently selected from C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$; hydroxy; halogen;

C_2-C_6 alkenyl and C_2-C_6 alkynyl; wherein

the alkenyl or alkynyl group is optionally substituted with C_1-C_4 alkyl, halogen, hydroxy, SH, cyano, CF_3, C_1-C_4 alkoxy, or NR_5R_6.

Other preferred compounds of formula A-III-12 include those compounds wherein

R_c and R_d are $-(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$, $-(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; $-(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl); $-(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl); $-(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl); $-(CH_2)_{0-4}$-N(H or R_{20})-CO-O-R_{20}; $-(CH_2)_{0-4}$-N(H or R_{20})-CO-$N(R_{20})_2$; $-(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; $-(CH_2)_{0-4}$-N(-H or R_{20})-CO-R_{21}; or $-(CH_2)_{0-4}$-$NR_{21}R_{22}$; wherein

R_{21} and R_{22} independently represent hydrogen, C_1-C_6 alkyl, hydroxyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, haloalkyl, C_3-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, phenyl, naphthyl, or heteroaryl;

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Still other preferred compounds of formula A-III-12 include those compounds wherein

R_c and R_d are $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl); $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl); $CH_2)_{0-4}-CO-(C_2-C_{12})$alkynyl; $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl); $-(CH_2)_{0-4}-CO$-phenyl; $-(CH_2)_{0-4}-CO$-naphthyl; $-(CH_2)_{0-4}-CO$-heteroaryl; $-(CH_2)_{0-4}-CO$-heterocycloalkyl; $-(CH_2)_{0-4}-CO_2R_{20}$; where

R_{20} is selected from C_1-C_6 alkyl, $-(CH_2)_{0-2}-$(phenyl), $-(CH_2)_{0-2}-$(naphthyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(CH_2)_{0-2}-$(heterocycloalkyl) and $-(CH_2)_{0-2}-$(heteroaryl);

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Yet still other preferred compounds of formula A-III-12 include those compounds wherein

R_c and R_d are $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl); $-(CH_2)_{0-4}-O-P(O)-(OR_5)_2$; $-(CH_2)_{0-4}-O-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-O-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-O-(R_{20})$; $-(CH_2)_{0-4}-O-(R_{20})-CO_2H$; $-(CH_2)_{0-4}-S-(R_{20})$; $-(CH_2)_{0-4}-O$-halo(C_1-C_6)alkyl; $-(CH_2)_{0-4}-O-(C_1-C_6)$alkyl; C_3-C_8 cycloalkyl; or $-(CH_2)_{0-4}-N(-H$ or $R_{20})-SO_2-R_{21}$; wherein

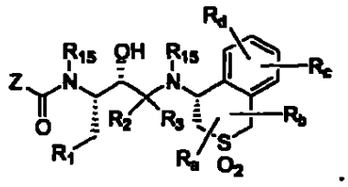
each aryl group and each heteroaryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, $-CO-(C_1-C_4$ alkyl), $-CO_2-(C_1-C_4$

alkyl), $-SO_2-NR_5R_6$, $-NR_7R_8$, $-CO-NR_5R_6$, $-CO-NR_7R_8$, $-SO_2-(C_1-C_4$ alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl; wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, $-NR_5R_6$, CN, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, NR_7R_8, and C_1-C_6 alkoxy.

Preferred compounds of formula A-III-6a include those of formula A-IV



Preferred compounds of formula A-IV include those wherein R_2 and R_3 are independently H or C_1-C_4 alkyl.

Other preferred compounds of formula A-IV include those of formula A-IV-1, i.e., compounds of formula A-IV wherein

R_a and R_b are independently H or C_1-C_3 alkyl; and

R_1 is phenyl, optionally substituted with 1, 2, or 3 R_{50} groups; and

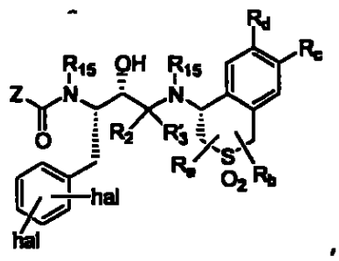
R_{15} at each occurrence is independently H or C_1-C_4 alkyl.

Preferred compounds of formula A-IV-1 include those of formula A-IV-2, i.e., compounds of formula A-IV-1 wherein

R_1 is a dihalophenyl; and

R_2 and R_3 are independently H or C_1-C_4 alkyl.

Preferred compounds of formula A-IV-2 include compounds of formula A-V



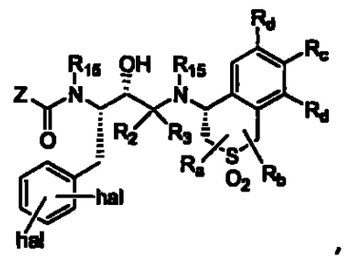
wherein

hal at each occurrence is independently selected from F, Cl, Br, and I.

More preferred compounds of formula A-V include those compounds wherein

R_c is a C_1-C_4 alkyl group.

Other preferred compounds of formula A-IV-2 include compounds of formula A-VI



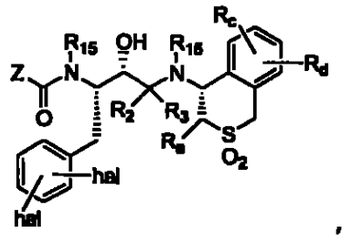
wherein

hal at each occurrence is independently selected from F, Cl, Br, and I.

Preferred compounds of formula A-VI include those compounds wherein

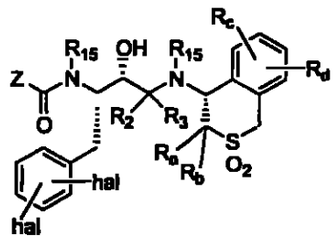
R_c is a C_1-C_4 alkyl group.

Other preferred compounds of formula A-IV-2 include compounds of formula A-VII

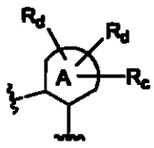


wherein R_b is H.

Still other preferred compounds of formula A-IV-2 include compounds of formula A-VIII



Other preferred compounds of formula A-I-1 include those compounds of formula A-IX, i.e., compounds of formula A-I-1 wherein



is a 5 or 6 membered heteroaryl group.

Preferred compounds of formula A-IX include compounds of formula A-IX-1, i.e., compounds of formula A-IX wherein

R_2 and R_3 are independently selected from H; C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents that are independently selected from C_1-C_4 alkyl, halogen, -CF_3, and C_1-C_4 alkoxy; C_2-C_6 alkenyl or C_2-C_6 alkynyl wherein each is optionally substituted with one, two, or three substituents selected from -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -NR_5R_6; or

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, -SO_2-, or -NR_7-; wherein

R_7 is selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, -NH_2, and halogen; -C_3-C_8 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl.

Preferred compounds of formula A-IX-1 include those of formula A-IX-2, i.e., compounds of formula A-IX-1, wherein

R_{15} at each occurrence is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_6 alkanoyl, benzyl optionally substituted with OCH_3, -C(O)-tertiary butyl, and -CO_2-benzyl.

Preferred compounds of formula A-IX-2 include those of formula A-IX-3, i.e., compounds of formula A-IX-2, wherein

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, -CF_3, -C_1-C_4 alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino OC(=O)-mono- and dialkylamino; or

R_1 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alkoxy, amino, and mono- or dialkylamino; or

R_1 is aryl, heteroaryl, heterocyclyl, aryl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, or heterocycloalkyl C_1-C_6 alkyl;

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, -CO-(C_1-C_4 alkyl), -CO_2-(C_1-C_4 alkyl), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl;

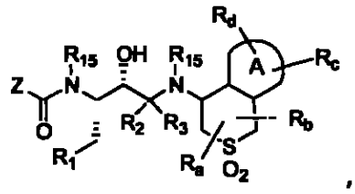
wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, -NR_5R_6, CN, C_1-C_4

haloalkyl, C_1-C_4 haloalkoxy, phenyl, NR_7R_8, and C_1-C_4 alkoxy.

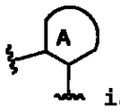
Preferred compounds of formula A-IX-3 include those of formula A-IX-4, i.e., compounds of formula A-IX-3, wherein

R_{50} at each occurrence is independently selected from halogen, OH, SH, $-NR_7R_8$, $-SO_2-(C_1-C_4$ alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl; wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, $-NR_5R_6$, CN, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, NR_7R_8, and C_1-C_4 alkoxy.

Preferred compounds of formula A-IX-4 include those of formula A-IX-5, i.e., compounds of formula A-X-4, of the formula



wherein



is selected from pyridinyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrazole, isoxazole, and pyrrolyl.

Preferred compounds of formula A-IX-5 include compounds of formula A-IX-6, i.e., compounds of formula A-IX-5 wherein wherein,

R_1 is phenyl C_1-C_6 alkyl or naphthyl C_1-C_6 alkyl, wherein the phenyl or naphthyl group is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups.

Preferred compounds of formula A-IX-6 include compounds of formula A-IX-7, i.e., compounds of formula A-IX-6 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, $-SO_2-$, or $-NR_7-$; wherein

R_7 is H, $-C_1-C_8$ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, $-NH_2$, and halogen; $-C_2-C_4$ alkenyl; or $-C_2-C_4$ alkynyl.

Preferred compounds of formula A-IX-7 include compounds of formula A-IX-8, i.e., compounds of formula A-IX-7 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms.

Other preferred compounds of formula A-IX-7 include compounds of formula A-IX-9, i.e., compounds of formula A-IX-7 wherein

R_2, R_3 and the carbon to which they are attached form a heterocycloalkyl group containing 2 to 5 carbon atoms and one group selected from -O-, -S-, $-SO_2-$, and $-NR_7-$; wherein

R_7 is H, $-C_1-C_6$ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, $-NH_2$, and halogen; $-C_2-C_4$ alkenyl; or $-C_2-C_4$ alkynyl.

Other preferred compounds of formula A-IX-6 include compounds of formula A-IX-10, i.e., compounds of formula A-IX-6 wherein

R_2 and R_3 are independently selected from H; C_1-C_4 alkyl optionally substituted with 1 substituent that is selected from halogen, $-CF_3$, and C_1-C_4 alkoxy; C_2-C_4 alkenyl; C_2-C_4 alkynyl; and $-CO_2-(C_1-C_4$ alkyl); wherein

R_5 and R_6 are at each occurrence are independently H or C_1-C_6 alkyl; or

R_5 and R_6 and the nitrogen to which they are attached, at each occurrence form a 5 or 6 membered heterocycloalkyl ring.

Preferred compounds of formulas A-IX-8, A-IX-9, or A-IX-10 include those of formula A-IX-11, i.e., compounds of formulas A-IX-8, A-IX-9, or A-IX-10 wherein

R_a and R_b are independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CN, OH, hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, and -C_1-C_6 alkyl-NR_5R_6; or

R_a and R_b are attached to the same carbon and form a C_3-C_7 spirocycle; and

R_{15} at each occurrence is independently H or C_1-C_4 alkyl.

Preferred compounds of formula A-IX-11 include those wherein

R_c and R_d are independently selected from C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and -NR_5R_6; hydroxy; halogen; C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein

the alkenyl or alkynyl group is optionally substituted with C_1-C_4 alkyl, halogen, hydroxy, SH, cyano, CF_3, C_1-C_4 alkoxy, or NR_5R_6.

Other preferred compounds of formula A-IX-11 include those wherein

R_c and R_d are -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$, -$(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl); -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl); -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl); -$(CH_2)_{0-4}$-N(H or R_{20})-CO-O-R_{20}; -$(CH_2)_{0-4}$-N(H or R_{20})-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N(-H or R_{20})-CO-R_{21}; or -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; wherein

R_{21} and R_{22} independently represent hydrogen, C_1-C_6 alkyl, hydroxyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, haloalkyl, C_3-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, phenyl, naphthyl, or heteroaryl;

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Still other preferred compounds of formula A-IX-11 include those wherein

R_c and R_d are $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl); $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl); $CH_2)_{0-6}-CO-(C_2-C_{12})$alkynyl; $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl); $-(CH_2)_{0-4}-CO$-phenyl; $-(CH_2)_{0-4}-CO$-naphthyl; $-(CH_2)_{0-4}-CO$-heteroaryl; $-(CH_2)_{0-4}-CO$-heterocycloalkyl; $-(CH_2)_{0-4}-CO_2R_{20}$; where

R_{20} is selected from C_1-C_6 alkyl, $-(CH_2)_{0-2}-$(phenyl), $-(CH_2)_{0-2}-$(naphthyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(CH_2)_{0-2}-$(heterocycloalkyl) and $-(CH_2)_{0-2}-$(heteroaryl);

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Yet still other preferred compounds of formula A-IX-11 include those wherein

R_c and R_d are $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl); $-(CH_2)_{0-4}-O-P(O)-(OR_5)_2$; $-(CH_2)_{0-4}-O-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-O-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-O-(R_{20})$; $-(CH_2)_{0-4}-O-(R_{20})-CO_2H$; $-(CH_2)_{0-4}-S-(R_{20})$; $-(CH_2)_{0-4}-O$-halo(C_1-C_6)alkyl; $-(CH_2)_{0-4}-O-(C_1-C_6)$alkyl; C_3-C_8 cycloalkyl; or $-(CH_2)_{0-4}-N(-H$ or $R_{20})-SO_2-R_{21}$; wherein

each aryl group and each heteroaryl group at each occurrence is optionally substituted with 1, 2, 3. 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, $-CO-(C_1-C_4$ alkyl), $-CO_2-(C_1-C_4$ alkyl), $-SO_2-NR_5R_6$, $-NR_7R_8$, $-CO-NR_5R_6$, $-CO-NR_7R_8$, $-SO_2-(C_1-C_4$ alkyl), C_1-C_6 alkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl;

wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, $-NR_5R_6$, CN, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, NR_7R_8, and C_1-C_6 alkoxy.

Other preferred compounds of formula A-IX-5 include those of formula A-IX-12, i.e., compounds of formula A-IX-5, wherein

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, $-CF_3$, $-C_1$-C_4 alkoxy, amino, mono- or dialkylamino, $-N(R)C(O)R'$, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino; or

R_1 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alkoxy, amino, and mono- or dialkylamino.

Preferred compounds of formula A-IX-12, include those of formula A-IX-13, i.e., compounds of formula A-IX-12 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms, wherein one carbon atom is optionally replaced by a group selected from -O-, -S-, $-SO_2-$, or $-NR_7-$; wherein

R_7 is selected from H or $-C_1$-C_4 alkyl optionally substituted with 1 group selected from -OH, $-NH_2$, and halogen.

Preferred compounds of formula A-IX-13, include those of formula A-IX-14, i.e., compounds of formula A-IX-13 wherein

R_2, R_3 and the carbon to which they are attached form a carbocycle of three thru six carbon atoms.

Other preferred compounds of formula A-IX-13, include those of formula A-IX-15, i.e., compounds of formula A-IX-13 wherein

R_2, R_3 and the carbon to which they are attached form a heterocycloalkyl group containing 2 to 5 carbon atoms and one group selected from -O-, -S-, $-SO_2-$, and $-NR_7-$; wherein

R_7 is selected from H and $-C_1-C_4$ alkyl optionally substituted with 1 group selected from -OH, $-NH_2$, and halogen.

Other preferred compounds of formula A-IX-13, include those of formula A-IX-16, i.e., compounds of formula A-IX-13 wherein

R_2 and R_3 are independently selected from H; C_1-C_4 alkyl optionally substituted with 1 substituent that is selected from halogen, $-CF_3$, and C_1-C_4 alkoxy; C_2-C_4 alkenyl; and C_2-C_4 alkynyl; wherein

R_5 and R_6 are at each occurrence are independently -H or C_1-C_6 alkyl; or

R_5 and R_6 and the nitrogen to which they are attached, at each occurrence form a 5 or 6 membered heterocycloalkyl ring.

Preferred compounds of formulas A-IX-14, A-IX-15, A-IX-16 include compounds of formula A-IX-17, i.e., compounds of formulas A-IX-14, A-IX-15, A-IX-16 wherein

R_a and R_b are independently selected from C_1-C_3 alkyl, F, OH, SH, C≡N, CF_3, C_1-C_6 alkoxy, and $-NR_5R_6$; and

R_{15} at each occurrence is independently H or C_1-C_4 alkyl.

Preferred compounds of formula A-IX-17, include those compounds wherein

R_c and R_d are independently selected from C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $-NR_5R_6$; hydroxy; halogen;

C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein

the alkenyl or alkynyl group is optionally substituted with C_1-C_4 alkyl, halogen, hydroxy, SH, cyano, CF_3, C_1-C_4 alkoxy, or NR_5R_6.

Other preferred compounds of formula A-IX-17, include those compounds wherein

R_c and R_d are $-(CH_2)_{0-4}-CO-NR_{21}R_{22}$, $-(CH_2)_{0-4}-SO_2-NR_{21}R_{22}$; $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl); $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl); $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl); $-(CH_2)_{0-4}-N(H$ or $R_{20})-CO_2R_{20}$; $-(CH_2)_{0-4}-N(H$ or $R_{20})-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-N-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-N(-H$ or $R_{20})-CO-R_{21}$; or $-(CH_2)_{0-4}-NR_{21}R_{22}$; wherein

R_{21} and R_{22} independently represent hydrogen, C_1-C_6 alkyl, hydroxyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, haloalkyl, C_3-C_7 cycloalkyl, $-(C_1-C_2$ alkyl$)-(C_3-C_7$ cycloalkyl), $-(C_1-C_6$ alkyl$)-O-(C_1-C_3$ alkyl), $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, phenyl, naphthyl, or heteroaryl;

each aryl group and each heteroaryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Still other preferred compounds of formula A-IX-17, include those compounds wherein

R_c and R_d are $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl); $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl); $CH_2)_{0-4}-CO-(C_2-C_{12})$alkynyl; $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl); $-(CH_2)_{0-4}-CO-$phenyl; $-(CH_2)_{0-4}-CO-$naphthyl; $-(CH_2)_{0-4}-CO-$heteroaryl; $-(CH_2)_{0-4}-CO-$heterocycloalkyl; $-(CH_2)_{0-4}-CO_2R_{20}$; where

R_{20} is selected from C_1-C_6 alkyl, $-(CH_2)_{0-2}-$(phenyl), $-(CH_2)_{0-2}-$(naphthyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(CH_2)_{0-2}-$(heterocycloalkyl) and $-(CH_2)_{0-2}-$(heteroaryl);

each aryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heteroaryl at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O.

Yet still other preferred compounds of formula A-IX-17, include those compounds wherein

R_c and R_d are $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl); $-(CH_2)_{0-4}-O-P(O)-(OR_5)_2$; $-(CH_2)_{0-4}-O-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-O-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-O-(R_{20})$; $-(CH_2)_{0-4}-O-(R_{20})-CO_2H$; $-(CH_2)_{0-4}-S-(R_{20})$; $-(CH_2)_{0-4}-O$-halo(C_1-C_6)alkyl; $-(CH_2)_{0-4}-O-(C_1-C_6)$alkyl; C_3-C_8 cycloalkyl; or $-(CH_2)_{0-4}-N(-H$ or $R_{20})-SO_2-R_{21}$; wherein

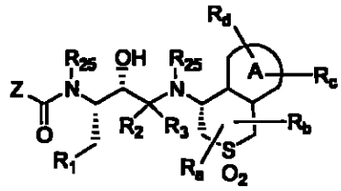
each aryl group and each heteroaryl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups;

each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently R_{50} or =O;

R_{50} at each occurrence is independently selected from halogen, OH, SH, CN, $-CO-(C_1-C_4$ alkyl), $-CO_2-(C_1-C_4$ alkyl), $-SO_2-NR_5R_6$, $-NR_7R_8$, $-CO-NR_5R_6$, $-CO-NR_7R_8$, $-SO_2-(C_1-C_4$ alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, or C_3-C_8 cycloalkyl;

wherein the alkyl, alkenyl, alkynyl, alkoxy, or cycloalkyl groups are optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_4 alkyl, halogen, OH, SH, $-NR_5R_6$, CN, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, NR_7R_8, and C_1-C_6 alkoxy.

Other preferred compounds of formula A-IX-4 include those of formula A-X



Preferred compounds of formula A-X include compounds of formula A-X-1, i.e., compounds of formula A-X wherein

R_1 is phenyl C_1-C_6 alkyl or naphthyl C_1-C_6 alkyl, wherein the phenyl or naphthyl group is optionally substituted with 1, 2, 3, 4, or 5 R_{50} groups; and

R_2 and R_3 are independently H or C_1-C_4 alkyl.

Preferred compounds of formula A-X-1 include compounds of formula A-X-2, i.e., compounds of formula A-X-1 wherein

R_a and R_b are independently H or C_1-C_4 alkyl; or

R_a and R_b are attached to the same carbon and form a C_3-C_6 carbocycle;

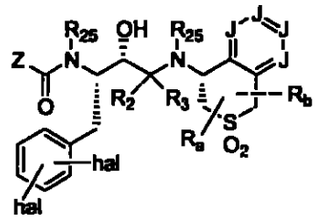
R_1 is phenyl, optionally substituted with 1, 2, or 3 R_{50} groups; and

R_{25} at each occurrence is independently H or C_1-C_4 alkyl.

Preferred compounds of formula A-X-2 include compounds of formula A-X-3, i.e., compounds of formula A-X-2 wherein

R_1 is a dihalophenyl.

Preferred compounds of formulas A-IX-5, A-X and A-X-3 include compounds of formula A-X-4, i.e., compounds of formulas A-IX-5, A-X and A-X-3 having the following structure,



wherein

wherein J at each occurrence is independently selected from N or CR_c, wherein

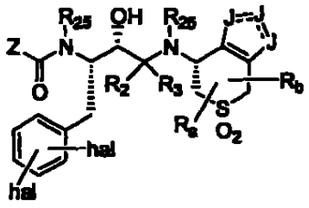
R_c at each occurrence is independently selected from C_1-C_6 alkyl, optionally substituted with 1, 2, or 3

substituents independently selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, and NR_5R_6; hydroxy; halogen; C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein

the alkenyl or alkynyl group is optionally substituted with C_1-C_4 alkyl, halogen, hydroxy, SH, cyano, CF_3, C_1-C_4 alkoxy, or NR_5R_6;

provided that at least two Js are CR_c.

Other preferred compounds of formulas A-IX-5, A-X and A-X-3 include compounds of formula A-X-5, i.e., compounds of formulas A-IX-5, A-X and A-X-3 having the following structure,



wherein

--- represents a single or double bond, provided that only one of the dashed bonds is a double bond;

J is selected from N, S, O, and CR_c, wherein

R_c at each occurrence is independently selected from C_1-C_6 alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from C_1-C_3 alkyl, halogen, OH, SH, C≡N, CF_3, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, and NR_5R_6; hydroxy; halogen; C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein

the alkenyl or alkynyl group is optionally substituted with C_1-C_4 alkyl, halogen, hydroxy, SH, cyano, CF_3, C_1-C_4 alkoxy, or NR_5R_6;

provided that at least one J is CR_c.

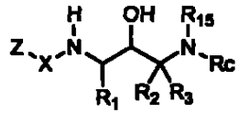
Other preferred compounds include those compounds according to any one of embodiments A-I to A-X-5, wherein

Z is C_1-C_6 alkyl, optionally substituted with 1 or 2 groups that are independently OH, halogen, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, CN, and NR_5R_6. More preferably, Z is C_1-C_4

alkyl. Another preferred embodiment, Z is phenyl, benzyl, imidazolyl, or -C_1-C_4-imidazolyl.

Still other preferred compounds include those compounds according to any one of embodiments A-I to A-X-5, wherein R_5 and R_6 at each occurrence are independently H or C_1-C_4 alkyl. Preferably, Z is C_1-C_4 alkyl.

In another aspect, the invention provides a method of preparing compounds of formula (I)



(I)

and a pharmaceutically acceptable salt thereof, wherein Z, X, R_1, R_2, R_3, R_{15} and R_c are as defined above.

In another aspect, the invention provides the intermediates that are useful in the preparation of the compounds of interest.

The invention also provides methods for treating a patient who has, or in preventing a patient from getting, a disease or condition selected from Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which includes administration of a therapeutically effective amount of a

compound of formula (I) and a pharmaceutically acceptable salts thereof.

In an embodiment, this method of treatment can be used where the disease is Alzheimer's disease.

In an embodiment, this method of treatment can help prevent or delay the onset of Alzheimer's disease.

In an embodiment, this method of treatment can be used where the disease is mild cognitive impairment.

In an embodiment, this method of treatment can be used where the disease is Down's syndrome.

In an embodiment, this method of treatment can be used where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

In an embodiment, this method of treatment can be used where the disease is cerebral amyloid angiopathy.

In an embodiment, this method of treatment can be used where the disease is degenerative dementias.

In an embodiment, this method of treatment can be used where the disease is diffuse Lewy body type of Alzheimer's disease.

In an embodiment, this method of treatment can treat an existing disease.

In an embodiment, this method of treatment can prevent a disease from developing.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 0.1 mg/day to about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration from about 0.5 to about 100 mg/day; for depo administration and implants from about 0.5 mg/day to about 50 mg/day; for topical administration from about 0.5 mg/day to about 200 mg/day; for rectal administration from about 0.5 mg to about 500 mg.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 1 mg/day to about 100 mg/day; and for parenteral administration from about 5 to about 50 mg daily.

In an embodiment, this method of treatment can employ therapeutically effective amounts for oral administration from about 5 mg/day to about 50 mg/day.

The invention also includes pharmaceutical compositions which include a compound of formula (I) and pharmaceutically acceptable salts thereof.

The invention also includes the use of a compound of formula (I) or pharmaceutically acceptable salts thereof for the manufacture of a medicament for use in treating a patient who has, or in preventing a patient from getting, a disease or condition selected from Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is Alzheimer's disease.

In an embodiment, this use of a compound of formula (I) can help prevent or delay the onset of Alzheimer's disease.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is mild cognitive impairment.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is Down's syndrome.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is cerebral amyloid angiopathy.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is degenerative dementias.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is diffuse Lewy body type of Alzheimer's disease.

In an embodiment, this use of a compound employs a pharmaceutically acceptable salt selected from salts of the following acids hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, HOOC-(CH$_2$)n-COOH where n is as defined above, HOOC-CH=CH-COOH, and phenyl-COOH.

The invention also includes methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype, or at a corresponding site of an isotype or mutant thereof; for inhibiting production of amyloid beta peptide (A beta) in a cell; for inhibiting the production of beta-amyloid plaque in an animal; and for treating or preventing a disease characterized by beta-amyloid deposits in the brain. These methods each include administration of a therapeutically effective amount of a compound of formula (I) and pharmaceutically acceptable salts thereof.

The invention also includes a method for inhibiting beta-secretase activity, including exposing said beta-secretase to an effective inhibitory amount of a compound of formula (I), and pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 nanomolar or less.

In an embodiment, this method includes exposing said beta-secretase to said compound *in vitro*.

In an embodiment, this method includes exposing said beta-secretase to said compound in a cell.

In an embodiment, this method includes exposing said beta-secretase to said compound in a cell in an animal.

In an embodiment, this method includes exposing said beta-secretase to said compound in a human.

The invention also includes a method for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, including exposing said reaction mixture to an effective inhibitory amount of a compound of formula (I), and a pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a cleavage site: between Met652 and Asp653, numbered for the APP-751 isotype; between Met 671 and Asp 672, numbered for the APP-770 isotype; between Leu596 and Asp597 of the APP-695 Swedish Mutation; between Leu652 and Asp653 of the APP-751 Swedish Mutation; or between Leu671 and Asp672 of the APP-770 Swedish Mutation.

In an embodiment, this method exposes said reaction mixture *in vitro*.

In an embodiment, this method exposes said reaction mixture in a cell.

In an embodiment, this method exposes said reaction mixture in an animal cell.

In an embodiment, this method exposes said reaction mixture in a human cell.

The invention also includes a method for inhibiting production of amyloid beta peptide (A beta) in a cell, including administering to said cell an effective inhibitory amount of a compound of formula (I), and a pharmaceutically acceptable salt thereof.

In an embodiment, this method includes administering to an animal.

In an embodiment, this method includes administering to a human.

The invention also includes a method for inhibiting the production of beta-amyloid plaque in an animal, including administering to said animal an effective inhibitory amount of a compound of formula (I), and a pharmaceutically acceptable salt thereof.

In an embodiment, this method includes administering to a human.

The invention also includes a method for treating or preventing a disease characterized by beta-amyloid deposits in the brain including administering to a patient an effective therapeutic amount of a compound of formula (I), and a pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 nanomolar or less.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 0.1 to about 1000 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 15 to about 1500 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 1 to about 100 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 5 to about 50 mg/day.

In an embodiment, this method can be used where said disease is Alzheimer's disease.

In an embodiment, this method can be used where said disease is Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type.

The invention also includes a composition including beta-secretase complexed with a compound of formula (I), and a pharmaceutically acceptable salt thereof.

The invention also includes a method for producing a beta-secretase complex including exposing beta-secretase to a compound of formula (I), and a pharmaceutically acceptable salt thereof, in a reaction mixture under conditions suitable for the production of said complex.

In an embodiment, this method employs exposing *in vitro*.

In an embodiment, this method employs a reaction mixture that is a cell.

The invention also includes a component kit including component parts capable of being assembled, in which at least

one component part includes a compound of formula I enclosed in a container.

In an embodiment, this component kit includes lyophilized compound, and at least one further component part includes a diluent.

The invention also includes a container kit including a plurality of containers, each container including one or more unit dose of a compound of formula (I):, and a pharmaceutically acceptable salt thereof.

In an embodiment, this container kit includes each container adapted for oral delivery and includes a tablet, gel, or capsule.

In an embodiment, this container kit includes each container adapted for parenteral delivery and includes a depot product, syringe, ampoule, or vial.

In an embodiment, this container kit includes each container adapted for topical delivery and includes a patch, medipad, ointment, or cream.

The invention also includes an agent kit including a compound of formula (I), and a pharmaceutically acceptable salt thereof; and one or more therapeutic agent selected from an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta antibody.

The invention also includes a composition including a compound of formula (I), and a pharmaceutically acceptable salt thereof; and an inert diluent or edible carrier.

In an embodiment, this composition includes a carrier that is an oil.

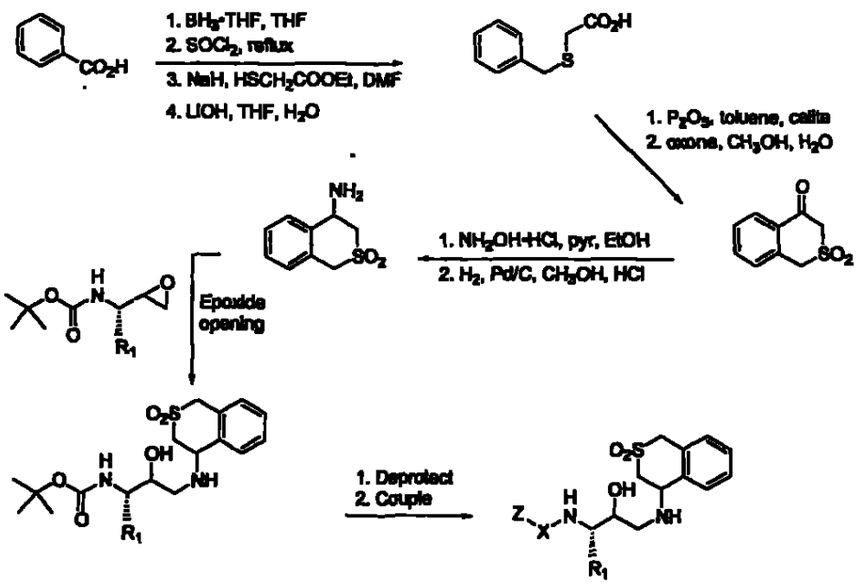
The invention also includes a composition including: a compound of formula (I), and a pharmaceutically acceptable salt thereof; and a binder, excipient, disintegrating agent, lubricant, or gildant.

The invention also includes a composition including a compound of formula (I), and a pharmaceutically acceptable salt thereof; disposed in a cream, ointment, or patch.

The invention provides compounds of formula (I), and the other formulas contained herein, that are useful in treating and preventing Alzheimer's disease. The compounds of the invention can be prepared by one skilled in the art based only on knowledge of the compound's chemical structure. The chemistry for the preparation of the compounds of this invention is known to those skilled in the art. In fact, there is more than one process to prepare the compounds of the invention. Specific examples of methods of preparation can be found in the art. For examples, see *J. Org. Chem.* 1998, *63*, 4898-4906; *J. Org. Chem.* 1997, *62*, 9348-9353; *J. Org. Chem.* 1996, *61*, 5528-5531; *J. Med. Chem.* 1993, *36*, 320-330; *J. Am. Chem. Soc.* 1999, *121*, 1145-1155; and references cited therein. See also U.S. Patent Nos. 6,150,530, 5,892,052, 5,696,270, and 5,362,912, which are incorporated herein by reference, and references cited therein.

An example of one of many various processes that can be used to prepare the compounds of the invention is set forth in Scheme I.

Scheme I



where R_1, X, and Z are as defined above or below.

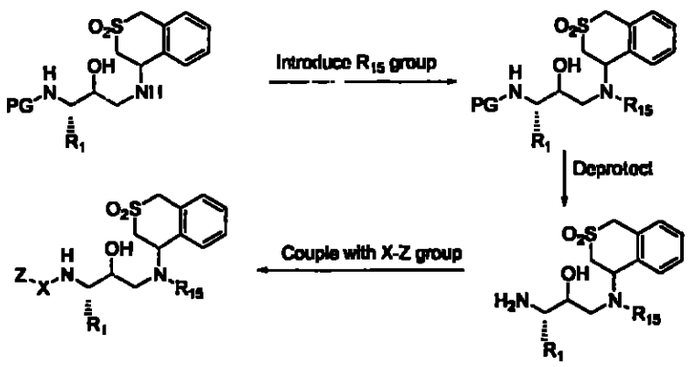
Scheme I illustrates the preparation of compounds wherein R_c is an isothiochroman 2,2-dioxide using an optionally substituted benzoic acid as the starting material. One of skill in the art will recognize that optionally substituted benzyl halides or benzyl alcohols may also be used as starting materials.

In Scheme I, the benzoic acid is reduced to a benzyl alcohol, which is then converted into a benzyl halide. Alternatively, the benzyl alcohol may be modified to include a leaving group such as, for example, a tosylate, brosylate, nosylate, triflate or mesylate. The benzyl compound is then reacted with a sulfide to generate the thioether. The carboxylic ester is then hydrolyzed to form a carboxylic acid, which is then subjected to annulation reaction conditions to form the desired bicyclic ring system. The annulation can be carried out using a Lewis acid, polyphosphoric acid, or P_2O_5. Other suitable reagents that effect cyclization are known in the art.

The resulting bicyclic sulfide is oxidized to form the sulfone. The keto group is converted into an amine directly via reductive amination or indirectly through the generation of an oxime, which is then reduced to form the amine. Transition metal catalysts and hydrogen or other reducing agents, such as $NaBH_4$, $LiAlH_4$ or $NaCNBH_3$, may be used to effect the reduction.

The resulting amine is used to open the epoxide to form the resulting coupled product. The coupled product is then deprotected to form a free amine, which is acylated or sulfonylated to generate the desired final product. In Scheme I, the use of a Boc protecting group is illustrated, but one of skill in the art will appreciate that other protecting groups, such as CBz, benzyl or others can also be used.

Scheme II

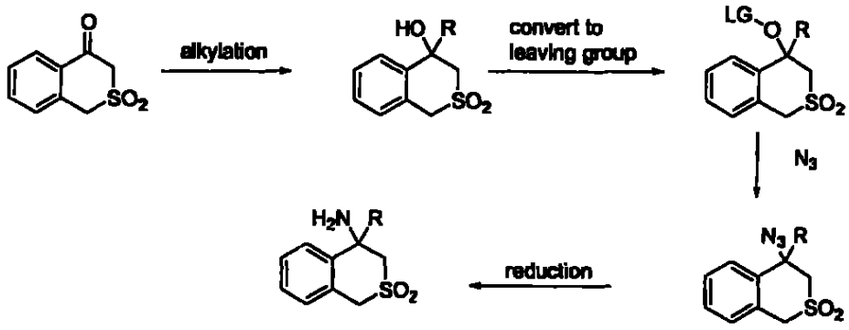


Scheme II illustrates the introduction of a non-hydrogen R_{15} group on the 3-position nitrogen atom in the 1,3-diaminopropane portion of the molecule. The free nitrogen is reacted with an electrophile, an aldehyde or ketone and a reducing agent, an acid chloride, an acid anhydride or an acid with a coupling agent, such as DCC (dicyclohexyl carbodiimide), DIC (1,3 diisopropyl carbodiimide), EDCI (1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride), BBC (1-benzotriazol-1-yloxy-bis(pyrrolidino)uronium hexafluorophosphate), BDMP (5-(1*H*-benzotriazol-1-yloxy)-3,4-

dihydro-1-methyl 2*H*-pyrrolium hexachloroanitimonate), BOMI (benzotriazol-1-yloxy-*N*,*N*-dimethylmethaniminium hexachloroantimonate), HATU (*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), HAPyU = *O*-(7-azabenzotriazol-1-yl)- 1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate, HBTU which is *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, TAPipU which is *O*-(7-azabenzotriazol-1-yl)- 1,1,3,3-bis(pentamethylene)uronium etrafluoroborate, AOP (*O*-(7-azabenzotriazol-1-yl)-tris(dimethylamino)phosphonium hexafluorophosphate), BDP (benzotriazol-1-yl diethyl phosphate), BOP (1-benzotriazolyoxytris(dimethylamino)phosphonium hexafluorophosphate), PyAOP (7-azobenzotriazolyoxytris(pyrrolidino)phosphonium hexafluorophosphate), PyBOP (1-benzotriazolyoxytris(pyrrolidino)phosphonium hexafluorophosphate), TDBTU (2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), TNTU (2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate), TPTU (2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate), TSTU (2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate), BEMT (2-bromo-3-ethyl-4-methyl thiazolium tetrafluoroborate), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride), BroP (bromotris(dimethylamino)phosphonium hexafluorophosphate), BTFFH (bis(tetramethylenefluoroformamidinium) hexafluorophosphate), ClP (2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate), DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one), Dpp-Cl (diphenylphosphinic chloride), EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline), FDPP (pentafluorophenyl diphenylphosphinate), HOTT (*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate), PyBroP

(bromotris(pyrrclydino)phophonium hexafluorophosphate), PyCloP (chlorotris(pyrrolydino)phophonium hexafluorophosphate), TFFH (tetramethylfluoroformamidinium hexafluorophosphate), and TOTT (*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate) to generate the monosubstituted product, which can then be deprotected and coupled to the "X-Z" group. Conversely, the monosubstituted product can be deprotected, and the free nitrogen reacted with an electrophile, an aldehyde or ketone and a reducing agent, an acid chloride, an acid anhydride or an acid with a coupling agent, such as those previously exemplified to generate the disubstituted product, which is then coupled to the "X-Z" group.

Scheme III

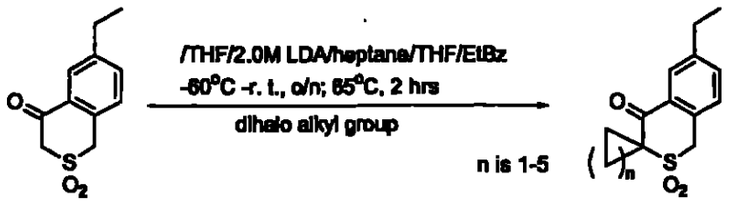


Scheme III illustrates the introduction of a tertiary amine (R is not hydrogen) or a secondary amine (R is hydrogen) onto the isothiochroman 2,2-dioxide scaffold. First, the sulfo-ketone is alkylated using, for example, a Grignard reagent or other alkylating agent, to generate the tertiary alcohol, which is then converted into a leaving group. One of skill in the art will appreciate that many possible leaving groups may be used. Particular examples include, but are not limited to triflate, mesylate, paratoluene sulfonate, nosylate, and brosylate. The leaving group is then displaced using an azide, such as DPPA or NaN_3. Substituted azides may be used in place of the unsubstituted azide. Alternatively, the desired compounds can be generated from the alcohol

directly without first converting the alcohol into a leaving group. Such transformations can be readily accomplished using conventional SN_1 conditions according to procedures available in the literature.

The resulting azide is then reduced to generate the desired amine. Many reducing agents that will effect the desired transformation are known. Examples include H_2 and Pd, H_2 and Pt, $NaBH_4$, and $NaCNBH_3$. Stronger reducing agents, such as $LiAlH_4$ and DIBAL may be used, but the sulfone may also be reduced. If the sulfone is reduced, it may be reoxidized using methods known in the art, such as MCPBA.

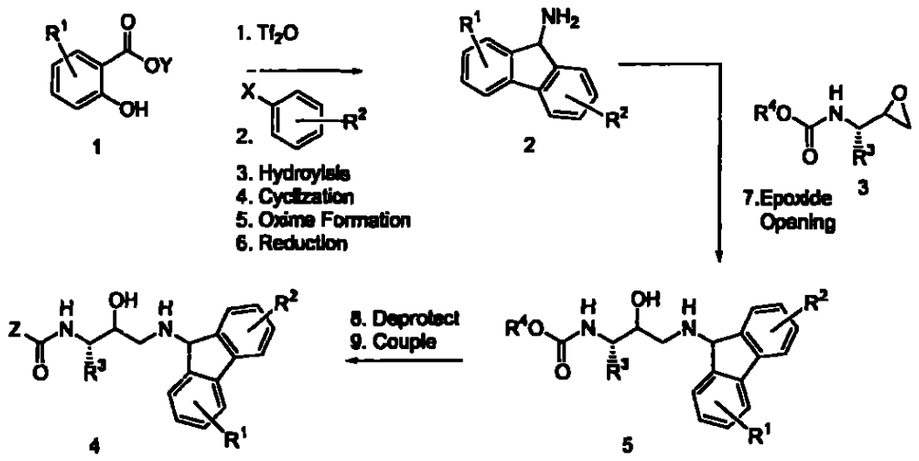
Scheme IV



As shown in scheme IV, spirocycles may be generated by alkylating a compound in the presence of a strong base. Examples of strong bases include, LDA, KHMDS, and tertiary-butyl lithium. One of skill in the art will appreciate that many other bases are strong enough to deprotonate the starting material and effect the desired transformation.

The alkylating agent dictates the size the of the spirocycle that is formed. Dibromo ethane, diiodoethane, or bromo iodoethane will generate a spirocyclopropyl compound, wherein n is 1. However, longer alkyl chains generate larger spirocycloalkyl compounds. For example, a 1,5-dihalopentane generates a spirocyclohexyl compound, wherein n is 4. Although dihalo compounds are illustrated, one of skill in the art will appreciate that other leaving groups, such as, for example, mesylate, tosylate, triflate, brosylate, and nosylate may be used. The leaving groups may, but need not, be identical.

Scheme V: Preparation of Fluorene Derivatives



Scheme V illustrates the preparation of fluorene derivatives using optionally substituted salicylic esters as starting materials. Non-commercially available substituted salicylic esters may be obtained by a variety of methods well known to those skilled in the art of organic synthesis. Such methods include, but are not limited to, halogenations [Rozen and Lerman (J. Org. Chem. 1993, 239 - 240)], Suzuki couplings [Miyaura and Suzuki (Chem. Rev. 1995, 2457 - 2483)], Sonagashiri couplings [Sonagashira (Metal-Catalyzed Cross-Coupling Reactions, 1998, Wiley-VCH publishers)], Negishi couplings [Zhu, *et al.* (J. Org. Chem. 1991, 1445 - 1453)], Stille cross-couplings [Littke et al. (Angew. Chem. Int. Ed. 1999, 2411 - 2413)], Heck couplings [Whitcombe *et al.* (Tetrahedron 2001, 7449 - 7476)], aminations [Wolfe et al. (J. Org. Chem. 2000, 1144 - 1157)], oxygenations [Fu and Littke (Angew. Chem. Int. Ed. 2002, 4177 - 4211)] and carbonylations [Cai *et al.* (J Chem Soc, Perkin Trans 1 1997, 2273 - 2274)]. One of skill in the art will recognize that optionally substituted ortho halo benzoates may also be used as starting materials.

Phenols of the general formula (1) are readily converted into triflates employing a triflating source and a base in an

inert solvent. Triflating sources include, but are not limited to, trifluoromethanesulfonic anhydride, trifluoromethanesulfonyl chloride and N-phenyltrifluoromethanesulfonimide. Bases include, but are not limited to, trialkyl amines (preferably diisopropylethylamine or triethylamine), aromatic amines (preferably pyridine, 4-dimethylaminopyridine or 2,6-lutidine) or alkali metal hydrides (preferably sodium hydride). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylforamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes (preferably dichloromethane). Preferred reaction temperatures range from 0 °C to room temperature. The progress of this conversion is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

Triflates may be treated with an aryl boronic acid or aryl boronic acid ester where X is equivalent to $B(OH)_2$ or $B(OR^a)(OR^b)$ (where R^a and R^b are lower alkyl, ie. C_1-C_6, or taken together R^a and R^b are lower alkylene, ie. C_2-C_{12}) in the presence of a metal catalyst with or without a base in an inert solvent to give birayls. Metal catalysts include, but are not limited to, salts or phosphine complexes of Cu, Pd or Ni (eg. $Cu(OAc)_2$, $Pd(PPh_3)_4$, $NiCl_2(PPh_3)_2$). Bases include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably sodium ethoxide or sodium methoxide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane),

N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylforamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes (preferably dichloromethane), alkyl alcohols (preferably methyl alcohol or ethyl alcohol), or water. Preferred reaction temperatures range from room temperature to the boiling point of the solvent employed. Non-commercially available boronic acids or boronic esters may be obtained from the corresponding optionally substituted aryl halide as described by Gao, *et al.* (Tetrahedron 1994, *50*, 979 -988). The progress of the coupling reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

Alternately, triflates may be treated with organozinc reagents as taught by Zhu, *et al.* (J. Org. Chem. 1991, 1445 - 1453).

One skilled in the art of organic synthesis will appreciate that the nature of the coupling partners described above could be reversed and the coupling reaction conducted in substantially the same manner as described above.

The biaryl ester is hydrolyzed to form a carboxylic acid. The hydrolysis reaction may be run under a wide variety of conditions familiar to one skilled in the art of organic synthesis. The hydrolysis reaction is run in the presence of a base such as, but not limited to, lithium hydroxide and sodium hydroxide. Typical solvents include, but are not limited to, tetrahydrofuran, diethyl ether, dichloromethane, alkyl alcohols (including methyl alcohol and ethyl alcohol) and water. The reactions may be successfully run at temperatures ranging from room temperature to the boiling point of the solvent employed. The progress of the hydrolysis reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

The carboxylic acid may be subjected to a cyclization reaction, under a wide variety of conditions known to one skilled in the art of organic synthesis, to form the desired tricycle. The cyclization reaction is carried out in the presence of an acidic reagent. Either Bronsted acids including, but not limited to, sulfuric acid, hydrochloric acid, methanesulfonic acid and polyphosphoric acid, or Lewis acids including, but not limited to, aluminum trichloride, titanium tetrachloride and tin tetrachloride are useful for effecting this transformation. The reaction may be performed neat or with the addition of a co-solvent. Typical co-solvents include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylforamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes (preferably dichloromethane) or alkyl alcohols (preferably methyl alcohol or ethyl alcohol). The reactions may be successfully run at temperatures ranging from room temperature to the boiling point of the solvent employed. The progress of the hydrolysis reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

Alternately, the carboxylic acid may be cyclized through the intermediacy of the corresponding activated acid as taught by Alder, *et al* (Justus Liebigs Ann. Chem. 1950; 230 - 238) Stiles and Libbey (J. Org. Chem 1957, 1243 - 1245) and Ladd, *et al*. (J. Med. Chem. 1986 1904 -1912).

The ketone may be converted to the corresponding oxime. The condensation reaction is carried out in the presence of a hydroxylamine (of the general formula $RONH_2$; where R = H, C_1-C_4) with or without a base in an inert solvent. Bases include, but are not limited to, alkaline earth metal

carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably sodium ethoxide or sodium methoxide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylforamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes (preferably dichloromethane), alkyl alcohols (preferably methyl alcohol or ethyl alcohol), or water. Preferred reaction temperatures range from room temperature to the boiling point of the solvent employed. The progress of the condensation reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

Reduction of the corresponding oxime to the desired amine proceeds in the presence of a reducing agent in an inert solvent. Suitable reducing agents include, but are not limited to, transition metals with or without hydrogen and hydride donating agents. Transition metals that may or may not be used catalytically with or without the addition of hydrogen include, but are not limited to, Pd, Pt and Zn. Hydride donating agents, include but are not limited to BH_3, $NaBH_4$, $LiBH_4$, $NaCNBH_3$ and $LiAlH_4$. Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylforamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes (preferably dichloromethane), alkyl alcohols (preferably methyl alcohol or ethyl alcohol), or

72

water. Preferred reaction temperatures range from 0 °C to the boiling point of the solvent employed. The progress of the condensation reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

One skilled in the art will appreciate, alternatively to the indirect procedure described above, that the ketone may be directly converted to the corresponding amine directly via a reductive amination as taught by Dei *et al.* (Bioorg. Med. Chem. 2001, 2673-2682).

The resulting amines of general formula (2) may be treated with a protected epoxide of general formula (3), including, but not limited to, Boc protected epoxides, with or without catalysis in an inert solvent. Catalysts include, but are not limited to, salts or complexes of Yb, Sn, Ti, B and Cu. Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylformamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes (preferably dichloromethane), alkyl alcohols (preferably isopropyl alcohol or tert-butyl alcohol). Preferred reaction temperatures range from room temperature to the boiling point of the solvent employed. The progress of the coupling reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

The resulting coupled products of general formula (4) may be deprotected to yield the amine by treatment with acidic additives in inert solvents. Acidic additives include, but are not limited to, TFA, HCl, HBr, AcOH and trichloroacetic acid. Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether),

water. Preferred reaction temperatures range from 0 °C to the boiling point of the solvent employed. The progress of the condensation reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

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The resulting coupled products of general formula (4) may be deprotected to yield the amine by treatment with acidic additives in inert solvents. Acidic additives include, but are not limited to, TFA, HCl, HBr, AcOH and trichloroacetic acid. Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether),

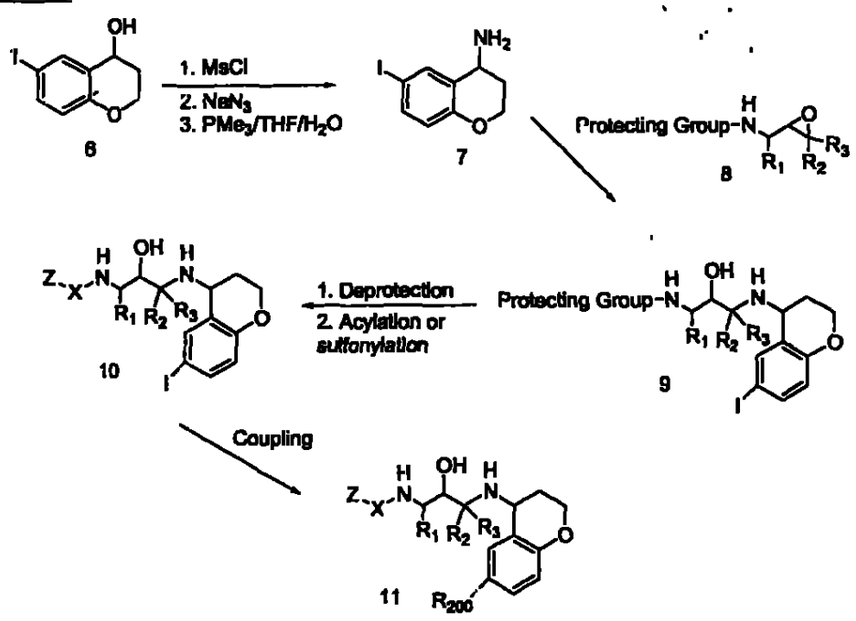
cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), haloalkanes (preferably dichloromethane), alkyl alcohols (preferably isopropyl alcohol or tert-butyl alcohol). Prefered reaction temperatures range from 0 °C to room temperature. The progress of the deprotection reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

The resulting amine may be treated with an acid to give the final product of general formula (5). The transformation may be effected utilizing an acid (or equivalent source) and a coupling reagent with or without a base and in an inert solvent. Coupling agents include, but are not limited to, DCC, EDC, HBTU, HATU, CDI, and PyBOP. Bases include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal alkoxides (preferably sodium ethoxide or sodium methoxide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylforamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes (preferably dichloromethane), alkyl alcohols (preferably methyl alcohol or ethyl alcohol), or water. Preferred reaction temperatures range from 0 °C to room temperature. The progress of the condensation reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

Alternately, the resulting amine may be treated with an activated acylating agent to give the final product of general formula (5). The transformation may be effected utilizing an active acylating agent and with or without a base and in an inert solvent. Active acylating agents include, but are not

limited to, acyl halides, acyl imidazoles, acyl anhydrides (symmetrical and unsymmetrical) and acyl oximes. Bases include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably sodium ethoxide or sodium methoxide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diether ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylforamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes (preferably dichloromethane), alkyl alcohols (preferably methyl alcohol or ethyl alcohol), or water. Preferred reaction temperatures range from 0 °C to room temperature. The progress of the condensation reaction is monitored by standard chromatographic and spectroscopic methods known to one skilled in the art of organic synthesis.

Scheme VI



Scheme VI

As described above and below, one aspect of the invention provides for compounds of formula (11) as shown above. These compounds may be made by methods known to those skilled in the art from starting compounds that are also known to those skilled in the art. The process chemistry is further well known to those skilled in the art. A suitable process for the preparation of compounds of formula (11) is set forth in Scheme VI above.

Scheme VI illustrates the preparation of the desired compounds using the readily obtainable 6-iodo-chroman-4-ol (6) as a starting material (see *Synthesis*, 1997, 23-25). One skilled in the art will recognize that there are several methods for the conversion of the alcohol functionality to the desired amino compounds of formula (7). In Scheme VI the alcohol (6) is first activated with methane sulfonyl chloride and the resulting mesylate displaced with sodium azide NaN_3. Alternative methods for the conversion of an alcohol to an azide are well known to one skilled in the art. The resulting

azide is subsequently reduced using trimthylphosphine in a mixture of THF and water. One skilled in the art will recognize that there are several methods for the reduction of an azide to the corresponding amine. For examples, see Larock, R.C. in *Comprehensive Organic Transformations*, Wiley-VCH Publishers, 1999. This reduction of the azide produces a mixture of enantiomers of the amine (7). This enantiomeric mixture can be separated by means known to those skilled in the art such as low temperature recrystallization of a chiral salt or by chiral preparative HPLC, most preferably by HPLC, employing commercially available chiral columns.

The resulting amine (7) is used to open the epoxide (8) to afford the protected (6-iodo-3,4-dihydro-2H-chromen-4-yl)amino propyl carbamate (9). Suitable reaction conditions for opening the epoxide (8) include running the reaction in a wide range of common and inert solvents. C_1-C_6 alcohol solvents are preferred and isopropyl alcohol most preferred. The reactions can be run at temperatures ranging from 20-25 °C up to the reflux temperature of the alcohol employed. The preferred temperature range for conducting the reaction is between 50°C and the refluxing temperature of the alcohol employed.

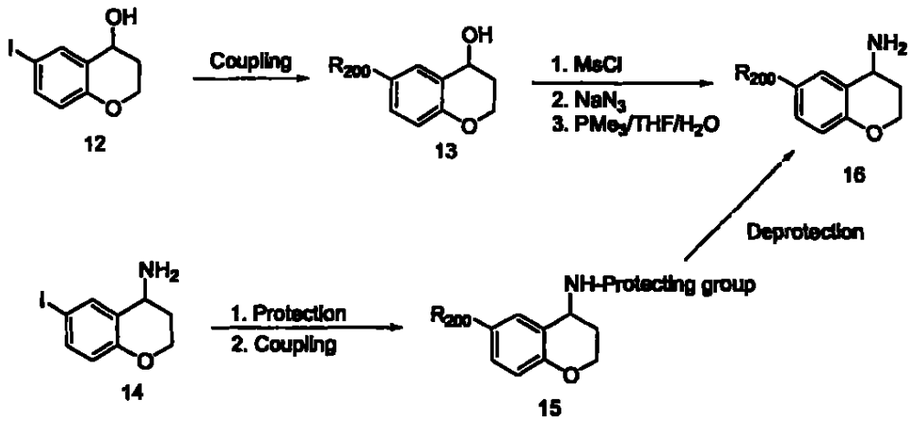
The protected iodo-chromen (9) is deprotected to the corresponding amine by means known to those skilled in the art for removal of amine protecting groups. Suitable means for removal of the amine protecting group depend on the nature of the protecting group. Those skilled in the art, knowing the nature of a specific protecting group, know which reagent is preferable for its removal. For example, it is preferred to remove the preferred protecting group, BOC, by dissolving the protected iodo-chroman in a trifluoroacetic acid/ dichloromethane (1/1) mixture. When complete the solvents are removed under reduced pressure to give the corresponding amine (as the corresponding salt, i.e. trifluoroacetic acid salt) which is used without further purification. However, if

desired, the amine can be purified further by means well known to those skilled in the art, such as for example recrystallization. Further, if the non-salt form is desired that also can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine via treatment of the salt with mild basic conditions. Additional BOC deprotection conditions and deprotection conditions for other protecting groups can be found in T. W. Green and P. G. M. Wuts in *Protecting Groups in Organic Chemistry*, 3rd edition, John 'Wiley and Sons, 1999.

The amine is then reacted with an appropriately substituted amide forming agent Z-(CO)-Y to produce coupled amides (10) by nitrogen acylation means known to those skilled in the art. Nitrogen acylation conditions for the reaction of amine with an amide forming agent Z-(CO)-Y are known to those skilled in the art and can be found in R.C. Larock in *Comprehensive Organic Transformations*, VCH Publishers, 1989, p. 981, 979, and 972. Y comprises -OH (carboxylic acid) or halide (acyl halide), preferably chlorine, imidazole (acyl imidazole), or a suitable group to produce a mixed anhydride.

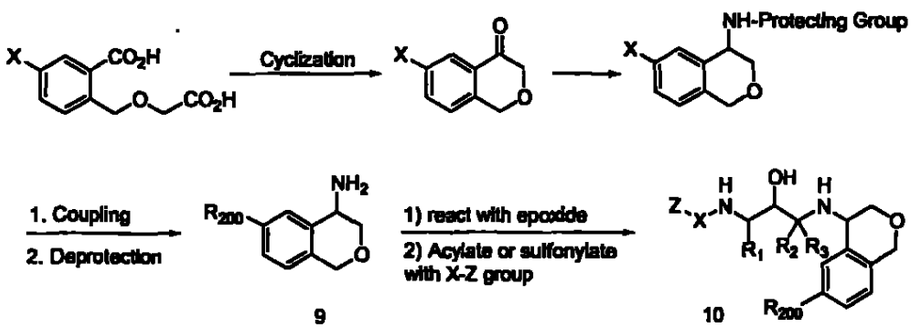
The acylated iodo-chromen (10) is coupled with an appropriately functionalzed organometallic $R_{200}M$ to afford compounds of formula (11) using conditions known to those skilled in the art. One skilled in the art will recognize that there are several methods for coupling various alkyl and aryl groups to an aromatic iodide. For examples, see L. S. Hegedus *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science, 1999.

Scheme VII



Scheme VII sets forth alternative routes to 4-aminochromanes, which are useful for preparing compounds of formula (11). Amines of formula (16) can be prepared by coupling the appropriately functionalized organometallic to 6-iodo-chroman-4-ol (12) or to the appropriately protected iodo-amino chroman of the formula (14). Further elaboration of the coupled products using methods known to one of skill in the art, ultimately yields the desired amines of formula (16). The chemistry from this point forward follows the generalizations described in Scheme VIII for converting compound 9 to 10.

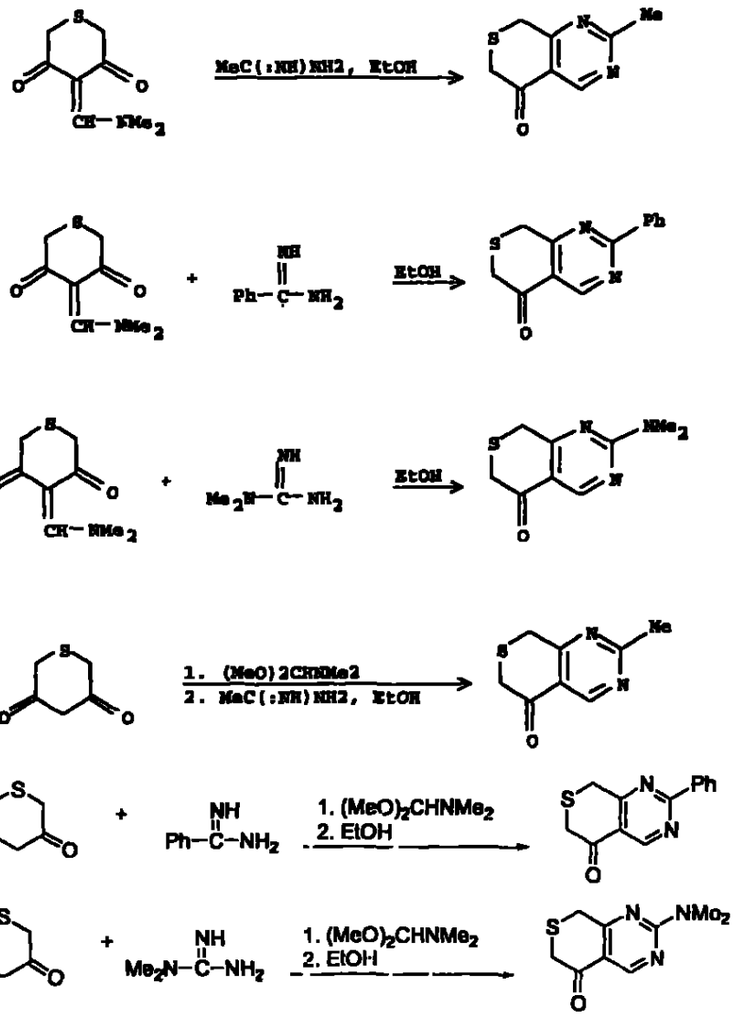
Scheme VIII



Scheme VIII illustrates another general preparation of amines of formula (9) that upon following the generalizations outlined in Schemes VI and VII will result in compounds of the

formula (10). From this point forward, the chemistry is essentially the same as described for Schemes VI and VII.

Scheme IX

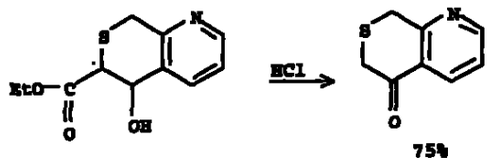


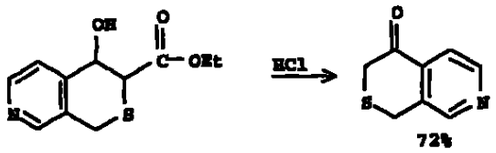
Scheme IX illustrates the synthesis of various 5H-thiopyranopyrimidinones from a variety of starting materials. Suitable reaction conditions are described in, for example, J. Heterocycl. Chem., 21(5), 1437-40; 1984.

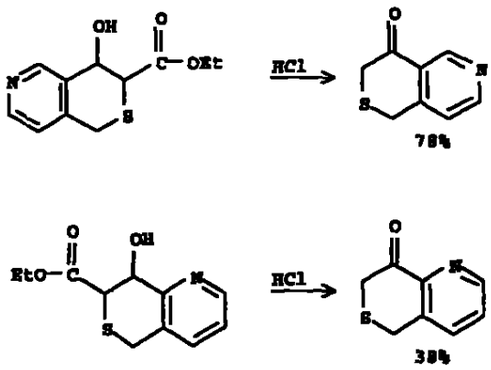
One of ordinary skill will appreciate that treating the sulfide with an oxidizing agent, such as parachlorobenzoic acid (MCPBA) or oxone, generates the sulfoxide or the sulfone. The oxidation of the sulfide can be done sequentially, i.e., generating and isolating the sulfoxide and then oxidizing it to the sulfone, or the sulfone can be generated directly from the sulfide. Further manipulations of the ketone are described in the application.

It is also understood that the pyrimidyl ring can be further substituted by means known in the art. For example, the pyridyl ring can be alkylated, halogenated, acylated, and/or nitrated. See Organic Transformations by Richard C. LaRock. All references are herein incorporated by reference in their entirety, for all purposes.

Scheme X





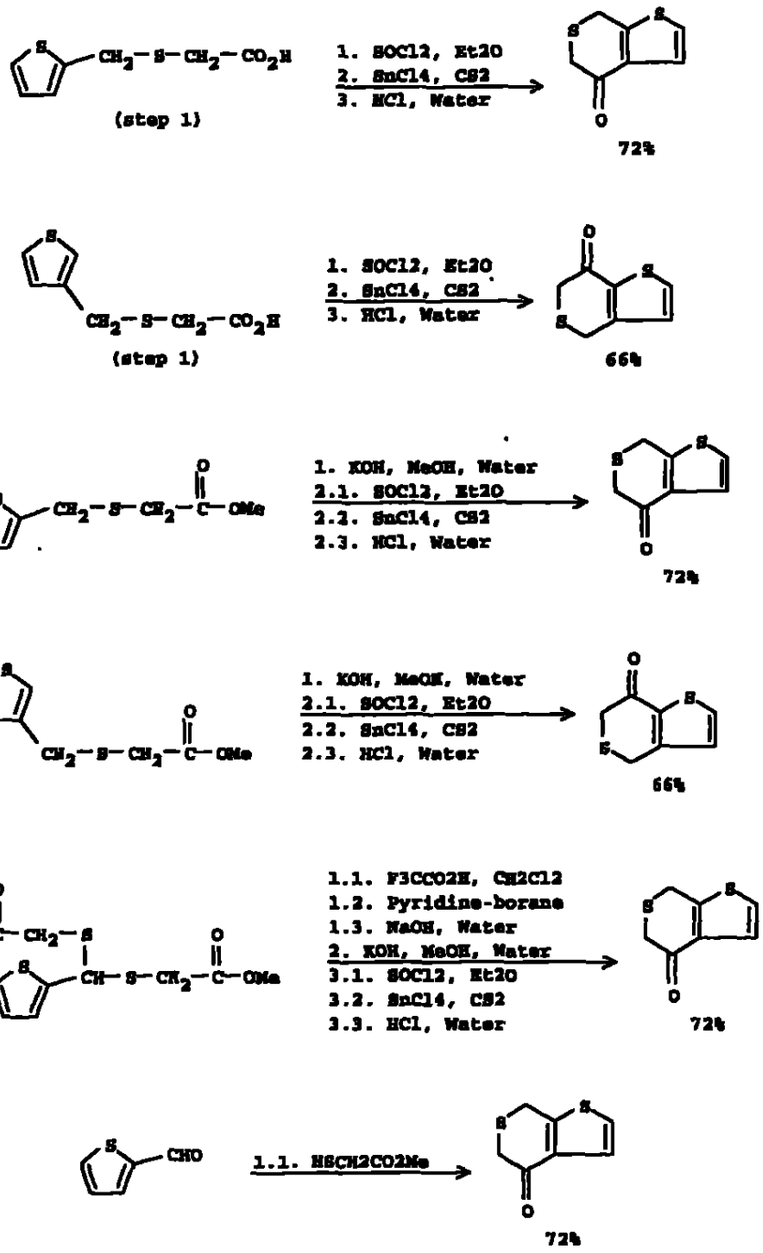


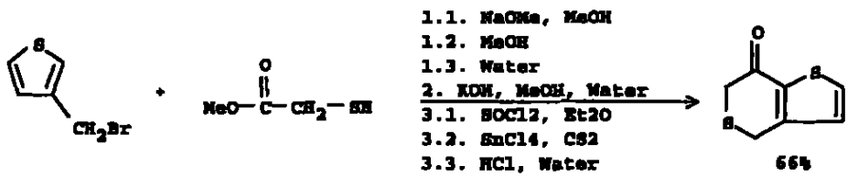
Scheme X illustrates the synthesis of various 1H-thiopyranopyridinones. Suitable reaction conditions are described in, for example, J. Chem. Soc., Perkin Trans. 1, (7), 1501-5; 1984

One of ordinary skill will appreciate that treating the sulfide with an oxidizing agent, such as parachlorobenzoic acid (MCPBA) or oxone, generates the sulfoxide or the sulfone. The oxidation of the sulfide can be done sequentially, i.e., generating and isolating the sulfoxide and then oxidizing it to the sulfone, or the sulfone can be generated directly from the sulfide. Further manipulations of the ketone are described in the application.

It is also understood that the pyridyl ring can be further substituted by means known in the art. For example, by way of illustration, the pyridyl ring can be alkylated, halogenated, acylated, and/or nitrated. See Organic Transformations by Richard C. LaRock.

Scheme XI


(step 1)
1. SOCl2, Et2O
2. SnCl4, CS2
3. HCl, Water
72%
(step 1)
1. SOCl2, Et2O
2. SnCl4, CS2
3. HCl, Water
66%
1. KOH, MeOH, Water
2.1. SOCl2, Et2O
2.2. SnCl4, CS2
2.3. HCl, Water
72%
1. KOH, MeOH, Water
2.1. SOCl2, Et2O
2.2. SnCl4, CS2
2.3. HCl, Water
66%
1.1. F3CCO2H, CH2Cl2
1.2. Pyridine-borane
1.3. NaOH, Water
2. KOH, MeOH, Water
3.1. SOCl2, Et2O
3.2. SnCl4, CS2
3.3. HCl, Water
72%
1.1. HSCH2CO2Me
72%





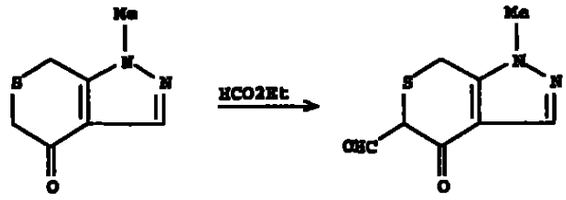
NOTE: 1) initially stirred with heating and then photochem.

Scheme XI illustrates the synthesis of various thienothiopyranones from a variety of starting materials. Suitable reaction conditions are described in, for example, Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry, (18), 2639-2644; 1999.

One of ordinary skill will appreciate that treating the sulfide with an oxidizing agent, such as parachlorobenzoic acid (MCPBA) or oxone, generates the sulfoxide or the sulfone. The oxidation of the sulfide can be done sequentially, i.e., generating and isolating the sulfoxide and then oxidizing it to the sulfone, or the sulfone can be generated directly from the sulfide. Further manipulations of the ketone are described in the application.

It is also understood that the thieno ring can be further substituted by means known in the art. For example, by way of illustration, the thieno ring can be alkylated, halogenated, acylated, and/or nitrated. See for example, Organic Transformations by Richard C. LaRock.

Scheme XII



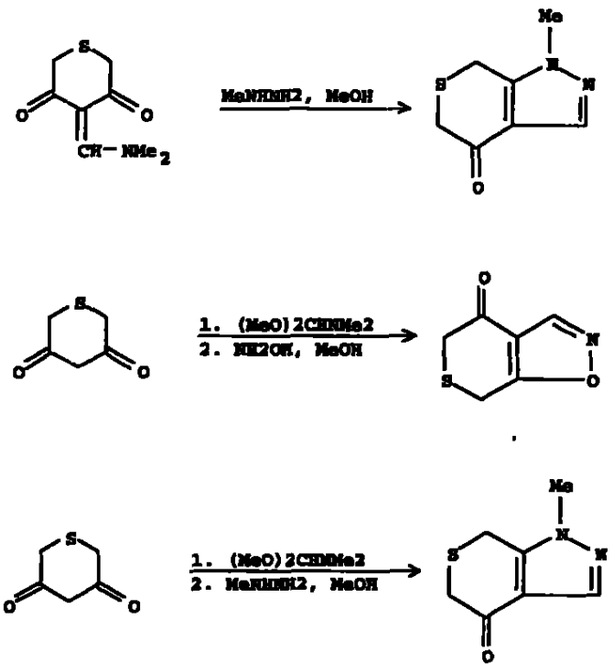
Scheme XII illustrates a method for introducing functionality into the sulfur containing ring. Suitable reaction conditions are described in, for example, U.S. Patent No. 4734431.

One of ordinary skill will appreciate that treating the sulfide with an oxidizing agent, such as parachlorobenzoic acid (MCPBA) or oxone, generates the sulfoxide or the sulfone. The oxidation of the sulfide can be done sequentially, i.e., generating and isolating the sulfoxide and then oxidizing it to the sulfone, or the sulfone can be generated directly from the sulfide. Further manipulations of the ketone are described in the application.

It is also understood that the pyrazole ring can be further substituted by means known in the art. For example, by way of illustration, the pyrazole ring can be alkylated, halogenated, and/or acylated. See for example, Organic Transformations by Richard C. LaRock.

Scheme XIII





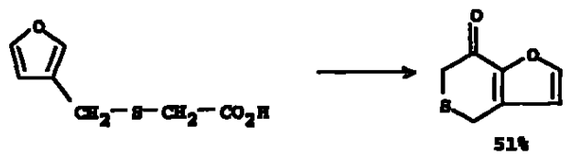
Scheme XIII illustrates the preparation of isoxazole and pyrazole containing bicyclic ring systems. Suitable reaction conditions are described in, for example, J. Heterocycl. Chem., 21(5), 1437-40; 1984. One of skill in the art will recognize that various reagents can be used to introduce functionality into the above ring systems. For example, substituted hydrazines are commercially available and can be used to prepare substituted pyrazoles. Furthermore, standard reactions such as alkylations and halogenations are known in the art.

One of ordinary skill will appreciate that treating the sulfide with an oxidizing agent, such as parachlorobenzoic acid (MCPBA) or oxone, generates the sulfoxide or the sulfone. The oxidation of the sulfide can be done sequentially, i.e., generating and isolating the sulfoxide and then oxidizing it to the sulfone, or the sulfone can be generated directly from

the sulfide. Further manipulations of the ketone are described in the application.

It is also understood that the pyrazole or isoxazole ring can be further substituted by means known in the art. For example, by way of illustration, the pyrazole and isoxazole rings can be alkylated, halogenated, and/or acylated. See for example, Organic Transformations by Richard C. LaRock.

Scheme XIV



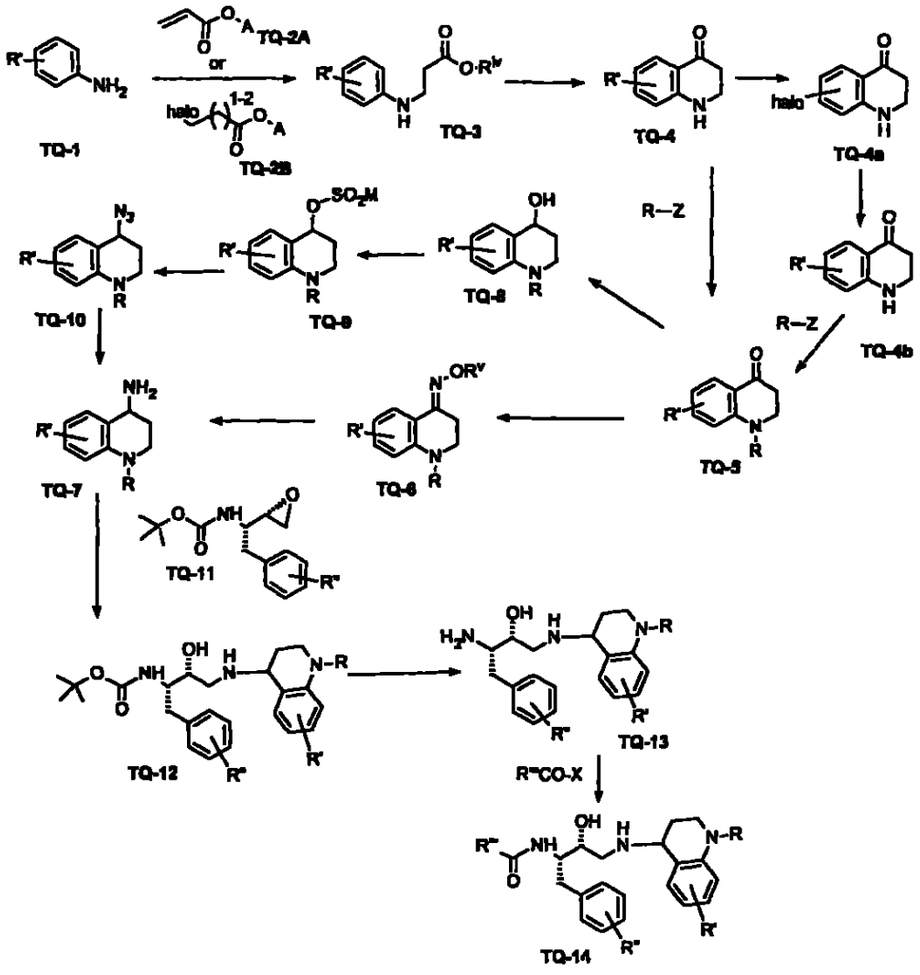
Scheme XIV illustrates the formation of a furan containing bicyclic ring system. Suitable reaction conditions are described in, for example, J. Heterocycl. Chem., 13(2), 365-7; 1976

One of ordinary skill will appreciate that treating the sulfide with an oxidizing agent, such as parachlorobenzoic acid (MCPBA) or oxone, generates the sulfoxide or the sulfone. The oxidation of the sulfide can be done sequentially, i.e., generating and isolating the sulfoxide and then oxidizing it to the sulfone, or the sulfone can be generated directly from the sulfide. Further manipulations of the ketone are described in the application.

It is also understood that the furyl ring can be further substituted by means known in the art. For example, by way of illustration, the furyl ring can be alkylated, halogenated, and/or acylated. See for example, Organic Transformations by Richard C. LaRock.

Scheme XV

The compounds of the invention that comprise tetrahydroquinoline moieties can be made by methods known in the art. The following general scheme can also be useful for tetrahydroquiniline compound synthesis.



Description of general synthetic scheme

Aniline TQ-1 is alkylated with a halide TQ-2B or acrylate TQ-2A to give TQ-3. TQ-3 is then treated with a strong acid or with a Lewis acid at temperatures ranging from 0 °C to 140 °C, preferably with phosphorus pentoxide and methanesulfonic acid at 130 °C, to give ketone TQ-4. The nitrogen of TQ-4 is

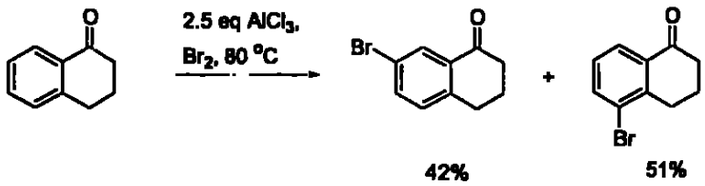
then either protected with a protecting group, many of which are listed in Protective Groups in Organic Synthesis, Greene and Wuts, 3rd edition, 1999, Wiley-Interscience, or is substituted with an alkyl group, an acyl group, or a sulfonyl group, using methods well known to those versed in the art, using R-Z, to give protected ketone TQ-5. An alternative preparation of TQ-5 starts with TQ-4 where R' is hydrogen. Halogenation with halogenating reagents such as N-bromosuccinimide, N-iodosuccinimide, dibromatin, and the like gives TQ-4a where R' is preferably bromine or iodine. Treatment of TQ-4a under cross coupling conditions such as those described by Negishi (Tet. Lett. 1983, 3823), Huo (Org. Lett. 2003, 423) and reviewed by Knochel (Tetrahedron 1998, 8275) provides TQ-4b where R' is alkyl. Further treatment of TQ-4b with R-Z as described above gives TQ-5.

Protected ketone TQ-5 is then converted to amine TQ-7 by several methods, the choice of which may depend on the nature of the R group. In the first method, TQ-5 is treated with a hydroxyl amine in the presence of a base and a catalytic amount of acid in solvents such as methanol, ethanol, butanol, and the like, at temperatures ranging from room temperature to the reflux temperature of the solvent, to give oxime TQ-6. TQ-6 is then reduced to amine TQ-7 using a suitable catalyst, preferably palladium, in solvents such as methanol, ethanol, or ethyl acetate, under a blanket of hydrogen at pressures ranging from atmospheric to 100 pounds per square inch. Alternatively, protected ketone TQ-5 is reduced to alcohol TQ-8 using reducing agents known to those well versed in the art, preferably and depending on the nature of group R using sodium borohydride in methanol or ethanol at temperatures ranging from 0 to 100 °C. Alcohol TQ-8 is then converted to sulfonate ester TQ-9 with reagents such as methanesulfonyl chloride or toluenesulfonyl chloride using methods known to those well-versed in the art. Displacement of the sulfonate ester with azide using, for example, sodium azide in solvents such as

dichloromethane and DMF at temperatures ranging from room temperature to 120 °C, gives azide TQ-10. Azide TQ-10 is then reduced to amine T-7 using, for example, trimethylphosphine in solvents such as THF and the like at temperatures between 0 °C to the reflux temperature of the solvent. Other methods of reduction of the azide group are known; the choice of reducing agent will depend on the nature of the R and R' groups and will be known to those well versed in the art and can be found in references such as Smith and March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th ed., 2001, Wiley-Interscience. Amine TQ-7 is then stirred in the presence of epoxide TQ-11 in preferably, but not limited to, alcoholic solvents such as ethanol, isopropropyl, tert-butyl, or n-butyl alcohol, at temperatures ranging from 50 °C to the reflux temperature of the solvent, to give Boc-amine TQ-12. Boc-amine TQ-12 is then treated with strong acid such as trifluoroacetic acid in non-reactive solvents such as dichloromethane or with dry HCl in solvents such as dialkyl ethers or alcoholic solvents at temperatures ranging from room temperature to 80 °C to give, after washing with base, triamine TQ-13. Triamine TQ-13 is acylated by means well-known to those versed in the art, for example condensation with a carboxylic acid using coupling agents such as EDC, DCC, HATU, or HBTU and the like. Preferred methods are acylation with acyl imidazole or acetylation with N, N-diacetylmethoxyamine to give TQ-14.

Experimental Procedures

Example 1: Preparation of 7-Bromo-1-tetralone

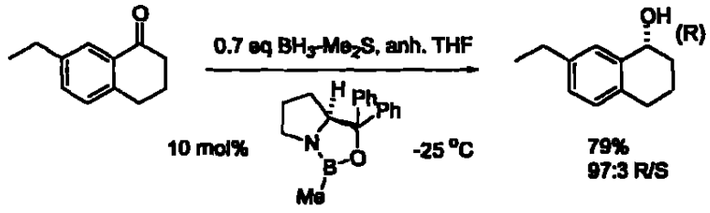


42% 51%

7-bromo-1-tetralone was prepared according to the procedure described in Cornelius, L. A.M.; Combs, D. W. *Synthetic Communications* 1994, *24*, 2777-2788. The above isomers were separated using silica gel flash chromatography (Biotage Flash 75, elution solvent 20/1 hexanes:MTBE) to yield 5-bromo-1-tetralone (11.59 g, 51%) and 7-bromo-1-tetralone (9.45 g, 42%).

Tetralin-1-ol compounds may be prepared as shown in Example 2 below. Mores specifically, (R)-7-ethyltetralin-1-ol was prepared in three steps starting from 7-ethyl-1-tetralone. The first step involves an asymmetric reduction of the ketone using borane and Corey's oxazaboralidine chiral auxilliary. This reduction produced a 97:3 mixture of (presumably) R/S enantiomers. A Mitsunobu-like S_n2 conversion to the azide and $LiAlH_4$ reduction to the amine produced material 98:2 S/R.

Example 2: Preparation of (R)-7-Ethyltetralin-1-ol

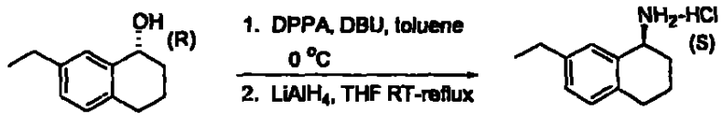


See generally: Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner-Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* 1991, *56*, 763-769. More particularly, 7-ethyl-1-tetralone (2.29 g, 13.1 mmol) was placed in a 100 mL round bottomed flask and dissolved in anhydrous THF (40 mL). Activated 4Å molecular sieves were added and the mixture was aged for 2 h before transferring via cannula to a 250 ml three-necked round bottom flask fitted with a dropping funnel, thermometer, and a nitrogen inlet. The solution was cooled to -25 °C and 1M (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrollo[1,2-c][1,3,2]oxazaborole in toluene (1.3 mL, 1.3 mmol) was added. The source of the oxazoborole was Aldrich, cat.

no. 45,770-1, "(S)-2-methyl-CBS-oxazaborolidine". Use of the S-auxilliary will produce R-alcohols. In accordance with the forging references, the use of 5 mol% oxazaborolidine catalyst should give comparable results.

The dropping funnel was charged with a solution of borane-methylsulfide (0.70 g, 0.87 mL, 9.3 mmol) in anhydrous THF (15 mL, dried over 4A sieves). The borane solution was added dropwise over 20 min keeping the reaction temperature less than -20 °C. The mixture was stirred for 1 h at -15 to -20 °C whereupon TLC analysis indicated consumption of the ketone. The reaction was quenched by careful addition of methanol (15 mL) at -20 °C and allowed to warm to ambient temperature and stir for 16 h. The volatiles were removed *in vacuo* and the residue was purified by silica gel chromatography (Biotage Flash 65, elution solvent 6/1 hexanes:ethyl acetate) to yield (R)-7-ethyltetralin-1-ol (1.82 g, 79%). Analytical chiral HPLC indicated a 96.6/3.4 mixture of enantiomers (Chirocel OD-H column, isocratic elution 2:98 IPA/hexane, 0.9 mL/min, RT 15.2 min (minor enantiomer), 17.5 min (major enantiomer).

Example 3: Preparation of (S)-7-Ethyl-1,2,3,4-tetrahydro-1-napthylamine hydrochloride



51%
98:2 S/R

See generally: Rover, S.; Adam, G.; Cesura, A. M.; Galley, G.; Jenck, F.; Monsma Jr., F. J.; Wichmann, J.; Dautzenberg, F. M. *J. Med. Chem.* **2000**, *43*, 1329-1338. The authors therein report a somewhat diminished yield due to partial formation of a dihydronapthalene via elimination of the hydroxyl moiety.

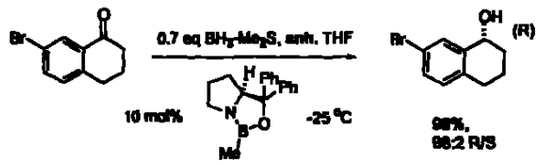
More specifically, a solution of (R)-7-ethyltetralin-1-ol (1.77 g, 10.1 mmol) in toluene (25 mL) was cooled in an ice bath and treated with diphenylphosphorylazide (DPPA, 3.3 g, 2.7 mL, 12 mmol). A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.8 g, 1.8 mL, 12 mmol) in toluene (8 mL) was added over 20 min and the mixture was allowed to stir at 0 °C for 2 h and ambient temp for 16 h. The mixture was filtered through a pad of silica gel (eluted 6:1 hexanes/ethyl acetate) to remove precipitates and the volatiles were removed *in vacuo* to give an oily residue of the crude S-azide. This material was used directly in the next step without further characterization.

The azide was dissolved in dry THF (20 mL) and added dropwise at RT to a slurry of lithium aluminum hydride (0.459 g, 12 mmol) in dry THF (20 mL). The mixture was stirred at RT for 1h and then heated to reflux for 1 h. The reaction was cooled to RT and quenched by successive addition of water (0.45 mL), 15% aq NaOH (0.45 mL) and water (1.4 mL). The resulting mixture was stirred for 1 h and then filtered through a pad of Celite (eluted diethyl ether). The volatiles were removed *in vacuo* and the residue taken up into ethyl acetate (40 mL) and treated with 4N HCl in dioxane (3 mL). The resulting precipitate was filtered (wash ethyl acetate), collected and vacuum dried to give (S)-7-ethyl-1,2,3,4-tetrahydro-1-napthylamine hydrochloride as a white solid (1.09 g, 51%). Analytical chiral HPLC indicated a 96:4 mixture of enantiomers (Daicel Crownpak (-) column, isocratic elution 10% methanol in water (0.1% TFA), 0.8 mL/min, RT 56.2 min (minor enantiomer), 78.2 min (major enantiomer).

Scheme VIII below depicts formation of a tetralinol, prepared in three steps starting from 7-bromo-1-tetralone. The first step involves an asymmetric reduction of the ketone using borane and Corey's oxazaboralidine chiral auxilliary. This reduction produced a 98:2 mixture of (presumably) R/S

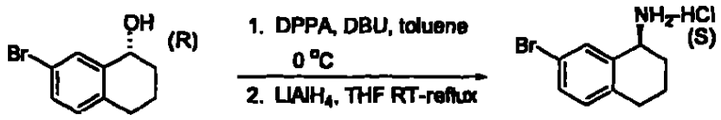
enantiomers. A Mitsunobu-like S_n2 conversion to the azide and $LiAlH_4$ reduction to the amine produced material 96:4 S/R.

Example 4: Preparation of (R)-7-Bromotetralin-1-ol



The reduction is performed using the general procedure described in example 2. Analytical chiral HPLC of the product indicated a 98:2 mixture of enantiomers (Chirocel OD-H column, isocratic elution 2:98 IPA/hexane, 0.9 mL/min, RT 18.4 min (minor enantiomer), 19.5 min (major enantiomer). Proton NMR was consistent with that previously reported for the racemate: Saito, M.; Kayama, Y.; Watanabe, T.; Fukushima, H.; Hara, T. *J. Med. Chem.* **1980**, *23*, 1364-1372.

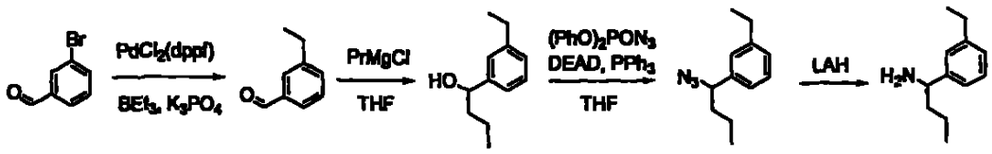
Example 5: Preparation of (S)-7-Bromo-1,2,3,4-tetrahydro-1-napthylamine hydrochloride



86%
96:4 S/R

The above compound is prepared essentially according to the procedure described in Example 3. The final compound is obtained as a white solid. Analytical chiral HPLC indicated a 96:4 mixture of enantiomers (Daicel Crownpak (-) column, isocratic elution 10% methanol in water (0.1% TFA), 0.8 mL/min, RT 39.4 min (minor enantiomer), 57.6 min (major enantiomer).

Example 6: Preparation of Precursor Substituted Amines



Precursore amines can generally be prepared as shown above. Specific examples are described below.

Example 7: Preparation of 3-Ethylbenzaldehyde from 3-bromobenzaldehyde

3-Bromobenzaldehyde (Aldrich, 1.17 mL, 10.0 mmol) was dissolved in THF (20 mL) at rt. To it was added $PdCl_2(dppf)\cdot CH_2Cl_2$ complex (Aldrich, 82 mg, 0.10 mmol), 2 M potassium phosphate (aq, 10 mL, 20 mmol), and triethylborane (Aldrich, 1.0 M solution in hexanes, 10 mL, 10 mmol). This was heated to reflux for 4 h, whereupon the mixture was allowed to cool to rt. The reaction mixture was partitioned between EtOAc and water. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes elution) to give a clear, colorless oil which was used without further purification: mass spec (CI) 135.1.

Example 8: Preparation of 3-Ethyl-α-propylbenzyl alcohol from 3-ethylbenzaldehyde

To a solution of 3-ethylbenzaldehyde (641 mg, 4.78 mmol) in THF (15 mL) cooled to 0 °C was added a solution of propylmagnesium chloride (Aldrich, 2.0 M in diethyl ether, 7.0 mL, 14.0 mmol) dropwise with stirring. Upon completion of addition, the reaction mixture was allowed to warm to rt for 2 h. Reaction was then quenched by addition of water (1 mL), then concentrated under reduced pressure. The residue was purified by flash chromatography (R_f = 0.71 in 30%

EtOAc/hexanes) to give a colorless oil as product (804 mg, 94%): mass spec (CI) 161.1 (M-OH).

Example 9: Preparatoin of 3-Ethyl-α-propylbenzyl azide from 3-ethyl-α-propylbenzyl alcohol

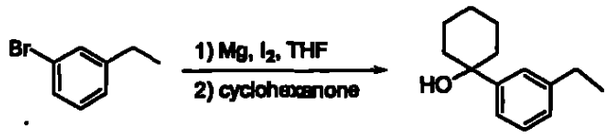
3-Ethyl-α-propylbenzyl alcohol (803 mg, 4.51 mmol) was dissolved in THF (10 mL), and cooled to 0 °C. Triphenylphosphine (Aldrich, 1.416 g, 5.40 mmol), diethyl azodicarboxylate (Aldrich, 0.85 mL, 5.40 mmol), and diphenyl phosphoryl azide (1.16 mL, 5.38 mmol) was added in succession by syringe. This was stirred at 0 °C for 1 ½ h, then at rt for 2 h, whereupon the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes elution) to give a clear, colorless oil as product: ^{1}H NMR (300 MHz) δ 7.35-7.25 (m, 1H), 7.20-7.05 (m, 2H), 4.39 (t, J = 7.2 Hz, 1H), 2.67 (q, J = 7.6 Hz, 2H), 1.95-1.60 (m, 2H), 1.52-1.25 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H).

Example 10: Preparation of 3-Ethyl-α-propylbenzyl amine from 3-ethyl-α-propylbenzyl azide

3-Ethyl-α-propylbenzyl azide (724 mg, 3.57 mmol) in dry THF (10 mL) was added to a suspension of lithium aluminum hydride (280 mg, 7.38 mmol) in THF (10 mL) at 0 °C. This was stirred at 0 °C for 30 min, then at rt for 1 h, whereupon the reaction was quenched using water (0.2 mL), 15% aq. NaOH (0.2 mL), and water (0.6 mL) in succession. This was stirred at rt for 1 h. The reaction mixture was then filtered through diatomaceous earth (CH_2Cl_2 elution), and the filtrate concentrated under reduced pressure. This material was used in subsequent reactions without further purification: ^{1}H NMR (300 MHz) δ 7.35-7.20 (m, 1H), 7.20-7.04 (m, 2H), 3.87 (t, J = 6.9

Hz, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.72-1.57 (m, 2H), 1.50-1.20 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H); mass spec (CI) 161.1 ($M-NH_3$).

Example 11: Preparation of 1-(3-Ethyl-phenyl)-cyclohexanol from 1-bromo-3-ethylbenzene



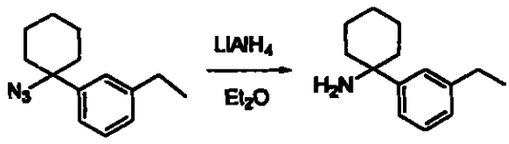
Magnesium turnings (1.35g, 55.53mmol) were activated via vigorous stirring overnight under N_2 (g) inlet. A few crystals of iodine were added to the flask, which was then flamed-dried under vacuum. Anhydrous THF (3 mL) was added to the reaction flask followed by 1-bromo-3-ethylbenzene (Avocado, 2.0mL, 14.59 mmol). The reaction was initiated after briefly heating with a heat gun. To this was added the remainder of 1-bromo-3-ethylbenzene (1.7mL, 12.43mmol) in a THF solution (15mL). The reaction mixture was refluxed for 2h. A cyclohexanone (2.2mL, 21.22mmol) in THF (8mL) solution was added once the flask was cooled to 0°C. After 3.5h the reaction mixture was quenched with H_2O over an ice bath and partitioned between Et_2O and H_2O. The organic layer was removed and acidified with 1N HCl. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (100% $CHCl_3$) to give the desired alcohol (4.152g, 96%): mass spec (CI) 187.1 (M-16).

Example 12: Preparatoin of 1-(1-Azido-cyclohexyl)-3-ethyl-benzene from 1-(3-Ethyl-phenyl)-cyclohexanol

1-(3-Ethyl-phenyl)-cyclohexanol (4.02g, 19.68mmol) in anhydrous chloroform (45mL) was cooled to 0°C under N_2 (g) inlet. Sodium azide (3.97g, 61.07mmol) was added followed by dropwise addition of trifluoroacetic acid (7.8mL, 101.25mmol).

The reaction mixture was refluxed for 2h and allowed to stir at rt o/n. This was then partitioned between H_2O and Et_2O. The aqueous layer was removed and the mixture was washed with H_2O followed by 1.0N NH_4OH. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was used without further purification (3.30g, 73%): mass spec (CI) 187.1 (M-42).

Example 13: Preparation of 1-(3-Ethyl-phenyl)-cyclohexylamine from 1-(1-azido-cyclohexyl)-3-ethyl-benzene



The above compound is prepared essentially according to the procedure described in Example 10. The final compound is used without further purification: mass spec (CI) 187.1 (M-16).

Example 14: Preparation of N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-7-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide.

Step 1: To 3.0 g (16.6 mmol) of methyl 5-ethyl-2-hydroxybenzoate in 100 mL of CH_2Cl_2 at 0 °C was added 5.8 mL (41.5 mmol, 2.5 eq.) of Et_3N. To this stirred solution was added dropwise 3.6 mL (21.6 mmol, 1.3 eq.) of Tf_2O. Following complete addition 0.2 g (cat.) of 4-dimethylamino pyridine was added and the reaction mixture was allowed to warm to room temperature. After 4 h stirring at this temperature the reaction was judged complete, and quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (100 mL). The resulting layers were separated and the aqueous layer extracted twice with CH_2Cl_2 (100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The resulting residue was purified by column chromatography to yield the desired methyl 5-ethyl-2-{[(trifluoromethyl)sulfonyl]oxy}benzoate. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 2.3 Hz, 1 H), 7.47 (dd, J = 2.3, 8.4 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 1 H), 4.00 (s, 3 H), 2.76 (q, J = 7.6 Hz, 2 H), 1.28 (t, J = 7.6 Hz, 3 H).

Step 2: To 1.5 g (4.8 mmol) of product from Step 1 in 12.5 mL of toluene at room temperature was added 0.28 g (0.24 mmol, 0.05 eq.) of $Pd(PPh_3)_4$. After stirring for 5 min, 1.1 g (5.7 mmol, 1.2 eq.) of 4-fluorophenylboronic acid in 5.5 mL of EtOH followed by 11.5 mL of 2 M aqueous Na_2CO_3 were added. After heating at 90 °C for 12 h the reaction was judged complete, cooled and diluted with Et_2O (100 mL) and water (50 mL). The resulting layers were separated and the aqueous layer extracted twice with Et_2O (100 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography to yield the desired methyl 4-ethyl-4'-fluoro-1,1'-biphenyl-2-carboxylate. $C_{16}H_{15}O_2F$+ H^+ requires 258 found 258..

Step 3: To 1.1 g (4.3 mmol) of the product from Step 2 in 50 mL of 2:2:1 THF:water:MeOH was added 0.9 g (21 mmol) of LiOH. The mixture was heated to 55 °C for 5 h at which point the reaction was judged complete. Upon cooling the volatiles were removed under reduced pressure and the residue portioned between 10% aqueous HCl (50 mL) and EtOAc (200 mL). The resulting layers were separated and the aqueous layer extracted twice with EtOAc (100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue, 4-ethyl-4'-fluoro-1,1'-biphenyl-2-carboxylic acid, was pure enough to use directly in the next step. $C_{15}H_{13}F_1O_2$ + H^+ requires 244, found 244.

Step 4: To 0.25 g (1 mmol) of product from Step 3 was added 1 mL of H_2SO_4 and the resulting mixture was heated to 110 °C for 20 min after which time the reaction was judged

complete. Upon cooling, the mixture was poured onto ice water (100 mL) and extracted twice with Et_2O (200 mL). The combined organic extracts were washed twice with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue, 2-ethyl-7-fluoro-9H-fluoren-9-one, was pure enough to use directly in the next step. $C_{15}H_{11}F_1O_1 + H^+$ requires 226, found 226.

Step 5: To 0.8 g (3.6 mmol) of the product from Step 4 was added 10 mL of EtOH and 3.2 mL of pyridine. To this stirred solution was added 1.0 g (14.6 mmol, 4 eq.) of $NH_2OH \cdot HCl$ and the mixture heated to 65 °C for 6 h after which time the reaction was judged complete. Upon cooling, the volatiles were removed under reduced pressure and the residue portioned between 10 % aqueous HCl (50 mL) and EtOAc (250 mL). The resulting layers were separated and the organic layers washed twice more with 10 % aqueous HCl (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue, (9Z)-2-ethyl-7-fluoro-9H-fluoren-9-one oxime, was pure enough to use directly in the next step. $C_{15}H_{12}F_1O_1N_1 + H^+$ requires 242, found 242.

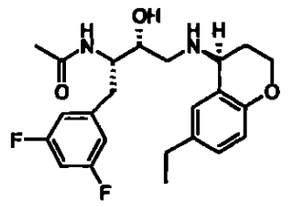
Step 6: To 0.8 g (3.3 mmol) of the product from Step 5 was added 3 mL of AcOH, 0.1 mL of water and 0.7 g (9.9 mmol, 3 eq.) of Zn. The resulting mixture was vigorously stirred for 20 min after which time the reaction was judged complete. After filtration to remove the solids the volatiles were removed under reduced pressure. The resulting residue was portioned between EtOAc (200 mL) and 10% aqueous KOH (100 mL). The resulting layers were separated and the organic layer washed once more with 10 % aqueous KOH (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue 2-ethyl-7-fluoro-9H-fluoren-9-aminewas pure enough to use directly in the next step. $C_{15}H_{14}F_1N_1 + H^+$ requires 227, found 211 ($-NH_3$)

Step 7: To 0.45 g (2.0 mmol) of the product of Step 6 was added 6 mL of isopropyl alcohol and 0.55 g (1.8 mmol, 0.9 eq.)

of Example 134. The mixture was heated at 65 °C for 12 h after which time the reaction was judged complete. Upon cooling, the volatiles were removed under reduced pressure. The resulting residue was purified by column chromatography to yield the desired tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-7-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropylcarbamate. $C_{30}H_{33}F_3N_2O_3$ + H^+ requires 527, found 527.

Steps 8&9: To 0.1 g (0.19 mmol) of product from Step 7 was added 3 mL of CH_2Cl_2 and 0.5 mL (excess) of TFA. The resulting mixture was stirred for 1 h at room temperature after which time the reaction was judged complete. The reaction mixture was diluted with toluene (2 mL) and the volatiles were removed under reduced pressure. After drying under high vacuum for 1 h, the residue was dissolved in 5 mL of CH_2Cl_2 and 0.061 mL (0.4 mmol, 2.2 eq.) of Et_3N followed by 0.02 g (0.2 mmol, 1.05 eq.) of acetyl-imidazole were added. After stirring for 12 h at room temperature the reaction was judged complete and poured in a saturated aqueous solution of $NaHCO_3$ (10 mL). The resulting layers were separated and the aqueous layer extracted once with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography to yield the desired N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-7-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide. $C_{27}H_{27}F_3N_2O_2$ + H^+ requires 469, found 469.

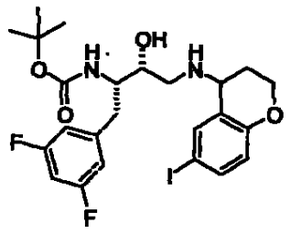
Example 15: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide



Step 1 Preparation of 6-Iodo-chroman-4-ylamine

To a CH_2Cl_2 (80 ml) solution of 6-iodo-4-chromanol (10.0 g, 36 mmol) and diisopropylethyl amine (19 ml, 108 mmol), at 0°C, was added the MsCl (4.2 ml, 54 mmol). After stirring for 1.5 h the solvent was removed *in vacuo* and the resulting residue dissolved in 150 ml of DMF followed by the addition of Na N_3 (3.5 g, 54 mmol). The reaction was heated to 70°C for 6.5 h then cooled to rt. followed by the addition of 900 ml 0f 1 N HCl and extraction with Et_2O (4 x 200 ml). The combined Et_2O layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield 9.5 g of the azide as yellow oil. MS (ESI+) for $C_9H_8IN_3O$ *m/z* 300.97 $(M+H)^+$. The crude azide (5.0 g, 16.6 mmol) was dissolved in THF (50 ml) and treated with PPh_3 (5.2 g, 20.0 mmol). The mixture stirred at rt. for 30 min. followed by the addition of 4 ml of H_2O. The mixture was then heated to 60°C overnight. After cooling the mixture was concentrated *in vacuo* and the resulting residue treated with 1 N HCl. The aqueous layer was washed with CH_2Cl_2 and then adjusted to pH = 12 with NaOH pellets. The basic aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried over Na_2SO_4 and treated with activated carbon. The mixture was filtered through Celite® and concentrated *in vacuo* to yield 6-Iodo-chroman-4-ylamine 3.6 g (79%) as clear oil that solidifies upon standing. MS (ESI+) for $C_9H_{10}INO$ *m/z* 275.98 $(M+H)^+$.

Step 2 Preparation of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propylcarbamate



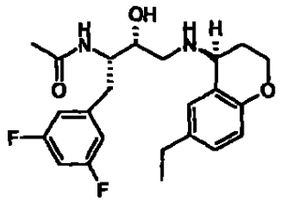
An isopropyl alcohol (25 ml) solution of Example 134 (2.2 g, 7.2 mmol) and 6-Iodo-chroman-4-ylamine (3.0 g, 10.9 mmol) was stirred at 75°C for 0 h. The IPA was removed in *vacuo* and the resulting residue dissolved in EtOAc (200 ml). The organic layer was washed with 1 N HCl (4 x 50 ml), followed by $NaHCO_3$ (2 x 50 ml), and brine (1 x 50 ml). The organic layer was dried over Na_2SO_4 and concentrated in *vacuo* to yield 3.5 g (85%) of the title compound as a mixture of diastereomers as an off white solid. MS (ESI+) for $C_{24}H_{29}F_2IN_2O_4$ *m/z* 574.8 $(M+H)^+$.

Step 3 Preparation of N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide

Tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propylcarbamate (3.0 g, 5.2 mmol) was dissolved in 30 mL of 25% TFA/CH_2Cl_2 and stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2 50 mL and washed with $NaHCO_3$ (2 x 30 mL). The organic layer was washed with brine (1 x 50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the resulting residue dissolved in 52 mL of CH_2Cl_2. The mixture was chilled to 0°C followed by the addition of Et_3N (1. mL, 11.9 mmol) and acetyl imidazole (0.68 g, 6.2 mmol). The mixture was warm spontaneously over night. The CH_2Cl_2 was removed *in vacuo* and the residue dissolved in EtOAc (100 mL) and washed with 1N HCl (2 x 30 mL), $NaHCO_3$ (1 x 30 mL), brine, dried over Na_2SO_4, and conc. *in vacuo* to yield 2.5 g (92%) of

the title compound as a light yellow solid. MS (ESI+) for $C_{21}H_{23}F_2IN_2O_3$ *m/z* 517.0 $(M+H)^+$.

Step 4 Preparation N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide



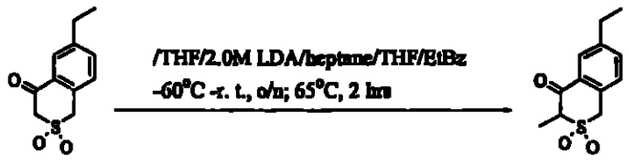
N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide (1.0 g, 1.9 mmol) and $Pd(dppf)Cl_2$ (0.078 g, 0.1 mmol) was dissolved in 20 mL of degassed THF. To the mixture was added 10 mL of 2.0 M K_3PO_4 followed by the addition of Et_3B (3.8 mL, 3.8 mmol, 1.0 M in THF) via syringe. The reaction mixture was heated to 65°C under a nitrogen atmosphere. After 2.5 h the reaction was determined to be complete and diluted with EtOAc (100 mL) and washed with brine (3 x 30 mL). The organic layer was dried over Na_2SO_4 and conc. *in vacuo* to yield brown solid. The diastereomers of the title compound were separated by preparative chiral HPLC (Chiralpak AD, 20% IPA/80%heptane, 0.1% DEA). MS (ESI+) for $C_{23}H_{26}F_2N_2O_3$ *m/z* 419 $(M+H)^+$.

The following compounds are prepared essentially according to the procedures described in the schemes and preparations set forth above:

Example 15 A	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide	MS (ESI+) for $C_{24}H_{30}F_2N_2O_3$ *m/z* 432.9 $(M+H)^+$
Example 15 B	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-3,4-	MS (ESI+) for $C_{25}H_{32}F_2N_2O_3$

	dihydro-2H-chromen-4-yl]amino}propyl)acetamide	*m/z* 447.4 $(M+H)^+$
Example 15 C	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide	MS (ESI+) for $C_{26}H_{34}F_2N_2O_3$ *m/z* 461.3 $(M+H)^+$
Example 15 D	N-[(1S,2R)-3-{[(4S)-6-cyano-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{22}H_{23}F_2N_3O_3$ *m/z* 416.4 $(M+H)^+$
Example 15 E	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1H-pyrrol-3-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{25}H_{27}F_2N_3O_3$ *m/z* 456.2 $(M+H)^+$
Example 15 F	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-2H-chromen-4-ylamino)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{21}H_{24}F_2N_2O_3$ *m/z* 391.3 $(M+H)^+$.

Example 16: Preparation of Representative Chroman Intermediates



To 0.9 g (4 mmole) of sulfone ketone in 40 ml of THF is added 2.5 ml (5 mmole, 1.25 eq.) of 2 M of Lithium diisopropylamine(LDA) in heptane/THF/ ethylbenzene at -60 °C. The mixture is stirred for about 15 minutes, and then 1.24 ml (20 mmole, 5 eq.) of methyl iodide is added. The reaction mixture is stirred for 1 hour at -60 °C, and then the cold bath is removed. After stirring overnight, the reaction mixture is partitioned between EtOAc and water, washed with 0.5N HCl, aqueous sodium bicarbonate solution, and brine, dried over

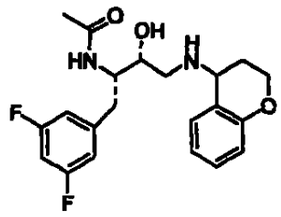
anhydrous sodium sulfate, filtered and concentrated. The concentrate was purified by column chromatography to afford 0.68 g of the desired product as an oil, which solidified upon standing. TLC (30%EtOAc/Hexane, Rf=0.39). Mass spec. m/e = 239.1.

The following compounds were prepared essentially according to the procedures described above:

Example 16 A	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-propionamide	(MS 481.1)
Example 16 B	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-(1H-imidazol-4-yl)-acetamide	(MS 533.1)
Example 16 C	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-methyl-2-methylamino-propionamide	(MS 524.1)
Example 16 D	{[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propylcarbamoyl]-methyl}-methyl-carbamic acid tert-butyl ester	(MS 596.1)
Example 16 E	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-phenyl-acetamide	(MS 543.1)
Example 16 F	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-butyramide	(MS 511.1)
Example 16 G	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-propionamide	(MS 497.1)
Example 16 H	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-2,2-dimethyl-propionamide	(MS 525.1)

Example 16 I	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-methyl-butyramide	(MS 509.1)
Example 16 J	2-Amino-N-[1-(3,5-difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-acetamide	(MS 482.1)
Example 16 K	N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-methylamino-acetamide	(MS 496.1).

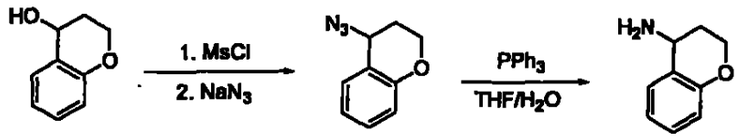
Example 17: N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-2H-chromen-4-ylamino)-2-hydroxypropyl]acetamide.



Step One: Chroman-4-ol.

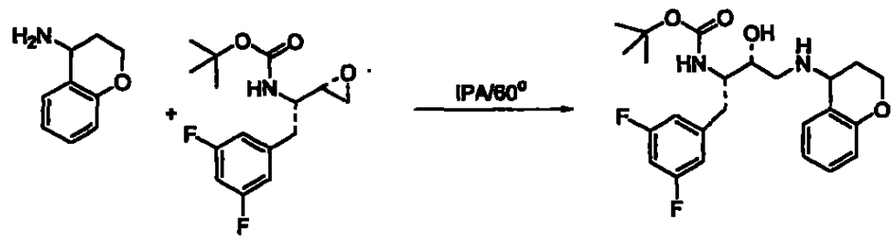
To a MeOH (250 ml) solution of 4-chromanone (16.6 g, 11 mmol), at 0°C, was added $NaBH_4$ (5.5 g, 145 mmol) in 1 g portions over a 30 min. period. After complete addition the mixture was stirred for 1 h with spontaneous warming. The reaction was quenched with the slow addition of aq. NH_4Cl (100 ml). The MeOH was removed *in vacuo* and the residue extracted with Et_2O (2 x 100 ml). The organic layers were dried over $MgSO_4$ and treated with activated carbon. After filtration the Et_2O was removed *in vacuo* to yield 15.8 g of chroman-4-ol as a clear oil. HRMS (ESI+) calcd for $C_9H_{10}O_2$ *m/z* 150.0681 $(M+H)^+$. Found 150.0679.

Step Two: 3,4-dihydro-2H-chromen-4-ylamine.



To a CH_2Cl_2 (80 ml) solution of chroman-4-ol (3.1 g, 20.6 mmol) and DIEA (8 ml, 42 mmol), at 0°C, was added the MsCl (2.1 ml, 27 mmol) via syringe. After complete addition the cold bath was removed and stirring continued at room temperature. After 15 h the CH_2Cl_2 was removed *in vacuo* and the residue dissolved in 80 ml of DMF followed by the addition of NaN_3 (1.8 g, 27 mmol). The mixture was heated to 75°C (oil bath) for 5h then cooled to room temperature. The mixture was diluted with Et_2O (400 ml) and washed with 1 N HCl (2 x 100 ml); $NaHCO_3$ (2 x 100 ml) and brine (100 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield the azide as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (m, 2 H), 6.97-6.87 (m, 2 H), 4.61 (appt, J = 3.84 Hz, 1 H), 4.31-4.19 (m, 2 H), 2.18 (m, 1 H), 2.03 (m, 1 H). MS (ESI-) for $C_9H_{10}N_3O$ *m/z* 173.0 $(M-H)^-$. The crude azide was dissolved in 60 ml of THF followed by the addition of PPh_3 (6.5 g, 25 mmol) and the mixture stirred at room temperature for 30 min. The mixture was treated with 8 ml of H_2O and heated to 60°C (oil bath) overnight. The mixture was concentrated *in vacuo* and the resulting residue treated with 1 N HCl. The aqueous mixture was extracted with CH_2Cl_2 then the pH was adjusted to 12 with NaOH and re-extracted with CH_2Cl_2. The second CH_2Cl_2 layers were combined; dried over Na_2SO_4 and concentrated *in vacuo* to yield 3,4-dihydro-2H-chromen-4-ylamine as a slightly yellow oil. HRMS (ESI+) calcd for $C_9H_{11}NO$ *m/z* 150.0919 $(M+H)^+$. Found 150.0920.

Step Three: tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-2H-chromen-4-ylamino)-2-hydroxypropylcarbamate.



An IPA (15 ml) solution of Example 134 (0.54 g, 1.8 mmol) and 3,4-dihydro-2H-chromen-4-ylamine (0.40 g, 2.6 mmol) was heated at 60°C (oil bath) with stirring overnight. The IPA was removed *in vacuo* and the residue dissolved in EtOAc and washed with 1 N HCl. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield 0.75 g of the desired product as a mixture of epimers. HRMS (ESI+) calcd for $C_{24}H_{30}N_2O_4F_2$ *m/z* 449.2252 $(M+H)^+$. Found 449.2258.

Step Four: N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-2H-chromen-4-ylamino)-2-hydroxypropyl]acetamide.

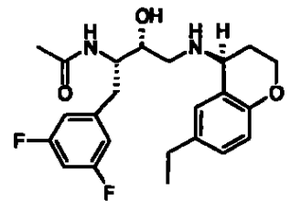
The above compound, which is obtained as a clear glass, is prepared essentially according to the procedure described in Example 15, step 3. Preparative reverse phase HPLC yields two fractions:

^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 1 H), 7.20 (m, 1 H), 6.92 (m, 1 H), 6.85 (dd, *J* = 6.85, 0.93 Hz, 1 H), 6.79-6.67 (m, 3 H), 5.69 (d, *J* = 8.91 Hz, 1 H), 4.35-4.23 (m, 2 H), 4.15 (m, 1 H), 3.87 (m, 1 H), 3.58 (m, 1 H), 3.03 (m, 1 H), 2.91-2.75 (m, 3 H), 2.15-2.08 (m, 1 H), 2.04-1.99 (m, 1H), 1.94 (s, 3 H). MS (ESI+) for $C_{21}H_{24}F_2N_2O_3$ *m/z* 391.3 $(M+H)^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 1 H), 7.21 (m, 1 H), 6.93 (m, 1 H), 6.86 (dd, *J* = 8.29, 1.04 Hz, 1 H), 6.79-6.67 (m, 3 H), 5.69 (d, *J* = 8.91 Hz, 1 H), 4.36-4.24 (m, 2 H), 4.17 (m, 1 H), 3.87 (appt, *J* = 4.04 Hz, 1 H), 3.54 (m, 1 H), 3.03 (dd, *J* = 14.31, 4.56 Hz, 1 H), 2.95 (m, 1 H), 2.88-2.79 (m, 2

H), 2.16-2.00 (m, 2 H), 1.92 (s, 3 H). MS (ESI+) for $C_{21}H_{24}F_2N_2O_3$ *m/z* 391.3 $(M+H)^+$.

Example 18: N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide:



Step One: 6-iodochroman-4-olTo a solution of chroman-4-ol (19.6g, 131 mmol) in CH_2Cl_2 (500 mL), at rt., was added HgO (29.7g, 137 mmol) and I_2 (34.8g, 137 mmol) under N_2. After stirring for 48 h. the mixture was filtered through a plug of silica gel and the plug washed plug with 30% EtOAc/Hexanes. The filtrate was washed with 15% $Na_2S_2O_3$ and the organic layer was dried over Na_2CO_3; filtered and concentrated *in vacuo*, yielding 6-iodochroman-4-ol as an off-white solid (32.44g, 90% crude yield). Recrystallization was performed by dissolving product in hot dichloromethane (250 mL) and slowly adding petroleum ether (250 mL). Overall yield 25.9g, 72% yield. Anal. Calcd for $C_9H_9IO_2$; C, 39.16, H, 3.29; found C, 39.26, H, 3.27.

Step Two: 6-Iodo-chroman-4-ylamine.

The above compound is prepared essentially according to the procedure described in Example 17, step 2. The above compound is obtained as a clear oil that solidifies upon standing. HRMS (ESI+) calcd for $C_9H_{10}INO$ *m/z* 275.9887 $(M+H)^+$. Found 275.9893.

Step Three: tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propylcarbamate

The above compound is prepared essentially according to the procedure described in Example 15, step 2; it is obtained as a mixture of diastereomers, which is used without purification.. MS (ESI+) for $C_{24}H_{29}F_2IN_2O_4$ *m/z* 574.8 $(M+H)^+$.

Step Four: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide

The title compound is obtained from the propylcarbamate, essentially according to the methods described herein, as a light yellow solid. MS (ESI+) for $C_{21}H_{23}F_2IN_2O_3$ *m/z* 517.0 $(M+H)^+$. Chiral preparative HPLC (20% IPA/Heptane, 0.1% DEA) yields the two diastereomers.

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, *J* = 9.12 Hz, 1 H), 7.62 (d, *J* = 2.07 Hz, 1 H), 7.40 (dd, *J* = 8.50, 2.28 Hz, 1 H), 7.01 (m, 1 H), 6.89 (m, 2 H), 6.58 (d, *J* = 8.50 Hz, 1 H), 4.97 (d, *J* = 6.01 Hz, 1 H), 4.23 (m, 1 H), 4.14 (m, 1 H), 3.93 (m, 1 H), 3.68 (m, 1 H), 3.47 (m, 1 H), 3.01 (dd, *J* = 13.89, 3.32 Hz, 1 H), 2.61 (m, 2 H), 1.90 (m, 2 H), 1.71 (s, 3 H).

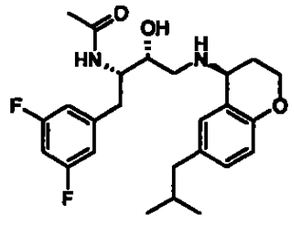
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4R)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 9.33 Hz, 1 H), 7.64 (d, *J* = 2.07 Hz, 1 H), 7.41 (dd, *J* = 8.60, 2.18 Hz, 1 H), 7.02 (m, 1 H), 6.92 (m, 2 H), 6.59 (d, *J* = 8.50 Hz, 1 H), 4.96 (d, *J* = 5.80 Hz, 1 H), 4.22 (m, 1 H), 4.15 (m, 1 H), 3.95 (m, 1 H), 3.68 (m, 1 H), 3.45 (m, 1 H), 2.98 (dd, *J* = 13.99, 2.80 Hz, 1 H), 2.73 (m, 1 H), 2.63-2.57 (m, 1 H), 1.87 (m, 2 H), 1.70 (s, 3 H).

Step Five: N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide (1.0 g, 1.9 mmol) and $Pd(dppf)Cl_2$ (0.078 g, 0.1 mmol) was dissolved in 20 mL of degassed THF. To the mixture was added 10 mL of 2.0 M K_3PO_4 followed by the addition of Et_3B (3.8 mL, 3.8 mmol, 1.0 M in THF) via syringe. The reaction mixture was heated to 65°C under a nitrogen atmosphere. After 2.5 h the reaction was determined to be complete and diluted with EtOAc (100 mL) and washed with brine (3 x 30 mL). The organic layer was dried over Na_2SO_4 and conc. *in vacuo* to yield brown solid. The diastereomers of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide were separated by preparative chiral HPLC (Chiralpak AD, 20% IPA/80%heptane, 0.1% DEA). MS (ESI+) for $C_{23}H_{26}F_2N_2O_3$ *m/z* 419 $(M+H)^+$.

To a MTBE (20 ml), CH_2Cl_2 (5 ml), MeOH (0.5 ml) solution of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide (0.2 g, 0.5 mmol) was added 1N HCl in Et_2O (0.38 ml) and the mixture stirred at room temperature. The final white solid was isolated by removing the solvent and tritration with Et_2O. HRMS (ESI+) calcd for $C_{23}H_{28}F_2N_2O_3$ *m/z* 419.2146 $(M+H)^+$. Found 419.2166.

Example 19: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



Step One: (4R)-6-iodochroman-4-ol

The above compound is prepared essentially according to the procedure described in Example 18, step1. Chiral HPLC separation is performed at this stage. HRMS (EI) calcd for $C_9H_9IO_2$ 275.9649, found 275.9646. (4S)-6-iodochroman-4-ol $[\alpha]^{20}_D$ = +13 (20 mg, MeOH) (4R)-6-iodochroman-4-ol $[\alpha]^{20}_D$ = -13 (20 mg, MeOH).

Step Two: (4S)-6-iodochroman-4-amine

To a solution of (4R)-6-iodochroman-4-ol (6.85 g, 24.81 mmol) and toluene (100 mL) under nitrogen at 0°C was added diphenylphosphoryl azide (6.42 mL, 29.76 mmol). To this mixture was added a chilled solution of DBU (4.45 mL, 29.76 mmol) as a toluene solution (25 mL) via syringe. Reaction mixture was allowed to warm to ambient temperature overnight. Azide solution was filtered through silica gel using 6:1 hexanes:EtOAc as eluant. Filtrate was concentrated in vacuo, then dissolved in anh. THF (100 mL) to which was added 1.0M Me_3P in THF (29.76 mL, 29.76 mmol). After 1h, deionized H_2O (5 mL) was added and reaction mixture was stirred overnight under nitrogen. Concentrated in vacuo, dissolved in EtOAc, washed with 10% $NaHCO_3$, brine, then the organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give (4S)-6-iodochroman-4-amine as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 2 H), 1.86 (m, 1 H), 2.13 (m, 1 H), 4.03 (t, J = 5 Hz, 1 H), 4.23 (m, 2 H), 6.60 (d, J = 9 Hz, 1 H), 7.42 (d, J = 9 Hz, 1 H), 7.64 (s, 1 H). MS (ESI+) for $C_9H_{10}INO$ *m/z* 258.8 $(M+H)^+$.

Step Three: *tert*-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.

The above compound was prepared essentially according to the method of Example 17, step 3. The crude product was purified via column chromatography using 3% MeOH/DCM as eluant. The desired compound was obtained as a colorless solid (6.89 g, 79%). HRMS (ESI); calcd for $C_{24}H_{29}N_2O_4IF_2$+H1 575.1220, found 575.1194; Specific Rotation (25 C D) = 30 (c = 1.04) MeOH.

Step Four: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.

The title compound is prepared using procedures described herein, and isolated as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3 H), 1.97 (m, 1 H), 2.08 (m, 1 H), 2.80 (m, 3 H), 3.09 (dd, *J* = 4, 14 Hz, 1 H), 3.55 (m, 1 H), 3.84 (m, 1 H), 4.13 (m, 1 H), 4.24 (m, 1 H), 4.31 (m, 1 H), 5.61 (m, 1 H), 6.62 (d, *J* = 9 Hz, 1 H), 6.70 (m, 1 H), 6.77 (d, *J* = 6 Hz, 2 H), 7.44 (dd, *J* = 2, 9 Hz, 1 H), 7.62 (s, 1 H).

Step Five: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.

To a solution of the product from step 4, (0.300 g, 0.58 mmol) and anh. THF (2.3 mL) was added $Pd(dppf)Cl_2$ (0.024 g, 0.03 mmol) under nitrogen with stirring. To this solution was added isobutylzinc bromide (9.2 mL of a 0.5M THF solution, 4.6 mmol) and reaction mixture was stirred overnight. Quenched with methanol, then added Dowex 50WX2-400 resin (used an excess, 4.6 meq/g). Filtered through a frit, washed resin with methanol. The alkylated material was released from the resin using 7N NH_3/MeOH. The filtrate was concentrated *in vacuo* and then purified via preparative HPLC to yield a colorless solid fully characterized as the HCl salt.

To a MeOH (10 ml) solution of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide (2.0 g, 4.5 mmol), at 0°C, was added 3 equiv. of HCl as a solution in MeOH. Results in 1.97 g of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide · hydrochloride as a white powder after tritration with CH_2Cl_2. HRMS (ESI+) calcd for $C_{25}H_{32}F_2N_2O_3$ *m/z* 447.2459 $(M+H)^+$. Found 447.2440. Anal calcd for $C_{25}H_{32}F_2N_2O_3 \cdot HCl$; C, 62.17; H, 6.89; N, 5.80; found C, 62.68; H, 7.05; N, 5.75.

Examples 20-50: General Procedure for Negishi Coupling to 6-Substituted Chromans:

To a solution of the product of Example 19, step 4 (0.300 g, 0.58 mmol) and anh. THF (2.3 mL) was added $Pd(dppf)Cl_2$ (0.024 g, 0.03 mmol) under nitrogen with stirring. To this solution was added the zinc bromide reagent (9.2 mL of a 0.5M THF solution, 4.6 mmol) and reaction mixture was stirred overnight. Quenched with methanol, then added Dowex 50WX2-400 resin (used an excess, 4.6 meq/g). Filtered through a frit, washed resin with methanol to remove impurities. Product was released from resin using 7N NH_3/MeOH. Filtrate was concentrated in vacuo and then purified via preparative HPLC. Final product was a colorless solid.

Example 20	N-[(1S,2R)-3-{[(4S)-6-(2-cyanophenyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{28}H_{27}F_2N_3O_3$ *m/z* 492.2205 $(M+H)^+$.
Example 21	N-[(1S,2R)-3-{[(4S)-6-(4-cyanophenyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{28}H_{27}F_2N_3O_3$ *m/z* 492.3219 $(M+H)^+$.

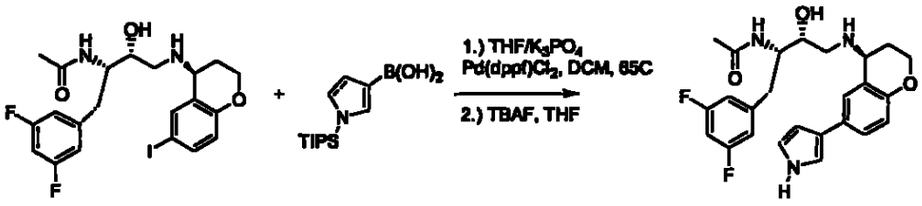
	.	$(M+H)^+$. .
Example 22	N-[(1S,2R)-3-{[(4S)-6-sec-butyl-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{25}H_{32}F_2N_2O_3$ m/z 447.316 $(M+H)^+$.
Example 23	N-[(1S,2R)-3-{[(4S)-6-cyclopentyl-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{26}H_{32}F_2N_2O_3$ m/z 459.3178 $(M+H)^+$.
Example 24	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-(1,1-dimethylpropyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide	MS (ESI+) for $C_{26}H_{34}F_2N_2O_3$ m/z 461.2516 $(M+H)^+$.
Example 25	N-[(1S,2R)-3-{[(4S)-6-cyclohexyl-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{27}H_{34}F_2N_2O_3$ m/z 473.3156 $(M+H)^+$.
Example 26	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(3-methylbutyl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{26}H_{34}F_2N_2O_3$ m/z 461.3249 $(M+H)^+$.
Example 27	N-[(1S,2R)-3-{[(4S)-6-(2-cyanobenzyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{29}H_{29}F_2N_3O_3$ m/z 506.2569 $(M+H)^+$.
Example 28	N-[(1S,2R)-3-{[(4S)-6-(4-cyanobenzyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{29}H_{29}F_2N_3O_3$ m/z 506.2145 $(M+H)^+$.
Example 29	N-[(1S,2R)-3-({(4S)-6-[(1S,4R)-bicyclo[2.2.1]hept-2-yl]-3,4-dihydro-2H-chromen-4-yl}amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{28}H_{34}F_2N_2O_3$ m/z 485.3293 $(M+H)^+$.

Example 30	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1-methylbutyl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{26}H_{34}F_2N_2O_3$ m/z 461.3311 $(M+H)^+$.
Example 31	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1-methylpentyl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{27}H_{36}F_2N_2O_3$ m/z 475.3686 $(M+H)^+$.
Example 32	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-(1-ethylpropyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide	MS (ESI+) for $C_{26}H_{34}F_2N_2O_3$ m/z 461.3334 $(M+H)^+$.
Example 33	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-(1-ethylbutyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide	MS (ESI+) for $C_{27}H_{36}F_2N_2O_3$ m/z 475.3723 $(M+H)^+$.
Example 34	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1-propylbutyl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{28}H_{38}F_2N_2O_3$ m/z 489.2886 $(M+H)^+$.
Example 35	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-(2-ethylbutyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide	MS (ESI+) for $C_{27}H_{36}F_2N_2O_3$ m/z 475.334 $(M+H)^+$.
Example 36	N-[(1S,2R)-3-{[(4S)-6-(cyclohexylmethyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{28}H_{36}F_2N_2O_3$ m/z 487.4099 $(M+H)^+$.
Example 37	N-[(1S,2R)-3-{[(4S)-6-(5-cyano-5-methylhexyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{29}H_{37}F_2N_3O_3$ m/z 514.1028 $(M+H)^+$.
Example	N-((1S,2R)-1-(3,5-	MS (ESI+) for

38	difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(4-methoxyphenyl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	$C_{28}H_{30}F_2N_2O_4$ m/z 497.2083 $(M+H)^+$.
Example 39	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(6-methylpyridin-2-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{27}H_{29}F_2N_3O_3$ m/z 482.3209 $(M+H)^+$.
Example 40	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(5-methylpyridin-2-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{27}H_{29}F_2N_3O_3$ m/z 482.2673 $(M+H)^+$.
Example 41	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(4-methylpyridin-2-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{27}H_{29}F_2N_3O_3$ m/z 482.3107 $(M+H)^+$.
Example 42	N-[(1S,2R)-3-{[(4S)-6-(4-cyanobutyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{26}H_{31}F_2N_3O_3$ m/z 472.2164 $(M+H)^+$.
Example 43	N-[(1S,2R)-3-{[(4S)-6-(6-cyanohexyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{28}H_{35}F_2N_3O_3$ m/z 500.2705 $(M+H)^+$.
Example 44	N-[(1S,2R)-3-{[(4S)-6-(3-cyanophenyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{28}H_{27}F_2N_3O_3$ m/z 492.1755 $(M+H)^+$.
Example 45	(2S)-3-((4S)-4-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3,4-dihydro-2H-chromen-6-yl)-2-Methylpropanoate	MS (ESI+) for $C_{26}H_{32}F_2N_2O_5$ m/z 491.3261 $(M+H)^+$.
Example	N-((1S,2R)-1-(3,5-	MS (ESI+) for

46	difluorobenzyl)-3-{[(4S)-6-(4-fluorophenyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide	$C_{27}H_{27}F_3N_2O_3$ *m/z* 485.3275 $(M+H)^+$.
Example 47	methyl (2R)-3-((4S)-4-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3,4-dihydro-2H-chromen-6-yl)-2-Methylpropanoate	MS (ESI+) for $C_{26}H_{32}F_2N_2O_5$ *m/z* 491.2724 $(M+H)^+$.
Example 48	N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({(4S)-6-[2-(1,3-dioxolan-2-yl)ethyl]-3,4-dihydro-2H-chromen-4-yl}amino)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{26}H_{32}F_2N_2O_5$ *m/z* 491.2323 $(M+H)^+$.
Example 49	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(6-methoxypyridin-2-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide	MS (ESI+) for $C_{27}H_{29}F_2N_3O_4$ *m/z* 498.3047 $(M+H)^+$.
Example 50	N-[(1S,2R)-3-{[(4S)-6-cyano-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	MS (ESI+) for $C_{22}H_{23}F_2N_3O_3$ *m/z* 416.4 $(M+H)^+$.

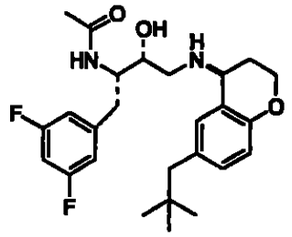
Example 51: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1H-pyrrol-3-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



To a solution of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide (0.300 g, 0.58 mmol) and anhydrous THF (5 mL) was added $Pd(dppf)Cl_2$ (0.030 g, 0.03 mmol) and K_3PO_4

(2.9 mL, 5.80 mmol). To this mixture was added boronic acid (0.310 g, 1.16 mmol) (*J. Org. Chem.* 1992, *57*, 1653) and the reaction mixture was heated to 65° C overnight under nitrogen with stirring. Reaction was quenched with deionized water and then extracted with ethyl acetate. Organic layers were washed with brine, then dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The TIPS-protected compound (0.100 g, 0.16 mmol) was dissolved in THF (3 mL) and then 0.1M solution of TBAF in THF (0.32 mL, 0.32 mmol) was added. Reaction mixture was stirred for 2 h, then concentrated in vacuo. Dissolved in ethyl acetate, filtered through silica gel plug, then concentrated *in vacuo* to give the desired product as an amber oil (130 mg), which is purified by reverse phase prep-HPLC. HRMS (ESI); calcd for C25H27N3O3F2 + H1 456.2099, found 456.2092.

Example 52: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



Step One: 6-neopentylchroman-4-ol.

To a solution of 6-iodochroman-4-ol (1.0 g, 3.6 mmol) in 18 ml of THF, at 0°C, was added the $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.15 g, 0.18 mmol), followed by neopentylmagnesium bromide (10.8 ml, 10.8 mmol, 1.0 M in Et_2O). The cold bath was maintained for 10 min., then removed and stirring continued overnight. The mixture was quenched with NH_4Cl (30 ml) and extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield a brown oil. The

crude oil was absorbed onto silica gel followed by flash chromatography (biotage 40S) 10% EtOAc/heptanes to yield 0.36 g (46%) of 6-neopentylchroman-4-ol as a white solid. R_f = 0.11. HRMS (ESI+) calcd for $C_{14}H_{20}O_2$ *m/z* 220.1463 $(M+H)^+$; found 220.1460.

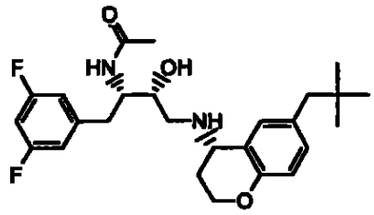
Step Two: 6-neopentyl-3,4-dihydro-2H-chromen-4-ylamine.

The above compound was prepared essentially according to the procedure of Example 19, Step 2. First, the azide was prepared. ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 8.40, 2.18 Hz, 1 H), 6.89 (d, *J* = 2.07 Hz, 1 H), 6.71 (d, *J* = 8.29 Hz, 1 H), 4.50 (appt, *J* = 3.73 Hz, 1 H), 4.15 (m, 2 H), 2.36 (s, 2 H), 2.08 (m, 1 H), 1.93 (m, 1 H), 0.83 (s, 9 H). Second, the azide was reduced to afford the amine as a slightly colored oil (1.6 g). The amine was taken to the next step without further purification. HRMS (ESI+) calcd for $C_{14}H_{21}NO$ *m/z* 219.1623 $(M+H)^+$. Found 219.1628.

Step Three: tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-3,4-dihydro-2H-chromen-4-yl)amino]propylcarbamate.

The above compound is prepared essentially according to the procedure of Example 17, step 3; it is obtained as an off white solid. Flash chromatography (3% MeOH/CHC_3, 1 ml of NH_4OH per liter) yields the desired product as a mixture of epimers. HRMS (ESI+) calcd for $C_{29}H_{40}N_2O_4F_2$ *m/z* 519.3034 $(M+H)^+$. Found 519.3040.

Step Four: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



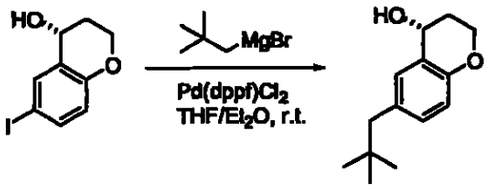
The above compound was prepared essentially according the method of Example 15, step 3, which resulted in a mixture of epimers. The epimers were then separated using chiral preparative HPLC (10% IPA/heptanes, 0.1% DEA) AD column:

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 1.87 Hz, 1 H), 6.96 (dd, J = 8.29, 2.07 Hz, 1 H), 6.79-6.67 (m, 4 H), 5.69 (d, J = 8.50 Hz, 1 H), 4.32-4.15 (m, 3 H), 3.85 (bs, 1 H), 3.60 (bs, 1 H), 3.02 (m, 1 H), 2.88 (m, 2 H), 2.76 (dd, J = 12.13, 6.74 Hz, 1 H), 2.46 (s, 2 H), 2.15-2.08 (m, 1 H), 2.04-1.98 (m, 1 H), 1.94 (s, 3 H), 0.91 (s, 9 H). HRMS (ESI+) calcd for $C_{26}H_{34}F_2N_2O_3$ m/z 461.2615 $(M+H)^+$. Found 461.2621.

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4R)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 2.07 Hz, 1 H), 6.96 (dd, J = 8.29, 1.87 Hz, 1 H), 6.77-6.67 (m, 4 H), 5.69 (d, J = 8.91 Hz, 1 H), 4.31-4.16 (m, 3 H), 3.86 (bs, 1 H), 3.57 (bs, 1 H), 3.00 (m, 2 H), 2.82 (m, 2 H), 2.44 (s, 2 H), 2.18-2.00 (m, 3 H), 1.90 (s, 3 H), 0.91 (s, 9 H). HRMS (ESI+) calcd for $C_{26}H_{34}F_2N_2O_3$ m/z 461.2615 $(M+H)^+$. Found 461.2630. Anal. Calcd for $C_{26}H_{34}F_2N_2O_3$; C, 67.81; H, 7.44; N, 6.08. Found C, 67.65; H, 7.51; N, 6.05.

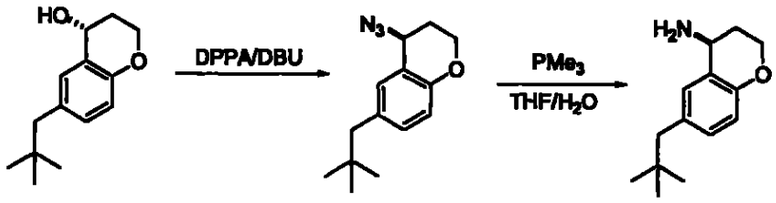
Example 52 A: Chiral Synthesis of Amine.

Step One: (4R)-6-neopentylchroman-4-ol.



(4R)-6-iodochroman-4-ol is converted into (4R)-6-neopentylchroman-4-ol essentially according to the procedure of Example 52, step 1. The produce is obtained as a white solid. Anal. Calcd for $C_{14}H_{20}O_2$; C, 76.33; H, 9.15. Found C, 76.31; H, 9.06. $[\alpha]_D$ = 22.3, c = 1.14 (CH_2Cl_2).

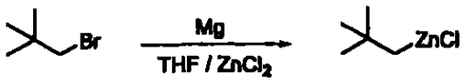
Step Two: (4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-ylamine.



(4R)-6-neopentylchroman-4-ol is converted into (4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-ylamine essentially according to the procedure of Example 19, step 2.

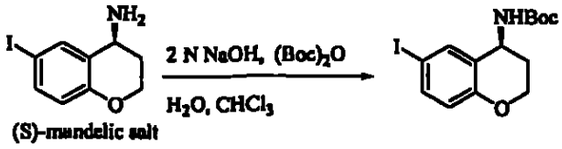
Example 52 B: Alternative chiral synthesis of amine

Step B-1



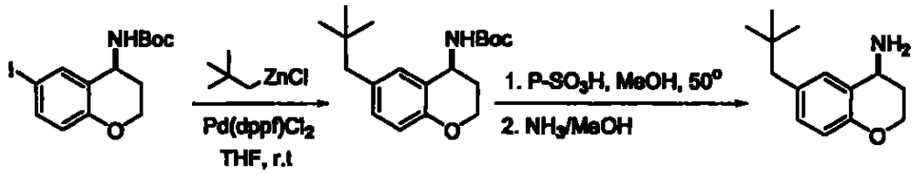
Neopentyl zinc was prepared according to the procedure described in *Tetrahedron Lett.* **1983**, *24*, 3823-3824.

Step B-2 *tert*-butyl (4S)-6-iodo-3,4-dihydro-2H-chromen-4-ylcarbamate.



To a suspension of amine (S)-mandelic salt (4.55 g, 10.6 mmol) in water (50 mL) was added sodium hydroxide (21 mL, 2 N, 42 mmol) followed by di-*tert*-butyl dicarbonate (2.58 g, 11.7 mmole) and chloroform (50 mL). The reaction mixture was stirred at room temperature for 2 h and then diluted with methylene chloride (100 mL) and water (50 mL). The organic layer was separated washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue was triturated with 1:1 hexanes/ethyl ether. The resulting white solid was collected by filtration and washed with hexanes to provided *tert*-butyl (4S)-6-iodo-3,4-dihydro-2H-chromen-4-ylcarbamate (3.30 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 1.8 Hz, 1H), 7.42 (dd, *J* = 8.6,2.2 Hz, 1H), 6.58 (d, *J* = 8.6 Hz, 1H), 4.78 (m, 2H), 4.28-4.20 (m, 1H), 4.18-4.10 (m, 1H), 2.19-2.10 (m, 1H), 2.06-1.96 (m, 1H), 1.49 (s, 9H).

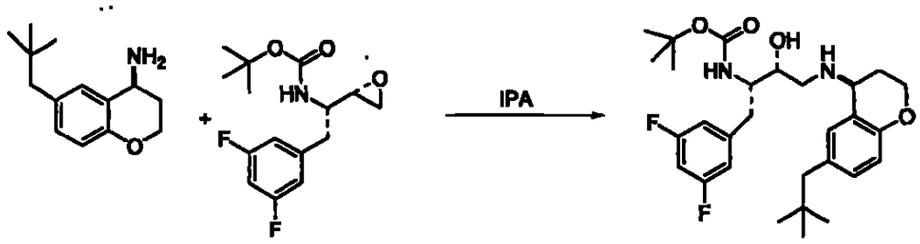
Step B-3 Coupling of neopentyl zinc reagent to *tert*-butyl (4S)-6-iodo-3,4-dihydro-2H-chromen-4-ylcarbamate.



To a suspension of the 0.3 M neopentyl zinc reagent in THF (60 ml, 15 mmol) was added the *tert*-butyl (4S)-6-iodo-3,4-dihydro-2H-chromen-4-ylcarbamate (1.8 g, 5.0 mmol) and $Pd(dppf)Cl_2$ (0.2 g, 0.25 mmol) as solids in one portion. The mixture was stirred at r.t. under nitrogen for 48 hours (progress monitored by LC/MS and HPLC). The mixture was quenched with aqueous NH_4Cl (20 ml) and extracted with EtOAc (3 x 50 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was dissolved in MeOH(25 ml) and treated with DOWEX® 50WX2-400 ion exchange resin. The mixture was heated to 50°C for six hours and then

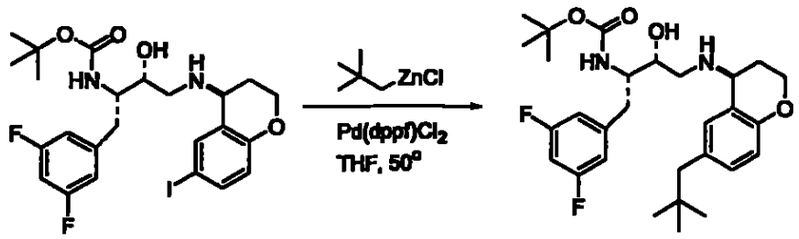
the resing was collected by filtration. The resin was washed successively with MeOH and CH_2Cl_2 these washings were discarded. The resin was then treated with 7 N NH_3/MeOH to elute the free amine from the resin. The elutions were concentrated *in vacuo* to yield a light brown oil (0.63 g, 57%) of (4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-ylamine. This material was consistent with previous preparations and was used as obtained for the subsequent opening of the difluoroPhe epoxide. S)-6-neopentyl-3,4-dihydro-2H-chromen-4-ylamine was previously characterized as the mono•HCl salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ); 7.25 (s, 1H), 7.02 (m, 1H,), 6.76 (m, 1H), 4.47 (bs, 1H), 4.21 (m, 2H), 2.38 (s, 2H), 2.24 (m, 1H), 2.10 (m, 1H), 0.87 (s, 9H). HRMS (ESI+) calculated for $C_{14}H_{21}N_1O_1$ 220.1701; found *m/z* 220.1698 $(M+H)^+$. Anal. Calcd for $C_{14}H_{21}NO$•HCl: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.62; H, 8.53; N, 5.42. $[\alpha]^{23}_D$ = 15.6, c = 1.17 in CH_3OH.

Example 52-C: Coupling of chiral amine with epoxide. Preparation of *tert*-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.



The above compound was prepared essentially according to the method of Example 15, step 2; it was obtained as a white foam. R_f = 0.25 (in 3% MeOH in $CHCl_3$ with 1 ml of NH_4OH per liter). HRMS (ESI+) calcd for $C_{29}H_{40}N_2O_4F_2$ *m/z* 519.3034 $(M+H)^+$. Found 519.3057.

Example 52-D: Alternative preparation of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.



To neopentyl zinc chloride (prepared as previously described) (51 ml, 11 mmol, 0.2 M in THF) under a nitrogen atmosphere at r.t. was added *tert*-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate (1.3 g, 2.2 mmol) and $Pd(dppf)Cl_2$ (0.09 g, 0.1 mmol) as solids. The reaction mixture was stirred at r.t. for 12 h and then heated to 50°C for 8h. The reaction was cooled to r.t. then quenched with 20 ml of aqueous NH_4Cl and extracted with EtOAc (3x100 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield a brown oil. The residue was dissolved in CH_2Cl_2 and absorbed onto 6g of silica gel. Flash chromatography (3-5% MeOH/$CHCl_3$ with 20 drops of NH_4OH/L, Biotage 40M) yields the desired product, which is identical to the material prepared by the previously described methods.

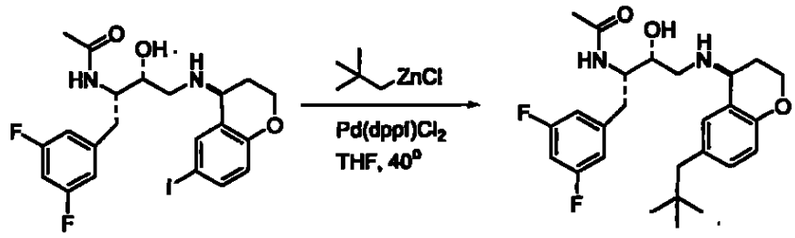
Example 52-E: Alternative preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.

The above compound is prepared essentially according to the method of Example 15, step 3. First, the Boc group is removed to afford the crude amine as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 2.07 Hz, 1 H), 6.95 (dd, J = 8.29, 2.28 Hz, 1 H), 6.78-6.68 (m, 4 H), 4.26 (m, 2 H), 3.82 (appt, J = 4.15 Hz, 1 H), 3.57 (ddd, J = 8.60, 5.29, 3.52 Hz, 1 H),

3.13 (ddd, J = 9.89, 5.55, 3.73 Hz, 1 H), 3.07 (dd, J = 11.82, 3.52 Hz, 1 H), 2.96 (dd, J = 13.58, 3.42 Hz, 1 H), 2.83 (dd, J = 11.71, 8.60 Hz, 1 H), 2.53 (dd, J = 13.58, 9.85 Hz, 1 H), 2.44 (s, 2 H), 2.14-1.99 (m, 2 H), 0.91 (s, 9 H).

Second, the crude amine was acylated. The crude acylated material was purified by flash chromatography (3.5% MeOH/CHC_3 with 1 ml of NH_4OH per liter), Biotage 40L, affording the desired product as a white powder. This material was spectroscopically identical to the N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide prepared by previous methods.

Example 52-F: Alternative preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



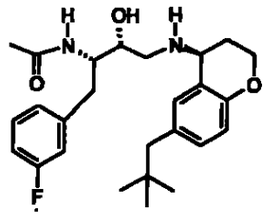
The above compound is prepared essentially according to the procedure of Example 19, step 5. The resulting residue was dissolved in CH_2Cl_2 and absorbed onto 6g of silica gel. Flash chromatography (3-5% MeOH/$CHCl_3$ with 20 drops of NH_4OH/L, Biotage 40M) yields two fractions. Fraction one yielded 650 mg of the desired product that was 93% pure by analytical HPLC. The second fraction (430 mg) was a 60:40 mixture of the desired product and the dehalogenated compound. The first fraction was re-subjected to preparative reverse phase HPLC (1% TFA in water/0.6% TFA in CH_3CN) to yield 500 mg (38%) of a white powder after neutralization. This material was spectroscopically identical to the N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-

chromen-4-yl]amino}propyl)acetamide prepared by previous methods.

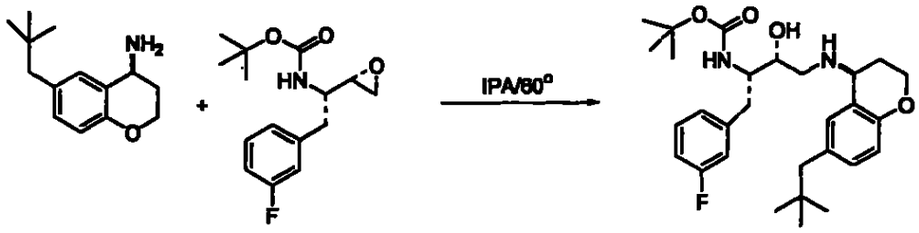
Example 52-G: Preparation of the HCl salt of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.

The free base (from Ex. 52-F, 0.5 g, 1.08 mmol) was dissolved in MeOH (10 ml) and treated with HCl/Et_2O (2.5 ml, 1.0 M). The solution was stirred at r.t. for 10 min. then the solvent removed *in vacuo* to yield a clear glass. The glass was tritrated with Et_2O to yield 536 mg of a white solid that was dried *in vacuo* at 40°C for 48h. Anal Calcd for $C_{26}H_{34}F_2N_2O_3 \cdot HCl \cdot 0.5\ H_2O$, C, 61.71; H, 7.17; N, 5.54. Found C, 61.69; H, 7.31; N, 5.64. HRMS (ESI+) calcd for $C_{26}H_{34}N_2O_3F_2$ *m/z* 461.2615 $(M+H)^+$. Found 461.2627.

Example 53: N-((1S,2R)-1-(3-fluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



Step One: tert-butyl (1S,2R)-1-(3-fluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.

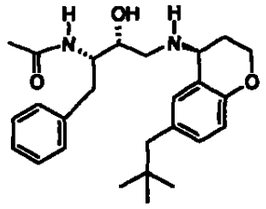


The above product was prepared essentially according to the method of Example 17, step 3. The crude product was then purified by flash chromatography (3% MeOH/$CHCl_3$). HRMS (ESI+) calcd for $C_{29}H_{41}N_2O_4F$ *m/z* 501.3128 $(M+H)^+$. Found 501.3150.

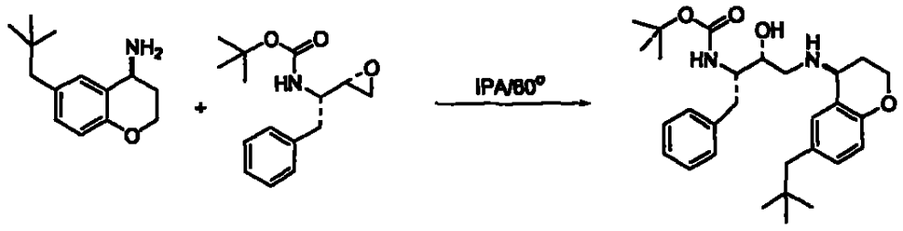
Step two: N-((1S,2R)-1-(3-fluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.

The above compound was prepared essentially according to the method of Example 15, step 3. The crude product was dissolved in MeOH and purified by reverse phase preparatory HPLC. HRMS (ESI+) calcd for $C_{26}H_{35}N_2O_3F$ m/z 443.2710 $(M+H)^+$. Found 443.2710.

Example 54: N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



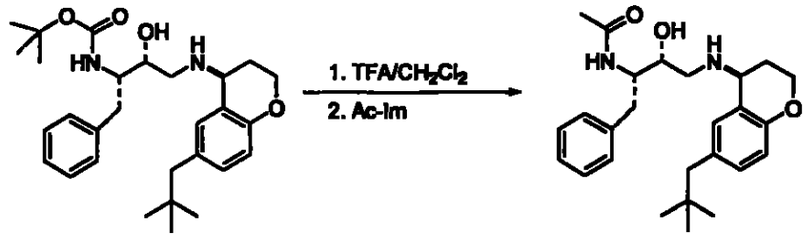
Step One: tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.



The above compound was prepared essentially according to the method of Example 17, step 3. The resulting crude product was purified by preparative HPLC (1% TFA in water/0.6% TFA in

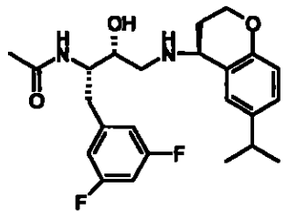
CH_3CN). HRMS (ESI+) calcd for $C_{29}H_{42}N_2O_4$ *m/z* 483.3222 $(M+H)^+$. Found 483.3219.

Step Two: N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



The above compound is prepared essentially according to the method of Example 17, step 3. The resulting crude product was dissolved in MeOH (5 mL) and purified by reverse phase preparatory HPLC which gave a white powder. HRMS (ESI+) calcd for $C_{26}H_{36}N_2O_3$ *m/z* 425.2804 $(M+H)^+$. Found 425.2801.

Example 55: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



Step One: 6-isopropyl-2,3-dihydro-4H-chromen-4-one.

A CH_2Cl_2 (350 ml) solution of 1-isopropyl-4-methoxy benzene (25 g, 166 mmol) and 3-chloro-propionly chloride (21 ml, 216 mmol), at r.t., was treated with $AlCl_3$ (33 g, 249 mmol) in 1-2 g portions over a 1 h period. Stirring was maintain at r.t. for 24 h at which time the mixture was poured onto crushed ice followed by the addition of 30 ml of conc. HCl. The mixture was diluted with 300 ml of CH_2Cl_2 and carefully

washed (avoid emulsion) with 2 N NaOH. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* a pale yellow oil. Flash chromatography (10% EtOAc/Heptanes) yields 6-isopropyl-2,3-dihydro-4H-chromen-4-one (7.5 g, 24%). R_f = 0.3. HRMS (ESI+) calcd for $C_{12}H_{14}O_2$ *m/z* 191.1072 $(M+H)^+$. Found 191.1071.

Step Two: 6-isopropylchroman-4-ol.

The above compound was prepared essentially according to the method of Example 17, step 1; it was obtained as a white solid. HRMS (ESI+) calcd for $C_{12}H_{16}O_2$ *m/z* 192.1150 $(M+H)^+$. Found 192.1152.

Step Three: 6-isopropyl-3,4-dihydro-2H-chromen-4-ylamine.

The above compound was prepared essentially according to the method of Example 17, step 2. First the azide was prepared as a yellow oil (7.53 g, 86% crude yield. HRMS calcd for $C_{12}H_{15}N_3O$ + H1 217.1215, found 217.1218. Second, the azide was reduced with 1.0M Me_3P in THF (42.00 mL, 41.59 mmol). The resulting amine was obtained as a yellow oil (3.5 g, 53% crude yield). HRMS calcd for $C_{12}H_{17}NO$ + H1 192.1388, found 192.1384. The crude racemic amine was purified and resolved using chiral preparative HPLC (5% EtOH/heptanes, 0.1% DEA) using a Chiralpak AD column. Obtained 1.5 g of (+)-(*4R*)- 6-isopropyl-chroman-4-ylamine retention time 15.5 min. $[\alpha]_D$ = 4.2 (c = 2.0 in MeOH) and 1.5 g of (-)-(*4S*)- 6-isopropyl-chroman-4-ylamin retention time 18.3 min. $[\alpha]_D$ = -3.9 (c = 2.0 in MeOH). ^1H NMR as the HCl salt (300 MHz, CD_3OD) δ 1.25 (d, *J* = 6 Hz, 6 H), 2.15 (m, 1 H), 2.38 (m, 1 H), 2.89 (m, 1 H), 4.27 (m, 2 H), 4.55 (t, *J* = 6 Hz, 1 H), 6.83 (d, *J* = 9 Hz, 1 H), 7.19 (dd, *J* = 3, 9 Hz, 1 H), 7.25 (d, *J* = 3 Hz, 1 H).

Step Four: tert-Butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropyl-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.

The above compound was prepared essentially according to the method of Example 17, step 3. The crude material was used in the next reaction without purification. ^{1}H NMR (crude-DMSO-d_6) δ 7.75 (d, J = 9 Hz, 1 H), 7.14 (br s, 1 H), 7.02 (m, 2 H), 6.9 (m, 1 H), 6.68 (d, J = 9 Hz, 1 H), 5.3 (br s, 2 H), 4.22 (m, 1 H), 4.12 (m, 1 H), 3.9 (m, 1 H), 3.68 (m, 1 H), 3.50 (m, 1 H), 3.02 (dd, J = 11, 3 Hz, 1 H), 2.78 (sept, J = 7 Hz, 1 H), 2.67 (s, 1 H), 2.57 (dd, J = 4, 10 Hz, 1 H), 1.59 (s, 9 H), 1.14 (d, J = 7 Hz, 6 H). LRMS (*m/z*) M+H: 490.3.

Step Five: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.

The product from step 4 was converted into the above compound essentially according to the method of Example 15, step 3. First, the free amine was obtained as a glassy solid/foam. ^{1}H NMR (crude-$CDCl_3$) δ 7.75 (d, J = 9 Hz, 1 H), 7.14 (br s, 1 H), 7.02 (m, 2 H), 6.9 (m, 1 H), 6.68 (d, J = 9 Hz, 1 H), 4.4 (br s, 2 H), 4.12 (m, 1 H), 3.9 (m, 1 H), 3.68 (m, 1 H), 3.50 (m, 1 H), 3.32 (m, 1 H), 3.02 (dd, J = 11, 3 Hz, 1 H), 2.78 (sept, J = 7 Hz, 1 H), 2.67 (s, 1 H), 2.57 (dd, J = 4, 10 Hz, 1 H), 1.11 (d, J = 7 Hz, 6 H). LRMS (*m/z*) M+H:390.2

Second, the amine was acylated to afford the acetamide as an oil, which was purified by prep-HPLC. HRMS (ESI+) calcd for $C_{24}H_{30}F_2N_2O_3$ *m/z* 433.2303 $(M+H)^+$. Found 433.2307.

The same procedure using (+)-(4*R*)- 6-isopropyl-chroman-4-ylamine results in the epimer N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4R)-6-isopropyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide. ^{1}H NMR (DMSO-d_6) δ 7.76

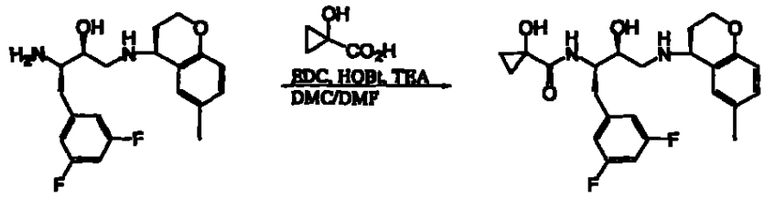
(d, J = 9 Hz, 1 H), 7.01 (m, 2 H), 7.14 (d, J = 2 Hz, 1 H), 6.99 (dd, J = 8.5, 2 Hz, 1 H), 6.91 (m, 1 H), 6.65 (d, J = 8.5 Hz, 1 H), 4.96 (d, J = 6 Hz, 1 H), 4.2 (dt, J = 10, 3.4 Hz, 1 H), 4.1 (m, 1 H), 3.99 (m, 1 H), 3.64 (br s, 1 H), 3.47 (m, 1 H), 3.0 (dd, J = 14, 3 Hz, 1 H), 2.78 (sept, J = 8 Hz, 1 H), 2.75 (m, 1 H), 2.6 (m, 2 H), 1.86 (m, 3 H), 1.7 (s, 3 H), 1.16 (d, J = 7 Hz, 6 H). HRMS (ESI+) calcd for $C_{24}H_{30}F_2N_2O_3$ m/z 433.2303 $(M+H)^+$. Found 433.2301.

Example 56: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)-2-hydroxy-2-methylpropanamide.



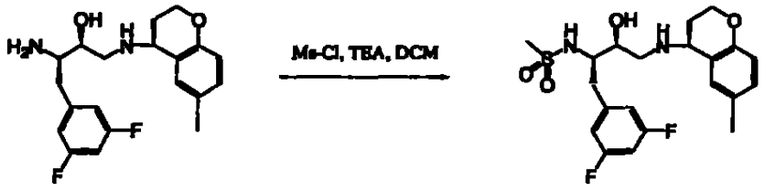
(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}butan-2-ol (1 equiv) was combined with 2-methylacetic acid, (1.25equiv), EDC (1.5equiv) and HOBt (1.5equiv) in DMF/DCM (1:1, 10mL). The reaction mixture was treated with Et_3N and stirred at ambient temperature for 6h. HPLC determined that the amine had been consumed by this time, and the reaction mixture was poured onto EtOAc and washed with 1M HCl, then the organics were dried over $MgSO_4$ and concentrated to give an oil which was purified by reverse phase preparative HPLC. HRMS (ESI+) calcd for $C_{23}H_{27}F_2IN_2O_4$ m/z 561.1063 $(M+H)^+$. Found 561.1047.

Example 57: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)-1-hydroxycyclopropanecarboxamide.



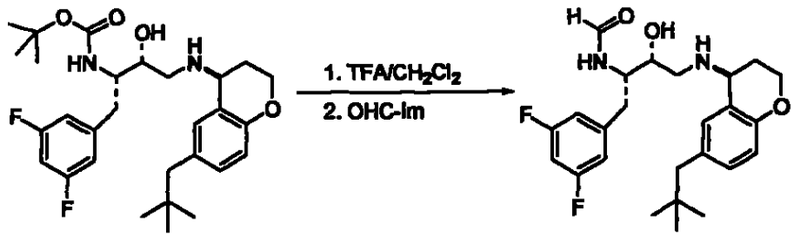
The above compound is prepared using the basic methodology described in Example 56. HRMS (ESI+) calcd for $C_{22}H_{25}F_2IN_2O_4$ m/z 559.0907 $(M+H)^+$. Found 559.0903.

Example 58: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)methanesulfonamide.



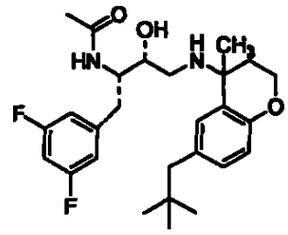
(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}butan-2-ol (1 equiv) was dissolved in DCM with TEA (2 equiv) then cooled to 0°C and treated with MsCl (1.25equiv)while stirring. The reaction mixture was removed from the cold bath, brought to ambient temperature, then quenched with MeOH and concentrated. The residue was dissolved in EtOAc and washed with 1M HCl (2x10mL). The organics were dried and concentrated and chromatographed over silica gel. ^1H NMR (CD_3OD) δ 7.74 (d, J = 2.0 Hz, 1 H), 7.53 (dd, J = 2.0, 8.7 Hz, 1 H), 6.88 (m, 2 H), 6.77 (m, 1 H), 6.67 (d, J = 8.7 Hz, 1 H), 4.23-4.39 (m, 2 H), 4.25 (br m, 1 H), 4.12 (m, 1 H), 3.87 (td, J = 3.1, 7.8 Hz, 1 H), 3.29 (dd, J = 3.5, 13.9 Hz, 1 H), 3.11 (s, 3H), 3.05 (dd, J = 3.2, 12.7 Hz, 1 H), 2.98 (dd, J = 7.9, 12.6 Hz, 1 H), 2.74 (dd, J = 11.0, 13.9 Hz, 1 H), 2.14 (br m, 2 H). MS (ESI+) calcd for $C_{20}H_{23}F_2IN_2O_4S$ m/z 553.38 $(M+H)^+$. Found 553.4.

Example 59: (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propylformamide.



The Boc protected amine (1 equiv) was dissolved in 10:1 DCM:TFA (to 0.1M) for 3h at ambient temperature. The reaction mixture was concentrated and the residue partitioned between EtOAc and 1M NaOH. The aqueous layer was removed and the organics washed with brine (50mL) then dried over $MgSO_4$ and concentrated to a glassy solid/foam. LRMS (m/z) M+H:418.5. This was dissolved in CH_2Cl_2 (to 0.1M), cooled to 0°C and treated with formyl imidizole (1.25equiv). The reaction was removed from the cold bath, then stirred for 2h at ambient temp. When done by HPLC, the reaction mixture was concentrated and dissolved in MeOH (1.5mL) and purified by reversed phase preparative HPLC (2 in. column) to give a film which scraped down to a white powder. ^1H NMR (DMSO-d_6) δ 8.46 (br s, 1H), 7.75 (d, J = 9 Hz, 1 H), 7.14 (br s, 1 H), 7.02 (m, 2 H), 6.91 (m, 1 H), 6.69 (d, J = 9 Hz, 1 H), 5.0 (br s, 2 H), 4.21 (m, 1 H), 4.09 (m, 1 H), 3.94 (m, 1 H), 3.72 (m, 1 H), 3.43 (m, 1 H), 3.08 (dd, J = 11, 3 Hz, 1 H), 2.77 (s, 2 H), 2.57 (dd, J = 4, 10 Hz, 1 H), 1.69 (s, 3 H), 1.04 (s, 9 H). MS (ESI+) for $C_{25}H_{32}F_2N_2O_3$ *m/z* 446.54 $(M+H)^+$. Found 446.3.

Example 60: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methyl-6-neopentyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide.



Step One: 6-iodo-2,3-dihydro-4H-chromen-4-one

To a CH_2Cl_2 (300 ml) suspension of 6-iodo-4-chromanol (15 g, 54.3 mmol) and 30 g of silica gel, at r.t., was added PCC (15.2 g, 70.6 mmol) as a solid. The mixture was stirred at r.t. for 3h at which time TLC (20% EtOAc/hexanes) indicated complete reaction. The reaction mixture was filtered through a silica gel plug and the filtrate concentrated *in vacuo* to yield 14.9 g (95%) of 6-iodo-2,3-dihydro-4H-chromen-4-one as a white solid consistent with the literature report (*Synthesis* 1997, 23-25). HRMS (ESI+) calcd for $C_9H_7IO_2$ *m/z* 273.9492; found 273.9500.

Step Two: 6-iodo-4-methylchroman-4-ol

$CeCl_3$ (4.9 g, 19.8 mmol) was dried *in vacuo* at 140°C for 3h and then slurried with dry THF (100 ml) for 1h. The white suspension was chilled to -78°C followed by the addition of MeLi•LiBr (14.2 ml, 21.4 mmol) over 15 minutes. The mixture was stirred for 30 min followed by the addition of a THF (20 ml) solution of 6-iodo-2,3-dihydro-4H-chromen-4-one dropwise via syringe. After 30 min TLC (15% EtOAc/hexanes) indicated complete reaction. The mixture was treated with NH_4Cl (aq.) 30 ml and diluted with water 150 ml. The mixture was extracted with EtOAc and the organic layer dried over Na_2SO_4 . The Na2SO4 was removed by filtration and the filtrate concentrated *in vacuo* to yield 6-iodo-4-methylchroman-4-ol as an off white solid 4.7 g (95%). HRMS (ESI+) calcd for $C_{10}H_{11}IO_2$ *m/z* 289.9806 $(M+H)^+$. Found 289.9803.

Step Three: 6-iodo-4-methylchroman-4-amine

To a mixture of 6-iodo-4-methylchroman-4-ol (1.0 g, 3.4 mmol) and NaN_3 (0.7 g, 10.3 mmol) in $CHCl_3$ (15 ml), at 0°C, was added TFA (1.3 ml, 17.2 mmol) as a solution in 10 ml of $CHCl_3$ dropwise via addition funnel. The addition was carried out over 2 h and stirring continued for an additional 2 h at 0°C. The mixture was warmed to r.t. and stirred over night. The mixture was diluted with 30 ml of water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield 4-azido-6-iodo-4-methylchroman as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.07 Hz, 1 H), 7.50 (dd, J = 8.71, 2.07 Hz, 1 H), 6.66 (d, J = 8.71 Hz, 1 H), 4.27 (m, 2 H), 2.06 (m, 2 H), 1.68 (s, 3 H). MS (ESI+) for $C_{10}H_{10}IN_3O$ *m/z* 273.0 $(M+H)^+$ loss of azide. The crude azide was dissolved in THF (15 ml) followed by the addition of trimethylphosphine (4 ml, 1.0 M in THF) at r.t. After 15 min. 3 ml of water was added and stirring continued at r.t. for 2h until complete as indicated by LC/MS. The solvent was removed *in vacuo* and the residue diluted with water (75 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacou* to yield 6-iodo-4-methylchroman-4-amine (0.900 g, 91%) as a yellow oil. This material was used in the next step without purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 2.07 Hz, 1 H), 7.40 (dd, J = 8.60, 2.18 Hz, 1 H), 6.59 (d, J = 8.50 Hz, 1 H), 4.25 (m, 2 H), 2.01 (m, 2 H), 1.53 (s, 3 H). MS (ESI+) for $C_{10}H_{12}INO$ *m/z* 273.2 $(M+H)^+$ loss of NH_3.

Step Four: tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-4-methyl-3,4-dihydro-2H-chromen-4-yl)amino]propylcarbamate.

The above compound was prepared essentially according to the method of example 17, step 3. The resulting crude

material was dissolved in CH_2Cl_2, absorbed onto 7.8 g of silica gel, and purified by flash chromatography using 50% EtOAc/Heptanes (Biotage 40 M column) as the eluent. Three fractions were obtained. The final fraction was recovered amine. Obtained 0.500 g of each of the following diastereomers overall yield from epoxide 83%.

Diastereomer A: ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (bs, 1 H), 7.42 (dd, J = 8.50, 2.07 Hz, 1 H), 6.71 (m, 3 H), 6.59 (d, J = 8.50 Hz, 1 H), 4.52 (d, J = 9.12 Hz, 1 H), 4.35 (m, 1 H), 4.21 (m, 1 H), 3.82 (m, 1 H), 3.42 (m, 1 H), 3.06 (m, 1 H), 2.81 (dd, J = 14.3, 8.7 Hz, 1 H), 2.62 (m, 2 H), 2.26 (m, 1 H), 1.84 (m, 1 H), 1.40 (m, 2 H), 1.35 (m, 12 H). HRMS (ESI+) for $C_{25}H_{31}N_2O_4F_2I$ +1H calcd for 589.1376 *m/z* found 589.1397 $(M+H)^+$.

Diastereomer B: ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.07 Hz, 1 H), 7.44 (d, J = 8.50 Hz, 1 H), 6.71 (m, 3 H), 6.67 (d, J = 8.71 Hz, 1 H), 4.54 (bs, 1 H), 4.34 (m, 1 H), 4.16 (m, 1 H), 3.77 (m, 1 H), 3.48 (m, 1 H), 3.10 (m, 1 H), 2.75 (m, 1 H), 2.75 (m, 1 H), 2.62 (m, 2 H), 2.24 (m, 1 H), 1.93 (m, 1 H), 1.60 (m, 2 H), 1.42 (s, 9 H), 1.39 (s, 3 H). HRMS (ESI+) for $C_{25}H_{31}N_2O_4F_2I$ + 1H calcd for m/z 589.1376; found 589.1375 $(M+H)^+$.

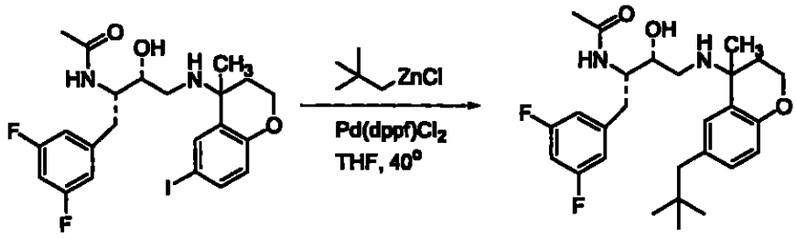
Step Five: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-4-methyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide.

To a CH_2Cl_2 (5 ml) solution of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-4-methyl-3,4-dihydro-2H-chromen-4-yl)amino]propylcarbamate (Diastereomer B). (0.47 g, 0.79 mmol), at r.t., was added 25 ml of 20% TFA/CH_2Cl_2. The mixture was stirred at r.t for 30 min. The solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (75 ml) and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield a white foam. The residue was dissolved in CH_2Cl_2 (5 ml) and

chilled to 0°C followed by the addition of Et_3N (0.24 ml, 1.7 mmol) and acetyl imidazole (0.10 g, 0.90 mmol). The mixture was then warmed to r.t. and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (25 ml) and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield a white foam (0.35 g, 84%) after flash chromatograph 5% MeOH/$CHCl_3$ (Biotage 40 S). R_f = 0.29. HRMS (ESI+) calcd for $C_{22}H_{25}N_2O_3IF_2$ + 1H calcd *m/z* 531.0958; found 531.0958 $(M+H)^+$.

Same procedure diastereomer A yields 0.28 g (70%) of the epimer. ^1H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 2.28 Hz, 1 H), 7.36 (dd, *J* = 8.71, 2.28 Hz, 1 H), 6.79 (m, 3 H), 6.57 (d, *J* = 8.50 Hz, 1 H), 4.31 (m, 1 H), 4.17 (m, 1 H), 4.08 (m, 1 H), 3.51 (m, 1 H), 3.11 (dd, *J* = 14.1, 3.73 Hz, 1 H), 2.62 (dd, *J* = 14.1, 10.4 Hz, 1 H), 2.52 (m, 1 H), 2.45 (dd, *J* = 11.9, 3.63 Hz, 1 H), 2.25 (m, 1 H), 1.79 (s, 3 H), 1.74 (m, 1 H), 1.47 (s, 3 H). Anal. Calcd for $C_{22}H_{25}F_2IN_2O_3$; C, 49.82; H, 4.75; N, 5.28. Found C, 49.87; H, 4.94; N, 5.05.

Step Six:: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methyl-6-neopentyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide.



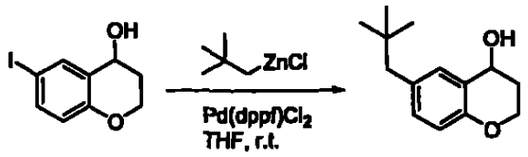
To a 20 ml serum capped vial containing N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-4-methyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide (0.20 g, 0.37 mmol) and $Pd(dppf)Cl_2$ (0.015 g, .018 mmol) under nitrogen was added 3.7 ml of a 0.5 M neopentyl zinc chloride (1.85 mmol) prepared as previously described. The mixture was shaken on an orbital shaker for 12 h at which time LC/MS indicated only

a trace of the desired compound. An additional 5 eq. of the zinc reagent and another 5 mol% of catalyst was added and the reaction mixture was warmed to 40 °C. After 6 h LC/MS indicated complete consumption of SM. The reaction mixture was quenched with NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated *in vacou* to yield a light brown solid (150 mg) after flash chromatography (4% MeOH/$CHCl_3$ Biotage 40S). This material was subjected to a final reverse phase preparative column (1% TFA in H_2O/0.6% TFA in CH_3CN) to yield 50 mg of a light yellow solid. This material was dissolved in 4 ml of CH_2Cl_2 and treated with 0.5 g of 3-mercaptopropyl functionalized silica gel and stirred at r.t. for 30 min. The mixture was filtered through Celite® to remove the resin and the filtrate concentrated *in vacuo* to yield a white powder (44 mg, 20%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.08 (d, J = 2.07 Hz, 1 H), 6.87 (dd, J = 8.29, 2.07 Hz, 1 H), 6.78 (m, 3 H), 6066 (d, J = 8.29 Hz, 1 H), 4.27 (m, 1 H), 4.12 (m, 1 H), 4.04 (m, 1 H), 3.54 (m, 1 H), 3.06 (dd, J = 13.99, 3.63 Hz, 1 H), 2.56 (m, 2 H), 2.45 (bs, 2 H), 2.37 (dd, J = 11.82, 7.67 Hz, 1 H), 2.25 (m, 1 H), 1.81 (s, 3 H), 1.78 (m, 1 H); 1.49 (s, 3 H), 0.91 (s, 9 H). MS (ESI+) for $C_{27}H_{36}N_2O_3F_2$ *m/z* 475.2772 $(M+H)^+$; found, 475.2774.

Same procedure yields 0.049 g (28%) of the epimer ^1H NMR (400 MHz, DMSO-d_6) δ 7.17 (d, J = 2.07 Hz, 1 H), 6.87 (dd, J = 8.29, 2.07 Hz, 1 H), 6.77 (m, 3 H), 6.66 (d, J = 8.29 Hz, 1 H), 4.27 (m, 1 H), 4.11 (m, 2 H), 3.53 (m, 1 H), 3.06 (dd, J = 14.10, 3.52 Hz, 1 H), 2.53 (m, 3 H), 2.43 (s, 2 H), 2.27 (m, 1 H), 1.78 (m, 4 H), 1.49 (s, 3 H), 0.90 (s, 9 H). MS (ESI+) calcd for $C_{27}H_{36}N_2O_3F_2$ *m/z* 475.2772 $(M+H)^+$; found, 475.2788.

Example 60 A: An alternative synthesis of 4-methyl-6-neopentylchroman-4-ol

Step 1: 6-neopentylchroman-4-ol.

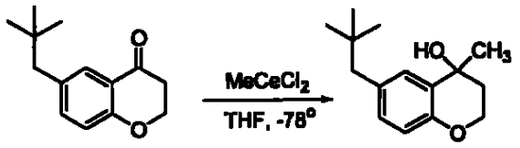


To a flame dried round bottom flask containing 6-iodo-chroman-4-ol (3.0 g, 10.8 mmol) and $Pd(dppf)Cl_2$ (0.44 g, 0.54 mmol) was added 6 ml of anhydrous THF and the mixture chilled to 0°C. The mixture was treated with neopentyl zinc chloride (prepared as previously described) (50 ml, 30 mmol, 0.6 M in THF) and stirred under nitrogen at r.t. for 19 h. followed by 5 h at 50°C (oil bath). The reaction was cooled to r.t. and quenched with NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to 1.9 g (79%) of a white solid after flash chromatography (10% EtOAc/heptanes, Biotage 40M) R_f = 0.11. HRMS (ESI+) calcd for $C_{14}H_{20}O_2$ m/z 220.1463 $(M+H)^+$; found 220.1460.

Step 2: 6-neopentyl-2,3-dihydro-4H-chromen-4-one.

The alcohol was oxidized to the ketone essentially according to the method of Example 60, step 1; the ketone was obtained as a clear oil. This material was carried forward without further purification.. HRMS (ESI+) calcd for $C_{14}H_{18}O_2$ m/z 219.1385 $(M+H)^+$; found 219.1393.

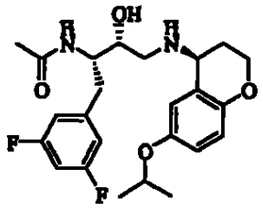
Step 3: 4-methyl-6-neopentylchroman-4-ol.



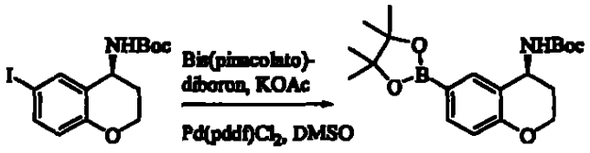
The aboye compound was prepared essentially according to the method of Example 60, step 2; the product was obtained as a clear oil, which was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.07 Hz, 1 H), 6.95 (dd, *J* = 8.29, 2.26 Hz, 1 H), 6.73 (d, *J* = 8.29 Hz, 1 H), 4.25 (m, 2

H), 2.44 (s, 2 H), 2.09 (m, 2 H), 1.64 (s, 3 H), 0.91 (s, 9 H). MS (ESI+) calcd for $C_{15}H_{22}O_2$ *m/z* 234.2 $(M+H)^+$; found 217.3 loss of water.

Example 61: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



Step One: tert-butyl (4S)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-chromen-4-ylcarbamate.



To a mixture of tert-butyl (4S)-6-iodo-3,4-dihydro-2H-chromen-4-ylcarbamate (3.30 g, 8.8 mmol) and bis(pinacolato)diboron (2.51 g, 9.7 mmol) in methyl sulfoxide (30 mL) was added potassium acetate (2.60 g, 26.4 mmol) followed by [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (410 mg, 0.5 mmol). The reaction mixture was heated under argon at 80 °C for 2 h and then cooled to room temperature. The reaction mixture was diluted with ethyl ether (100 mL) and washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 10-20% ethyl acetate/hexanes) provided the desired product (3.25 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.62 (dd, *J* = 8.2,1.5 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 4.79 (m, 2H), 4.31-4.24 (m,

1H), 4.21-4.15 (m, 1H), 2.14-2.11 (m, 2H), 1.48 (s, 9H), 1.34 (s, 6 H), 1.33 (s, 6 H).

Step Two: tert-butyl (4S)-6-hydroxy-3,4-dihydro-2H-chromen-4-ylcarbamate

To a solution of tert-butyl (4S)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-chromen-4-ylcarbamate (1.09 g, 2.90 mmol) in tetrahydrofuran (10 mL) was added sodium hydroxide (6 mL, 1 N, 6 mmol) followed by hydrogen peroxide (10 mL, 30%). The reaction mixture was stirred at room temperature for 2 h and then quenched with sodium hydrogen sulfite (5 g in 10 mL of water). The mixture was adjusted to pH 4 with 2 N sodium hydroxide and then extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Flash chromatography (silica gel, 10-25% ethyl acetate/hexanes) provided (650 mg, 85%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.75 (d, J = 2.7 Hz, 1H), 6.72-6.63 (m, 1H), 5.03 (d, J = 7.5 Hz, 1 H), 4.77-4.75 (m, 1H), 4.16-4.08 (m, 2H), 2.30 (s, 1H), 2.16-2.13 (m, 1H), 2.05-1.99 (m, 1H), 1.47 (s, 9H).

Step Three: tert-butyl (4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-ylcarbamate

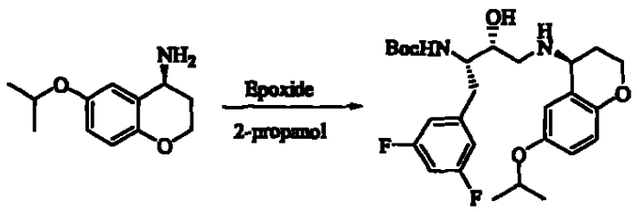
To a solution of the alcohol, from step two, (325 mg, 1.22 mmol) in acetone (10 mL) was added cesium carbonate (800 mg, 2.45 mmol) followed by 2-bromopropane (360 mg, 2.93 mmol). The reaction mixture was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (100 mL) and water (50 mL). The organic layer was separated and washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated

under reduced pressure to provide tert-butyl (4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-ylcarbamate (340 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, J = 2.1 Hz, 1H), 6.77-6.62 (m, 2H), 4.81 (m, 2 H), 4.45-4.35 (m, 1H), 4.23-4.16 (m, 1H), 4.14-4.06 (m, 1H), 2.22-2.14 (m, 1H), 2.05-1.95 (m, 1H), 1.48 (s, 9H), 1.29 (d, J = 6.2 Hz, 6H). This material was used in the next step without further purification.

Step Four: (4S)-6-isopropoxychroman-4-amine.

To a solution of tert-butyl (4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-ylcarbamate (340 mg, 1.11 mmol) in methanol (2 mL) was added hydrochloric acid (2 mL, 4 N in 1,4-dioxane, 8 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was diluted with methylene chloride (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 50 mL). The combined extracts were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide (4S)-6-isopropoxychroman-4-amine (240 mg, 99% crude yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 2.7 Hz, 1H), 6.90-6.86 (m, 1H), 6.80 (d, J = 9.0 Hz, 1H), 4.55-4.46 (m, 2H), 4.24-4.17 (m, 2H), 2.40-2.31 (m, 1H), 2.18-2.08 (m, 1H), 1.28 (d, J = 6.0 Hz, 6H). This material was used in the next step without further purification.

Step Five: *tert*-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.



The above compound was prepared essentially according to the method of Example 17, step 3. Flash chromatography of the crude product (silica gel, 20-50% ethyl acetate/hexanes) afforded 95 mg of amine and the desired product (330 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.79-6.73 (m, 4H), 6.70-6.63 (m, 1H), 4.52 (d, *J* = 9.4 Hz, 1H), 4.45-4.37 (m, 1H), 4.25-4.13 (m, 2H), 3.77-3.69 (m, 2H), 3.45-3.39 (m, 1H), 3.09-3.03 (m, 1H), 2.83-2.75 (m, 3H), 2.05-2.01 (m, 1H), 1.95-1.87 (m, 1H), 1.37 (s, 9H), 1.30 (d, *J* = 6.1 Hz, 6H).

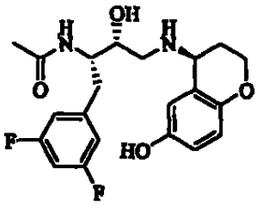
Step Six: (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-yl]amino}butan-2-ol hydrochloride.

To a solution of the product from step 6 (330 mg, 0.65 mmol) in 1,4-dioxane (2 mL) was added hydrochloric acid (2 mL, 4 N in 1,4-dioxane, 8 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure. The residue was triturated with ethyl ether. The resulting white solid was collected by filtration and washed with ethyl ether to provide (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-yl]amino}butan-2-ol hydrochloride (302 mg, 97%): ESI MS *m/z* 407 $[C_{22}H_{28}F_2N_2O_3 + H]^+$. This material was used in the next step without further purification.

Step Seven: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropoxy-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.

To a solution of the product from step 7 (302 mg, 0.63 mmol) in methylene chloride (5 mL) was added triethylamine (322 mg, 3.15 mmol) followed by 1-acetylimidazole (71 mg, 0.63 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was washed successively with 1N hydrochloric acid, water, saturated sodium bicarbonate and saturated sodium chloride, and dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 0-5% methanol/methylene chloride provided the desired product (190 mg, 67%) as a white solid: ESI MS *m/z* 449 $[C_{24}H_{30}F_2N_2O_4 + H]^+$; HPLC (Method A) 98.7% (AUC), t_R = 8.69 min. Anal. Calcd for $C_{24}H_{30}F_2N_2O_4$: C, 64.27; H, 6.74; N, 6.24. Found: C, 64.11; H, 6.65; N, 6.17.

Example 62: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-hydroxy-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



Step One: *tert*-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-hydroxy-3,4-dihydro-2H-chromen-4-yl]amino}propylcarbamate.

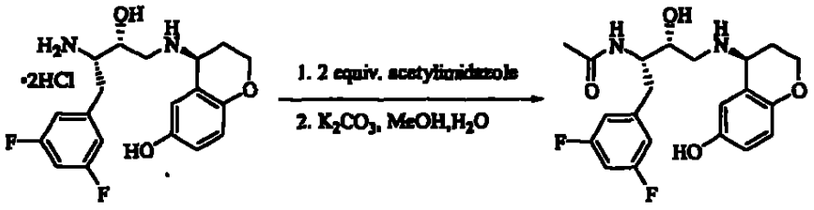
A mixture of (4S)-4-aminochroman-6-ol (165 mg, 1.0 mmol) and Example 134 (300 mg, 1.0 mmol) in 2-propanol (5 mL) was stirred at 60 °C for 16 h. The solvent was removed under reduced pressure. Flash chromatography (silica gel, 0-5% methanol/methylene chloride) recovered 54 mg of starting amine and provided the desired product (200 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-6.63 (m, 6H), 4.55 (d, *J* = 9.0 Hz, 1H), 4.21-4.14 (m, 2H), 3.73-3.71 (m, 2H), 3.47-3.44 (m, 1H), 3.10-

3.02 (m, 1H), 2.84-2.75 (m, 3H), 2.10-2.02 (m, 1H), 1.94-1.90 (m, 1H), 1.37 (s, 9H).

Step Two: (4S)-4-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}chroman-6-ol hydrochloride.

The above compound was prepared essentially according to the method of Example 61, step 7. ESI MS *m/z* 365 $[C_{19}H_{22}F_2N_2O_3 + H]^+$. This material was used in the next step without further purification.

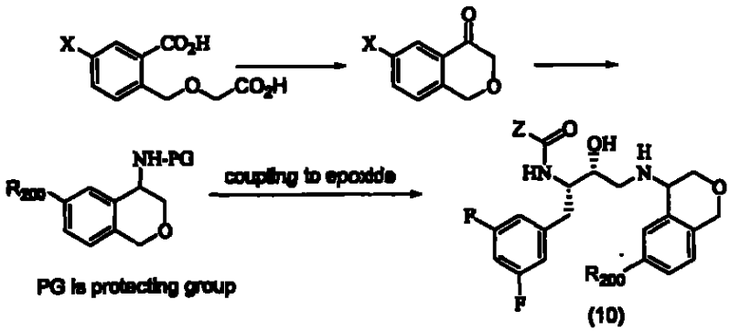
Step Three: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-hydroxy-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide.



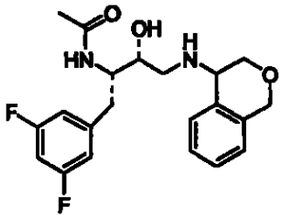
To a solution of the product from step 2 (200 mg, 0.43 mmol) in methylene chloride (5 mL) was added triethylamine (217 mg, 2.15 mmol) followed by 1-acetylimidazole (95 mg, 0.86 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure. The residue was dissolved in methanol (6 mL) and water (3 mL) and treated with potassium carbonate (300 mg, 2.17 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was acidified with 1N hydrochloric acid and extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with saturated sodium chloride, and dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 0-5% methanol/methylene chloride provided the desired product (85 mg, 49%) as a white foam. ESI MS *m/z* 407 $[C_{21}H_{24}F_2N_2O_4 + H]^+$;

HPLC (Method B) 98.0% (AUC), t_R = 7.01 min. Anal. Calcd for $C_{21}H_{24}F_2N_2O_4 \cdot 0.25\ H_2O$: C, 61.38; H, 6.01; N, 6.82. Found: C, 61.60; H, 5.68; N, 6.59.

Scheme for preparing isochromen-4-yl compounds



Example 63: N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-1H-isochromen-4-ylamino)-2-hydroxypropyl]acetamide.



Step One: 2-[(carboxymethoxy)methyl]benzoic acid.

A mixture of (2-cyano-benzyloxy)-acetic acid ethyl ester (*J. Org. Chem.* 1985, *50*, 2128) (30 g, 136 mmol) and KOH (38 g, 680 mmol) in 1:1 EtOH/H_2O (270 ml) was heated to 90°C (oil bath) for 15 h. After cooling to room temperature the mixture was treated with conc. HCl until the pH = 1 and extracted with CH_2Cl_2. The combined organic layers were dried concentrated *in vacuo* to yield an orange oil. The oil was dissolved in aq. Na_2CO_3, treated with activated carbon, filtered and the pH adjusted to 1 with conc. HCl. The resulting solid was collected by filtration and dried to yield 8.2 g of 2-[(carboxymethoxy)methyl]benzoic acid as a tan solid. ^1H NMR

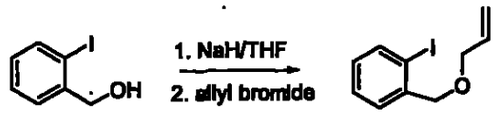
(400 MHz, DMSO-d_6) δ 12.9 (bs, 1 H), 7.87 (dd, J = 7.77, 1.14 Hz, 1 H), 7.66 (m, 1 H), 7.59 (m, 1 H), 7.39 (m, 1 H), 4.90 (s, 2 H), 4.15 (m, 2 H).

Step Two: 1H-isochromen-4(3H)-one.

A mixture of the product of step one(8.2 g, 39.0 mmol), KOAc (16.5 g, 167.8 mmol) and Ac_2O (117 ml) was heated to reflux for 2 h. The mixture was cooled to room temperature then poured onto ice. The mixture was extracted with Et_2O (3 x 100 ml) and the combined organic layers dried over Mg SO_4 and concentrated *in vacuo*. The resulting residue was dissolved in 40 ml of EtOH followed by the addition of 15 ml of 2 N NaOH. Stirring was continued at room temperature for 2h then the EtOH was removed *in vacuo*. The resulting aqueous layer was extracted with Et_2O (3 x 75 ml) and the combined organic layers dried over $MgSO_4$, concentrated *in vacuo* to yield 2.7 g of 1H-isochromen-4(3H)-one as a slight yellow oil after flash chromatography (10% EtOAc/Hexanes) R_f = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.88 Hz, 1 H), 7.59 (m, 1 H), 7.43 (appt, J = 7.36 Hz, 1 H), 7.24 (d, J = 7.67 Hz, 1 H), 4.91 (s, 2 H), 4.39 (s, 2 H). Anal calcd for $C_9H_8O_2$; C, 72.96; H, 5.44; found C, 72.50; H, 5.29. MS (ESI+) for $C_9H_8O_2$ m/z 148.8 $(M+H)^+$.

Alternative Preparation of 1H-isochromen-4(3H)-one

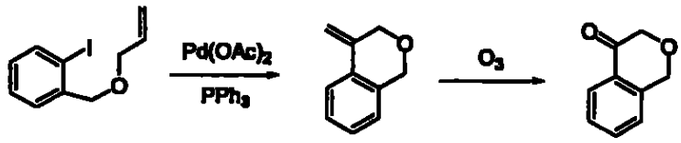
Step 1 A: 1-[(allyloxy)methyl]-2-iodobenzene.



To a THF (200 ml) solution of 2-iodo-benzyl alcohol (25 g, 107 mmol), at r.t., was added the NaH (5.12 g, 128 mmol) in small portions. After complete addition of the NaH the allyl bromide (11.1 ml , 128 mmol) was added via syringe. The mixture was stirred overnight at room temperature. The

resulting white heterogeneous mixture was quenched with H_2O (100 ml) and diluted with 300 ml of Et_2O followed by washing with H_2O (2 x 100 ml) and brine (1 x 100 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield 31 g of 1-[(allyloxy)methyl]-2-iodobenzene as a faint yellow oil. HRMS (ESI+) calcd for $C_{10}H_{11}IO$ *m/z* 273.9857 $(M+H)^+$. Found 273.9855.

Step 2 A: 1H-isochromen-4(3H)-one.



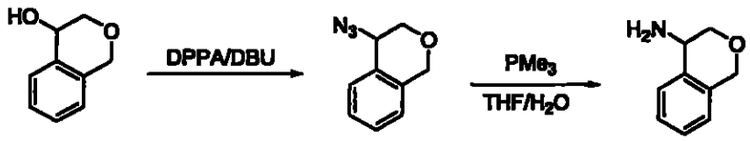
1-[(allyloxy)methyl]-2-iodobenzene (23 g, 83.9 mmol) was dissolved in 100 ml of CH_3CN and 58 ml of Et_3N. The solution was vacuum degassed (3 cycles) followed by the addition of $Pd(OAc)_2$ (0.9 g, 4.2 mmol) and PPh_3 (2.2 g, 8.4 mmol). The mixture was heated to 80°C until HPLC indicated complete reaction. The mixture was cooled to room temperature and diluted with Et_2O (200 ml). The mixture was washed with 1N HCl (2x 50 ml); $NaHCO_3$ (2 x 50 ml); brine (1 x 50 ml); dried over Na_2SO_4 and concentrated *in vacuo* to yield 4-methylene-3,4-dihydro-1H-isochromene (*Heterocycles* 1994, *39*, 497) as an oil. HRMS (ESI+) calcd for $C_{10}H_{10}O$ *m/z* 146.0732 $(M+H)^+$. Found 146.0728. The crude oil was dissolved in 1:1 CH_3OH/CH_2Cl_2 (500 ml) and 5 ml of pyridine added. The mixture was chilled to -78°C and ozone was bubbled through the mixture for 1 h, at which time TLC indicated complete reaction. The mixture was purged with N_2 at -78°C and treated with Me_2S, then allowed to warm to room temperature and stir for 3h. The reaction was then diluted with CH_2Cl_2 and washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield 5.1 g of 1H-isochromen-4(3H)-one as a slight yellow oil after flash chromatography (10% EtOAc/Hexanes) R_f = 0.25. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.88 Hz, 1 H), 7.59 (m,

1 H), 7.43 (appt, J = 7.36 Hz, 1 H), 7.24 (d, J = 7.67 Hz, 1 H), 4.91 (s, 2 H), 4.39 (s, 2 H. Anal calcd for $C_9H_8O_2$; C, 72.96; H, 5.44; found C, 72.50; H, 5.29. MS (ESI+) for $C_9H_8O_2$ m/z 148.8 $(M+H)^+$.

Step Three: 3,4-dihydro-1H-isochromen-4-ol.

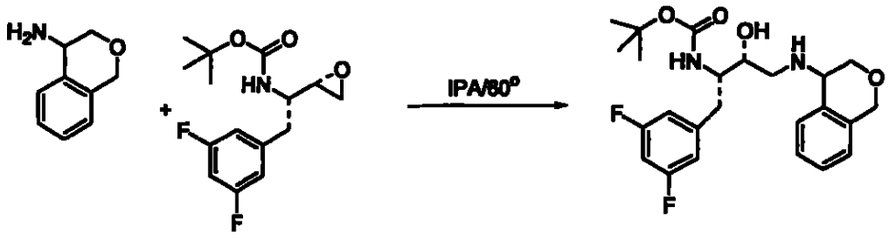
The alcohol was prepared from the ketone essentially according to the method of Example 17, step 1; it was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 1 H), 7.31 (m, 2 H), 7.04 (m, 1 H), 4.84 (d, J = 15 Hz, 1 H), 4.72 (d, J = 15 Hz, 1 H), 4.58 (appt, J = 2.38 Hz, 1 H), 4.14 (dd, J = 12.02, 2.70 Hz, 1 H), 3.91 (dd, J = 12.02, 2.70 Hz, 1 H), 2.24 (bs, 1 H). Anal calcd for $C_9H_{10}O_2$; C, 71.98; H, 6.71; found C, 71.80; H, 6.94.

Step Four: 3,4-dihydro-1H-isochromen-4-amine.



The above compound was prepared from the alcohol, essentially according to the method of Example 19, step 2. First, the alcohol is converted to the azide, which is obtained as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.09 (m, 4 H), 4.90 (d, J = 15.26 Hz, 1 H), 4.75 (d, J = 15.26 Hz, 1 H), 4.23 (m, 2 H), 3.98 (dd, J = 12.43, 3.39 Hz, 1 H). The crude azide was then reduced using PMe_3, affording the amine. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 1 H), 7.30-7.22 (m, 2 H), 7.01 (m, 1 H), 4.85 (d, J = 15 Hz, 1 H), 4.75 (d, J = 15 Hz, 1 H), 4.00-3.86 (m, 3 H), 1.80 (bs, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.6, 128.6, 127.5, 127.4, 124.5, 72.75, 68.61, 48.23.MS (ESI+) for $C_9H_{11}NO$ m/z 133.2 $(M+H)^+$ (loss of NH_2).

Step Five: tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-1H-isochromen-4-ylamino)-2-hydroxypropylcarbamate.



The coupled product was prepared essentially according to the method of Example 17, step 3; the resulting mixture of epimers was obtained as an off white solid and was used in the next step without further purification.. HRMS (ESI+) calcd for C24 $H_{30}F_2N_2O_4$ *m/z* 449.2252 $(M+H)^+$. Found 449.2244.

Step Six: N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-1H-isochromen-4-ylamino)-2-hydroxypropyl]acetamide.

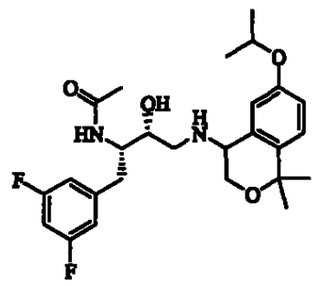
The above compound was prepared essentially according to the method of Example 15, step 3; the acetamide was obtained as a white foam. Small scale reverse phase HPLC of the mixture of epimers results in partial separation.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 1 H), 7.28 (m, 2 H), 7.04 (m, 1 H), 6.77 (m, 2 H), 6.68 (m, 1 H), 5.90 (d, *J* = 8.50 Hz, 1 H), 4.83 (d, *J* = 15.13 Hz, 1 H), 4.73 (d, *J* = 15.13 Hz, 1 H), 4.18 (m, 2 H), 3.85 (dd, *J* = 11.82, 2.90 Hz, 1 H), 3.70 (m, 1 H), 3.62 (m, 1 H), 3.00-2.84 (m, 3 H), 2.71 (dd, *J* = 12.34, 7.15 Hz, 1 H), 1.93 (s, 3 H). MS (ESI+) for $C_{21}H_{24}F_2N_2O_3$ *m/z* 391.5 $(M+H)^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 1 H), 7.29 (m, 2 H), 7.05 (m, 1 H), 6.77 (m, 2 H), 6.68 (m, 1 H), 5.88 (d, *J* = 8.91 Hz, 1 H), 4.87 (d, *J* = 15.13 Hz, 1 H), 4.74 (d, *J* = 15.13 Hz, 1 H), 4.26-4.16 (m, 2 H), 3.84 (m, 2 H), 3.75 (bs, 1 H), 3.57

(m, 2 H), 3.04-2.85 (m, 3 H), 2.76 (dd, J = 12.34, 6.53 Hz, 1 H), 1.90 (s, 3 H). MS (ESI+) for $C_{21}H_{24}F_2N_2O_3$ m/z 391.5 $(M+H)^+$.

Example 64: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromen-4-yl)amino]propyl}acetamide.



Step One: 6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromene.

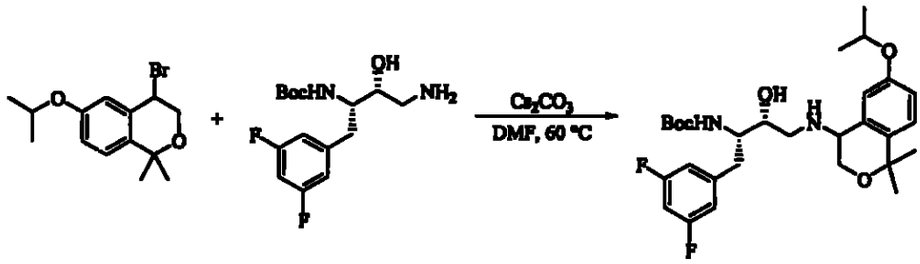
The ether was prepred from the alcohol essentially according to the method of Example 61, step 3; the ether was obtained as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.6 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 4.54-4.46 (m, 1H), 3.92 (t, J = 5.5 Hz, 2H), 2.77 (t, J = 5.5 Hz, 2H), 1.49 (s, 6H), 1.32 (d, J = 6.0 Hz, 6H).

Step Two: 4-bromo-6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromene

A solution of the product from step 1 (0.22 g, 1.0 mmol), *N*-bromosuccinimide (0.19 g, 1.05 mmol), and AIBN (catalytic) in carbon tetrachloride (3 mL) was degassed with nitrogen for 10 min, and then stirred at 65 °C for 2.5 h. The reaction mixture was cooled in an ice-water bath, diluted with methylene chloride (150 mL) and washed with water (2 × 50 mL), saturated sodium chloride (50 mL), dried (sodium sulfate),

filtered, and concentrated. The crude product was purified by flash chromatography (silica, 10:1 hexanes/ethyl acetate) to afford the bromide (1.02 g, 53%) as a pale-yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.5 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.18 (m, 1H), 4.54–4.48 (m, 1H), 4.19 (dd, *J* = 12.8, 3.0 Hz, 1H), 4.11 (dd, *J* = 12.8, 3.0 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 6H).

Step Three: *tert*-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromen-4-yl)amino]propylcarbamate.

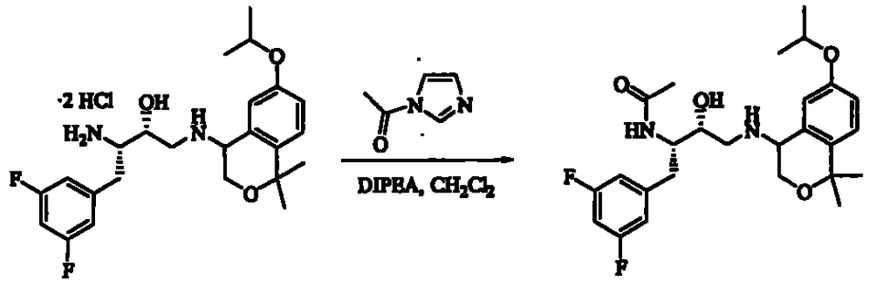


A solution of 4-bromo-6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromene (0.61 g, 2.04 mmol), cesium carbonate (1.33 g, 4.08 mmol), and *tert*-butyl (1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (0.64 g, 2.04 mmol) in *N*,*N*-dimethylformamide (10 mL) was stirred at 60 °C, under nitrogen, for 24 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 5% lithium chloride (3 x 40 mL), water (2 x 30 mL), saturated sodium chloride (30 mL), dried (sodium sulfate), and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, 95:5 methylene chloride/methanol) to afford the desired product (0.51 g, 47%) as a pale-yellow foam: ESI MS *m/z* 535 $[C_{29}H_{40}F_2N_2O_5 + H]^+$.

Step Four: (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromen-4-yl)amino]butan-2-ol hydrochloride.

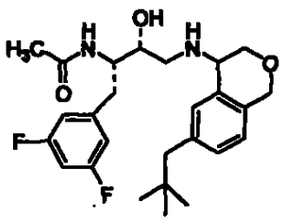
The free amine was prepared from the Boc-amine essentially according to the method of Example 61, step 7; the amine was obtained as a yellow solid: ESI MS m/z 435 $[C_{24}H_{32}F_2N_2O_3 + H]^+$.

Step Five: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromen-4-yl)amino]propyl}acetamide.

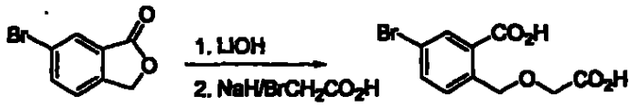


The acetamide was prepared from the free amine essentially according to the method of Example 61, step 7. The crude product was purified by flash chromatography (silica, 95:5 methylene chloride/methanol) to afford the acetamide as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.4 Hz, 1H), 6.82-6.74 (m, 4H), 6.69-6.63 (m, 1H), 5.81-5.78 (m, 1H), 4.56-4.52 (m, 1H), 4.21-4.17 (m, 1H), 3.94 (d, *J* = 2.1 Hz, 2H), 3.50-3.48 (m, 2H), 3.00-2.85 (m, 3H), 2.71-2.64 (m, 1H), 1.88 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 6H); ESI MS *m/z* 477 $[C_{26}H_{34}F_2N_2O_4 + H]^+$; HPLC (Method A) >99% mixture of diastereomers (AUC), t_R = 6.12 and 6.77 min.

Example 65: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-3,4-dihydro-1H-isochromen-4-yl)amino]propyl}acetamide



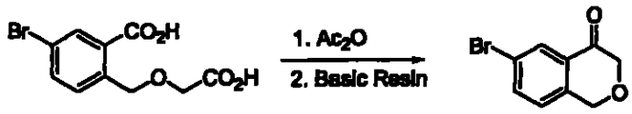
Step One: 5-Bromo-2-carboxymethoxymethyl-benzoic acid



Lithium hydroxide monohydrate (11.80 g, 281.6 mmol) was added at room temperature over several minutes to a solution of 5-bromophthalide (20.0 g, 93.88 mmol) in a 2:1:1 solution of tetrahydrofuran/methanol/water (570 mL) and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and azeotropically dried with benzene to give 5-Bromo-2-hydroxymethyl-benzoic acid as a white solid. The material was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.89 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 1.9 Hz, 1H), 7.50 (dd, J = 8.3, 1.9 Hz, 1H), 3.99 (s, 2H); ESI MS (negative mode) m/z 229 $[C_8H_7BrO_3 - H]^-$. Sodium hyride (15.0 g, 375 mmol, 60% dispersion in mineral oil) was added in small portions over the course of 0.5 h at room temperature to a solution of 5-Bromo-2-hydroxymethyl-benzoic acid in tetrahydrofuran (235 mL) containing bromoacetic acid (14.35 g, 103.2 mmol) and sodium iodide (1.41 g, 9.4 mmol). The reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and poured into water and then extracted with diethyl ether. The aqueous phase was acidified with 10% hydrochloric acid to pH 3-4 and extracted several times with ethyl acetate. The combined ethyl acetate phases were washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield . -Bromo-2-carboxymethoxymethyl-benzoic acid as a white solid. The material was used without further purification: ^{1}H NMR (300

MHz, CD_3OD) δ 7.93-7.86 (m, 2H), 7.55-7.50 (m, 1H), 4.98 (s, 2H), 4.23 (s, 2H); ESI MS (negative mode) *m/z* 287 $[C_{10}H_9BrO_5 - H]^-$.

Step Two: 6-Bromo-isochroman-4-one

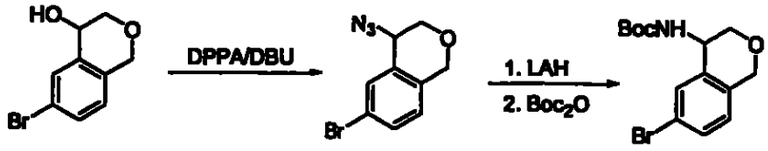


A solution of Bromo-2-carboxymethoxymethyl-benzoic acid in acetic anhydride (350 mL) containing potassium acetate (170 g) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure and the residue partitioned between ethyl acetate and water. The phases were separated and the aqueous phase extracted with ethyl acetate. The combined ethyl acetate phase was then washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield a red semi-solid. Purification by flash column chromatography over silica (85:15 hexanes/ethyl acetate) gave the enol acetate (7.59 g, 29% for three steps) as a golden syrup: ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.19 (d, *J* = 1.9 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.04 (s, 2H), 2.29 (s, 3H). Unactivated Dowex 500A OH anion exchange resin (1 g) added in one portion to a solution of the acetate enol acetate (5.95 g, 22.11 mmol) in methanol (50 mL) and the reaction mixture stirred at room temperature overnight. The reaction mixture was gravity filtered and the resin washed with fresh methanol. The combined filtrate was then concentrated under reduced pressure to yield 6-Bromo-isochroman-4-one (4.32 g, 86%) as a yellow oil, which solidified on standing: ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.41 (d, *J* = 1.7 Hz, 1H), 4.86 (s, 2H), 4.36 (s, 2H).

Step Three: 6-Bromo-isochroman-4-ol

A solution of sodium borohydride (300 mg, 7.93 mmol) dissolved in a minimum amount of ice cold water was added dropwise at 0 °C to a solution of 6-Bromo-isochroman-4-one (1.49 g, 6.56 mmol) in absolute ethanol (27.0 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The phases were separated and the organic phase washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield 6-Bromo-isochroman-4-ol (1.44 g, 95%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.3, 1.8 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 1.8 Hz, 1H), 4.63 (ABq, J = 15.3 Hz, 2H), 4.49 (d, J = 8.6 Hz, 1H), 4.07 (dd, J = 12.0, 2.8 Hz, 1H), 3.83 (dd, J = 12.0, 2.8 Hz, 1H), 2.60 (d, J = 9.2 Hz, 1H).

Step Four: (6-Bromo-isochroman-4-yl)-carbamic acid tert-butyl ester.

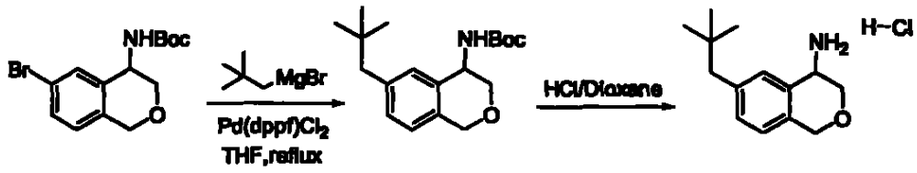


Diphenyphosphoryl azide (2.11 mL, 9.8 mmol) was added at 0 °C to a solution of 6-Bromo-isochroman-4-ol (1.87 g, 8.16 mmol) in toluene (17 mL). To this was added dropwise over 0.5 h a mixture of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.46 ml, 9.8 mmol) in toluene (5.0 ml). The reaction mixture was then stirred at room temperature overnight. The reaction mixture was then passed through a plug of silica and the plug rinsed with 6:1 hexanes/ethyl acetate. The combined filtrates were concentrated under reduced pressure to provide the azide as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.33 (m, 3H), 4.76 (ABq, J = 15.5 Hz, 2H), 4.22-4.16 (m, 3H), 3.93 (dd, J = 11.7, 2.6 Hz, 1H). A solution of lithium aluminum hydride (391 mg,

9.79 mmol) in a minimum amount of tetrahydrofuran (2.0 mL) was added dropwise at 0 °C to a solution of the azide in tetrahydrofuran (30 mL) and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and quenched with water (0.5 mL), 15% sodium hydroxide (1.2 ml), water (0.5 mL) and the reaction mixture stirred at room temperature for 1 h. The resulting mixture was then passed through a plug of silica and the plug rinsed with ether. The combined filtrates were concentrated under reduced pressure to afford a oil which was dissolved in a minimum amount of ethyl acetate to which was added hydrogen chloride (3.0 ml, 4 N in 1,4-dioxane, 12 mmol) and the reaction mixture stirred at room temperature overnight. The reaction mixture was vacuum filtered to afford the desired amine salt (1.54 g, 72 % for two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.44 (m, 2H), 7.37 (s, 1H), 4.80 (ABq, *J* = 15.5 Hz, 2H), 4.42 (d, *J* = 12.8 Hz, 1H), 4.34 (s, 1H), 3.87 (dd, *J* = 12.8, 2.2 Hz, 1H), 3.66 (s, 3 H); ESI MS *m/z* 228 $[C_9H_{10}BrNO + H]^+$.

Di-tert-butyl dicarbonate (1.40 g, 6.40 mmol) was added in portions to a solution of amine (1.54 g, 5.82 mmol) in acetonitrile (25 mL) containing *N,N*-diisopropylethylamine (4.0 mL, 23.28 mmol) and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a yellow syrup. Purification by flash column chromatography over silica (80:20 hexanes/ethyl acetate) yielded the desired product (1.05 g, 55%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.23 (m, 2H), 7.15 (s, 1H), 5.10-5.07 (m, 1H), 4.69 (ABq, *J* = 15.5 Hz, 2H), 4.04-4.00 (m, 1H), 3.89-3.81 (m, 1H), 1.45 (s, 9 H).

Step Five: 6-(2,2-Dimethyl-propyl)-isochroman-4-ylamine hydrochloride.



Neo-pentylmagnesium bromide (10 mL, 9.1 mmol, 1.0 M in ether) was added dropwise to a solution of zinc chloride (18.2 mL, 0.5 M in tetrahydrofuran, 9.1 mmol) over 0.5 h and the reaction mixture stirred at RT for an additional 0.5 h. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (250 mg, 0.30 mmol) was added to the reaction mixture followed by (6-Bromo-isochroman-4-yl)-carbamic acid tert-butyl ester (1.00 g, 3.04 mmol) and the reaction mixture heated at reflux for 1 h. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate and washed with water, sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography over silica (83:17 hexanes/ethyl acetate) yielded the desired protected amine (303 mg, 31%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.23 (m, 1H), 7.00 (d, *J* = 6.3 Hz, 1H), 6.74 (s, 1H), 5.09-5.06 (m, 1H), 4.79-4.65 (m, 3H), 4.13-3.85 (m, 2H), 2.45 (s, 2H), 1.46 (s, 9 H), 0.89 (s, 9H); ESI MS *m/z* 320 $[C_{19}H_{29}NO_3 + H]^+$. A solution of protected amine (303 mg, 0.95 mmol) in hydrogen chloride (20 mL, 4 N in 1,4-dioxane, 80 mmol) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to give 6-(2,2-Dimethyl-propyl)-isochroman-4-ylamine hydrochloride (210 mg, quantitative) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6, 1.2 Hz, 1H), 6.73 (d, *J* = 1.2 Hz, 1H), 4.75 (ABq, *J* = 15.0 Hz, 2H), 3.96-3.80 (m, 3H),

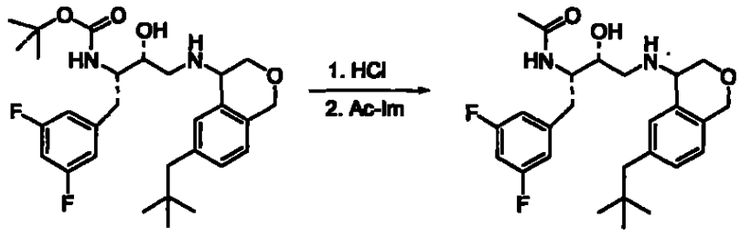
117

2.44 (s, 2H), 1.73 (m, 2H), 0.89 (s, 9H); ESI MS *m/z* 220 $[C_{14}H_{21}NO + H]^+$.

Step Six: tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-3,4-dihydro-1H-isochromen-4-yl)amino]propylcarbamate.

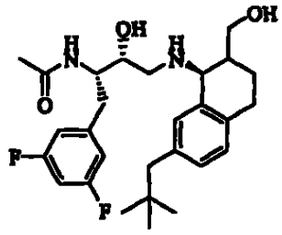
The above compound was prepared essentially according to the method of Example 17, step 3. The resulting crude material was purified by flash column chromatography over silica (94:6 chloroform/methanol) to yield the desired product as a white foam: ESI MS *m/z* 519 $[C_{29}H_{40}F_2N_2O_4 + H]^+$.

Step Seven: N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-3,4-dihydro-1H-isochromen-4-yl)amino]propyl}acetamide.



The acetamide was prepared from the Boc-protected amine essentially according to the method of Example 61, steps 7 and 8. First, the Boc-protected amine was deprotected to afford the free amine as a white solid. Second, the free amine was acylated to form the acetamide, as a mixture of epimers. ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.16 (m, 2H), 7.01-6.98 (m, 1H), 6.76-6.66 (m, 4H), 5.83 (ABq, *J* = 15.0 Hz, 2H), 4.10-4.05 (m, 2H), 3.83-3.79 (m, 1H), 3.55-3.51 (m, 2H), 2.93-2.72 (m, 3H), 2.69-2.65 (m, 1H), 2.45 (s, 2H), 1.89 (m, 4H), 0.89 (s, 9H); ESI MS *m/z* 461 $[C_{26}H_{34}F_2N_2O_3 + H]^+$; HPLC (1-99, 220) 68.1% Major Epimer (AUC), t_R = 10.89 min and 31.8% Minor Epimer (AUC), t_R = 11.19 min.

Example 66: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-2-(hydroxymethyl)-7-neopentyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)acetamide.



Step One: 7-(2,2-Dimethyl-propyl)-1-hydroxy-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester.



To a solution of tetralone (2.16 g, 10 mmol) in tetrahydrofuran (50 mL) was added sodium hydride (60%, 1.49 g, 37.1 mmol) followed by dimethyl carbonate (2.73g, 30 mmol). The reaction mixture was heated at reflux for 3 h and then allowed to cool to room temperature and quenched with acetic acid (3.6 mL). The solvent was removed under reduced pressure and the residue was diluted with ethyl ether (100 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl ether (2 x 50 mL). The combined extracts were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10-20% ethyl acetate/hexanes) provided the desired product (2.50 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.48 (s, 1H), 7.60 (s, 1H), 7.17-7.08 (m, 2H), 3.85 (s, 3H), 2.84-2.79 (m, 2H), 2.62-2.57 (m, 2H), 2.54 (s, 2H), 0.94 (s, 9H).

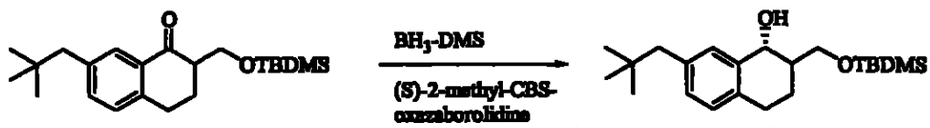
Step Two: 2-(tert-Butyl-dimethyl-silanyloxymethyl)-7-(2,2-dimethyl-propyl)-3,4-dihydro-2H-naphthalen-1-one.

To an ice-cooled solution of 7-(2,2-Dimethyl-propyl)-1-hydroxy-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (2.49 g, 9.07 mmol) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (1 M in tetrahydrofuran, 9 mL, 9 mmol). The reaction mixture was stirred at 0 °C for 2 h and then quenched with saturated ammonium chloride and ethyl acetate. The resulting emulsion was filtered through diatomaceous earth. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10-20% ethyl acetate/hexanes) provided hydroxymethyl tetralone (1.55 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.4 Hz, 1H), 7.27 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 4.00-3.90 (m, 1H), 3.85-3.75 (m, 1H), 3.20-3.10 (m, 1H), 3.08-2.90 (m, 2H), 2.75-2.60 (m, 1H), 2.52 (s, 2H), 2.15-2.05 (m, 1H), 2.00-1.85 (m, 1H), 0.90 (s, 9H).

To a solution of hydroxymethyl tetralone (1.50 g, 6.09 mmol) in *N,N*-dimethyl formamide (6 mL) was added imidazole (500 mg, 7.25 mmol) followed by tert-butyldimethylsilyl chloride (1.03 g, 6.64 mmol). The reaction mixture was stirred at room temperature for 2 h and then diluted with 1:1 hexanes/ethyl acetate (100 mL). The mixture was washed successively with 1N hydrochloric acid, water, saturated sodium bicarbonate and saturated sodium chloride, and dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 2-(tert-Butyl-dimethyl-silanyloxymethyl)-7-(2,2-dimethyl-propyl)-3,4-dihydro-2H-naphthalen-1-one (2.20g, 99% crude yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 4.16-4.08 (m, 2H), 3.90-3.84 (m, 1H), 3.01-2.95 (m, 2H), 2.68-2.60 (m, 1H), 2.51 (s, 2H), 2.42-2.33 (m, 1H), 2.03-1.95 (m, 1H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H),

0.06 (s, 3H). This material was used in the next step without further purification..

Step Three: 2-(tert-Butyl-dimethyl-silanyloxymethyl)-7-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-naphthalen-1-ol.



To a -30 °C cooled solution of 2-(tert-Butyl-dimethyl-silanyloxymethyl)-7-(2,2-dimethyl-propyl)-3,4-dihydro-2H-naphthalen-1-one (2.20 g, 6.09 mmol) in tetrahydrofuran (20 mL) was added (S)-2-methyl-Cbs-oxazaborolidine (1 M in toluene, 0.61 mL, 0.61 mmol) and a solution of borane-methyl sulfide complex (2 M in tetrahydrofuran, 2.15 mL, 4.3 mmol) in tetrahydrofuran (5 mL). The reaction mixture was heated at -20 to -5 °C for 5 h. The reaction mixture was quenched with methanol (8.3 mL) at -5 °C and then allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure. Flash column chromatography (silica gel, 0-5% ethyl acetate/hexanes) recovered 790 mg of ketone and provided chiral 2-(tert-Butyl-dimethyl-silanyloxymethyl)-7-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-naphthalen-1-ol (980 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.03-6.96 (m, 2H), 4.84 (d, J = 2.5 Hz, 1H), 3.92-3.82 (m, 2H), 3.04 (d, J = 3.7 Hz, 1H), 2.92-2.67 (m, 2H), 2.46 (s, 2H), 2.04-1.86 (m, 2H), 1.75-1.63 (m, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

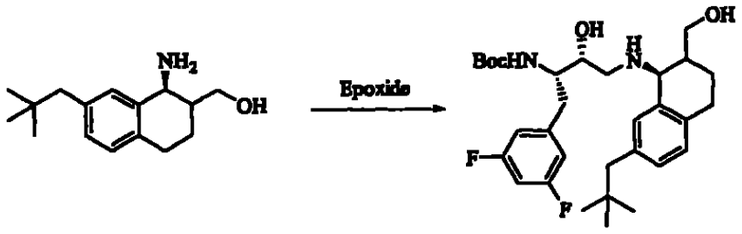
Step Four: [1-Amino-7-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-naphthalen-2-yl]-methanol.

The alcohol was converted into an amine essentially according to the method of Example 65, step 4. However, the resulting amine was not protected, as in Example 65, step 4.

First the alcohol was converted to the azide, which was purified by flash column chromatography (silica gel, 0-5% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.03-6.97 (m, 2H), 4.42 (d, *J* = 2.5 Hz, 1H), 3.75 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.67 (dd, *J* = 10.1, 4.8 Hz, 1H), 2.81-2.67 (m, 2H), 2.48 (s, 2H), 2.07-1.98 (m, 2H), 1.80-1.67 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

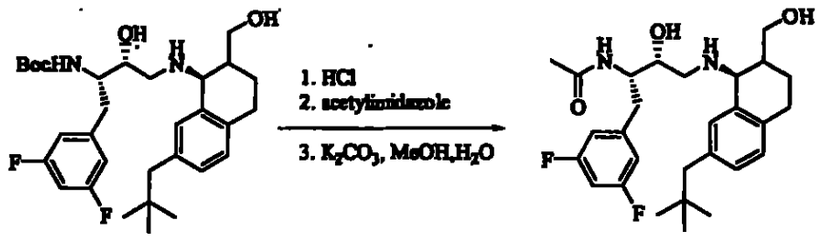
Second, the azide was reduced to the amine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 7.01-6.92 (m, 2H), 3.83-3.70 (m, 3H), 2.92-2.72 (m, 3H), 2.47 (s, 2H), 1.85-1.69 (m, 2H), 1.48-1.33 (m, 1H), 0.90 (s, 9H).

Step Five: *tert*-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-2-(hydroxymethyl)-7-neopentyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propylcarbamate.



The coupling was performed essentially according to the method of Example 17, step 3. The resulting crude product was purified by flash chromatography (silica gel, 1-10% methanol/methylene chloride). : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01-6.91 (m, 3H), 6.76-6.60 (m, 5H), 4.62 (d, *J* = 8.9 Hz, 1H), 4.34-4.30 (m, 1H), 4.07-3.89 (m, 2H), 3.83-3.61 (m, 4H), 3.53-3.47 (m, 2H), 2.95-2.86 (m, 2H), 2.80-2.63 (m, 3H), 2.59-2.57 (m, 2H), 2.45 (s, 2H), 2.15-2.05 (m, 1H), 1.81-1.77 (m, 1H), 1.36 (s, 9H), 0.89 (s, 9H).

Step Six: N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-2-(hydroxymethyl)-7-neopentyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)acetamide.



The above compound was prepared essentially according to the method of Example 15, step 3. First the Boc-protected amine was deprotected. ESI MS *m/z* 447 $[C_{26}H_{36}F_2N_2O_2 + H]^+$.

Second, the amine was acetylated. Then the residue was dissolved in methanol (6 mL) and water (3 mL) and treated with potassium carbonate (300 mg, 2.17 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was acidified with 1N hydrochloric acid and extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with saturated sodium chloride, and dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 0-5% methanol/methylene chloride provided the desired product (80 mg, 44%) as a white foam: IR (ATR) 3265, 3072, 2948, 2864, 1626, 1595, 1550, 1459, 1364, 1315, 1115, 1071, 984, 842 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.15 (s, 1H), 7.07-7.00 (m, 2H), 6.83-6.72 (m, 3H), 4.18 (d, *J* = 5.9 Hz, 1H), 4.06-3.99 (m, 1H), 3.74-3.64 (m, 2H), 3.57 (t, *J* = 8.4 Hz, 1H), 3.34 (s, 2H), 3.13-3.07 (m, 1H), 2.94-2.59 (m, 5H), 2.49 (s, 2H), 2.30-2.20 (m, 1H), 2.04-1.98 (m, 1H), 1.81 (s, 3H), 1.64-1.57 (m, 1H), 0.91 (s, 9H); ESI MS *m/z* 489 $[C_{28}H_{38}F_2N_2O_3 + H]^+$; HPLC (Method C) 98.2% (AUC), t_R = 9.41 min. Anal. Calcd for $C_{21}H_{24}F_2N_2O_4 \cdot H_2O$: C, 66.38; H, 7.96; N, 5.53. Found: C, 66.18; H, 7.80; N, 5.45.

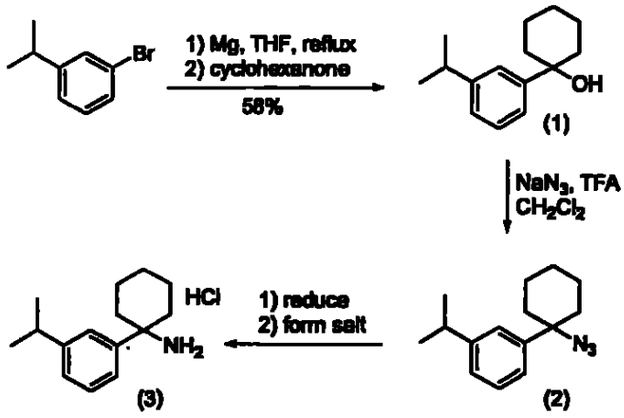
Example 67: 5-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)amino]-5-oxopentanoic acid.

To a solution of 3-amino-4-(3,5-difluoro-phenyl)-1-(7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-butan-2-ol (0.240g, 0.64 mmol), triethylamine (0.268 mL, 1.92 mmol), and chloroform (3 mL) was added glutaric anhydride (0.073 g, 0.64 mmol) and reaction was stirred overnight at 60°C. Reaction was washed with 1N HCl, 10% $NaHCO_3$, brine, dried over $MgSO_4$, filtered, concentrated *in vacuo* to give 5-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)amino]-5-oxopentanoic acid (100 mg). Purified via prep-HPLC. ^1H NMR (400 MHz, CD_3OD) δ 1.26 (t, J = 8 Hz, 3 H), 1.73 (m, 2 H), 1.89 (m, 1 H), 2.01 (m, 1 H), 2.17 (m, 6 H), 2.68 (d, J = 8 Hz, 2 H), 2.93 (d, J = 6 Hz, 1 H), 3.02 (m, 1 H), 3.30 (m, 2 H), 3.88 (m, 1 H), 4.09 (m, 1 H), 4.57 (m, 1 H), 6.79 (m, 1 H), 6.88 (m, 3 H), 6.93 (d, J = 6 Hz, 1 H), 7.20 (m, 2 H), 7.31 (s, 1 H); OAMS: ES+ 488.9 ES- 486.9

Example 68: 4-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)amino]-4-oxobutanoic acid.

The above compound was prepared essentially according to the method of Example 67. The crude product was purified via prep-HPLC. ^1H NMR (400 MHz, CD_3OD) δ 1.27 (t, J = 8 Hz, 3 H), 1.88 (m, 1 H), 2.04 (m, 1 H), 2.25 (m, 3 H), 2.48 (m, 2 H), 2.70 (m, 4 H), 2.81 (m, 1 H), 2.93 (m, 1 H), 3.12 (dd, J = 8, 13 Hz, 1 H), 3.32 (m, 2 H), 3.87 (m, 1 H), 4.04 (m, 1 H), 4.51 (s, 1 H), 6.80 (m, 1 H), 6.86 (d, J = 6 Hz, 2 H), 7.18 (dd, J = 8, 19 Hz, 2 H), 7.32 (s, 1 H); OAMS: ES+ 474.9, ES- 472.9.

EXAMPLE 69: Preparation of 1-(3-isopropylphenyl)cyclohexanamine hydrochloride 3.



Step 1. Preparation of 1-(3-isopropylphenyl)cyclohexanol 1.

To 1.2 g (50 mmol) of magnesium turnings in 15 mL of dry THF is added a small crystal of iodine followed by 40 µL of dibromoethane. This mixture is placed in a water bath at 50 °C and 3-isopropylbromobenzene (5.0 g, 25 mmol) in 15 mL of dry tetrahydrofuran (THF) is added dropwise over 20 min, while the bath temperature is raised to 70 °C. The mixture is stirred and refluxed for 40 additional min. The solution is cooled in an ice-water bath and cyclohexanone (2.0 mL, 19 mmol) in 10 mL of dry THF is added dropwise over 15 min. The ice bath is removed and the mixture is allowed to warm to ambient temperature over 1h. The solution is decanted into aqueous saturated NH_4Cl, and combined with an ether wash of the residual magnesium turnings. The organic phase is washed twice more with aqueous NH_4Cl, dried over anhydrous Na_2SO_4, filtered and concentrated. Chromatography on silica gel, eluting with 10% ethyl acetate in heptane, affords 2.7 g (12 mmol, 60%) of compound 1 as an oil: ^1H NMR ($CDCl_3$) δ 7.39 (m, 1 H), 7.3 (m, 2 H), 7.12 (m, 1 H), 2.92 (m, 1 H), 1.84-1.54 (m, 10 H), 1.26 (d, J = 7 Hz, 6 H).

Step 2. Preparation of 1-(3-isopropylphenyl)cyclohexylazide (2).

To 3.20 g (14.7 mmol) of compound 1 in 60 mL of CH_2Cl_2 under nitrogen is added 2.10g (32.3 mmol) of sodium azide. The stirred suspension is cooled to -5°C and a solution of trifluoroacetic acid (9.0 mL, 120 mmol) in 35 mL of dichloromethane is added dropwise over 1 h. The resulting suspension is stirred at 0 °C for an additional hour. To the cold, vigorously stirred mixture is added, dropwise, 10 mL of water, followed by dropwise addition of a mixture of 10 mL of water and 10 mL of concentrated ammonium hydroxide. After 30 min the mixture is poured into a separatory funnel containing 350 mL of a 1:1 mixture of heptane and ethyl acetate, and 100 mL of water. The organic phase is washed with an additional portion of water, followed successively by 1 N KH_2PO_4, water, and brine. It is then dried over anhydrous Na_2SO_4, filtered and concentrated to afford 3.6 g (14.7 mmol, 100%) of 2 as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.3 (m, 2 H), 7.25 (m, 1 H), 7.16 (m, 1 H), 2.92 (m, 1 H), 2.01 (m, 2 H), 1.83 (m, 2 H), 1.73-1.64 (m, 5 H), 1.3 (m, 1 H), 1.26 (d, J = 7 Hz, 6 H).

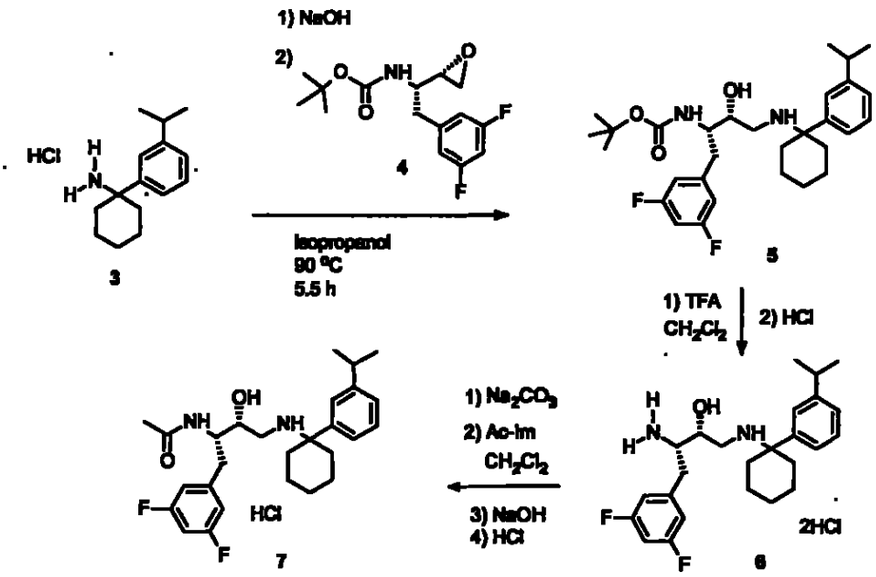
Step 3. Preparation of 1-(3-isopropylphenyl)cyclohexanamine hydrochloride 3.

To 1-(3-isopropylphenyl)cyclohexylazide 2 (2.7 g, 11 mmol) in 200 mL of ethanol is added 20 mL of glacial acetic acid and 0.54 g of 10% palladium on carbon. The mixture is evacuated and placed under 16 psi of hydrogen, with shaking, for 2.5 h. The reaction mixture is filtered, the catalyst is washed with ethanol, and the solvents are removed *in vacuo*. Residual acetic acid is removed by chasing the residue with toluene. The acetate salt is dissolved in ethyl acetate and 1 N NaOH is added. The organic phase is washed with more 1 N NaOH and then with water, dried over Na_2SO_4, filtered and

concentrated. The residue is dissolved in ether and ethereal HCl (concentrated HCl in ether which has been stored over $MgSO_4$) is added to afford a white solid. This is filtered, washed with ether, collected as a solution in dichloromethane, and concentrated to afford 2.1 g (8.3 mmol, 75%) of hydrochloride 3 as a white solid: ^1H NMR ($CDCl_3$) δ 8.42 (br s, 3 H), 7.43 (m, 2 H), 7.25 (m, 1 H), 7.15 (m, 1 H), 2.92 (hept, *J* = 7 Hz, 1 H), 2.26 (m, 2 H), 2.00 (m, 2 H), 1.69 (m, 2 H), 1.45-1.3 (m, 4 H), 1.24 (d, *J* = 7 Hz, 6 H); IR (diffuse reflectance) 2944, 2864, 2766, 2707, 2490, 2447, 2411, 2368, 2052, 1599, 1522, 1455, 1357, 796, 704 cm -1. MS (EI)m/z(rel intensity) 217 (M+,26), 200 (13), 175 (18), 174 (99), 157 (15), 146 (23), 132 (56), 131 (11), 130 (16), 129 (18). HRMS (ESI) calcd for $C_{15}H_{23}N+H_1$ 218.1909, found 218.1910. Anal. Calcd for $C_{15}H_{23}N.HCl$: C, 70.98; H, 9.53; N, 5.52; Cl, 13.97. Found: C, 70.98; H, 9.38; N, 5.49.

EXAMPLE 70: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 7

Scheme 2



Step 1. Preparation of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propylcarbamate (5).

Compound 3 (2.1 g, 8.3 mmol) is shaken with aqueous 1 N NaOH and ethyl acetate. The layers are separated and the organic phase is washed sequentially with aqueous NaOH and then with 1N $NaHCO_3$. The organic layer is then dried over Na_2SO_4, filtered, and concentrated to afford a quantitative yield (1.8 g) of the free amine as an oil. Example 134 (4, 1.5 g, 5.0 mmol) is combined with the free amine in 35 mL of isopropyl alcohol, and the mixture is heated at reflux for 5.5 h, under nitrogen. The mixture is cooled and concentrated in vacuo. The resulting residue is dissolved in 250 mL of ethyl ether, which is washed four times with 30 mL portions of aqueous 10% HCl to remove much of the excess amine 3. The ether phase is then washed twice with 1N $NaHCO_3$, once with

brine, dried over Na_2SO_4, filtered, and concentrated. The concentrate is chromatographed over silica gel, eluting with 4% to 6% methanol (containing 2% NH_4OH) in CH_2Cl_2 to afford 1.98g (3.8 mmol, 77%) of 5 as a viscous oil: ^1H NMR ($CDCl_3$) δ 7.28-7.21 (m, 3 H), 7.09 (m, 1 H), 6.69 (m, 2 H), 6.62 (m, 1 H), 4.68 (d, J = 10 Hz, 1 H), 3.74 (m, 1 H), 3.47 (m, 1 H), 2.93-2.86 (m, 2 H), 2.67 (dd, J = 8, 14 Hz, 1 H), 2.32 (m, 2 H), 1.88 (m, 4 H), 1.63-1.52 (m, 5 H), 1.36 (s +m, 10 H), 1.24 (d, J = 7 Hz, 6 H); MS (CI) m/z 517.4 (MH+).

Step 2. Preparation of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-isopropylphenyl)cyclohexyl] amino}butan-2-ol dihydrochloride 6

To 1.98 g (3.8 mmol) of compound 5 in 15 mL of CH_2Cl_2 is added 6.5 mL of trifluoroacetic acid. The mixture is stirred under a nitrogen atmosphere for 1 h and then concentrated. The resulting residue is taken up in ethyl acetate and washed twice with 10% Na_2CO_3 and once with 1 N $NaHCO_3$. The organic layer is dried over anhydrous Na_2SO_4, filtered, and concentrated to afford 1.6 g (quant.) of a pale yellow oil (free base of 6), which is generally carried on in the next step without characterization. The yellow oil may be dissolved in ether and treated with ethereal HCl to precipitate (dihydrochloride 6 as a white solid after trituration with ether: ^1H NMR ($CDCl_3$ +CD_3OD drop) δ 7.55 (s, 1 H), 7.45-7.15 (m, 3 H), 6.85 (m, 2 H), 6.75 (m, 1 H), 4.4 (d, J = 9.5 Hz, 1 H), 3.82 (m, 1 H), 2.97 (m, 2 H), 2.81 (dd, J = 8, 14 Hz, 1 H), 2.65 (m, 2 H), 2.5 (obscured by water) 2.26 (m, 1 H), 2.13 (m, 2 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.45-1.25 (m, 3 H), 1.28 (d, J = 7 Hz, 6 H); MS (CI) m/z 417.3 (MH+).

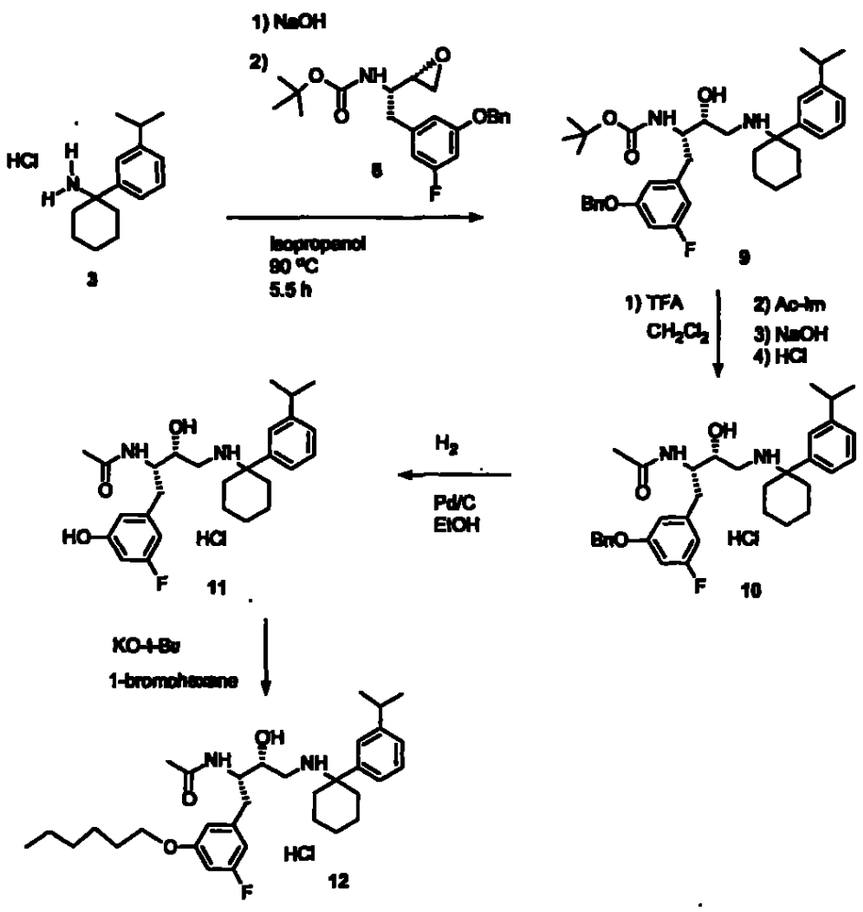
Step 3. Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-

isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 7

The free base of compound 6 (1.6 g, 3.8 mmol) is dissolved in 20 mL of CH_2Cl_2 under nitrogen, and 0.87 g (7.9 mmol) of acetyl imidazole is added with stirring. After 15 min., 30 mL of methanol is added, followed by 15 mL of 1 N NaOH to saponify the ester that is formed along with the amide. The CH_2Cl_2 is removed *in vacuo*, and the mixture is neutralized with 1N KH_2PO_4. The product is extracted into ethyl acetate and the organic phase is washed with water, with 1 N $NaHCO_3$, and with brine. The solution is dried over Na_2SO_4, filtered and concentrated to an oil, which is chromatographed over silica gel, eluting with 5%-7% methanol (containing 1% of NH_4OH) in CH_2Cl_2. Product-containing fractions are pooled, concentrated, dissolved in a small volume of ethanol, and acidified with 0.6 N HCl in dry ether. Concentration from this solvent mixture affords a gel-like material. This can be dissolved in ethanol and ethyl acetate, and concentrated to 1.65 g (3.3 mmol, 87%) an off-white solid. This solid is triturated with ethyl acetate to remove a pale yellow mother liquor, leaving hydrochloride 7 as a white solid: ^1H NMR ($CDCl_3$ +CD_3OD drop) δ 7.44 (s, 1 H), 7.37 (m, 2 H), 7.29 (m, 1 H), 6.70 (m, 2 H), 6.62 (m, 1 H), 3.94 (m, 1 H), 3.87 (m, 1 H), 3.0-2.94 (m, 2 H), 2.64 (m, 4 H), 2.36 (m, 1 H), 2.09 (m, 2 H), 1.84 (s, 3 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.5-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); IR (diffuse reflectance) 3343, 3254, 2958, 2937, 2866, 2497, 2442, 2377, 1660, 1628, 1598, 1553, 1460, 1116, cm $^{-1}$. MS (EI) m/z (rel intensity) 458 (M+, 7), 415 (20), 230 (35), 202 (18), 201 (99), 200 (26), 159 (35), 157 (32), 133 (41), 129 (28), 117 (17). HRMS (ESI) calcd for $C_{27}H_{36}N_2O_2F_2+H_1$ 459.2823, found 459.2837. Anal. Calcd for $C_{27}H_{36}F_2N_2O_2.HCl$: C, 65.51; H, 7.53; N, 5.66; Cl, 7.16; F, 7.68. Found: C, 65.19; H, 7.70; N, 5.67. Found; Cl, 7.08.

EXAMPLE 71: Preparation of N-((1S,2R)-1-(3-(hexyloxy)-5-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 12

Scheme 3



Step 1. Preparation of tert-butyl (1S,2R)-1-(3-(benzyloxy)-5-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propylcarbamate (9).

Following essentially the procedure described in Step 1 of EXAMPLE 70, the free base of compound 3 (3.9 mmol) is reacted with compound 8 (0.80 g, 2 mmol) in 20 mL of isopropyl alcohol at reflux overnight. After workup and chromatography over silica gel, eluting with 4% methanol (containing 2% NH_4OH) in CH_2Cl_2, compound 9 is obtained as a colorless syrup (0.92 g, 1.5 mmol, 74%): MS (CI) m/z 605.5 (MH+).

Step 2. Preparation of N-((1S,2R)-1-(3-(benzyloxy)-5-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride (10).

Following essentially the procedures of Steps 2 and 3 of EXAMPLE 70, compound 9 (0.92 g, 1.5 mmol) is converted to hydrochloride 10, which is a white solid: ^1H NMR ($CDCl_3$ +CD_3OD drop) δ 7.46-7.25 (m, 9 H), 6.26 (s, 1 H), 6.53-6.47 (m, 2 H), 5.00 (s, 2 H), 4.01 (m, 1 H), 3.88 (m, 1 H), 2,98-2,89 (m, 2 H), 2.68-2.62 (m, 4 H), 2.3 (m, 1H, obscured by water), 2.14 (m, 2 H), 1.88 (s, 3 H), 1.78 (m, 2 H), 1.58 (m, 1 H), 1.5-1.3 (m, 3 H), 1.26 (d, J = 7 Hz, 6 H); MS (CI) m/z 547.5 (MH+).

Step 3. Preparation of N-((1S,2R)-1-(3-hydroxy-5-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 11.

To a solution of compound 10 (0.70 g, 1.2 mmol) in 70 mL of ethanol in a Parr bottle is added 0.33 g of 10% palladium on carbon. The mixture is placed under 20 psi of hydrogen and shaken for 21 h. The mixture is filtered and the catalyst is washed with ethanol. Concentration *in vacuo* affords a colorless oil, which is treated with ethereal HCl to give a quantitiative yield of hydrochloride 11 as a white solid: ^1H

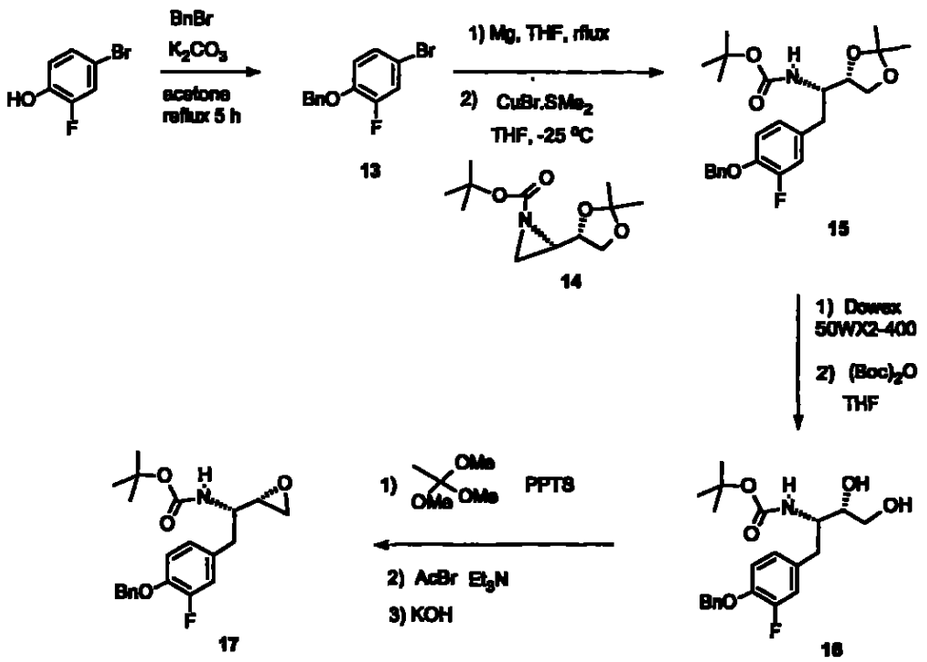
NMR ($CDCl_3$ +CD_3OD drop) δ 7.44 (s, .1 H), 7.37 (m, 2 H), 7.28 (m, 1 H), 6.59 (s, 1 H), 6.40 (m, 1 H), 6.31 (m, 1 H), 4.0 (m, 1 H), 3.79 (m, 1 H), 2.95 (m, 2 H), 2.63 (m, 4 H), 2.44 (m, 1 H), 2.05 (m, 2 H), 1.90 (s, 3 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.5-1.3 (m, 3 H), 1.26 (d, *J* = 7 Hz, 6 H); MS (CI) m/z 457.4 (MH+).

Step 4. Preparation of N-((1S,2R)-1-(3-(hexyloxy)-5-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 12

To 0.40 mmol of hydrochloride 11 in 3 mL of acetone is added 0.29 mL (2.1 mmol) of 1-bromohexane. The mixture is heated to reflux, and 0.6 mL of a 1 M solution of potassium t-butoxide in THF (0.6 mmol) is added. After 1.2 h the mixture is cooled and aqueous 1 N KH_2PO_4 and ethyl acetate are added. The organic phase is washed twice with 1 N $NaHCO_3$ and once with brine, dried over Na_2SO_4, and concentrated. Chromatography over silica gel, eluting with 7%-9% methanol (containing 1% of NH_4OH) in CH_2Cl_2, affords a colorless oil. Treatment with ethereal HCl produces 147 mg (0.25 mmol, 64%) of hydrochloride 12 as a white solid: ^1H NMR ($CDCl_3$ +CD_3OD drop) δ 7.45 (s, 1 H), 7.37 (m, 2 H), 7.27 (m, 1 H), 6.50 (s, 1 H), 6.43 (m, 2 H), 3.98 (m, 1 H), 3.88 (m + t, *J* = 6.5 Hz, 3 H), 2.93 (m, 2 H), 2.63 (m, 4 H), 2.38 (m, 1 H), 2.09 (m, 2 H), 1.89 (s, 3 H), 1.75 (m, 4 H), 1.59 (m, 1 H), 1.43-1.32 (m, 10 H), 1.27 (d, *J* = 7 Hz, 6 H), 0.90 (t, *J* = 7 Hz, 3 H); MS (CI) m/z 541.5 (MH+).

EXAMPLE 72: Preparation of tert-butyl (1S)-2-[4-(benzyloxy)-3-fluorophenyl]-1-[(2S)-oxiran-2-yl]ethylcarbamate 17

Scheme 4



Step 1. Preparation of 1-Benzyloxy-2-fluoro-4-bromobenzene 13.

To a stirred suspension of pulverized K_2CO_3 (49 g, 350 mmol) in 250 mL of acetone is added 6.5 mL (11.3 g, 59 mmol) of 2-fluoro-4-bromophenol and 7 mL (10 g, 59 mmol) of benzyl bromide. The mixture is refluxed under nitrogen 5 h. It is cooled and filtered, washing the residual K_2CO_3 with acetone. Removal of the solvent leaves 17 g of an off-white solid. This is triturated twice with hexanes, redissolved in 250 mL of CH_2Cl_2, and washed successively with 10% Na_2CO_3, water, and brine. The organic phase is dried over Na_2SO_4 and treated with decolorizing charcoal. Filtration and evaporation affords

1-benzyloxy-2-fluoro-4-bromobenzene 13 (13.7g, 49 mmol, 83%) as a colorless oil which crystallizes to a white solid: ^{1}H NMR ($CDCl_3$) δ 7.43-7.33 (m, 5 H), 7.24 (dd, J = 2.3, 10 Hz, 1

H), 7.14 (dt, J = 2, 8.7 Hz, 1 H), 6.86 (t, J = 8.7 Hz, 1 H), 5.12 (s, 2 H).

Step 2. Preparation of tert-butyl (1S)-2-(4-(benzyloxy)-3-fluorophenyl)-1-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]ethylcarbamate (15).

A solution of 1-benzyloxy-2-fluoro-4-bromobenzene 13 (7.0 g, 25 mmol) in 20 mL of dry THF is added dropwise over 20 min to 1.22 g (50 mmol) of magnesium turnings in 10 mL of refluxing THF under nitrogen and the mixture is refluxed for an additional 25 min to form the Grignard reagent. The Grignard solution is cooled and added by cannula to a suspension of CuBr-dimethylsulfide complex (0.52 g, 2.5 mmol) in 15 mL of dry THF at -25 °C. The brown suspension is stirred at -25 °C for 20 min, and then a solution of tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1-carboxylate 14 (3.4 g, 14 mmol) in 15 mL of THF is added dropwise over 5 min. The mixture is allowed to gradually warm to ambient temperature over 3 h. Saturated aqueous NH_4Cl and ethyl ether are added, and the organic phase is washed with two more portions of saturated NH_4Cl and once with brine. The solution is dried over Na_2SO_4 and treated with decolorizing carbon. Filtration and concentration gives a yellow solid, which is triturated twice with ether/heptane to afford 5.4 g (12 mmol, 86%) of compound 15 as a cream-colored solid: MS (CI) m/z 468.3 (MNa+), 446.3 (MH+).

Step 3. Preparation of tert-butyl (1S,2S)-1-[4-(benzyloxy)-3-fluorobenzyl]-2,3-dihydroxypropylcarbamate 16

To a solution of crude (combined solid and mother liquor) compound 15 (maximum 14 mmol) in 90 mL of methanol is added 12 g of Dowex 50WX2-400 which has been extensively washed with

water, methanol, and CH_2Cl_2, and air-dried. The mixture is warmed to 50 °C and stirred for 2 h. It is filtered, washing first with methanol and a 1:1 mixture of methanol and CH_2Cl_2. The receiver is then changed and the product is eluted from the resin with 1:1 methanol:CH_2Cl_2 containing 10% of NH_4OH. The filtrate is concentrated to afford 2.7 g of a white solid. This solid is dissolved in 60 mL of dry THF under nitrogen, cooled to 0 °C, and 2.0 g (9.2 mmol) of di-tert-butyldicarbonate is added. The ice bath is removed and the mixture is stirred at ambient temperature for 18 h. It is concentrated and chromatographed over silica gel, eluting with 49:49:2 to 58:38:4 ethyl acetate:heptane:methanol, affording 3.0 g (7.4 mmol, 53%, two steps) of compound 16 as a white solid: ^1H NMR ($CDCl_3$) δ 7.45-7.30 (m, 5 H), 7.01-6.88 (m, 3 H), 5.12 (s, 2 H), 4.52 (d, J = 9 Hz, 1 H), 3.78 (m, 1 H), 3.62 (m, 2 H), 3.32 (m, 2 H), 3.02 (dd, J = 4, 14 Hz, 1 H), 2.82 (m, 2 H), 1.39 (s, 9 H); MS (CI) m/z 428.2 (MNa+), 406.3 (MH+).

Step 4. Preparation of tert-butyl (1S)-2-[4-(benzyloxy)-3 fluorophenyl]-1-[(2S)-oxiran-2-yl]ethylcarbamate (17)

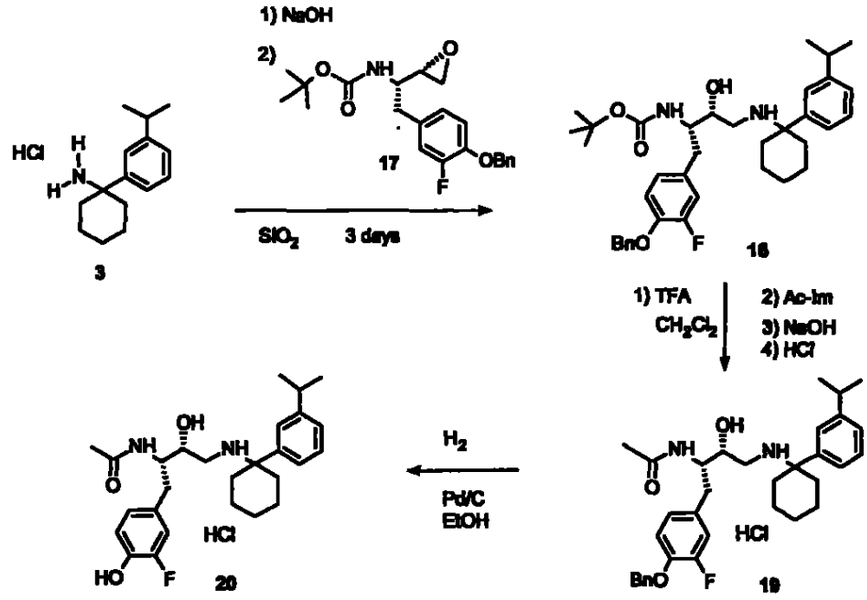
Trimethyl orthoacetate (0.94 mL, 7.4 mmol) is added to a suspension of compound 16 (2.9 g, 7.2 mmol) in 30 mL of CH_2Cl_2 stirred under nitrogen. Pyridinium *p*-toluenesulfonate (18 mg, 0.07 mmol) is added and the resulting pale yellow solution is stirred for 30 min and then concentrated to a white solid. This solid is dissolved in 30 mL of CH_2Cl_2, triethylamine (0.10 mL, 0.72 mmol) is added, and the mixture, under nitrogen, is cooled in an ice bath. Freshly distilled acetyl bromide (0.55 mL, 7.4 mmol) is added dropwise over 3-4 min with stirring. After 1 h, the ice bath is removed and aqueous 1 N $NaHCO_3$ and CH_2Cl_2 are added. The aqueous phase is extracted with additional CH_2Cl_2 and the combined organic phases are dried over $MgSO_4$ and concentrated to a white solid. This solid is

suspended in 25 mL of methanol and 6 mL of THF, and cooled in an ice bath, under nitrogen. Pulverized KOH (0.60 g, 11 mmol) in 6 mL of methanol is added all at once. After 15 min the ice bath is removed and the mixture is allowed to come to ambient temperature over 70 min. The mixture is concentrated and taken up in ethyl acetate and aqueous 1N KH_2PO_4. The organic phase is washed with 1N $NaHCO_3$ and then brine, dried over Na_2SO_4, and concentrated. Chromatography over silica gel, eluting with 20% ethyl acetate and 5% to 10% CH_2Cl_2 in heptane affords 2.0 g (5.2 mmol, 72%) of compound 17 as a white solid: ^1H NMR ($CDCl_3$) δ 7.45-7.30 (m, 5 H), 6.99-6.86 (m, 3 H), 5.12 (s, 2 H), 4.43 (br, 1 H), 3.63 (br, 1 H), 2.90 (m, 2 H), 2.79 (m, 2 H), 2.74 (m, 1 H), 1.39 (s, 9 H); MS (CI) m/z 410.3 (MNa+), 388.3 (MH+).

EXAMPLE 73: Preparation of N-((1S,2R)-1-(3-fluoro-4-hydroxybenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 20

127

Scheme 5



Step 1. Preparation of tert-butyl (1S,2R)-1-(3-fluoro-4-(benyloxy)benzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propylcarbamate (18).

The free base (270 mg, 1.24 mmol) of 1-(3-isopropylphenyl) cyclohexanamine hydrochloride 3 is obtained as a colorless oil by neutralization of the salt with 1N NaOH, extraction into ethyl acetate, drying over Na_2SO_4, and concentration. This is dissolved in 10 mL of CH_2Cl_2, and to it is added compound 17 (280 mg, 0.73 mmol) and 1.25 g of silica gel. The solvent is removed *in vacuo* and the reactants on silica are allowed to stand at ambient temperature for three days. The product mixture is eluted from the silica with 10% methanol in CH_2Cl_2, concentrated, and chromatographed on silica gel, eluting with 4% methanol (containing 2% NH_4OH) in CH_2Cl_2, to afford compound 18 (238 mg, 0.39 mmol, 54%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.43-7.26 (m, 8 H), 7.12 (m, 1 H), 6.94-6.84 (m, 3 H), 5.09 (s, 2 H), 4.64 (d, J = 9 Hz, 1 H), 3.80

(br, 1 H), 3.31 (br, 1 H), 2.92-2.83 (m, 2 H), 2.7 (m, 1 H), 2.37 (m, 2 H), 2.0-1.95 (m, 4 H), 1.67-1.50 (m, 5 H), 1.35 (s+m, 10 H), 1.25 (d, J = 7 Hz, 6 H).

Step 2. Preparation of N-((1S,2R)-1-(3-fluoro-4-(benzyloxy)benzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride (19).

Following essentially the procedures of Steps 2 and 3 of EXAMPLE 70, compound 18, (0.238 g, 0.39 mmol) as prepared in step 1, above, is deprotected with trifluoroacetic acid and reacted with an excess of acetyl imidazole. This is followed by alkaline hydrolysis to afford, after workup and chromatography over silica gel, eluting with 7%-10 % methanol (containing 1% NH_4OH) in CH_2Cl_2, and conversion to the HCl salt, 0.19g (0.32 mmol, 75%) hydrochloride 19 as a white solid: MS (CI) m/z 547.5 (MH+).

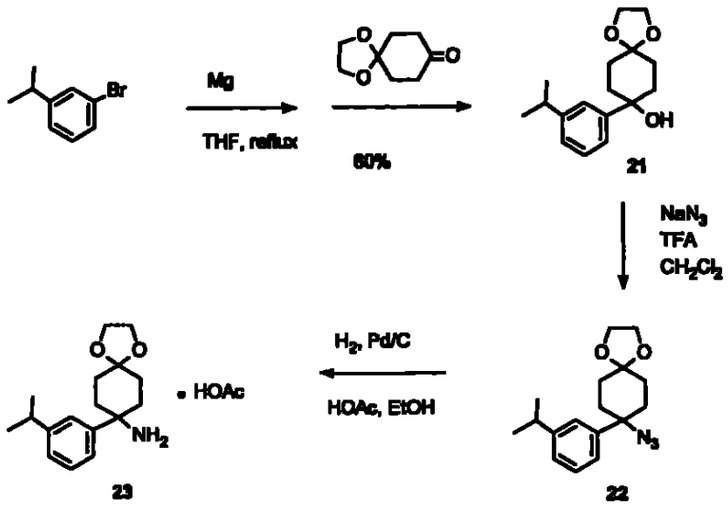
Step 3. Preparation of N-((1S,2R)-1-(3-fluoro-4-hydroxybenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 20

Following essentially the procedure of EXAMPLE 71, Step 3, the product from step 2, compound 19, (0.19 g, 0.32 mmol) is deprotected under 20 psi of H_2 in the presence of 54 mg of 10% palladium on carbon in 3.5 h, affording, after filtration, concentration and treatment with ethereal HCl, 20 (0.16 g, 0.32 mmol, quant.) as a cream-white solid: ^1H NMR ($CDCl_3$ + CD_3OD drop) δ 7.43-7.27 (m, 4 H), 6.86-6.77 (m, 3 H), 3.95 (br, 1 H), 3.8 (br, 1 H), 2.93 (m, 2 H), 2.6 (m, 4 H), 2.4 (m, 1 H), 2.06 (m, 2 H), 1.85 (s, 3 H), 1.8 (m, 2 H), 1.59 (m, 1 H), 1.5-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); IR (diffuse reflectance) 3251, 3113, 3087, 3061, 3053, 3028, 2956, 2941,

2865, 2810, 1645, 1596, 1520, 1446, 1294 cm -1. MS (CI) m/z (rel intensity) 457 (MH+,99), 459 (5), 458 (25), 457 (99), 439 (3), 257 (7), 218 (5), 202 (3), 201 (9), 96 (4), 77 (3). HRMS (ESI) calcd for $C_{27}H_{37}N_2O_3F+H_1$ 457.2866, found 457.2855. Anal. Calcd for $C_{27}H_{37}FN_2O_3.HCl.1.5\ H_2O$: C, 62.35; H, 7.95; N, 5.39; Found: C, 62.63; H, 7.76; N, 5.47.

EXAMPLE 74: Preparation of 8-(3-isopropylphenyl)-1,4-dioxa-spiro[4.5]decane-8-amine acetate 23.

Scheme 6



Step 1. Preparation of 8-(3-isopropylphenyl)-1,4-dioxa-spiro[4.5]decane-8-alcohol (21)

Following essentially the procedure described in EXAMPLE 72, Step 2, the Grignard reagent formed from 3-bromoisopropylbenzene (25 mmol) is reacted with 1,4-cyclohexanedione, monoethylene ketal (3.9 g, 25 mmol) to afford, after chromatography over silica gel, eluting with 20% to 30% ethyl acetate in heptane, alcohol 21 (5.6 g, 20 mmol, 80%) as a colorless oil which crystallizes to a white solid on cooling: ^1H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 7.33 (m, 1 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.13 (d, J = 7.5 Hz, 1 H), 4.0 (m, 4 H), 2.91 (hept, J = 7 Hz, 1 H), 2.15 (m, 4 H), 1.82 (br d, J =

11.5 Hz, 2 H), 1.70 (br d, J = 11.5 Hz, 2 H), 1.25 (d, J = 7 Hz, 6 H);.MS (CI) m/z 259.2 (M-OH).

Step 2. Preparation of 8-(3-isopropylphenyl)-1,4-dioxa-spiro[4.5]decane-8-azide (22).

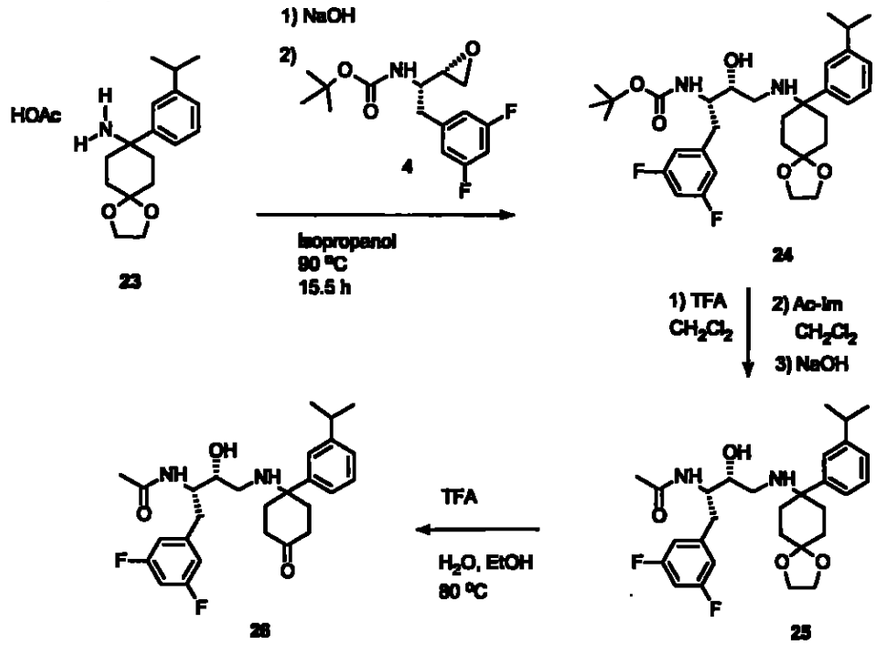
Following essentially the procedure described in EXAMPLE 69, Step 2, alcohol 21 (5.5 g, 20 mmol) is converted to the azide 22. The resulting crude material is purified by silica gel chromatography, eluting with 3% acetone in heptane. Concentration of the product-containing fractions affords 2.2 g (7.3 mmol, 36%) of compound 22 as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.33-7.26 (m, 3 H), 7.17 (m, 1 H), 3.98 (m, 4 H), 2.92 (hept, J = 7 Hz, 1 H), 2.2-2.12 (m, 2 H), 2.07-1.95 (m, 4 H), 1.72 (m, 2 H), 1.26 (d, J = 7 Hz, 6 H).

Step 3. Preparation of 8-(3-isopropylphenyl)-1,4-dioxa-spiro[4.5]decane-8-amine acetate 23.

Following essentially the procedure described in EXAMPLE 69, Step 3, 2.2 g (7.3 mmol) of compound 22 in 200 mL of ethanol is reduced under 16 psi of hydrogen in the presence of 0.7 g of 10% palladium on carbon for 4.5 h. Filtration and removal of solvents with a toluene azeotrope affords a white solid which is triturated with pentane to yield 2.14 g (6.4 mmol, 87%) of compound 23 as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.37-7.33 (m, 2 H), 7.30-7.26 (m, 1 H), 7.13 (d, J = 7.5 Hz, 1 H), 5.91 (br, 3 H), 3.96 (m, 4 H), 2.90 (hept., J = 7 Hz, 1 H), 2.32 (m, 2 H), 2.03 (s, 3 H), 2.0-1.85 (m, 4 H), 1.63 (m, 2 H), 1.25 (d, J = 7 Hz, 6 H); MS (CI) m/z 259.2 ($M-NH_2$).

EXAMPLE 75: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexan-4-one]amino}propyl) acetamide 26

Scheme 7



Step 1. Preparation of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{8-(3-isopropylphenyl)-1,4-dioxa-spiro[4.5]decane-8-amino}propylcarbamate (24)

Following essentially the procedure of EXAMPLE 70, compound 23 (3.2 mmol) is neutralized and reacted with Example 134 (4, 0.6 g, 2.0 mmol) in refluxing isopropanol (15 mL) for 15.5 h. The reaction mixture is concentrated and chromatographed over silica gel, eluting with 4% methanol (containing 2% of NH_4OH) in CH_2Cl_2 to separate the crude product from excess 8-(3-isopropylphenyl) -1,4-dioxa-spiro[4.5]decane-8-amine. The crude product is then re-chromatographed over silica gel, eluting with 10% to 20% acetone in CH_2Cl_2 to afford 0.600 g (1.04 mmol, 52%) of compound 24 as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.27-7.20 (m, 3 H), 7.09 (d, J = 7 Hz, 1 H), 6.69 (m, 2 H), 6.63 (m, 1 H), 4.64 (d, J = 9 Hz, 1 H), 3.95 (m, 4 H), 3.72 (m, 1 H), 3.28

(m, 1 H), 2.88 (m, 2 H), 2.69 (dd, J = 8.5, 14 Hz, 1 H), 2.32 (m, 2 H), 2.15 (m, 2 H), 1.99-1.86 (m, 4 H), 1.63 (m, 2 H), 1.35 (s, 9 H), 1.24 (d, J = 7 Hz, 6 H); MS (CI) m/z 575.4 (MH+)

Step 2. Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{8-(3-isopropylphenyl)-1,4-dioxa-spiro[4.5]decane-8-amino}propyl)acetamide (25)

Following essentially the procedures described in EXAMPLE 70, Steps 2 and 3, compound 24 (0.600 g, 1.04 mmol) is deprotected, acetylated, and saponified to afford, after chromatography on silica gel, eluting with 32.5% acetone and 2.5% methanol in CH_2Cl_2, acetamide 25 (335 mg, 0.65 mmol, 62%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.31-7.26 (m, 3 H), 7.15 (m, 1 H), 6.69-6.61 (m, 3 H), 5.9 (br, 1 H), 4.13 (m, 1 H), 3.95 (m, 4 H), 3.48 (m, 1 H), 2.92-2.83 (m, 2 H), 2.73 (dd, J = 8.5, 14 Hz, 1 H), 2.45-2.25 (m, 4 H), 2.10 (m, 2 H), 1.88 (s+m, 5 H), 1.62 (m, 2 H), 1.25 (d, J = 7 Hz, 6 H); MS (CI) m/z 517.4 (MH+).

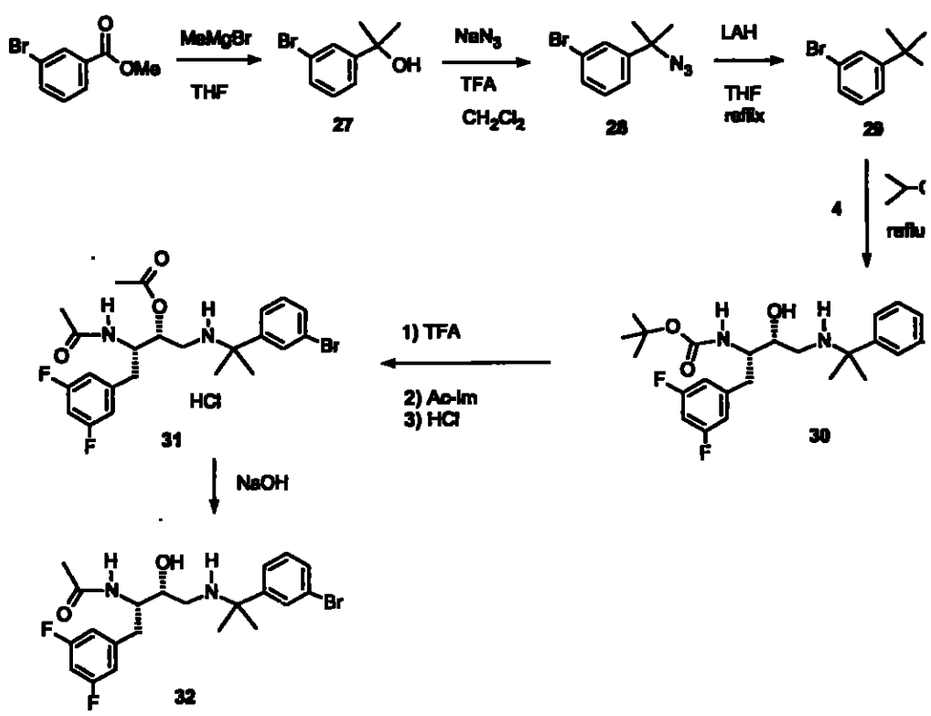
Step 3. Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexan-4-one]amino}propyl)acetamide 26

To acetamide 25 (255 mg, 0.49 mmol) in 5 mL of ethanol and 5 mL of water is added 6 mL of trifluoroacetic acid, and the mixture is refluxed for 2 h under nitrogen. It is concentrated and taken up in aqueous 10% Na_2CO_3 and ethyl acetate. The organic phase is washed twice more with 10% Na_2CO_3 and then with brine. It is dried over Na_2SO_4, and concentrated to a colorless oil. Evaporation *in vacuo* from ethyl ether affords compound 26 (140 mg, 0.30 mmol, 60 %) as a white solid: ^1H NMR ($CDCl_3$) δ 7.35-7.18 (m, 4 H), 6.71-6.64 (m, 3 H), 5.65 (br, 1 H), 4.12 (m, 1 H), 3.43 (m, 1 H), 2.95-2.90 (m, 2

H), 2.75 (dd, J = 8.5, 14 Hz, 1 H), 2.64 (m, 2 H), 2.4-2.25 (m, 8 H), 1.87 (s, 3 H), 1.25 (d, J = 7 Hz, 6 H); MS (CI) m/z 473.4 (MH+). The LC-MS spectrum in methanol solvent shows a small signal at 505.4 ($MH+CH_3OH$) due to hemiketal formation. IR (diffuse reflectance) 3311, 2958, 1710, 1646, 1628, 1595, 1550, 1544, 1460, 1372, 1315, 1116, 983, 846, 707 cm^{-1}. MS (EI)m/z(rel intensity) 472 (M+, 6), 472 (6), 417 (5), 416 (33), 415 (99), 398 (8), 397 (30), 327 (11), 244 (9), 215 (13), 214 (6). HRMS (ESI) calcd for $C_{27}H_{34}N_2O_3F_2+H_1$ 473.2615, found 473.2627. Anal. Calcd for $C_{27}H_{34}F_2N_2O_3+ 0.5\ H_2O$: C, 67.34; H, 7.33; N, 5.82; Found (av): C, 67.89; H, 7.32; N, 5.86.

EXAMPLE 76: Preparation of N-[(1S,2R)-3-{[1-(3-bromophenyl)-1-methylethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide 32

Scheme 8



Step 1. Preparation of 2-(3-bromophenyl)-2-propanol 27

To 75 mmol of methylmagnesium bromide in 25 mL of ether stirring at 6 °C is added, dropwise over 10 min, a solution of methyl-3-bromobenzoate (4.3 g, 20 mmol) in 25 mL of dry THF. The mixture is then allowed to warm to ambient temperature and stirred for 3.5 h, then cooled to 0°C and quenched by dropwise addition of aqueous 10% HCl. The acidified mixture is extracted twice with ethyl acetate, and the combined organic phases are washed with 1 N $NaHCO_3$ and with brine. The solution is dried over Na_2SO_4, concentrated, and chromatographed over silica gel, eluting with 15% ethyl acetate in heptane, to afford 4.00 g (18.6 mmol, 93%) of 2-(3-bromophenyl)-2-propanol 27 as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.65 (t, J = 2 Hz, 1 H), 7.39 (m, 2 H), 7.20 (t, J = 8 Hz, 1 H), 1.78 (br s, 1 H), 1.57 (s, 6 H).

Step 2. Preparation of 2-(3-bromophenyl)-2-propylazide (28).

The above compound was prepared by essentially according to the method of Example 12. The crude product was purified by chromatography over silica gel, eluting with heptane, and thereby affording compound 28 as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.58 (t, J = 2 Hz, 1 H), 7.74-7.36 (m, 2 H), 7.24 (t, J = 8 Hz, 1 H), 1.62 (s, 6 H).

Step 3. Preparation of 2-(3-bromophenyl)-2-propylamine 29.

The above compound was prepared essentially according to the method of Example 10. The crude product was purified by chromatography over silica gel, eluting with 6% methanol (containing 1% NH_4OH) in CH_2Cl_2 to afford compound 29 (7 mmol,

50%) as a pale amber oil: ^{1}H NMR ($CDCl_3$) δ 7.67 (t, J = 2 Hz, 1 H), 7.43 (m, 1 H), 7.35 (m, 1 H), 7.20 (t, J = 8 Hz, 1 H), 1.68 (br s, 2 H), 1.48 (s, 6 H).

Step 4. Preparation of 2-(3-bromophenyl)-2-propylamine hydrochloride

To 2-(3-bromophenyl)-2-propylamine 29 in ether is added ethereal HCl. Solvent removal affords a tan solid, which is dissolved in a small volume of ethanol and diluted with ethyl acetate. The tan crystals which form are filtered to afford 2-(3-bromophenyl)-2-propylamine hydrochloride :^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.65 (n m, 1 H), 7.51 (app t, 2 H), 7.32 (m, 1 H), 1.77 (s, 6 H); MS (CI) m/z 214.0 (MH+)

Step 5. Preparation of tert-butyl (1S,2R)-3-{[1-(3-bromophenyl)-1-methylethyl] amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate 30

The above compound was prepared essentially according to the method of example 17, step 3. Purification of the crude material over silica gel, eluting with 4% to 6% of methanol (containing 1% of NH_4OH) in CH_2Cl_2 affords 365 mg (0.71 mmol, 69%) of compound 30 as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 1 H), 7.35 (m, 2 H), 7.19 (t, J = 8 Hz, 1 H), 6.73 (m, 2 H), 6.64 (m, 1 H), 4.54 (d, J = 9 Hz, 1 H), 3.73 (m, 1 H), 3.29 (m, 1 H), 2.99 (dd, J = 4, 14 Hz, 1 H), 2.73 (dd, J = 8.5, 14 Hz, 1 H), 2.46-2.35 (m, 2 H), 1.45 (s, 6 H), 1.37 (s, 9 H); MS (CI) m/z 514.2 (MH+).

Step 6. Preparation of (1R,2S)-2-(acetylamino)-1-({[1-(3-bromophenyl)-1-methylethyl]amino}methyl)-3-(3,5-difluorophenyl)propyl acetate hydrochloride 31

To 365 mg (0.71 mmol) of tert-butyl (1S,2R)-3-{[1-(3-bromophenyl)-1-methylethyl] amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate 30 in 2 mL of CH_2Cl_2 is added 1 mL of trifluoroacetic acid, and the mixture is stirred for 30 min. It is concentrated *in vacuo*, diluted with ethyl acetate, and washed with 10% Na_2CO_3 and then brine. The solution is dried over Na_2SO_4, filtered and concentrated to a colorless oil. This is dissolved in 3 mL of CH_2Cl_2 and 172 mg (1.56 mmol) of acetyl imidazole is added. After 2.5 h the mixture is concentrated and taken up in ethyl acetate and 1 N KH_2PO_4. The organic phase is washed with 1N KH_2PO_4, with brine, dried over Na_2SO_4, concentrated, and chromatographed over silica gel. Elution with 4% methanol (containing 1% of NH_4OH) in CH_2Cl_2 affords a sticky solid. This is dissolved in ether and treated with ethereal HCl. Concentration afford 260 mg (0.49 mmol, 68%) of compound 31 as a white solid: ^1H NMR ($CDCl_3$ + CD_3OD drop) δ 7.79 (n m, 1 H), 7.59 (m, 2 H), 7.36 (t, *J* = 8 Hz, 1 H), 6.69-6.62 (m, 3 H), 5.15 (m, 1 H), 4.17 (m, 1 H), 3.07 (d, *J* = 12.5 Hz, 1 H), 2.87-2.75 (m, 2 H), 2.61 (dd, *J* = 7, 13.5 Hz, 1 H), 2.21 (s, 3 H), 1.95 (s, 3 H), 1.92 (s, 3 H), 1.84 (s, 3 H); IR (diffuse reflectance) 2985, 2958, 2940, 2755, 2738, 2730, 1749, 1645, 1628, 1596, 1569, 1463, 1372, 1227, 1118 cm -1. MS (CI)m/z(rel intensity) 497 (MH+, 86), 500 (15), 499 (99), 497 (86), 419 (28), 283 (18), 231 (22), 136 (17), 77 (46), 60 (13), 58 (18). HRMS (ESI) calcd for $C_{23}H_{27}N_2O_3F_2Br+H_1$ 497.1252, found 497.1248. Anal. Calcd for $C_{23}H_{27}BrF_2N_2O_3$ + HCl + 0.5H_2O: C, 50.89; H, 5.38; N, 5.16; Found: C, 50.95; H, 5.37; N, 5.05.

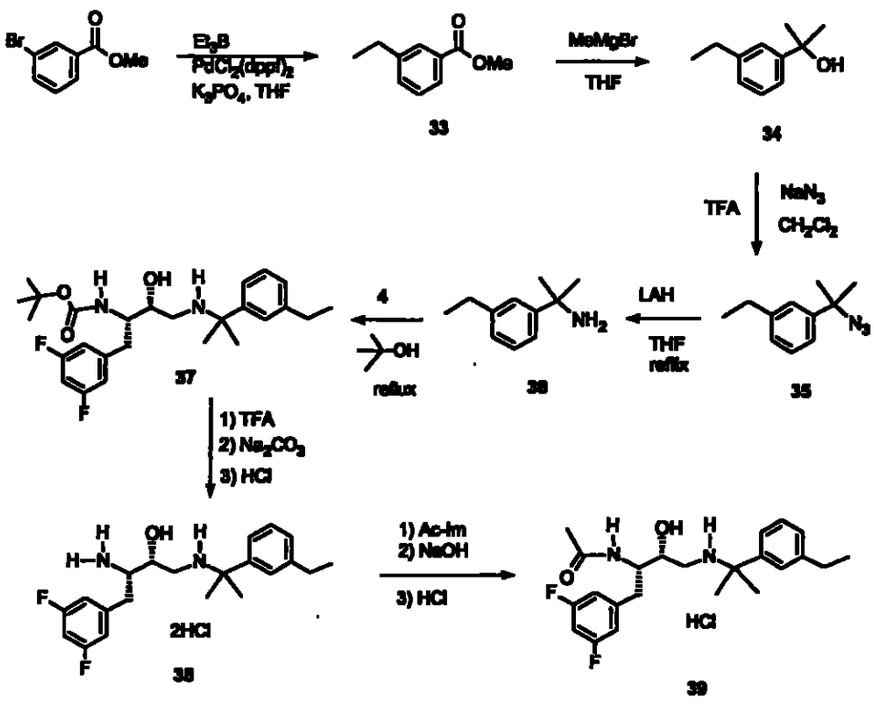
Step 7. Preparation of N-[(1S,2R)-3-{[1-(3-bromophenyl)-1-methylethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide 32

To a solution of 107 mg (0.21 mmol) of hydrochloride 31 in 10 mL of methanol is added 1 mL of 1N NaOH. The mixture is stirred for 45 min at ambient temperature, then quenched with

1N KH_2PO_4 and diluted with ethyl acetate. The organic phase is washed with brine, dried over Na_2SO_4, filtered and concentrated to a glassy solid. This is dissolved in methanol and treated with ethereal HCl to afford 70 mg (0.14 mmol, 68%) of compound 32 as a white solid: ^1H NMR ($CDCl_3$+ CD_3OD drop) δ 7.69 (s, 1 H), 7.56 (m, 2 H), 7.35 (t, J = 8 Hz, 1 H), 6.71 (m, 2 H), 6.63 (m, 1 H), 3.98 (m, 2 H), 2.98 (m, 1 H), 2.8 (m, 1 H), 2.68 (m, 1 H), 2.39 (m, 1 H), 1.92 (s, 3 H), 1.83 (s, 6 H); IR (diffuse reflectance) 3311, 3283, 3257, 3249, 3058, 3007, 2757, 1655, 1646, 1628, 1596, 1551, 1459, 1116, 697 cm^{-1}. MS (CI)m/z(rel intensity) 457 (15), 455 (MH+,97), 458 (17), 457 (99), 456 (15), 455 (97), 377 (5), 259 (9), 216 (6), 214 (6), 96 (27), 69 (5). HRMS (ESI) calcd for $C_{21}H_{25}N_2O_2F_2Br+H_1$ 455.1146, found 455.1145. Anal. Calcd for $C_{21}H_{25}BrF_2N_2O_2.HCl+ H_2O$: C, 49.47; H, 5.54; N, 5.49; Found: C, 49.45; H, 5.50; N, 5.54.

EXAMPLE 77: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)acetamide hydrochloride 39

Scheme 9



Step 1. Preparation of methyl-3-ethylbenzoate 33.

Compound 33 was prepared essentially according to the method of Example 7. The crude product was purified by chromatography over silica gel eluting with 2% to 3% of ethyl acetate in hexanes, to afford 6.1 g (37 mmol, 93%) of methyl-3-ethylbenzoate 33 as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.89-7.84 (m, 2 H), 7.40-7.33 (m, 2 H), 3.91 (s, 3 H), 2.70 (q, J = 7.6 Hz, 2 H), 1.26 (t, J = 7.6 Hz, 3 H).

Step 2. Preparation of 2-(3-ethylphenyl)-2-propanol 34.

Following essentially the procedure of Example 76, Step 1, methyl-3-ethylbenzoate 33 (6.0 g, 37 mmol) is converted to

2-(3-ethylphenyl)-2-propanol 34 (6 g, quantitative) which is obtained as a pale yellow oil, sufficiently pure without chromatography: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 1 H), 7.28 (m, 2 H), 7.09 (m, 1 H), 2.66 (q, *J* = 7.6 Hz, 2 H), 1.75 (s, 1 H), 1.59 (s, 6 H), 1.25 (t, *J* = 7.6 Hz, 3 H).

Step 3. Preparation of 2-(3-ethylphenyl)-2-propylazide 35

Following essentially the procedure of EXAMPLE 69, Step 2, but only stirred at ambient temperature for 1 h, alcohol 34 (6.0 g, 37 mmol) is converted to azide 35 (6.6 g, 35 mmol, 94%) which is obtained as a pale yellow oil, and is sufficiently pure without chromatography: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 3 H), 7.12 (m, 1 H), 2.67 (q, *J* = 7.6 Hz, 2 H), 1.64 (s, 6 H), 1.25 (t, *J* = 7.6 Hz, 3 H).

Step 4. Preparation of 2-(3-ethylphenyl)-2-propylamine 36.

Following essentially the procedure described in EXAMPLE 76, Step 3, azide 35 (6.6 g, 35 mmol) is converted to amine 36 (3.2 g, 20 mmol, 56%) which is obtained as a pale yellow oil after chromatography: ^{1}H NMR ($CDCl_3$) δ 7.35-7.24 (m, 3 H), 7.07 (d, *J* = 7.4 Hz, 1 H), 2.66 (q, *J* = 7.6 Hz, 2 H), 1.55 (s, 2 H), 1.49 (s, 6 H), 1.25 (t, *J* = 7.6 Hz, 3 H).

Step 5. Preparation of 2-(3-ethylphenyl)-2-propylamine hydrochloride

To amine 36 in ether is added ethereal HCl. Removal of the mother liquor affords, 2-(3-ethylphenyl)-2-propylamine hydrochloride as a white solid: 1H NMR (CDCl3) δ 8.93 (s, 3 H), 7.44 (s, 1 H), 7.36 (m, 1 H), 7.26 (t, J = 7.6 Hz, 1 H),

7.13 (d, J = 7.6 Hz, 1 H), 2.63 (q, J = 7.6 Hz, 2 H), 1.81 (s, 6 H), 1.22 (t, J = 7.6 Hz, 3 H); MS (CI) m/z 147.0 (MH $-NH_2$)

Step 6. Preparation of tert-butyl (1S,2R)-3-{[1-(3-ethylphenyl)-1-methylethyl] amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate 37.

Following essentially the procedure described in EXAMPLE 76, Step 5, except that t-butanol is used in place of isopropanol, 2-amine 36 (3.0 g, 18.4 mmol) is reacted with Example 134 (4, 3.0 g, 10 mmol) to afford, after chromatography, protected amine 37 (3.8 g, 8.2 mmol, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 3 H), 7.09 (m, 1 H), 6.74 (m, 2 H), 6.65 (m, 1 H), 4.69 (d, *J* = 9.4 Hz, 1 H), 3.76 (m, 1 H), 3.32 (m, 1 H), 2.97 (dd, *J* = 4, 14 Hz, 1 H), 2.72 (m, 1 H), 2.67 (q, *J* = 7.6 Hz, 2 H), 2.45 (m, 2 H), 1.49 (s, 6 H), 1.40 (s, 9 H), 1.26 (t, *J* = 7.6 Hz, 3 H).

Step 7. Preparation of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethylphenyl)-1-methylethyl]amino}butan-2-ol hydrochloride 38.

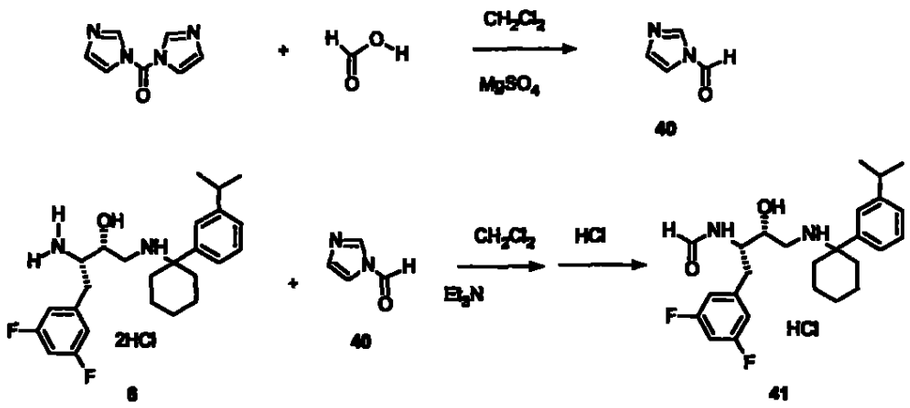
Following essentially the procedure described in EXAMPLE 76, Step 6, protected amine 37 (3.5 g, 7.6 mmol) is deprotected with TFA to afford a quantitative yield of a slightly yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 3 H), 7.08 (m, 1 H), 6.72-6.6 (m, 3 H), 3.39 (m, 1 H), 3.02 (m, 1 H), 2.82 (dd, *J* = 3.8, 13.6 Hz, 1 H), 2.67 (q, *J* = 7.6 Hz, 2 H), 2.59 (dd, *J* = 3.6, 11.8 Hz, 1 H), 2.45-2.37 (m, 2 H), 1,48 (s, 6 H), 1.24 (t, *J* = 7.6 Hz, 3 H). Treatment with ethereal HCl affords hydrochloride 38 (86%) as a white solid: MS (CI) m/z 363.3 (MH+).

Step 8. Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)acetamide hydrochloride 39

Following essentially the procedure described for EXAMPLE 76, Step 6, hydrochloride 38 (1.1 mmol) is converted to acetamide 39, which, following chromatography on silica gel, eluting with 8% to 10% methanol (containing 1% NH_4OH) in CH_2Cl_2, is obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.28-7.20 (m, 3 H), 7.07 (d, J = 7 Hz, 1 H), 6.69-6.61 (m, 3 H), 6.28 (d, J = 9 Hz, 1 H), 4.11 (m, 1 H), 3.40 (m, 1 H), 2.83 (dd, J = 5.2, 14.3 Hz, 1 H), 2.73 (dd, J = 8.4, 14.2 Hz, 1 H), 2.65 (q, J = 7.6 Hz, 2 H), 2.44 (dd, J = 4, 12 Hz, 1 H), 2.34 (dd, J = 5.3, 12 Hz, 1 H), 1.89 (s, 3 H), 1.47 (s, 3 H), 1.46 (s, 3 H), 1.24 (t, J = 7.6 Hz, 3 H). Treatment with ethereal HCl and concentration affords the hydrochloride 39 (0.22 g, 0.49 mmol, 45%), which is obtained as a white solid: ^1H NMR ($CDCl_3$+ CD_3OD drop) δ 7.37 (m, 3 H), 7.24 (m, 1 H), 6.71 (m, 2 H), 6.62 (m, 1 H), 3.98 (m, 2 H), 3.0 (dd, J = 4, 14.7 Hz, 1 H), 2.78-2.65 (m+q, J = 7.6 Hz, 4 H), 2.46 (m, 1 H), 1.91 (s, 3 H), 1.84 (s, 3 H), 1.83 (s, 3 H), 1.26 (t, J = 7.6 Hz, 3 H); IR (diffuse reflectance) 3250, 3229, 3053, 2967, 2933, 2876, 2786, 2764, 1645, 1628, 1595, 1550, 1459, 1377, 1116 cm^{-1}. MS (CI)m/z(rel intensity) 405 (MH+,99), 407 (6), 406 (41), 405 (99), 387 (7), 259 (23), 176 (8), 164 (18), 148 (7), 147 (19), 77 (15). HRMS (ESI) calcd for $C_{23}H_{30}N_2O_2F_2+H_1$ 405.2353, found 405.2369. Anal. Calcd for $C_{23}H_{30}F_2N_2O_2.HCl+ 0.5\ H_2O$: C, 61.39; H, 7.17; N, 6.23; Found: C, 61.27; H, 7.07; N, 6.20.

EXAMPLE 78: Preparation of (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propylformamide hydrochloride 41

Scheme 10



Step 1. Preparation of formyl imidazole 40.

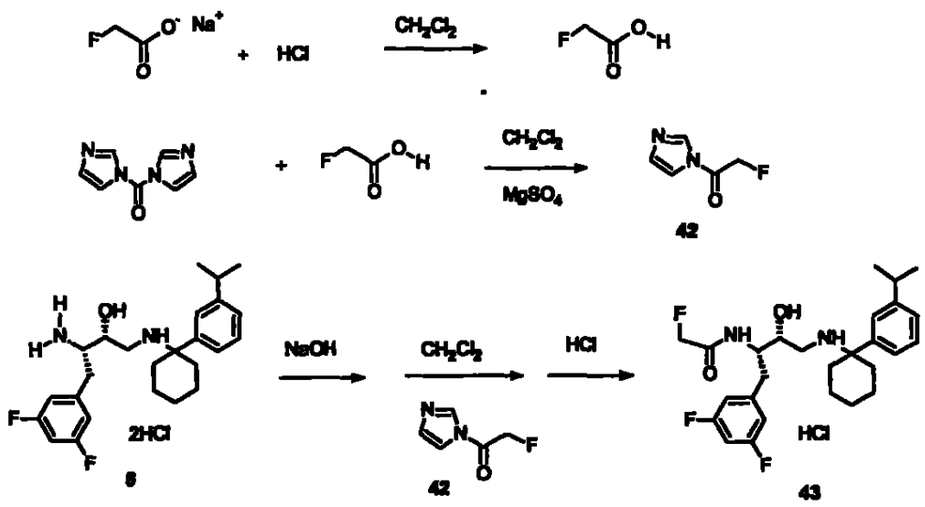
To a solution of formic acid (0.76 mL, 20 mmol, 96%) in CH_2Cl_2 stirring under nitrogen is added, portionwise over 10 min, 3.6 g (22 mmol) of carbonyldiimidazole, and the mixture is allowed to stir overnight. Anhydrous $MgSO_4$ is added, and after several hours the mixture is filtered and concentrated *in vacuo* (note: formyl imidazole is volatile and this operation should be carefully monitored for maximum recovery) to afford 0.7 g of iridescent crystals. The NMR spectrum showed the presence of formyl imidazole 40: ^1H NMR ($CDCl_3$) δ 9.15 (s, 1 H), 8.14 (s, 1 H), 7.53 (s, 1 H), 7.20 (s, 1 H). The crystals also contain imidazole (δ 7.71 (s,1H), 7.13 (s, 2H)) and the relative peak intensity and relative molecular weights are used to determine the weight % of formyl imidazole in the product.

Step 2. Preparation of (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl) cyclohexyl]amino}propylformamide hydrochloride 41

To a solution of amine 6 (209 mg, 0.43 mmol) in 4 mL of CH_2Cl_2 under nitrogen is added 125μL (0.9 mmol) of triethylamine. To this mixture is added 75 mg of the solid from Step 1, which is determined by NMR to contain 63% by weight of formyl imidazole (47 mg, 0.49 mmol) and the solution is stirred for 20 min. Methanol (5 mL is added, followed by 2 mL of 1 N NaOH. The mixture is concentrated *in vacuo* and diluted with 1 N KH_2PO_4 and ethyl acetate. The organic phase is washed with 1 N $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration and chromatography over silica gel, eluting with 5% to 7.5 % of methanol (containing 1% of NH_4OH) in CH_2Cl_2 affords a colorless oil. Ether and ethereal HCl are added, and the gel-like precipitate is concentrated *in vacuo* from ethanol and then ethyl acetate to afford 176 mg (0.37 mmol, 85%) of hydrochloride 41 as a white solid: ^1H NMR ($CDCl_3$+ CD_3OD drop) δ 7.86 (s, 1 H), 7.39-7.28 (m, 4 H), 6.67 (m, 2 H), 6.60 (m, 1 H), 3.96 (m, 1 H), 3.79 (m, 1 H), 3.08 (dd, 1 H), 2.93 (m, 1 H), 2.7-2.5 (m, 4 H), 2.37 (dd, 1 H), 2.05 (m, 2 H), 1.78 (m, 2 H), 1.6 (m, 1 H), 1.45-1.3 (m, 3 H), 1.25 (dd, *J* = 1, 7 Hz, 6 H); MS (CI) m/z 445.3 (MH+).

EXAMPLE 79: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)-2-fluoroacetamide hydrochloride 43

Scheme 11



Step 1. Preparation of fluoroacetyl imidazole 42.

To a slurry of 1.2 g (12 mmol) of sodium fluoroacetate in 25 mL of CH_2Cl_2 is added, with swirling of the flask, 1 mL (12 mmol) of concentrated HCl (note: this operation must be carried out in an efficient hood; fluoroacetic acid is highly toxic!). About 1 teaspoonful of anhydrous $MgSO_4$ is added to the flask, and the contents are filtered, rinsing the filter paper with 15 mL of CH_2Cl_2. The combined filtrate and wash are placed under nitrogen, and 1.3 g (8 mmol) of carbonyldiimidazole is added portionwise to the stirring mixture over 20 min. NMR analysis of an aliquot removed 40 min later indicates nearly complete reaction. After 1 h a teaspoonful of $MgSO_4$ is added, and the mixture is allowed to stir overnight. It is filtered and concentrated to remove most of the CH_2Cl_2, leaving 1.6 g of a pale yellow oil. The NMR spectrum indicates the presence of CH_2Cl_2, fluoroacetic acid, imidazole, and fluoroacetyl imidazole 42 : ^1H NMR ($CDCl_3$) δ 8.26 (s, 1 H), 7.53 (s, 1 H), 7.15 (s, 1 H), 5.40 (d, J = 47 Hz, 2 H). Integration reveals the oil to be 28% by weight fluoroacetyl imidazole 42 (0.45 g,

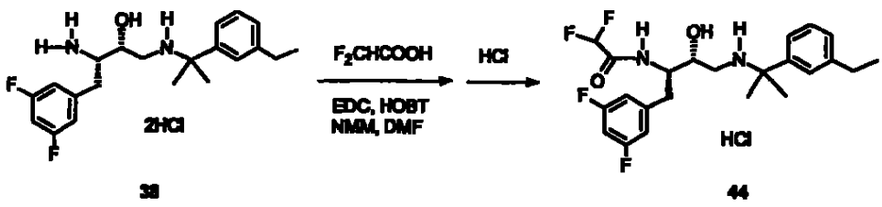
3.5 mmol, 44%). The oil is diluted with CH_2Cl_2 to make a solution that is 0.2 M in 42.

Step 2. Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)-2-fluoroacetamide hydrochloride 43.

To amine 6 (0.64 mmol) is added 1 N NaOH and ethyl acetate. The organic phase is washed with more 1N NaOH, brine, and then dried over Na_2SO_4 and concentrated to 265 mg of a colorless oil. This free base is dissolved in 3 mL of CH_2Cl_2 under nitrogen and 3.2 mL (0.64 mmol) of a 0.2 M solution of fluoroacetyl imidazole 42 in CH_2Cl_2 is added. The mixture is stirred for 5 min, and then aqueous 1N KH_2PO_4 and ethyl acetate are added. The organic phase is washed with 1N KH_2PO_4, 1N $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. Chromatography over silica gel, eluting with 5 % methanol (containing 2% of NH_4OH) in CH_2Cl_2 affords a colorless oil. Ether and ethereal HCl are added, and the solvents are removed *in vacuo* to yield 256 mg (0.50 mmol, 78%) of hydrochloride 43 as a white solid: ^1H NMR ($CDCl_3$) δ 9.85 (m, 1 H), 8.0 (m, 1 H), 7.51 (s, 1 H), 7.37 (m, 2 H), 7.27 (m, 1 H), 6.80 (d, J = 7 Hz, 1 H), 6.68 (m, 2 H), 6.63 (m, 1 H), 4.63 (d, J = 47 Hz, 2 H), 4.16 (m, 1 H), 4.10 (m, 1 H), 2.98-2.93 (m, 2 H), 2.77-2.64 (m, 4 H), 2.35-2.2 (m, 3 H), 1.80 (m, 2 H), 1.59 (m, 1 H), 1.44-1.25 (m, 3 H), 1.28 (d, J = 7 Hz, 6 H); MS (CI) m/z 477.4 (MH+).

EXAMPLE 80: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl] amino}-2-hydroxypropyl)-2,2-difluoroacetamide hydrochloride 44

Scheme 12

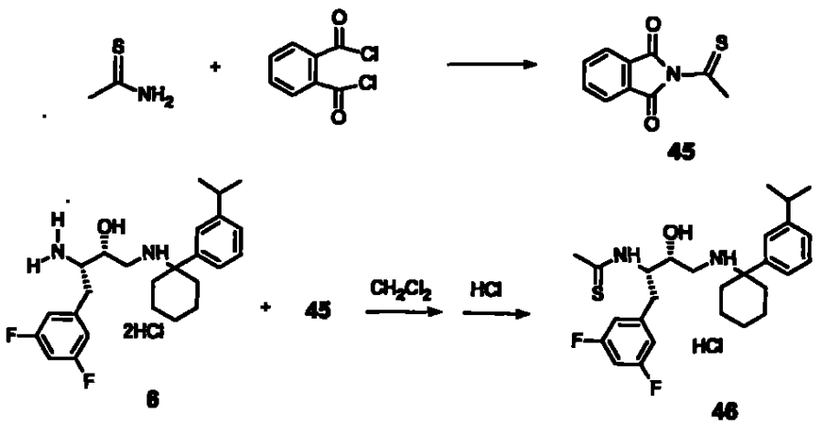


38 44

Following the general procedure of Example 56, compound 38 is converted into hydrochloride 44, which is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.9 (m, 1 H), 8.1 (m, 1 H), 7.35 (m, 4 H), 7.23 (d, *J* = 7 Hz, 1 H), 6.66-6.58 (m, 3 H), 5.95 (t, *J* = 54 Hz, 1 H), 4.6 (v br, 1 H), 4.37 (m, 1 H), 4.10 (m, 1 H), 2.89 (dd, *J* = 5, 14 Hz, 1 H), 2.80-2.66 (m+q, *J* = 7.6 Hz, 4 H), 2.34 (m, 1 H), 1.87 (s, 6 H), 1.26 (t, *J* = 7.6 Hz, 3 H); MS (CI) m/z 441.3 (MH+).

EXAMPLE 81: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl) cyclohexyl]amino}propyl)ethanethioamide hydrochloride 46

Scheme 13



6 46

Step 1. Preparation of thioacetyl-N-phthalimide 45

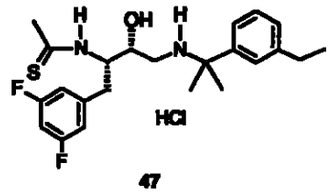
Thioacetamide (1.9 g, 25 mmol) is suspended in 40 mL of CH_2Cl_2 and cooled in an ice bath under nitrogen. Phthaloyldichloride (3.6 mL, 25 mmol) is added slowly over 10 min via syringe while the mixture is stirred. The mixture becomes a clear orange solution transiently, eventually depositing a precipitate. After stirring for 40 h, the mixture is concentrated *in vacuo* (in the hood!). The oily coral solid is triturated with hexanes. Within minutes the hexanes mother liquor drops a precipitate, which is filtered off to afford 0.2 g of a light coral solid: ^1H NMR ($CDCl_3$) δ 7.99 (m, 2 H), 7.86 (m, 2 H), 3.08 (s, 3 H). The residual solids remaining after trituration with hexanes are further triturated with ether and then with CH_2Cl_2. The combined mother liquors are concentrated to about 3 g of a red oily solid, which is chromatographed over silica gel, eluting with 10% to 20% ethyl acetate in heptane. The red fractions contained a product (concentrated to a coral solid, 0.77 g) with the same TLC retention (R_f = 0.32, 20% ethyl acetate in heptane) as the coral solid which had precipitated from hexanes. The total recovery is 0.97 g, 4.7 mmol, 19%.

Step 2. Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl) cyclohexyl]amino}propyl)ethanethioamide hydrochloride 46.

To 164 mg (0.39mmol) of the free base of compound 6 in 3 mL of approximately 0°C CH_2Cl_2 under nitrogen, is added solid thioacetyl-N-phthalimide 45 (80 mg, 0.39 mmol). The mixture is stirred for 20 min, and then 3 mL of methanol and 3 mL of 1N NaOH are added. The mixture is taken up in ethyl acetate and washed twice with 1N NaOH, once with water, and once with brine. It is dried over Na_2SO_4, concentrated, and chromatographed over silica gel, eluting with 4% methanol (containing 2% NH_4OH) in CH_2Cl_2. Product-containing fractions are concentrated to a colorless oil, which is dissolved in

ether and treated with ethereal HCl. Concentration affords 97 mg (0.19 mmol, 49%) of hydrochloride 46 as a white solid: ^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.42-7.37 (m, 2 H), 7.29 (m, 2 H), 6.73 (m, 2 H), 6.62 (m, 2 H), 4.67 (m, 1 H), 4.10 (m, 1 H), 3.11 (dd, *J* = 5, 14 Hz, 1 H), 2.96 (hept, *J* = 7 Hz, 1 H), 2.83 (m, 1 H), 2.65-2.4 (m, 4 H, obscured by solvent), 2.38 (s, 3 H), 2.07 (m, 2 H), 1.78 (m, 2 H), 1.59 (m, 1 H), 1.44-1.35 (m, 3 H), 1.28 (d, *J* = 7 Hz, 6 H); MS (CI) m/z 475.3 (MH+).

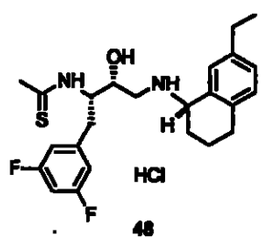
EXAMPLE 82: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)ethanethioamide hydrochloride 47



47

Following essentially the procedure described for EXAMPLE 81, compound 38 (220 mg, 0.5 mmol) is converted to the title compound 47, which is obtained as a white solid (79 mg, 0.17 mmol, 34%): MS (CI) m/z 421.3 (MH+).

EXAMPLE 83: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)ethanethioamide hydrochloride 48

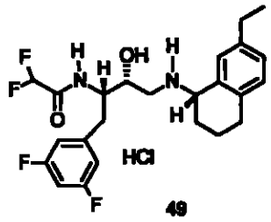


48

Following essentially the procedure described in EXAMPLE 81, (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(1S)-7-ethyl-

1,2,3,4-tetrahydronaphthalen-1-yl]amino}butan-2-ol dihydrochloride (0.71 mmol) is converted to the title compound 48 (158 mg, 0.34 mmol, 47%), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 9.1 (d, 1 H), 7.95 (br , 1 H), 7.39 (s, 1 H), 7.15-7.07 (m, 2 H), 6.73 (m, 2 H), 6.60 (m, 1 H), 4.77 (m, 1 H), 4.47 (m, 1 H), 4.34 (m, 1 H), 3.0 (d, J = 7 Hz, 2 H), 2.97 (m, 1 H), 2.73 (m, 3 H), 2.61 (q, J = 7.5 Hz, 2 H), 2.53 (s, 3 H), 2.15 (m, 1 H), 2.02 (m, 1 H), 1.87 (m, 1 H), 1.79 (m, 1 H), 1.23 (t, J = 7.5 Hz, 3 H); IR (diffuse reflectance) 3194, 3029, 2964, 2932, 2872, 1627, 1597, 1459, 1439, 1420, 1384, 1153, 1119, 982, 847 cm^{-1}. MS (CI)m/z(rel intensity) 433 (MH+,24), 221 (36), 184 (51), 176 (27), 174 (49), 172 (99), 159 (49), 156 (27), 77 (31), 60 (27), 58 (52). HRMS (ESI) calcd for $C_{24}H_{30}N_2OSF_2+H_1$ 433.2125, found 433.2114. Anal. Calcd for $C_{24}H_{30}F_2N_2OS.HCl+ H_2O$: C, 59.19; H, 6.83; N, 5.75; Cl, 7.28; S, 6.58; Found: C, 59.84; H, 6.70; N, 5.88; Cl, 6.91; S, 6.40.

EXAMPLE 84: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2,2-difluoroacetamide hydrochloride 49

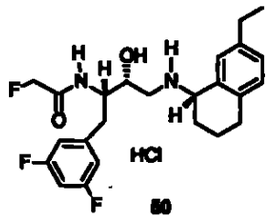


49

Using methods analogus to those previously described, (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}butan-2-ol dihydrochloride (0.33 mmol) is converted to compound 49 (88 mg, 0.18 mmol, 54%), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1 H), 7.12 (m, 2 H), 6.71 (m, 2 H), 6.64 (m, 1 H), 5.81 (t, J = 54 Hz, 1 H), 4.46 (m, 1 H), 4.18 (m, 1 H), 4.07 (m, 1 H), 3.12 (m, 2 H), 2.77 (m, 4 H), 2.63 (q, J = 7.5

Hz, 2 H), 2.2 (m, 1 H), 2.05 (m, 1 H), 1.96 (m, 1 H), 1.86 (m, 1 H), 1.23 (t, J = 7.5 Hz, 3 H); MS (CI) m/z 453.5 (MH+).

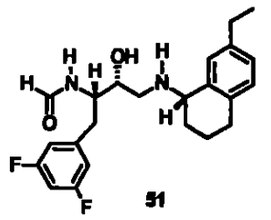
EXAMPLE 85: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2-fluoroacetamide hydrochloride 50



80

Using methods analogus to those previously described, (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}butan-2-ol dihydrochloride (0.0.71 mmol) is converted to compound 50 (248 mg, 0.53 mmol, 74%), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.85 (br, 1 H), 8.41 (br, 1 H), 7.45 (s, 1 H), 7.09 (m, 2 H), 6.97 (d, J = 8.6 Hz, 1 H), 6.68 (m, 2 H), 6.62 (m, 1 H), 4.70 (dq, J ~ 50, 11 Hz, 2 H), 4.48 (m, 1 H), 4.29 (m, 1 H), 4.16 (m, 1 H), 3.1-3.0 (m, 2 H), 2.83-2.69 (m, 4 H), 2.59 (q, J = 7.5 Hz, 2 H), 2.21 (m, 1 H), 2.02 (m, 2 H), 1.78 (m, 1 H), 1.21 (t, J = 7.5 Hz, 3 H); MS (CI) m/z 435.3 (MH+).

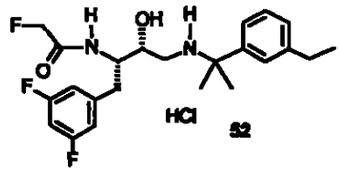
EXAMPLE 86: Preparation of (1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropylformamide 51



51

Using methods analogus to those previously described, but without making the HCl · salt, (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}butan-2-ol dihydrochloride (0.0.31 mmol) is converted to compound 51 (70 mg, 0.17 mmol, 56%), which is obtained as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1 H), 7.16 (s, 1 H), 7.03 (s, 2 H), 6.76 (m, 2 H), 6.67 (m, 1 H), 5.83 (d, J = 9 Hz, 1 H), 4.25 (m, 1 H), 3.74 (m, 1 H), 3.53 (m, 1 H), 3.03 (dd, J = 4.8, 14.4 Hz, 1 H), 2.90-2.69 (m, 5 H), 2.61 (q, J = 7.6 Hz, 2 H), 1.85 (m, 3 H), 1.76 (m, 1 H), 1.23 (t, J = 7.6 Hz, 3 H); MS (CI) m/z 403.3 (MH+). A trace NMR doublet (J = 11.8 Hz) appears at δ 7.73, tentatively attributed to an intramolecularly cyclized form of the product in the deuterochloroform solution.

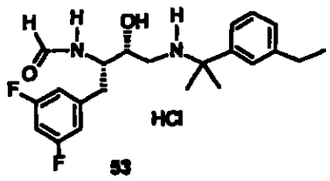
EXAMPLE 87: Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl] amino}-2-hydroxypropyl)-2-fluoroacetamide hydrochloride 52



52

Using methods analogus to those previously described, compound 38 (150 mg, 0.34 mmol) is converted to compound 52 (80 mg, 50%), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.95 (br, 1 H), 8.37 (br m, 1 H), 7.39-7.34 (m, 3 H), 7.23 (d, J = 7 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), 6.67 (m, 2 H), 6.60 (m, 1 H), 4.68 (dq, J = 47, 14 Hz, 2 H), 4.27 (m, 1 H), 4.16 (m, 1 H), 2.97 (dd, 1 H), 2.80 (m, 2 H), 2.70 (q, J = 7.6 Hz, 2 H), 2.38 (m, 1 H), 1.88 (s, 3 H), 1.87 (s, 3 H), 1.27 (t, J = 7.6 Hz, 3 H); MS (CI) m/z 423.3 (MH+).

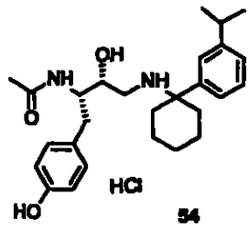
EXAMPLE 88: Preparation of (1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl] amino}-2-hydroxypropylformamide hydrochloride 53



53

Using methods analogus to those previously described, compound 38 (0.60 mmol) is converted to compound 53 (130 mg, 50%), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.95 (s, 1 H), 7.39-7.31 (m, 3 H), 7.24 (d, *J* = 7 Hz, 1 H), 6.71 (m, 2 H), 6.62 (m, 1 H), 4.05 (m, 1 H), 3.95 (m, 1 H), 3.07 (dd, 1 H), 2.80 (m, 1 H), 2.70 (q, *J* = 7.6 Hz, 2 H), 2.6 (m, obscured, 1 H), 2.47 (m, 1 H), 1.83 (s, 3 H), 1.82 (s, 3 H), 1.26 (t, *J* = 7.6 Hz, 3 H); MS (CI) m/z 391.3 (MH+). The NMR spectrum of the free base in pure deuterochloroform shows a small doublet (J = 11.6 Hz) at δ 7.58 which is tentatively attributed to an intramolecularly cyclized form of the product.

EXAMPLE 89: Preparation of N-((1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-{[1-(3-isopropylphenyl) cyclohexyl]amino}propyl)acetamide hydrochloride 54

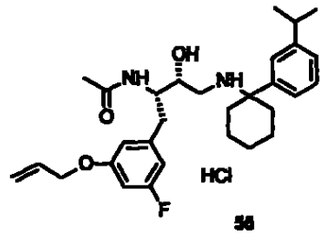


54

Using methods analogus to those previously described, tert-butyl (1S)-2-(4-hydroxyphenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (0.78 mmol) is converted to compound 54 (70

mg, 0.15 mmol, 19%, 3 steps), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.49 (s, 1 H), 7.39 (d, J = 4.6 Hz, 2 H), 7.28 (m, 1 H), 6.91 (d, J = 8 Hz, 2 H), 6.69 (d, J = 8 Hz, 2 H), 3.97 (m, 1 H), 3.90 (m, 1 H), 2.96 (hept, J = 7 Hz, 1 H), 2.83 (dd, 1 H), 2.62 (m, 4 H), 2.45 (m, 1 H), 2.13 (m, 2 H), 1.89 (s, 3 H), 1.78 (m, 2 H), 1.58 (m, 1 H), 1.45-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); MS (CI) m/z 439.3 (MH+).

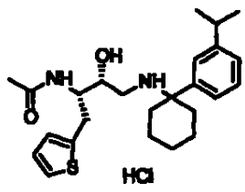
EXAMPLE 90: Preparation of N-((1S,2R)-1-[3-(allyloxy)-5-fluorobenzyl]-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 55



55

Using methods analogus to those previously described, tert-butyl (1S)-2-[3-(allyloxy)-5-fluorophenyl]-1-[(2S)-oxiran-2-yl]ethylcarbamate (0.61 mmol) is converted to compound 55 (0.31 mmol, 51%, 3 steps), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.42-7.27 (m, 4 H), 6.54 (m, 1 H), 6.48 (m, 1 H), 6.45 (m, 1 H), 6.05-5.98 (m, 1 H), 5.39 (m, 1 H), 5.28 (m, 1 H), 4.48 (m, 2 H), 3.95 (m, 1 H), 3.77 (m, 1 H), 2.96 (m, 2 H), 2.60 (m, 4 H), 2.4 (m, obscured, 1 H), 2.1 (m, 2 H), 1.81 (s+m, 5 H), 1.6 (m, 1 H), 1.45-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); MS (CI) m/z 497.4 (MH+).

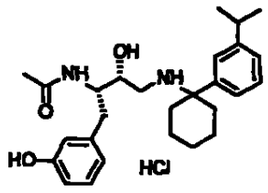
EXAMPLE 91: Preparation of N-[(1S,2R)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}-1-(thien-2-ylmethyl)propyl]acetamide hydrochloride 56



56

Using methods analogus to those previously described, tert-butyl (1S)-1-[(2S)-oxiran-2-yl]-2-thien-2-ylethylcarbamate (0.92 mmol) is converted to compound 56 (0.51 mmol, 55%, 3 steps), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.8 (br, 1 H), 8.03 (br, 1 H), 7.47 (s, 1 H), 7.37 (m, 2 H), 7.26 (m, 1 H), 7.21 (m, 1 H), 7.0 (br, 1 H), 6.95 (m, 1 H), 6.90 (d, J = 5 Hz, 1 H), 4.15 (m, 1 H), 3.96 (m, 1 H), 3.9 (v br, 1 H), 2.96 (hept, J = 7 Hz, 1 H), 2.86 (m, 2 H), 2.7-2.55 (m, 3 H), 2.24 (m, 3 H), 2.00 (s, 3 H), 1.8-1.7 (m, 2 H), 1.59 (m, 1 H), 1.45-1.3 (m, 3 H), 1.28 (dd, J = 1.7, 7 Hz, 6 H); MS (CI) m/z 429.3 (MH+).

EXAMPLE 92: Preparation of N-((1S,2R)-2-hydroxy-1-(3-hydroxybenzyl)-3-{[1-(3-isopropylphenyl) cyclohexyl]amino}propyl)acetamide hydrochloride 57

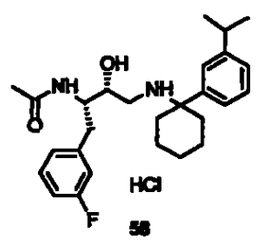


57

Using methods analogus to those previously described, tert-butyl (1S)-2-[3-(benzyloxy)phenyl]-1-[(2S)-oxiran-2-yl]ethylcarbamate (1.0 mmol) is converted to compound 57 (0.28 mmol, 28%, 4 steps), obtained as a colorless glass-like solid which can be pulverized into a beige powder: ^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.43 (s, 1 H), 7.37 (m, 2 H), 7.28 (m, 1 H), 7.08 (t, J = 7.7 Hz, 1 H), 6.78 (s, 1 H), 6.69 (d, J = 8 Hz, 1 H),

6.57 (d, J = 7.5 Hz, 1 H), 4.03 (m, 1 H), 3.75 (m, 1 H), 2.97 (m, 2 H), 2.65 (m, 4 H), 2.43 (m, 1 H), 2.12-2 (m, 2 H), 1.85 (s, 3 H), 1.78 (m, 2 H), 1.59 (m, 1 H), 1.45-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); MS (CI) m/z 439.3 (MH+).

EXAMPLE 93: Preparation of N-((1S,2R)-1-(3-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl) cyclohexyl]amino}propyl)acetamide hydrochloride 58

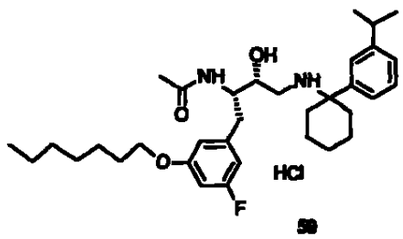


58

Using methods analogus to those previously described, tert-butyl (1S)-2-(3-fluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (0.82 mmol) is converted to compound 58 (0.37 mmol, 45%, 3 steps), which is obtained as a white solid:

^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.45 (s, 1 H), 7.4-7.35 (m, 2 H), 7.28 (m, 1 H), 7.20 (m, 1 H), 6.93 (m, 1 H), 6.88 (m, 2 H), 4.00 (m, 1 H), 3.87 (m, 1 H), 2.96 (m, 2 H), 2.7-2.6 (m, 4 H), 2.39 (m, 1 H), 2.11 (m, 2 H), 1.88 (s, 3 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.45-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); MS (CI) m/z 441.5 (MH+).

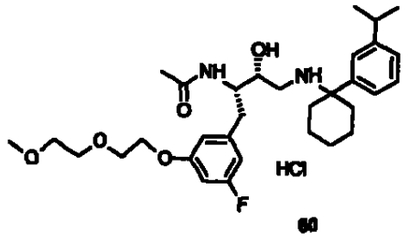
EXAMPLE 94: Preparation of N-((1S,2R)-1-(3-(heptyloxy)-5-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 59 .



59

Using methods analogus to those previously described, hydrochloride 11 (0.4 mmol) is reacted with 1-bromoheptane to afford the title compound 59 (0.14 mmol, 34%) as a glass, which can be pulverized to an off-white solid: ^{1}H NMR ($CDCl_3$+ CD_3OD drop) δ 7.49 (s, 1 H), 7.37 (m, 2 H), 7.27 (m, 1 H), 6.51 (s, 1 H), 6.45 (s, 1 H), 6.43 (s, 1 H), 4.05 (m, 1 H), 3.98 (m, 1 H), 3.88 (t, *J* = 6.5 Hz, 2 H), 2.96 (hept, *J* = 7 Hz, 1 H), 2.84 (m, 1 H), 2.6 (3H obscured by solvent), 2.36 (m, 1 H), 2.16 (m, 2 H), 2.01 (s, 3 H), 1.85-1.75 (m, 4 H), 1.58 (m, 1 H), 1.5-1.26 (m, 18 H), 0.89 (t, *J* = 6.6 Hz, 3 H); MS (CI) m/z 555.5 (MH+).

EXAMPLE 95: Preparation of N-((1S,2R)-1-(3-(2-(2-methoxyethoxy)ethoxy)-5-fluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide hydrochloride 60

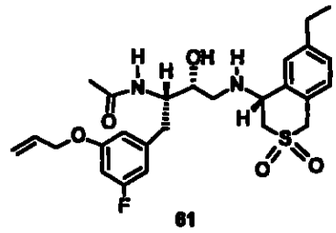


60

Using methods analogus to those previously described, compound 11 (0.4 mmol) is reacted with 1-bromo-2-(2-methoxyethoxy)ethane to afford the title compound 60 (0.21 mmol, 52%) as a hygroscopic white solid: ^{1}H NMR ($CDCl_3$) δ 9.4 (br, 1 H), 8.5 (br, 1 H), 8.32 (br, 1 H), 7.54 (s, 1 H), 7.38

(m, 2 H), 7.26 (m, 1 H), 6.56 (s, 1 H), 6.47 (m, 2 H), 4.34 (v br, water H), 4.1 (m, 4 H), 3.83 (m, 2 H), 3.70 (m, 2 H), 3.58 (m, 2 H), 3.38 (s, 3 H), 2.96 (hept, J = 7 Hz, 1 H), 2.8-2.6 (m, 5 H), 2.4-2.2 (m, 3 H), 2.15 (s, 3 H), 1.80 (m, 2 H), 1.6 (m, 1 H), 1.5-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); MS (CI) m/z 559.5 (MH+).

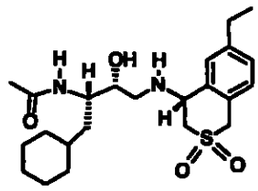
EXAMPLE 96: Preparation of N-((1S,2R)-1-[3-(allyloxy)-5-fluorobenzyl]-3-{[(4R)-6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}-2-hydroxypropyl)acetamide 61



61

Using methods analogus to those previously described, tert-butyl (1S)-2-[3-(allyloxy)-5-fluorophenyl]-1-[(2S)-oxiran-2-yl]ethylcarbamate (0.37 mmol) and (4R)-6-ethyl-3,4-dihydro-1H-isothiochromen-4-amine 2,2-dioxide (0.78 mmol) are reacted together, and the product is further converted, Using methods analogus to those previously described, (except that the HCl salt is not formed) to the title compound 61 (0.16 mmol, 43%), which is obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.22-7.19 (m, 2 H), 7.13 (m, 1 H), 6.57 (m, 1 H), 6.51 (m, 2 H), 6.06-5.99 (m, 1 H), 5.75 (br, 1 H), 5.41 (d, J = 17 Hz, 1 H), 5.30 (d, J = 12 Hz, 1 H), 4.67 (d, J = 15 Hz, 1 H), 4.50 (m, 2 H), 4.26 (m, 1 H), 4.17 (d, J = 15 Hz, 1 H), 4.1 (m, 1 H), 3.66 (m, 2 H), 3.48 (m, 1 H), 3.36 (dd, 1 H), 2.90 (m, 2 H), 2.78 (m, 2 H), 2.67 (q, J = 7.6 Hz, 2 H), 1.91 (s, 3 H), 1.25 (t, J = 7.6 Hz, 3 H); MS (CI) m/z 505.4 (MH+).

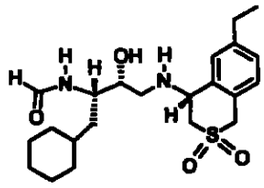
EXAMPLE 97: Preparation of N-((1S,2R)-1-(cyclohexylmethyl)-3-{[(4R)-6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}-2-hydroxypropyl)acetamide 62



62

Using methods analogus to those previously described, tert-butyl (1S)-2-cyclohexyl-1-[(2S)-oxiran-2-yl]ethylcarbamate (0.91 mmol) and (4R)-6-ethyl-3,4-dihydro-1H-isothiochromen-4-amine 2,2-dioxide (1.15 mmol) are coupled. The resulting product is recovered by chromatography over silica gel, eluting with 3% methanol (containing 1 % NH_4OH) in CH_2Cl_2. This material is then converted to compound 62, which is obtained as a white solid: MS (CI) m/z 437.3 (MH+).

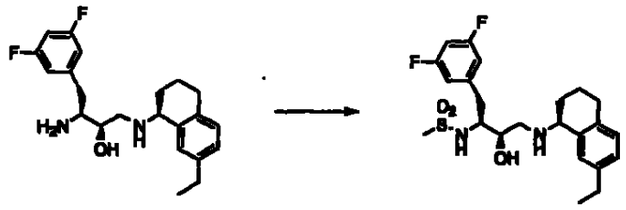
EXAMPLE 98: Preparation of (1S,2R)-1-(cyclohexylmethyl)-3-{[(4R)-6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}-2-hydroxypropylformamide 63.



63

Using methods analogus to those previously described, tert-butyl (1S)-2-cyclohexyl-1-[(2S)-oxiran-2-yl]ethylcarbamate (0.91 mmol) and (4R)-6-ethyl-3,4-dihydro-1H-isothiochromen-4-amine 2,2-dioxide (1.15 mmol) are coupled. The resulting product (0.63 mmol, 69%) is purified by chromatography over silica gel, eluting with 3% methanol (containing 1 % NH_4OH) in CH_2Cl_2. The purified coupled material is then converted to the title compound 63 (which is obtained as a white solid), using methods analogous to those disclosed herein. : MS (CI) m/z 423.3 (MH+).

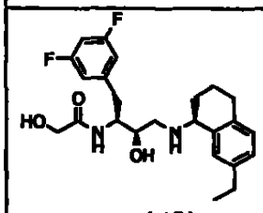
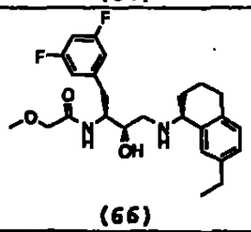
Example 99: Preparation of N-[(1*S*, 2*R*)-1-(3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-methanesulfonamide (64)

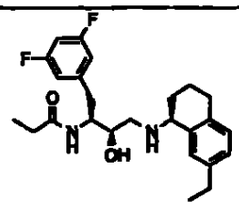
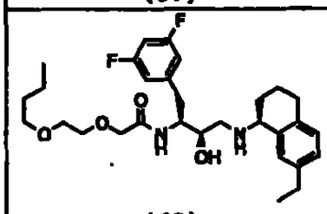
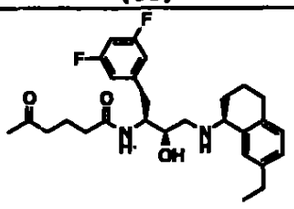
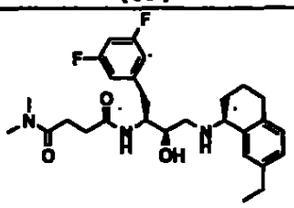
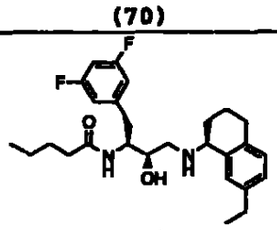
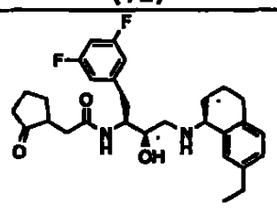


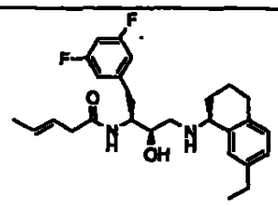
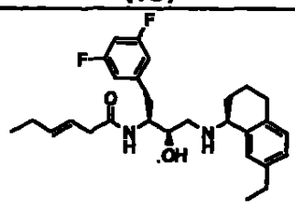
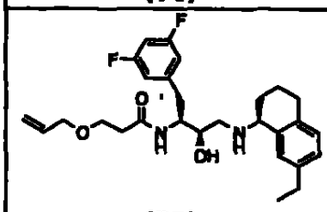
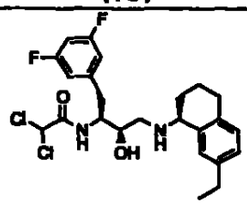
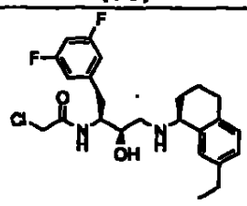
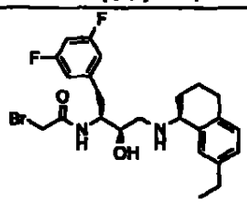
64

A 30 mg sample of the starting amine in 1 mL of dichloromethane was treated with 33 uL of triethylamine. A solution of 6 uL of methanesulfonyl chloride in 0.5 mL of dichloromethane was added and the solution was stirred overnight. The solvent was evaporated and the product was isolated by reverse-phase HPLC. Mass spectroscopy gave m/z = 453.2.

Compounds 65-78 are synthesized in an analogous manner, substituting methansefulfonyl chloride with various reagents.

Structure (Compound No.)	Name	Mass Spec.
 (65)	N-[(1*S*, 2*R*)-1-(3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxypropyl]-2-hydroxy-acetamide	432.8
 (66)	N-[(1*S*, 2*R*)-1-(3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-2-methoxy-acetamide	446.9

Structure (Compound No.)	Name	Mass Spec.
 (67)	N-[(1*S*, 2*R*)-1-(3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-propionamide	430.9
 (68)	2-(2-Butoxy-ethoxy)-N-[(1*S*, 2*R*)-1-(3,5-difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-acetamide	532.9
 (69)	5-Oxo-hexanoic acid [(1*S*, 2*R*)-1-(3,5-difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-amide	486.9
 (70)	N-[(1*S*, 2*R*)-1-(3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-N',N'-dimethyl-succinamide	501.9
 (71)	Pentanoic acid [(1*S*, 2*R*)-1-(3,5-difluoro-benzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-amide	458.9
 (72)	N-[(1*S*, 2*R*)-1-(3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-2-(2-oxo-cyclopentyl)-acetamide	498.9

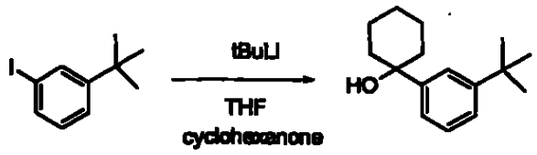
Structure (Compound No.)	Name	Mass Spec.
 (73)	Pent-3-enoic acid [(1*S*, 2*R*)-1-(3,5-difluoro-benzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-amide	456.9
 (74)	Hex-3-enoic acid [(1*S*, 2*R*)-1-(3,5-difluoro-benzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-amide	470.9
 (75)	3-Allyloxy-N-[(1*S*, 2*R*)-1-(3,5-difluoro-benzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-propionamide	486.9
 (76)	2,2-Dichloro-N-[(1*S*, 2*R*)-1-(3,5-difluoro-benzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-acetamide	485.7
 (77)	2-Chloro-N-[(1*S*, 2*R*)-1-(3,5-difluoro-benzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-acetamide	451.7
 (78)	2-Bromo-N-[(1*S*, 2*R*)-1-(3,5-difluoro-benzyl)-3-((1*S*)-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-acetamide	495.7

EXAMPLE 100:

A. Preparation of 1-tert-Butyl-3-iodo-benzene from 3-(tert-Butyl)aniline

3-(tert-Butyl)aniline (Oakwood, 6.0 g, 40.21mmol) was slowly added to a cold solution of 12 N HCl (24.5 mL) while stirring over an ice/acetone bath in a three-neck round bottom flask equipped with a thermometer. A 2.9M solution of sodium nitrite (16 mL) was added via addition funnel to the reaction flask at a rate so as maintain the temperature below 2°C. The solution was stirred for 30 min. prior to being added to a reaction flask containing a 4.2M solution of potassium iodide (100 mL). The reaction mixture was allowed to stir overnight while warming to RT. The mixture was then extracted with a hexane/ether solution (1:1) followed by washing with H_2O (2X), 0.2N citric acid (2X) and sat. NaCl. The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (100% Hexane) to give the desired iodo intermediate (8.33g, 80%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 9H), 7.07 (t, J = 8.0 Hz, 1H), 7.39(d, J = 8.0 Hz, 1H), 7.55(d, J = 8.0 Hz, 1H), 7.77 (t, J = 2.0 Hz, 1H).

B. Preparation of 1-(3-tert-Butyl-phenyl)-cyclohexanol from 1-tert-Butyl-3-iodo-benzene



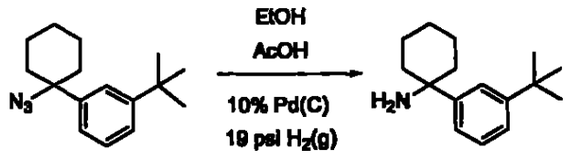
1-tert-Butyl-3-iodo-benzene(8.19g, 31.49mmol) in anh. THF (35mL) was cooled to -78°C. A solution of 1.7M tert-butyl lithium was added and the reaction mixture was allowed to stir while under N_2 (g) inlet for 2 h. A solution of cyclohexanone

in anh. THF (5mL) was added and the reaction mixture was stirred for 1 h. before transferring to a 0°C bath for 1 h and warming to RT for 1 h. The reaction was quenched with H_2O and extracted with ether. The organic layer was separated, dried ($NaSO_4$) and concentrated under reduce pressure. The residue was purified by flash chromatography (100% $CHCl_3$) to give the desired alcohol (4.73g, 65%): mass spec (CI) 215.2 (M-OH).

C. Preparation of 1-(1-Azido-cyclohexyl)3-tert-*butyl*-benzene from 1-(3-tert-Butyl-phenyl)-cyclohexanol

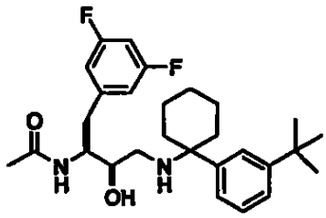
The above compound was prepared essentially according to the procedure of Example 12. The crude reaction product was purified by flash chromatography (100% hexane) to give the desired azide. mass spec (CI) 215.2 ($M-N_3$).

D. Preparation of 1-(3-tert-Butyl-phenyl)-cyclohexylamine from 1-(1-Azido-cyclohexyl)3-tert-*butyl*-benzene



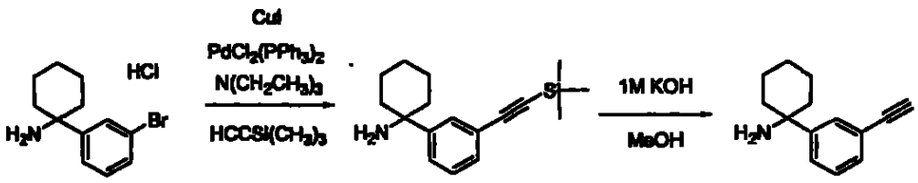
To a solution of 1-(1-Azido-cyclohexyl)-3-tert-butylbenzene dissolved in ethanol (5mL) was added acetic acid (0.5mL) and 10% palladium on carbon (0.10g, 0.94mmol). The reaction mixture was placed on the hydrogenator at 19 psi for 3.5hand then filtered through Celite and rinsed with ethanol. The filtrate was collected and concentrated under reduce pressure. This was then partitioned between EtOAc and 1N NaOH. The aqueous layer was removed and the mixture was washed with H_2O. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was used without further purification: mass spec (CI) 215.2 ($M-NH_2$).

E. Preparation of (1S,2R)-N-[3-[1-(3-tert-Butyl-phenyl)cyclohexylamino]-1-(3,5-Difluorobenzyl)-2-hydroxy-propyl]acetamide (79)



The product from step D is transformed into the above product using methods that are analogous to others described in the application. Mass spec: (CI) 473.2 (M+H).

F. Preparation of 1-(3-Ethynylphenyl)cyclohexylamine from 1-(3-Bromo-phenyl)-cyclohexylamine

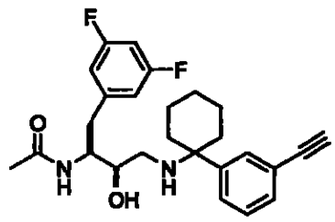


1-(3-Bromo-phenyl)-cyclohexylamine (Pharmacia, 1.04 g, 4.09 mmol) was free based and then dissolved in triethylamine (20 mL, 143mol) prior to the addition of dicholorbis(triphenylphosphine) palladium(II) (0.119 g, 0.170 mmol) and copper iodide (0.040 g, 0.211 mmole). The reaction mixture was heated to reflux at which point trimethylsilylacetylene (0.85 mL, 6.01 mmole) was added via syringe. After refluxing for 3h, the reaction mixture was cooled to RT before partitioning between EtOAc and sat. $NaHCO_3$ (aq). The aqueous phase was collected and extract with EtOAc (3X). The organic phases were then collect and washed with sat. NaCl (aq), separated, dried (Na_2SO_4) and concentrated

under reduced pressure. The crude product was used without further purification.

The trimethylsilyl intermediate was dissolved in methanol (5mL) and 1 N KOH (6 mL) and stirred at RT for 5.5 h. The reaction mixture was then partitioned between EtOAc and sat. $NaHCO_3$ (aq). The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (5%MeOH, 94.5% $CHCl_2$, 0.5% NH_4OH) to give the desired amine (0.35g, 31%): mass spec (CI) 183.1 (M-16).

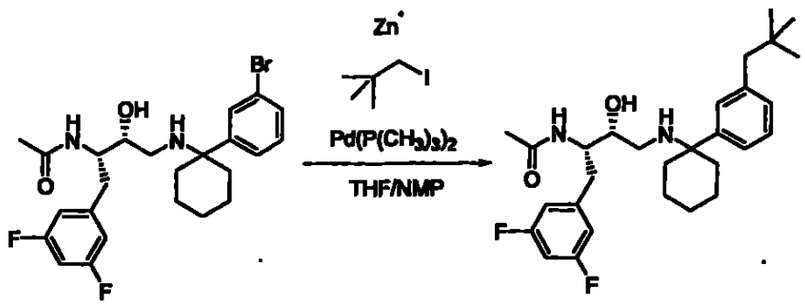
G. Preparation of (1*S*, 2*R*)-*N*-{1-(3,5-Difluorobenzyl)-3-[1-(3-(ethynylphenyl)cyclohexylamino]-2-hydroxy-propyl}acetamide (80)



(80)

The product from step F is transformed into the above product using methods that are analogous to others described in the application. Mass spectrometic analysis: (CI) 441.2 (M+H).

H. Preparation of (1*S*,2*R*)-*N*-(1-(3,5-Difluorobenzyl)-3-{1-[3-(2,2-dimethylpropyl)phenyl]cyclohexylamino}-2-hydroxypropyl)acetamide (81)

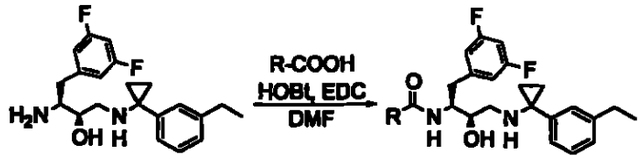


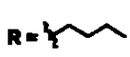
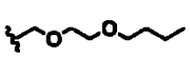
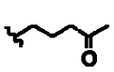
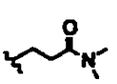
(81)

The desired product is prepared using methods that are analogous to others described in the application. Mass spec: (CI) 487.2 (M+H), 509 (M+Na).

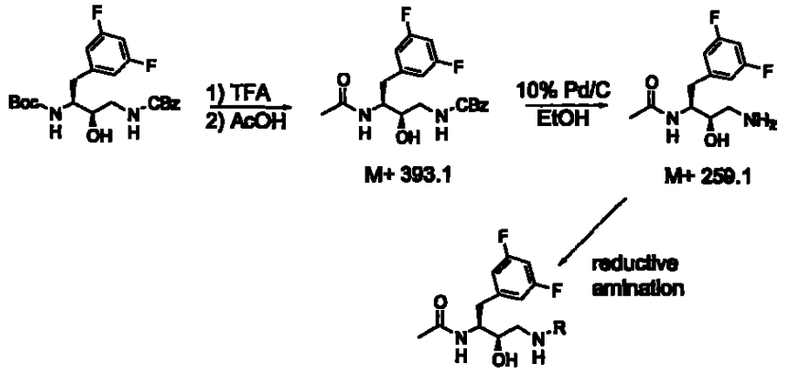
EXAMPLE 101:

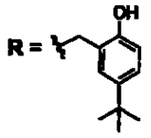
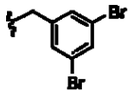
A. Synthesis of the following inhibitors was performed using essentially the same coupling conditions described above in Example 56, except with the variation of carboxylic acid starting materials as described below.



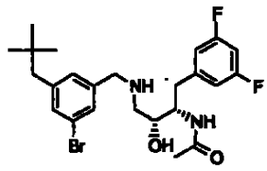
	MH+		Compound No.
R = 	445.2	(*1S, 2R*) Pentanoic acid {1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide	(82)
	473.3	(*1S, 2R*) Heptanoic acid {1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide	(83)
	485.3	(*1S, 2R*) 2-Cyclohexyl-*N*-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-acetamide	(84)
	519.2	(*1S, 2R*) 2-(2-Butoxy-ethoxy)-*N*-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-acetamide	(85)
	473.2	(*1S, 2R*) 5-Oxo-hexanoic acid {1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide	(86)
	488.2	(1S, 2R) *N*-{1-(3,5-Difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-*N',N'*-dimethyl-succinamide	(87)

B. Preparation of disubstituted benzylamine derivatives was generally performed as follows:



R =	M+		Compound No.
	421.2	*(1S, 2R)* *N*-[3-(5-*tert*-Butyl-2-hydroxy-benzylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	(88)
	506.9	*(1S, 2R)* *N*-[3-(2,5-Dibromo-benzylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	(89)

Example 101A Preparation of [(*1S,2R*) N-[3-[3-Bromo-5-(2,2-dimethyl-propyl)-benzylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide] (90)

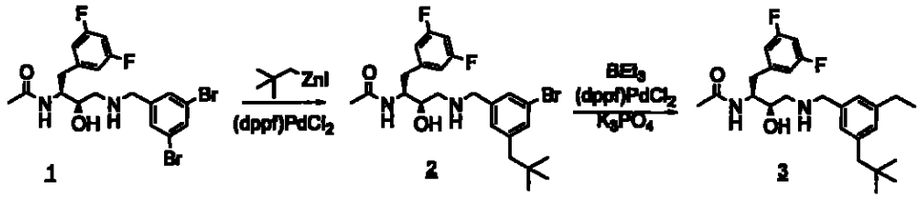


To dibromobenzylamine (*1S,2R*) N-[3-(2,5-Dibromo-benzylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide (0.504 g, 1.0 mM, 1 eq) was added 0.5 M THF solution of neopentylzinc iodide (20 mL, 10 eq) and 0.082 g, (0.1 mM, 0.1 eq) of [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane ($Pd(dppf)Cl_2 \cdot CH_2Cl_2$). A reaction mixture was stirred overnight at room temperature. The reaction was quenched with a

saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3 x 30 mL). Combined organic layers were washed with brine, dried and concentrated.

Compound (90) was purified by HPLC, yielding 0.055 g (11%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.60-9.00 (m, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.61 (s, 1H), 7.39 (s, 1H), 7.08 (s, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 6.9 Hz, 2H), 4.16 (bs, 2H), 3.85 (m,1H), 3.70 (m, 1H), 3.02 (m, 2H), 2.81 (m, 1H), 2.57 (m, 1H), 2.47 (s, 2H), 1.69 (s, 3H), 0.87 (s, 9H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 170.0, 164.4, 164.2, 161.1, 160.9, 144.2, 142.9, 134.2, 133.9, 131.8, 131.0, 121.6, 112.9, 112.6, 102.2, 69.3, 53.5, 50.1, 49.1, 35.4, 32.1, 29.6, 23.0; MH+ (CI): 497.2.

Example 101B

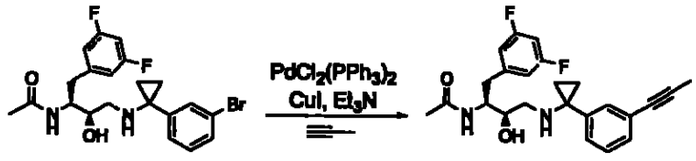


1 2 3

Compound 3 [(*1S,2R*) N-{1-(3,5-Difluorobenzyl)-3-[3-(2,2-dimethylpropyl)-5-ethyl-benzylamino]-2-hydroxypropyl}-acetamide] was prepared by reacting Example 101A (compound 2) with BEt_3, a palladium catalyst and potassium phosphate. MH+ (CI): 447.2.

Example 101C

Preparation of [(*1S, 2R*) N-{1-(3,5-Difluorobenzyl)-2-hydroxy-3-[1-(3-prop-1-ynyl-phenyl)-cyclopropylamino]-propyl}-acetamide] 5

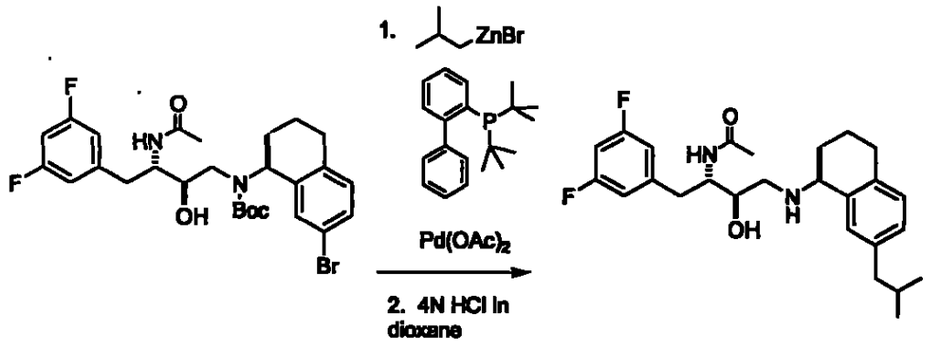


4 5

To a solution of (*1S, 2R*) N-[3-[1-(3-Bromo-phenyl)-cyclopropylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide 4 (0.227 g, 0.5 mM) in Et_3N (2 mL) and DMF (0.5 mL) was added $PdCl_2(PPh_3)_2$. A reaction mixture was cooled down to -30°C and propene gas was bubbled through for 1 minute. A reaction tube was sealed and the mixture was stirred for 2 min. before CuI (0.001g) was added. After stirring for additional 10 min. in a sealed tube at RT color of the reaction mixture changed from yellow to dark brown. The reaction was heated at 50°C for 48 hrs, cooled down to rt, filtered and stripped solvent. Purified by HPLC; yield 0.030g (15%); MH+ (CI): 413.2.

EXAMPLE 102

A. Preparation of N-(1*S*, 2*R*)-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[(1*S*)-(7-isobutyl-1,2,3,4-tetrahydronaphthalen-1-ylamino)]-propyl]-acetamide

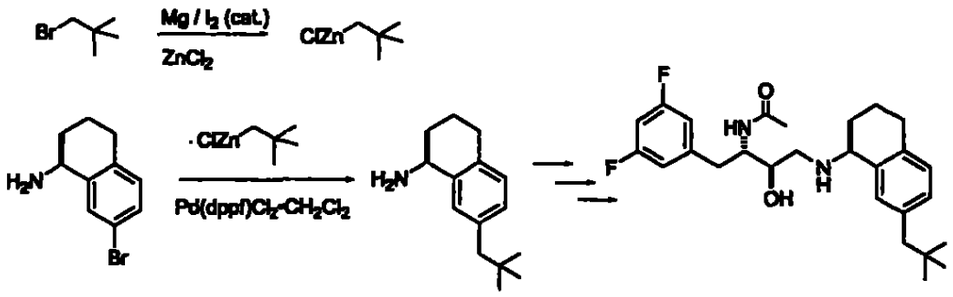


Palladium(II) acetate (0.2 equiv, 0.07 mmol, 15.8 mg) and 2-(di-t-butylphosphino)biphenyl (0.1 equiv, 0.035 mmol, 10.5 mg) were dissolved in THF (2 mL) and deoxygenated with a subsurface N_2 (g) purge for 5 minutes. The bromide (1 equiv, 0.352 mmol, 200 mg) was then added to this solution as a solid, followed by isobutyl zinc bromide (0.5 M solution in THF, 3 equiv, 1.1 mmol, 2.1 mL). The reaction was stirred overnight at ambient temperature under a N_2 (g) atmosphere. After 12 hours, the reaction was partitioned between EtOAc and

H_2O, and extracted 3x into EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography on SiO_2 with 30 → 50 % EtOAc in hexanes gave the pure desired Boc protected product. (148 mg, 77 % yield) $M+Na^+$ (CI) = 567.2

Removal of the Boc group was achieved by dissolving the above compound in 4N HCl in dioxane (1 mL) and stirring at ambient temperature for 1 hour under a N_2 (g) atmosphere. The resulting white cloudy mixture was concentrated to give the final product. (100 mg, 85% yield) ^{1}HNMR (CD_3OD): δ 7.3 (s, 1H), 7.15 (s, 2H), 6.9 (m, 2H), 6.8 (m, 1H), 4.6 (t, 1H), 4.05 (m, 1H), 3.9 (m, 1H), 3.2 (m, 2H), 3.0 (m, 1H, 2.8 (m, 2H), 2.7 (m, 2H), 2.5 (d, 2H), 2.2 (m, 2H), 2.0 (m, 1H), 1.85 (s, 3H), 1.85, m, 1 H), 0.9 (m, 6H). $M+H^+$ (CI) = 445.2

B. Preparation of *N*-(1*S*, 2*R*)-{1-(3,5-Difluoro-benzyl)-3-[(1*S*)-7-(2,2-dimethylpropyl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-2-hydroxypropyl}-acetamide



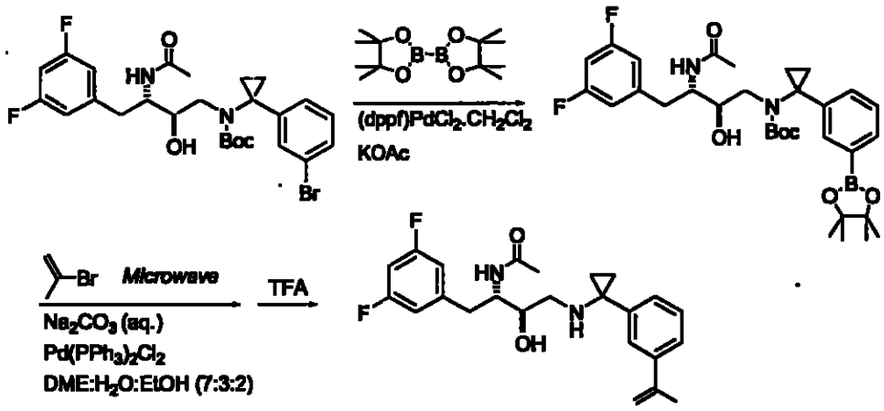
The neopentyl zinc was prepared according to the procedure in Tetrahedron Letters, 1983, volume 24, page 3823-3824.

To the bromotetralin amine (1 equiv, 8 mmol, 1.71 g) was added the crude neopentylzinc chloride suspension (3 equiv, 24 mmol, 48 mL), followed by $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.05 equiv, 0.4 mmol, 330 mg). The reaction was stirred at ambient temperature under N_2 (g) overnight. The suspension quickly turned yellow, and eventually turned purplish overnight.

After 12 h, the reaction was quenched with NH_4Cl (aq) and extracted 3x with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography on SiO_2 with 2 → 10 % MeOH in CH_2Cl_2 gave the desired neopentyl tetralin amine. (1.5 g, 86% yield) ^{1}HNMR ($CDCl_3$): δ 7.15 (s,1H), 6.95 (m, 2H), 3.95 (m, 1H), 2.8 (m, 2H), 2.4 (s, 2H), 2.0 (m, 2H), 1.7 (m, 2H), 1.6 (broad s, 2H), 1.0 (s, 9H); M-NH_3^+ (CI) = 201.2.

The final compound was synthesized via epoxide opening, protecting group deprotection, and acetylation as previously described: M+H^+ (CI) = 459.2.

C. Preparation of *N*-(1*S*, 2*R*)-{1-(3,5-Difluorobenzyl)-2-hydroxy-3-[1-(3-isopropenyl-phenyl)-cyclopropylamino]-propyl}-acetamide



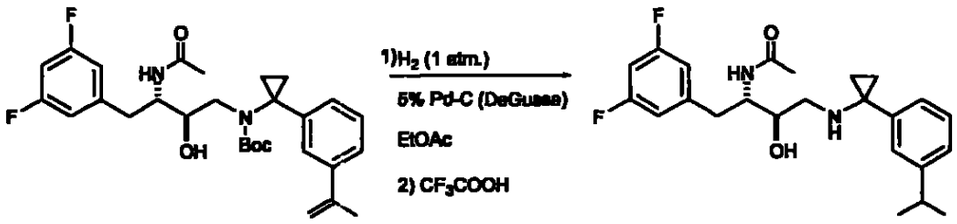
Potassium acetate (5 equiv, 8.8 mmol, 0.864 g), (dppf)$PdCl_2$·CH_2Cl_2 (0.04 equiv, 0.0704 mmol, 57.5 mg), and diboron reagent (1.15 equiv, 2.03 mmol, 0.515g), followed by the bromide (1 equiv, 1 g, 1.76 mmol) and DMF (7 mL) were added to a flask. The mixture was deoxygenated via a subsurface N_2 (g) purge, and stirred at 80°C under N_2 (g) overnight. As soon as heating began, the reaction turned brown. After 18 h, the reaction was partitioned between EtOAc and H_2O, and extracted 3x with EtOAc. The combined organic

extracts were washed with brine, dried over Na_2SO_4, and filtered before removal of solvent under vacuum. A quick SiO_2 column with 20→50% EtOAc in hexanes gave the pure boronic ester. (0.75 g, 69% yield) ^{1}HNMR (CD_3OD): δ 7.6 (t, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.8 (dd, 2H), 6.6 (m, 1H), 4.05 (m, 1H), 3.8 (m, 1H), 3.5 (m, 2H), 2.9 (m, 2H), 1.8 (s, 3H), 1.4 (s, 9H), 1.2 (m, 12 H), 1.2 (m, 4 H). $M+Na^+$ (CI) = 623.2

The boron ester (1 equiv, 0.167 mmol, 100 mg) followed by $Pd(PPh_3)_2Cl_2$ (0.1 equiv, 0.017 mmol, 11.7 mg), 2-bromopropene (1.2 equiv, 0.2 mmol, 24.2 mg, 17.8 µL), 2M Na_2CO_3 (aq) (1.5 equiv, 0.25 mmol, 0.125 mL), and finally 7:3:2 DME:H_2O:EtOH (0.7 mL) were placed in a reaction vial equipped with a stir bar. The vial was sealed and the reaction was prestirred for 15 s before being microwaved at 160 °C for 7 minutes at Normal Absportion Level and with Fixed Hold Time on. (A Personal Chemistry Microwave Reactor was used.) The reaction was partitioned between EtOAc and H_2O, and extracted 3x with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered before removal of solvent under vacuum. Purification via SiO_2 column run with 10→35% EtOAc in hexanes gave the pure Boc protected styrene compound. (45.9 mg, 53% yield) $M+Na^+$ (CI) = 537.2

Boc group removal was achieved by treating the above protected compound with 1:4 TFA:CH_2Cl_2 at 0°C. The reaction was stirred for 2 h at 0°C, and then concentrated to give the desired product. HPLC purification gave the pure desired product (7 mg, 36% yield): $M+H^+$ (CI) = 415.2

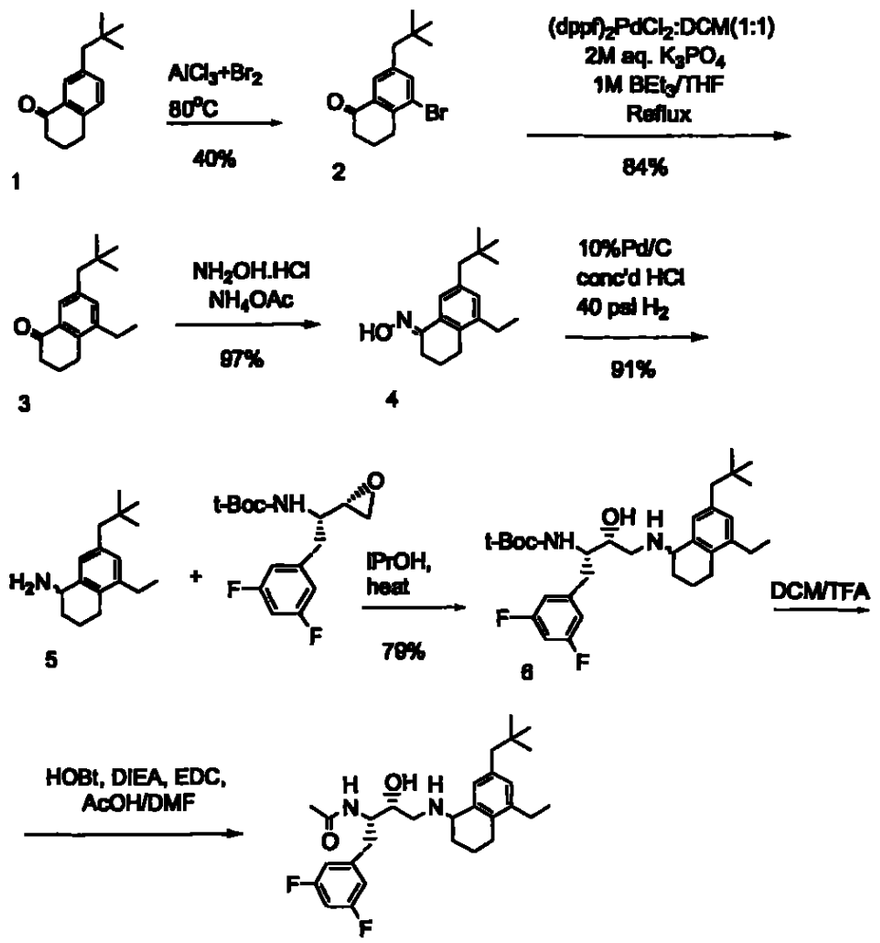
D. Preparation of *N*-(1*S*, 2*R*)-{1-(3,5-Difluorobenzyl) -2-hydroxy-3-[1-(3-isopropylphenyl)-cyclopropylamino]-propyl}-acetamide



The Boc amine (1 equiv, 0.1 mmol, 55.4 mg) was dissolved in EtOAc before the addition of 5% Pd-C DeGussa catalyst (an unmeasured amount). The air was evacuated from the flask before a balloon of N_2 (g) was applied. The mixture was stirred for 4 h at ambient temperature, at which point HPLC-MS determined the reaction was complete. Filtration through diatomaceous earth followed by removal of solvent by vacuum resulted in the clean crude reduced material. (56.7 mg, quantitative) $M+H^+$ (CI) = 517.3.

Removal of the Boc group was achieved by dissolving the above compound in 50:50 TFA:CH_2Cl_2 and stirring at ambient temperature for 1 hour under a N_2 (g) atmosphere. The resulting solution was concentrated to give the final product. (41.6 mg, quantitative): ^1H NMR (CD_3OD) δ 7.4 (s, 1H), 7.25 (m, 3H), 6.7 (m, 2H), 6.6 (m, 1H), 4.0 (m, 1H), 3.9 (m, 1H), 2.9 (m, 4H), 2.7 (m, 1H), 1.8 (s, 3H), 1.2 (d, 6 H), 1.2 (m, 4H). $M+H^+$ (CI) = 417.2

EXAMPLE 103



Step 1:

The conversion of compound 1 to compound 2 was performed essentially according to the method of Example 1. The resulting crude product was purified by flash column chromatography to afforded compound 2 as a solid: TLC (10% EtOAc/Hexane) R_f = 0.48; MH+ (CI) 295.0 (^{79}Br).

Step 2:

Palladium-mediated transfer of the ethyl group onto the aryl bromide was described previously to give compound 3: Yield: 84%; MH+ (CI) 245.2.

Step 3:

Formation of the oxime was performed as previously described to give compound 4. Yield: 97%; MH+ (CI) 260.2.

Step 4:

Reduction of the oxime to the amine was achieved as previously described to give compound 5: yield: 91%; MH+ (CI) 229.2.

Step 5:

Epoxide opening was performed as previously described: yield: 79%; MH+ (CI) 545.3.

Step 6:

Boc deprotection and acetylation was performed as previously described. The resultant diastereomeric mixture was purified by reverse-phase HPLC to give both isomers of:

N-(1*S*,2*R*)-{1-(3,5-Difluorobenzyl)-3-[7-(2,2-dimethylpropyl)-5-ethyl-1,2,3,4-tetrahydronaphthalen-1-ylamino]-2-hydroxypropyl}acetamide.

Isomer 1: MH+ (CI) 487.3.

Isomer 2: MH+ (CI) 487.3.

EXAMPLE 104: *Synthesis* Of 3, 5-Disubstituted Benzylamine Derivatives

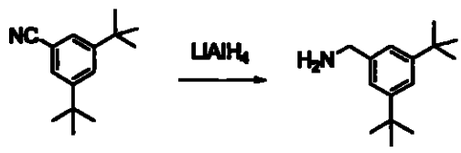
A. 3,5-di-*tert*-butylbenzonitrile from 3,5-di-*tert*-butylbromobenzene.



The nitrile is introduced essentially according to the procedure detailed in Dudley, D. A. et al. *J. Med. Chem.* 2000, *43*, 4063-4070. The crude product was purified by flash

chromatography (R_f = 0.68 in 10% EtOAc/hexanes) to give the desired product as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.48 (d, J = 1.8 Hz, 2H), 1.33 (s, 18H); mass spec (CI): 175.1.

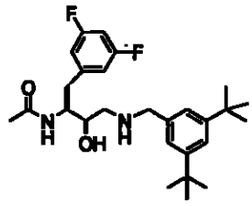
B. 3,5-di-tert-butylbenzylamine



To 3, 5-di-tert-butylbenzonitrile (863 mg, 4.02 mmol) in dry THF (10 mL) at 0 °C was added lithium aluminum hydride (304 mg, 8.0 mmol) in one portion. The reaction mixture was allowed to warm to rt for 2 h, whereupon the reaction was quenched (0.2 mL water, followed by 0.2 mL 15% potassium hydroxide solution and 0.6 mL water). The reaction mixture was stirred at rt for 1 h, then filtered through diatomaceous earth (CH_2Cl_2 elution). The filtrate was then concentrated and used in the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.16 (d, J = 1.8 Hz, 2H), 3.86 (s, 2H), 1.33 (s, 18H); mass spec (CI): 203.2 (M-NH_2).

The free amine was further elaborated, using methods analogous to those disclosed herein, to form the final product.

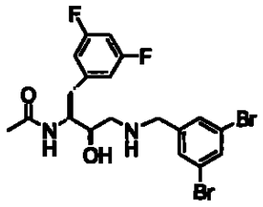
C. *N*-[(1*S*, 2*R*)-3-(3,5-Di-tert-butyl-benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide



The above compound was prepared using methods analogous to those previously described. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.16 (d, J = 1.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 1H),

6.70 (d, J = 6.2 Hz, 2H), 6.61 (tt, J = 9.0, 2.0 Hz, 1H), 4.22-4.10 (m, 1H), 4.03 (br s, 1H), 3.80 (d, J = 12.9 Hz, 1H), 3.74 (d, J = 12.9 Hz, 1H), 3.72-3.60 (m, 1H), 2.90-2.65 (m, 4H), 1.85 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 162.8 (dd, J = 248.2, 13.0 Hz, 2C), 151.0, 142.1 (t, J = 9.1 Hz, 1C), 137.3, 122.6, 121.5, 111.9 (dd, J = 16.9, 7.5 Hz, 2C), 101.8 (t, J = 25.3 Hz, 1C), 70.1, 54.2, 53.6, 50.7, 36.1, 34.7, 31.4, 23.2; MH+ (CI): 461.3.

D. ***N*-[(1S,2R)-3-(3,5-Dibromobenzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide**



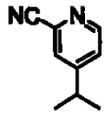
The titled compound was prepared using methods analogous to those previously described. The required dibromo benzylamine is prepared by treating the commercially available aldehyde with a nitrogen source and a reducing agent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (t, J = 1.5 Hz, 1H), 7.40 (d, J = 1.5 Hz, 2H), 6.74 (d, J = 6.2, 1.8 Hz, 2H), 6.68 (tt, J = 9.0, 2.2 Hz, 1H), 5.63 (d, J = 8.9 Hz, 1H), 4.20-4.05 (m, 1H), 3.78 (d, J = 13.9 Hz, 1H), 3.71 (d, J = 13.9 Hz, 1H), 3.51 (q, J = 5.3 Hz, 1H), 2.99 (dd, J = 14.3, 4.7 Hz, 1H), 2.82 (dd, J = 14.3, 8.7 Hz, 1H), 2.67 (d, J = 3.0 Hz, 2H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 163.0 (dd, J = 248.2, 13.0 Hz, 2C), 143.9, 141.7 (t, J = 9.1 Hz, 1C), 132.8, 129.8, 123.0, 112.0 (dd, J = 16.9, 7.5 Hz, 2C), 102.2 (t, J = 25.3 Hz, 1C), 70.7, 52.9, 52.8, 50.5, 36.1, 23.3; MH+ (CI): 505.0 (^{79}Br X 2).

EXAMPLE 105: Synthesis Of Pyridine Derivatives



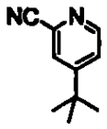
The nitrile was introduced essentially according to the method of Ornstein, P. L. et al. *J. Med. Chem.* 1991, *34*, 90-97. The crude product was filtered through silica (CH_2Cl_2 elution) to give the product as a white crystalline solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 5.3 Hz, 1H), 7.72 (d, J = 1.7 Hz, 1H), 7.56 (dd, J = 5.3, 1.7 Hz, 1H); MH+ (CI): 139.0 (^{35}Cl).

A. 2-Cyano-4-isopropylpyridine



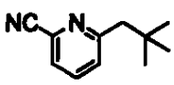
2-Cyano-4-isopropylpyridine was synthesized according to the method of Ornstein, P. L. et al. *J. Med. Chem.* 1991, *34*, 90-97: MH+ (CI): 147.1.

B. 2-Cyano-4-tert-butylpyridine



2-Cyano-4-tert-butylpyridine was synthesized according to the method of Ornstein, P. L. et al. *J. Med. Chem.* 1991, *34*, 90-97: ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 5.3 Hz, 1H), 7.68 (d, J = 1.5 Hz, 1H), 7.49 (dd, J = 5.3, 1.9 Hz, 1H), 1.33 (s, 9H); MH+ (CI): 161.1.

C. 2-Cyano-6-neopentylpyridine



2-Cyano-6-neopentylpyridine was synthesized from 2-neopentylpyridine according to the method of Ornstein, P. L. et al. *J. Med. Chem.* 1991, *34*, 90-97: R_f = 0.62 in 20% EtOAc/hexanes; MH+ (CI): 175.1.

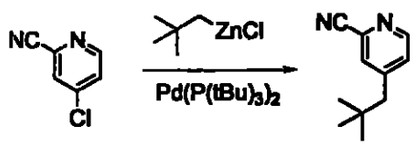
D. 2-Neopentylpyridine from 2-bromopyridine



A solution of neopentylzinc chloride was prepared according to the method of Negishi, E.-I. et al. *Tetrahedron Lett.* 1983, *24*, 3823-3824.

2-Bromopyridine (Aldrich, 0.48 mL, 5.0 mmol) and [1, 1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (Aldrich, 200 mg, 0.25 mmol) were added to the neopentylzinc chloride suspension. The resulting suspension was stirred at rt for 21 h, whereupon saturated ammonium chloride solution (25 mL) was added. The mixture was extracted with ethyl acetate (3X). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was dissolved in methylene chloride, and washed with 1 N HCl. The aqueous layer was separated, basified with 10 N NaOH (aq), and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 2-neopentylpyridine as an oil: R_f = 0.33 in 5% MeOH/CH_2Cl_2.

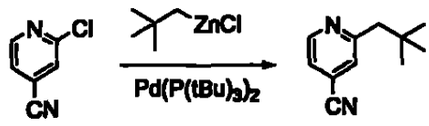
E. 2-cyano-4-neopentylpyridine



This transformation was performed according to the method of Dai, C. and Fu, G. *J. Am. Chem. Soc.* 2001, *123*, 2719-2724.

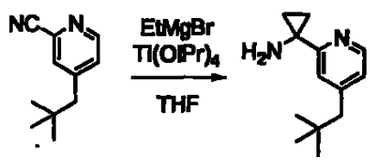
The crude residue was purified by filtration through a small plug of silica (20% ether/hexanes elution) to give the 2-cyano-4-neopentylpyridine: R_f = 0.25 in 20% Et_2O/hexanes; MH+ (CI): 175.1.

F. 4-cyano-2-neopentylpyridine



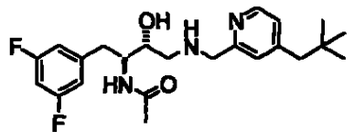
The method for the synthesis of 2-cyano-4-neopentylpyridine was used to convert 2-chloro-4-cyanopyridine (Oakwood) into 4-cyano-2-neopentylpyridine: R_f = 0.47 in 10% EtOAc/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (dd, J = 4.9, 0.7 Hz, 1H), 7.55-7.40 (m, 2H), 2.75 (s, 2H), 0.96 (s, 9H); MH+ (CI): 175.1.

G. 2-Cycloalkylamino-4-neopentylpyridine



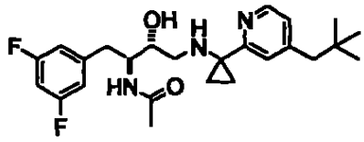
To a solution of 2-cyano-4-neopentylpyridine (380 mg, 2.2 mmol) in dry THF (6 mL) at rt was added titanium(IV) isopropoxide (0.7 mL, 2.4 mmol) and ethylmagnesium bromide (1.0 M in THF, 4.3 mL, 4.3 mmol) in succession with vigorous stirring. After 30 min, 1 mL water was added. The quenched reaction mixture was stirred at rt for 30 min, then filtered through diatomaceous earth (10% iPrOH/$CHCl_3$ elution). The filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography (R_f = 0.26 in 10% MeOH/CH_2Cl_2) to give 166 mg of the desired product as an oil: MH+ (CI): 205.1.

H. ***N*-((1*S*,2*R*)-1-(3,5-Difluorobenzyl)-3-{[4-(2,2-dimethylpropyl)pyridin-2-ylmethyl]amino}-2-hydroxypropyl) acetamide**



The above compound was prepared from 2-cyano-4-neopentylpyridine by methods analogous to those disclosed herein. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 5.0 Hz, 1H), 7.03-6.92 (m, 2H), 6.72 (app d, J = 6.3 Hz, 2H), 6.63 (tt, J = 9.0, 2.2 Hz, 1H), 6.44 (d, J = 9.0 Hz, 1H), 4.25-4.10 (m, 1H), 3.93 (s, 2H), 3.72-3.62 (m, 1H), 2.94 (dd, J = 14.3, 4.7 Hz, 1H), 2.88-2.70 (m, 3H), 2.48 (s, 2H), 1.87 (s, 3H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 162.8 (dd, J = 248.2, 13.0 Hz, 2C), 157.7, 149.8, 148.3, 142.3 (t, J = 9.1 Hz, 1C), 124.62, 124.56, 112.0 (dd, J = 16.9, 7.4 Hz, 2C), 101.8 (t, J = 25.1 Hz, 1C), 71.0, 54.1, 52.9, 51.5, 49.5, 35.7, 31.7, 29.3, 23.1; MH+ (CI): 420.2.

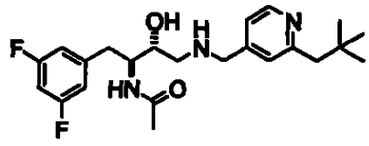
I. ***N*-((1*S*,2*R*)-1-(3,5-Difluorobenzyl)-3-{1-[4-(2,2-dimethylpropyl)pyridin-2-yl]cyclopropylamino}-2-hydroxypropyl) acetamide**



The above compound was prepared by coupling 2-Cycloalkylamino-4-neopentylpyridine and example 134 by methods analogous to those disclosed herein. The coupled product was then further elaborated using to afford the above compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 5.1 Hz, 1H), 6.89 (dd, J = 5.1, 1.0 Hz, 1H), 6.80 (s, 1H), 6.73 (dd, J = 6.2, 2.0 Hz, 2H), 6.64 (tt, J = 9.0, 2.0 Hz, 1H), 5.93 (d, J = 9.2 Hz, 1H),

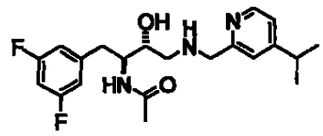
4.22-4.07 (m, 1H), 3.72 (s, 2H), 3.50 (dt, *J* = 6.6, 3.3 Hz, 1H), 2.96 (dd, *J* = 14.3, 4.6 Hz, 1H), 2.90-2.70 (m, 3H), 2.46 (s, 2H), 1.88 (s, 3H), 1.16 (d, *J* = 2.4 Hz, 4H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 163.3 (dd, *J* = 248.2, 13.0 Hz, 2C), 162.2, 149.4, 147.5, 142.1 (t, *J* = 9.1 Hz, 1C), 123.2, 120.9, 112.0 (dd, *J* = 16.9, 7.4 Hz, 2C), 101.9 (t, *J* = 25.1 Hz, 1C), 71.1, 63.6, 53.4, 52.6, 49.7, 49.4, 42.7, 35.8, 31.7, 29.3, 23.2, 19.0, 18.5; MH+ (CI): 446.2.

J. ***N***-((1*S*,2*R*)-1-(3,5-Difluorobenzyl)-3-{[2-(2,2-dimethylpropyl)pyridin-4-ylmethyl]-amino}-2-hydroxypropyl) acetamide



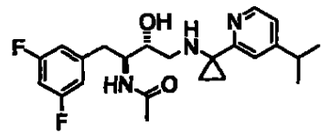
The above compound was prepared essentially according to the previously described methods. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J*= 5.0 Hz, 1H), 7.07 (d, *J* = 5.0 Hz, 1H), 7.06 (s, 1H), 6.72 (d, *J* = 6.3 Hz, 2H), 6.64 (tt, *J* = 9.0, 2.2 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 4.25-4.10 (m, 1H), 3.82 (d, *J* = 14.4 Hz, 1H), 3.76 (d, *J* = 14.4 Hz, 1H), 3.62 (q, *J* = 5.0 Hz, 1H), 3.42 (br s, 2H), 2.93 (dd, *J* = 14.2, 4.9 Hz, 1H), 2.78 (dd, *J* = 14.2, 8.9 Hz, 1H), 2.73 (d, *J* = 4.8 Hz, 2H), 2.66 (s, 2H), 1.88 (s, 3H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 162.7 (dd, *J* = 248.2, 13.0 Hz, 2C), 160.2, 148.7, 148.0, 142.0 (t, *J* = 9.1 Hz, 1C), 123.9, 120.3, 111.8 (dd, *J* = 16.9, 7.5 Hz, 2C), 101.9 (t, *J* = 25.3 Hz, 1C), 70.5, 53.4, 52.6, 51.7, 50.8, 36.0, 31.9, 29.5, 23.1; MH+ (CI): 420.2.

K. ***N***-{(1*S*,2*R*)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(4-isopropylpyridin-2-ylmethyl)-amino]propyl}acetamide



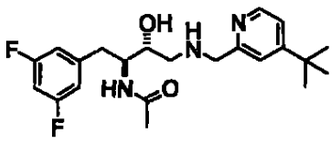
The above compound was prepared essentially according to the previously described methods. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J= 4.7 Hz, 1H), 7.10 (s, 1H), 7.06 (d, J = 5.2 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 6.72 (d, J = 6.3 Hz, 2H), 6.61 (tt, J = 9.0, 2.2 Hz, 1H), 4.77 (br s, 2H), 4.25-4.10 (m, 1H), 3.93 (s, 2H), 3.80-3.70 (m, 1H), 3.05-2.70 (m, 5H), 1.86 (s, 3H), 1.23 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 162.7 (dd, J = 248.2, 13.0 Hz, 2C), 158.8, 157.4, 148.9, 142.4 (t, J = 9.1 Hz, 1C), 120.9, 112.0 (dd, J = 16.9, 7.5 Hz, 2C), 101.7 (t, J = 25.3 Hz, 1C), 70.8, 54.0, 53.2, 51.6, 35.7, 33.5, 22.9; MH+ (CI): 392.2.

L. *N*-{(1*S*,2*R*)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[1-(4-isopropylpyridin-2-yl)-cyclopropylamino]propyl}acetamide



The above compound was prepared essentially according to the previously described methods. MH+ (CI): 418.2.

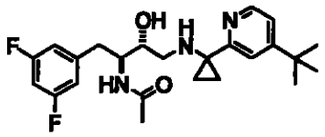
M. *N*-[(1*S*,2*R*)-3-[(4-tert-Butylpyridin-2-ylmethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide



The above compound was prepared essentially according to the previously described methods. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J= 5.3 Hz, 1H), 7.22 (s, 1H), 7.19 (dd, J = 5.3, 1.7

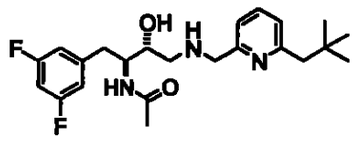
Hz, 1H), 6.73 (d, J = 6.3 Hz, 2H), 6.65 (tt, J = 9.0, 2.2 Hz, 1H), 4.26 (br s, 2H), 4.25-4.10 (m, 1H), 3.94 (s, 2H), 3.77-3.67 (m, 1H), 3.05-2.70 (m, 4H), 1.88 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 162.8 (dd, J = 248.2, 13.0 Hz, 2C), 161.2, 157.9, 148.8, 142.4 (t, J = 9.1 Hz, 1C), 119.6, 119.5, 112.1 (dd, J = 16.9, 7.5 Hz, 2C), 101.8 (t, J = 25.3 Hz, 1C), 70.9, 54.3, 53.1, 51.7, 35.8, 34.7, 30.4, 28.7, 23.1; MH+ (CI): 406.2.

N. *N*-[(1*S*,2*R*)-3-[1-(4-tert-Butylpyridin-2-yl)cyclopropylamino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl] acetamide



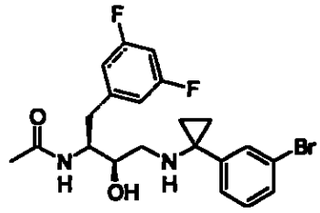
The above compound was prepared essentially according to the previously described methods. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J= 5.2 Hz, 1H), 7.15-7.05 (m, 2H), 6.73 (d, J = 6.3 Hz, 2H), 6.64 (tt, J = 9.0, 2.2 Hz, 1H), 5.88 (d, J = 9.1 Hz, 1H), 4.22-4.08 (m, 1H), 3.75 (br s, 2H), 3.50 (td, J = 6.5, 3.5 Hz, 1H), 2.99 (dd, J = 14.2, 4.5 Hz, 1H), 2.90-2.70 (m, 3H), 1.89 (s, 3H), 1.30 (s, 9H), 1.25-1.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 162.9 (dd, J = 248.2, 13.0 Hz, 2C), 162.5, 160.8, 148.2, 142.1 (t, J = 9.1 Hz, 1C), 118.2, 115.6, 112.0 (dd, J = 16.9, 7.5 Hz, 2C), 101.9 (t, J = 25.3 Hz, 1C), 70.9, 52.6, 49.4, 43.1, 35.9, 34.8, 30.5, 23.2, 18.8, 18.7; MH+ (CI): 432.2.

O. *N*-((1*S*,2*R*)-1-(3,5-Difluorobenzyl)-3-{[6-(2,2-dimethylpropyl)pyridin-2-ylmethyl]-amino}-2-hydroxypropyl) acetamide

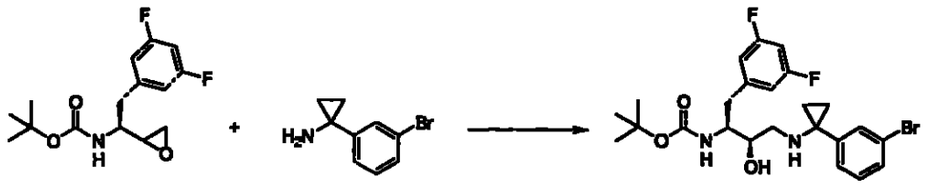


The above compound was prepared essentially according to the previously described methods. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (t, J= 7.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.74 (dd, J = 6.3, 2.0 Hz, 2H), 6.64 (tt, J = 9.0, 2.2 Hz, 1H), 6.11 (d, J = 9.0 Hz, 1H), 4.25-4.10 (m, 1H), 3.92 (d, J = 1.2 Hz, 2H), 3.70-3.55 (m, 1H), 3.25 (br s, 1H), 2.93 (dd, J = 14.2, 4.9 Hz, 1H), 2.88-2.70 (m, 3H), 2.68 (s, 2H), 1.88 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.0, 162.8 (dd, J = 248.2, 13.0 Hz, 2C), 159.8, 157.6, 142.2 (t, J = 9.1 Hz, 1C), 136.3, 123.3, 119.6, 112.0 (dd, J = 16.9, 7.5 Hz, 2C), 101.9 (t, J = 25.3 Hz, 1C), 70.8, 54.2, 52.8, 51.6, 51.5, 35.7, 32.0, 29.5, 23.2; MH+ (CI): 420.2.

EXAMPLE 106



Step 1. Epoxide opening with 1-(3-bromophenyl) cyclopropyl amine.



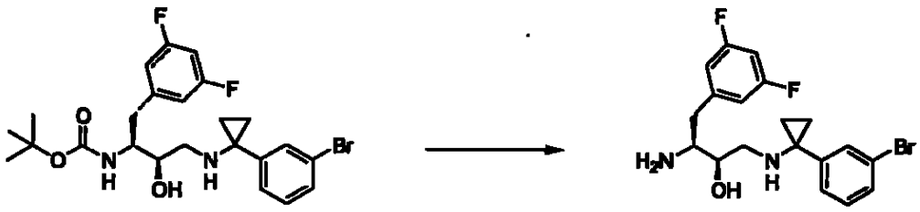
N-BOC-1-(3-bromophenyl)aminocyclopropane (15.60g, 50.2 mmol) was treated with 4N HCl in dioxane (50 mL) and stirred for 2 h. The volatiles were evaporated *in vacuo* and the

residue taken up into 1N NaOH (250 mL). The mixture was extracted with diethyl ether (2 X 200 mL). The combined ether extracts were washed with brine (50 mL), dried (sodium sulfate), then filtered and evaporated *in vacuo* to provide the amine free base.

The amine free base was dissolved in 2-propanol (250 mL) and the epoxide (15.0g, 50.2 mmol) was added. The mixture was heated to reflux for 22 h and allowed to stand at ambient temperature for 3 d. Analysis by HPLC indicated that the desired product predominated, and that some starting cyclopropylamine remained unreacted. The starting epoxide was consumed. The volatiles were removed *in vacuo* and the residue was purified by silica gel flash chromatography (eluted 2:1 hexane/ethyl acetate) to provide the final product (13.68 g, 53%).

LC-MS: [M+H] = 511, 513, Rt=2.31 min, Phenomenex Luna C18 (30cm X 4.6 mm), 20-70% CH_3CN / water / 0.1% trifluoroacetic acid in 2.33 min, flow rate 1.5 mL/min.

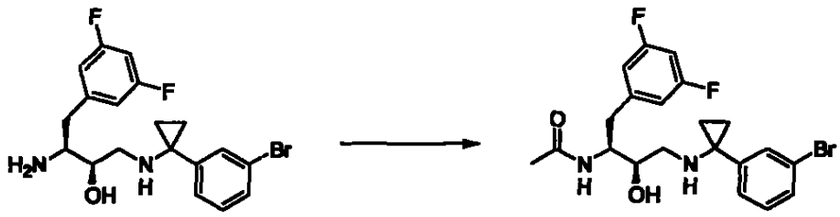
Step 2. Preparation of S,R 1-(3,5-Difluorobenzyl)-3-[1-(3-Bromophenyl)Cyclopropylamino)]-2-Hydroxypropyl Amine.



The Boc-protected amine (13.5 g, 26.7 mmol) was treated with 4N HCl in dioxane (30 mL). Methanol (15 mL) was added and the mixture became homogeneous before depositing a precipitate. The mixture was stirred for 3 h before the volatiles were removed *in vacuo*. The residue was taken up in 1N NaOH (150 mL) and the mixture was extracted with diethyl ether (3 X 100 mL). The combined ether extracts were washed

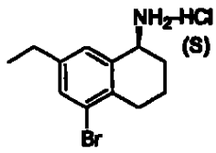
with brine (50 mL), dried (magnesium sulfate), filtered and evaporated *in vacuo* to give the desired amine (6.5g), which was used directly in the next step.

Step 3. Preparation of N-[3-[1-(3-Bromo-phenyl)-cyclopropylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide

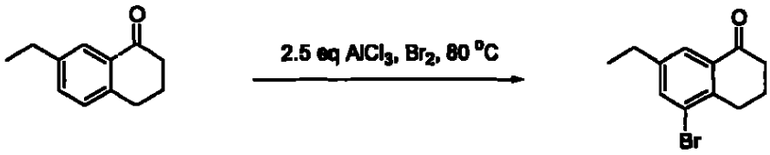


The above product was prepared essentially according to the procedure of Example 56, using acetic acid as the acid. The desired product was obtained as a white solid (11.75g, 97%). LC-MS analysis indicated a purity of 94%. LC-MS: [M+H] = 453, 455, Rt=1.86 min, Phenomenex Luna C18 (30cm X 4.6 mm), 20-70% CH_3CN / water / 0.1% trifluoroacetic acid in 2.33 min, flow rate 1.5 mL/min.

EXAMPLE 107



A. Preparation of 5-Bromo-7-ethyl-1-tetralone

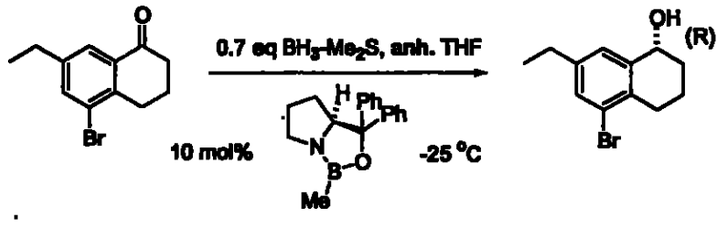


The bromination was performed essentially according to the procedure of Cornelius, L.A.M. Combs, D.W., *Synthetic Communications* 1994, *24*, 2777-2788). The product was

separated using silica gel flash chromatography (Biotage Flash 75, 10:1 hexanes:MTBE) to yield the purified product (7.4 g, 75%).

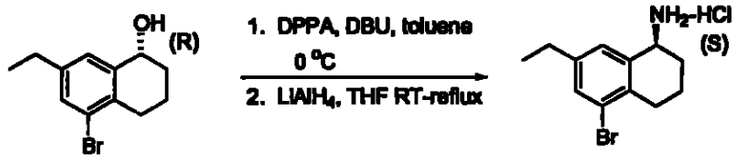
LC-MS analysis indicated the presence of a dibromoproduct co-eluting with desired product. This material was taken on to the next step and separated.

B. (R)-7-Ethyl-5-bromotetralin-1-ol



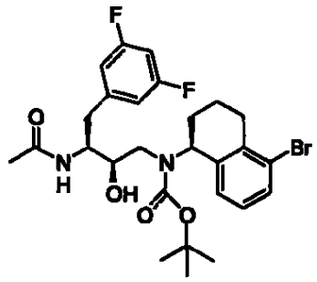
The above product was prepared essentially according to the method of Example 2. The resulting product was purified by silica gel chromatography (Biotage Flash 65, 10/1 hexanes/ethyl acetate) to yield (R)-7-ethyl-5-bromotetralin-1-ol (4.0 g, 53%).

C. (S)-7-Ethyl-5-bromo-1,2,3,4-tetrahydro-1-napthylamine hydrochloride.



The above compound was prepared essentially according to the method of Example 3. First the azide was prepared. Second, the azide was reduced with lithium aluminum hydride to afford the product as a white solid. LC-MS: [M-NH2] = 237, 239, Rt=6.34 min, Phenomenex Luna C18 (30cm X 4.6 mm), 5-20% CH_3CN/water/0.1% trifluoroacetic acid in 3.33 min, flow rate 1.5 mL/min.

Example 108



Step 1. Epoxide opening with (S)-7-bromo-1-aminotetralin .

The above compound was prepared essentially according to the method of Example 17, step 3. The coupled product was crystallized from isopropyl alcohol. LC-MS analysis indicated about 99% purity. LC-MS: [M+H] = 527, Rt=2.34 min, Phenomenex Luna C18 (30cm X 4.6 mm), 20-70% CH_3CN / water / 0.1% trifluoroacetic acid in 2.33 min, flow rate 1.5 mL/min.

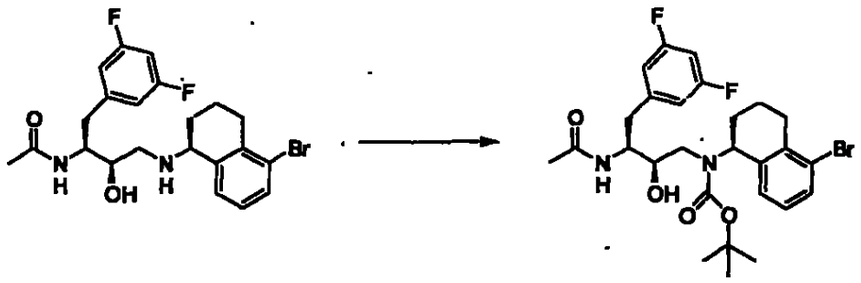
Step 2. Deprotection Of Boc Group.

The above compound was prepared essentially using the method of example 106, step 2. The resulting material was used directly in the next step.

Step 3. Acylation of N-terminal amine

The above compound was prepared essentially using the method of example 106, step 3. LC-MS analysis indicated a purity of 99%. LC-MS: [M+H] = 467, 469, Rt=1.94 min, Phenomenex Luna C18 (30cm X 4.6 mm), 20-70% CH_3CN / water / 0.1% trifluoroacetic acid in 2.33 min, flow rate 1.5 mL/min.

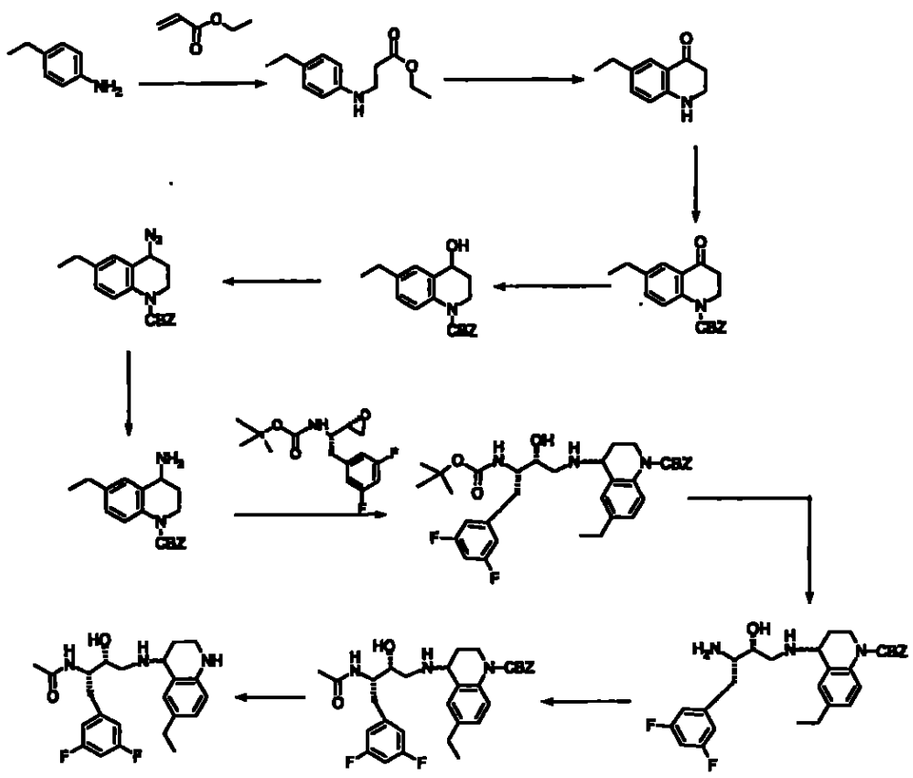
Step 4. Adding Boc Group



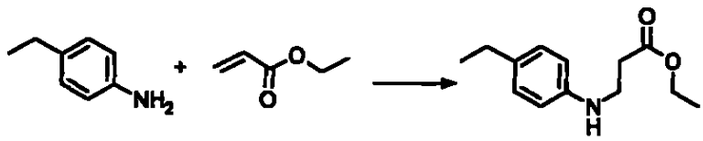
The starting compound (7.80g, 16.7 mmol) was dissolved in dichloromethane (150 mL). Di-tert-butyldicarbonate (3.82g, 17.5 mmol) was added and the mixture was stirred for 3 days. The mixture was then concentrated *in vacuo* and the residue passed through a pad of silica gel (eluted 1L 2:1 hexanes/ethyl acetate, 0.5L 5% MeOH/dichloromethane) to give the desired product (8.52g, 90%).

LC-MS analysis indicated a purity of 99%. LC-MS: [M+Na] = 589, 591, Rt=5.12 min, Phenomenex Luna C18 (30cm X 4.6 mm), 20-70% CH_3CN / water / 0.1% trifluoroacetic acid in 2.33 min, flow rate 1.5 mL/min.

Example 109. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide



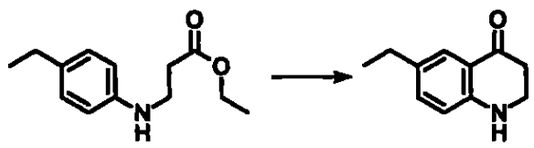
A.1. Ethyl N-(4-Ethylphenyl)-beta-alaninate



To a solution of 4-ethyl aniline (10.0 g) in acetic acid (25 mL) was added ethyl acrylate (10.8 g). The mixture was heated to 80 °C for 2 hours. Additional ethyl acrylate (1.0 mL) was added, and the mixture was again heated to 80 °C for 1 hour. The mixture was allowed to cool to room temperature and stir for two days. Sodium hydroxide (8N) was added until the pH equaled 9. The mixture was partitioned between dichloromethane and water and the combined organics were washed once with 1N sodium hydroxide, once with brine, dried with sodium sulfate, filtered, and concentrated. The mixture

was chromatographed using a 20% ethyl acetate in heptane solvent solution. A mixture of the mono and di ester product (19.5 g) were obtained (1:1 mixture). MS (ESI+) for $C_{13}H_{19}NO_2$ m/z 221.99 $(M+H)^+$.

A.2. 6-Ethyl-2,3-dihydroquinolin-4(1H)-one



A solution of phosphorus pentoxide (19.53 g) in methane sulfonic acid (200 mL) was heated to 130 °C. The mixture was stirred at 130 °C for one hour until all the phosphorus pentoxide had dissolved. The mixuture was allowed to cool for 15 minutes and ethyl N-(4-ethylphenyl)-beta-alaninate (19.53 g of mono and di-ester mixture) was added. The mixture was heated to 130 °C for one hour and allowed to slowly cool overnight. The mixture was then cooled in an ice bath and 10N sodium hydroxide was added until the pH reached 9.5. Ethyl acetate was added to the mixture to help dissolve solids. The remaining gummy dark solids were dissolved in methanol and added to the ethyl acetate-aq. sodium hydroxide mixture. Semi-crystalline solids precipitated and were removed by filtration through Celite. The filtrate was washed with water, followed by 1N sodium hydroxide and brine, dried with magnesium sulfate, filtered, and concentrated.. Silica gel chromatography using 0.25% ammonium hydroxide in dichloromethane gave mixed fractions. The mixed fractions were combined and re-chromatographed using 30% ethyl acetate in heptane. The resulting material was further upgraded by formation of the hydrochloride salt using 2N HCl in ether. The salt was collected by filtration and washed with heptane and dried in an oven under vacuum at 50 °C overnight. The salt was then partitioned between dichloromethane and 1N sodium hydroxide. The organic layer was extracted twice with

dichloromethane, washed with 1N sodium hydroxide, dried with sodium sulfate, filtered, and concentrated to give 3.83 g of the title compound. MS (ESI+) for $C_{11}H_{13}NO$ *m/z* 175.96 $(M+H)^+$.

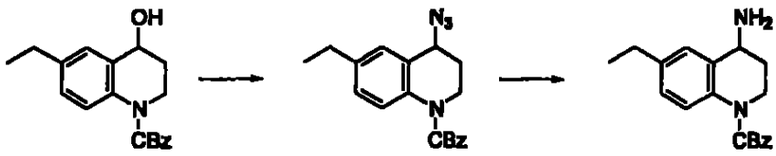
A.3. Benzyl 6-ethyl-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

To a solution of 6-ethyl-2,3-dihydroquinolin-4(1H)-one (1.25 g) in THF (15 mL) was added sodium bicarbonate (0.84 g). Water (5 mL) followed by benzyl chloroformate (1.58 g) were added to the mixture,and it was stirred at room temperature overnight. The reaction was not complete as determined by TLC, so an additional 0.60 g of $NaHCO_3$ were added to the mixture and it was stirred at room temperature for two additional hours. The mixture was then concentrated under reduced pressure and the residue was partitioned between water and ethyl acetate and the organic layer was washed with brine, dried with magnesium sulfate, filtered, and concentrated. Chromotography on silicia gel using 25% ethyl acetate in heptane solvent solution gave 1.84 g of the title compound. MS (ESI+) for $C_{19}H_{19}NO_3$ *m/z* 310.03 $(M+H)^+$.

A.4. Benzyl 6-ethyl-4-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate

The above compound was prepared essentially according to the procedure of Example 17, step 1. The crude product was purified by chromatography on silica gel using a 2% MeOH in dichloromethane solvent solution with 0.5% ammonium hydroxide. ^{1}HNMR ($CDCl_3$) δ 1.22 (t, *J* = 8 Hz, 3 H), 1.89 (s, 1 H), 2.04 (m, 2 H), 2.61 (q, *J* = 8 Hz, 2 H), 3.66 (m, 1 H), 4.11 (m, 1 H), 4.74 (t, *J* = 4 Hz, 1 H), 5.25 (dd, *J* = 12, 20 Hz, 2 H), 7.09 (dd, *J* = 2, 9 Hz, 1 H), 7.21 (d, *J* = 2 Hz, 1 H), 7.35 (m, 5 H), 7.6 (d, *J* = 8 Hz, 1 H).

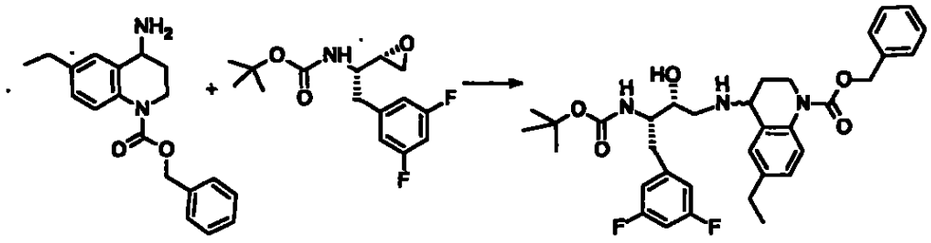
A.5. Benzyl 4-amino-6-ethyl-3,4-dihydroquinoline-1(2H)-carboxylate



The above compound was prepared essentially according to the method of Example 17, step 2. First, the alcohol was converted to the azide. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, *J* = 8 Hz, 3 H), 2.09 (m, 2 H), 2.62 (q, *J* = 8 Hz, 2 H), 3.67 (m, 1 H), 4.12 (m, 1 H), 4.58 (t, *J* = 4 Hz, 1 H), 5.24 (m, 2 H), 7.09 (d, *J* = 2 Hz, 1 H), 7.13 (dd, *J* = 2, 9 Hz, 1 H), 7.35 (m, 5 H), 7.82 (d, J = 8 Hz, 1 H).

Second the azide was reduced using PMe_3. MS (ESI+) for $C_{19}H_{22}N_2O_2$ *m/z* 311.05 $(M+H)^+$.

A.6. Benzyl 4-{[(2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3,4-dihydroquinoline-1(2H)-carboxylate



The above compound was prepared essentially according to the method of Example 17, step 3. The crude product was purified by silcica gel chromatography using 2% MeOH in dichloromethane with 0.25% NH_4OH as the solvent system. MS (ESI+) for $C_{34}H_{41}F_2N_3O_5$ *m/z* 610.51 $(M+H)^+$.

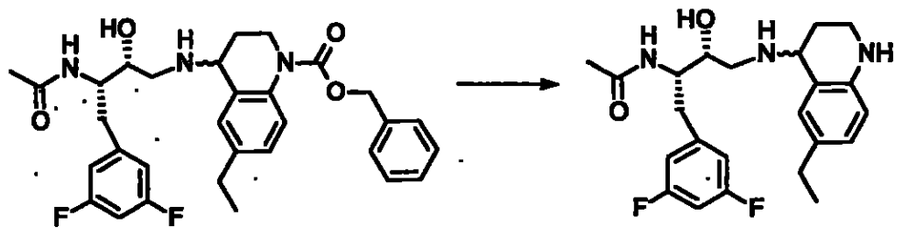
A.7. Benzyl 4-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-6-ethyl-3,4-dihydroquinoline-1(2H)-carboxylate

To a solution of the produce from step A.6 (0.76 g) in MeOH (10 mL) was added 2N HCl in Et_2O (1.6 mL). The mixture was stirred at room temperature for two hours and an additional 1.0 mL of 2N HCl in Et_2O were added. The mixture was stirred for four more hours. The reaction was still not complete, so an additional 3.0mL of HCl in Et_2O were added. The mixture was stirred for two hours and then stripped of solvent under reduced pressure. The residue was dissolved in ethyl acetate washed two times with 1N NaOH, dried with magnesium sulfate, filtered, and concentrated. A silica gel column was run for purification using 4% MeOH in dichloromethane with 0.25% NH_4OH as the solvent solution and gave 0.44 g of the title compound. MS (ESI+) for $C_{29}H_{33}F_2N_3O_3$ *m/z* 510.36 $(M+H)^+$.

A.8. Benzyl 4-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-6-ethyl-3,4-dihydroquinoline-1(2H)-carboxylate

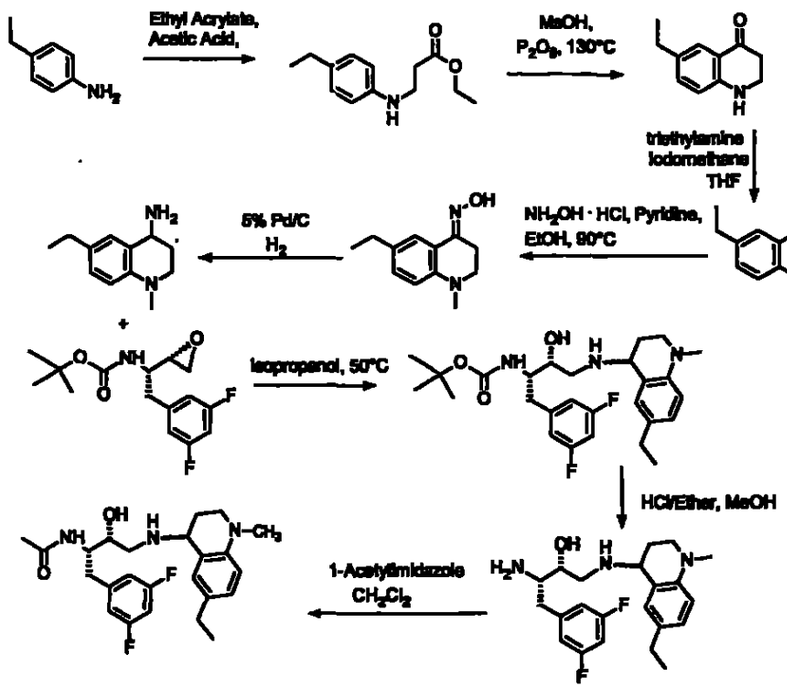
To a solution of the product from step A.7 (0.43 g) in dichloromethane (15 mL) was added N,N-diacetyl-O-methylhydroxylamine (0.11 g). The mixture was stirred overnight at room temperature. An additional 0.10 g of N,N-diacetyl-O-methylhydroxylamine were then added and the mixture was stirred for 6 hours. Another 0.10 g of N,N-diacetyl-O-methylhydroxylamine were added and the mixture was stirred overnight and then partitioned between dichloromethane and 1N HCl and brine. The organic layer was dried with magnesium sulfate, filtered, and concentrated. A silica gel column was run for purification using 4% MeOH in dichloromethane with 0.25% NH_4OH as the solvent solution and gave 0.35 g of the title compound. MS (ESI+) for $C_{31}H_{34}F_2N_3O_4$ *m/z* 552.32 $(M+H)^+$.

A.9. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide



Nitrogen was bubbled through a solution of the product from step A.8 (0.35 g), EtOH (25 mL), and acetic acid (0.75 mL). 10% palladium on carbon (0.29 g) was added to the mixture and it was shaken on a hydrogenation apparatus under 52 psi of hydrogen for 1.25 h. The catalyst was filtered off using Celite and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate, aq. sodium hydroxide (pH 10), and brine, and then dried with magnesium sulfate, filtered, and concentrated. A silica gel column was run using 6% MeOH in dichloromethane with 0.25% NH_4OH as the solvent solution and gave 0.04 g of the title compound. MS (ESI+) for $C_{23}H_{29}F_2N_3O_2$ *m/z* 418.31 $(M+H)^+$.

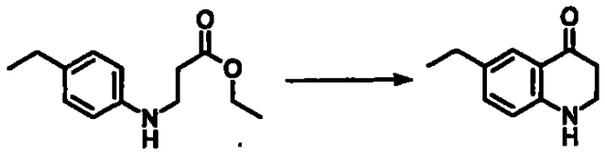
A.10. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide



A.11. Ethyl N-(4-ethylphenyl)-beta-alaninate

To a solution of 4-ethyl aniline (10.00g) in acetic acid (20mL) was added ethyl acrylate (8.26). The mixture was heated to 70° for 3.5 hours. The mixture was allowed to cool to room temperature. The mixture was partitioned between dichloromethane and water, and was extracted three times. The combined organics were washed once with brine, dried with sodium sulfate, filtered, and concentrated. The mixture was taken on to the next step. MS (ESI+) for $C_{13}H_{19}NO_2$ *m/z* 223.1 $(M+H)^+$.

A.12. 6-ethyl-2,3-dihydroquinolin-4(1H)-one



A solution of phosphorus pentoxide (11.14g) in methane sulfonic acid (114mL) was heated to 130°. The mixture was stirred at 130° for one hour until all the phosphorus pentoxide had dissolved. The mixture was allowed to cool for 15 minutes, and ethyl N-(4-ethylphenyl)-beta-alaninate (11.14g of mono and di-ester mixture) was added. The mixture was heated to 130° for 1.5 hours, and the mixture was allowed to cool to room temperature. The mixture was cooled in an ice bath, and 50% sodium hydroxide was added until the pH reached 8. The gummy dark solids were dissolved in MeOH, and added to the mixture. Solids began to crash out, so they were filtered off with celite. The liquids were combined, and were partitioned between dichloromethane and water, and the organics were extracted three times with dichloromethane. The combined organics were washed with brine, dried with sodium sulfate, filtered, and concentrated. The product was chromatographed using a 30% ethyl acetate in heptane solvent solution. 4.10g of the title product were recovered. (28% yield through first two steps) MS (ESI+) for $C_{11}H_{13}NO$ *m/z* 176.00 $(M+H)^+$.

A.13. 6-ethyl-1-methyl-2,3-dihydroquinolin-4(1H)-one

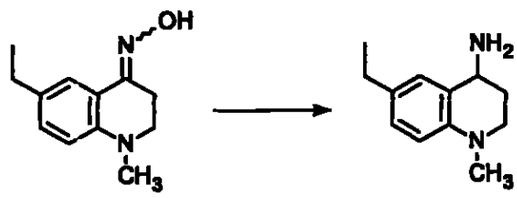
To a solution of 6-ethyl-2,3-dihydroquinolin-4(1H)-one (1.00g) in THF (25mL) was added triethylamine (0.64g) followed by iodomethane (0.89g). The mixture was refluxed at 70°C overnight. The solvent was stripped under reduced pressure, and the residue was partitioned between aqueous sodium bicarbonate and dichloromethane. The organics were extracted three times, washed with brine, dried with sodium sulfate, filtered, and concentrated. Chromatography was used to purify

the title compound using a 40% ethyl acetate in heptane solvent solution. 0.32g of the title product were recovered. (30% yield). MS (ESI+) for $C_{12}H_{15}NO$ *m/z* 190.10 $(M+H)^+$.

A.14. (4E)-6-ethyl-1-methyl-2,3-dihydroquinolin-4(1H)-one oxime

To a solution of 6-ethyl-1-methyl-2,3-dihydroquinolin-4(1H)-one (0.32g) in ethanol (25mL) were added pyridine (0.53g) and hydroxylamine hydrochloride (0.59g). The mixture was heated to 90°C for two hours with a reflux condensor attatched. The mixture was cooled to room temperature, and the solvent was stripped under reduced pressure. The residue was portioned between water and dichloromethane and the organics were extracted three times. The combined organics were washed once with brine, dried with sodium sulfate, filtered, and concentrated. 0.34g of the title product were recovered. (98% yield). MS (ESI+) for $C_{12}H_{16}N_2O$ *m/z* 205.02 $(M+H)^+$.

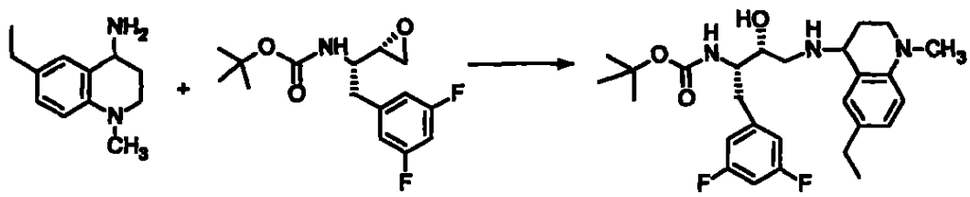
A.15. 6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-amine



(4E,Z)-6-ethyl-1-methyl-2,3-dihydroquinolin-4(1H)-one oxime (0.34g), ethanol (20mL), and acetic acid (0.27g) were combined in a hydrogenation flask and degassed with nitrogen. 5% Palladium on carbon was carefully added to the mixture (0.04g) and the mixture was degassed for several more minutes. The mixture was set up on the hydrogenation apparatus, and was put under 50 psi of hydrogen. The mixture was shaken for five and ½ hours, and was taken off the machine, but was not complete by TLC. The mixture was again degassed, and an

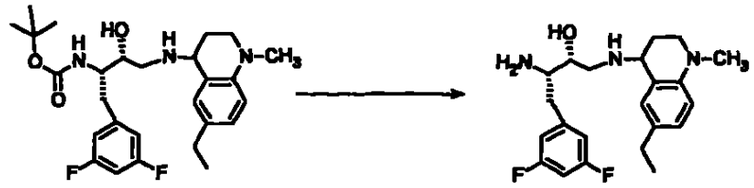
additional 0.10g of 5% palladium on carbon were added to the mixture. The mixture was put back on the hydrogenation apparatus, and was shaken overnight. The palladium on carbon was filtered off using celite, and the liquids were concentrated under reduced pressure. The residue was partitioned between aqueous sodium bicarbonate and dichloromethane, and the organics were extracted three times. The combined organics were dried with sodium sulfate, filtered, and concentrated. 0.26g of the title compound were recovered. (82% yield).

A.16. tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropylcarbamate



The above compound was prepared essentially according to the method of Example 15, step 2. MS (ESI+) for $C_{27}H_{37}F_2N_3O_2$ *m/z* 490.59 $(M+H)^+$.

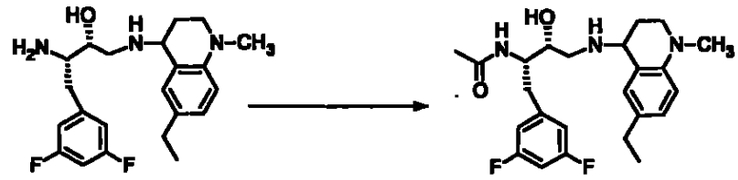
A.17. (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]butan-2-ol



To a solution of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropylcarbamate

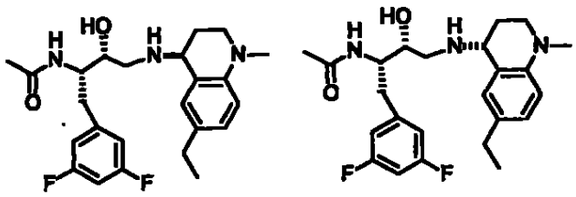
(0.412g) in MeOH (5mL) was added 2N HCl in Et_2O (2.1mL). The mixture was stirred at room temperature for fifteen minutes. The mixture was stripped of solvent under reduced pressure. The residue was partitioned between dichloromethane and aqueous sodium bicarbonate, and the organic was extracted three times, washed with brine, dried with sodium sulfate, filtered, and concentrated. A silica gel column was run for purification using 5% MeOH in dichloromethane with as the solvent solution. 0.255g of the title product were recovered. (78% yield). MS (ESI+) for $C_{22}H_{29}F_2N_3O$ *m/z* 390.18 $(M+H)^+$.

A.18. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide



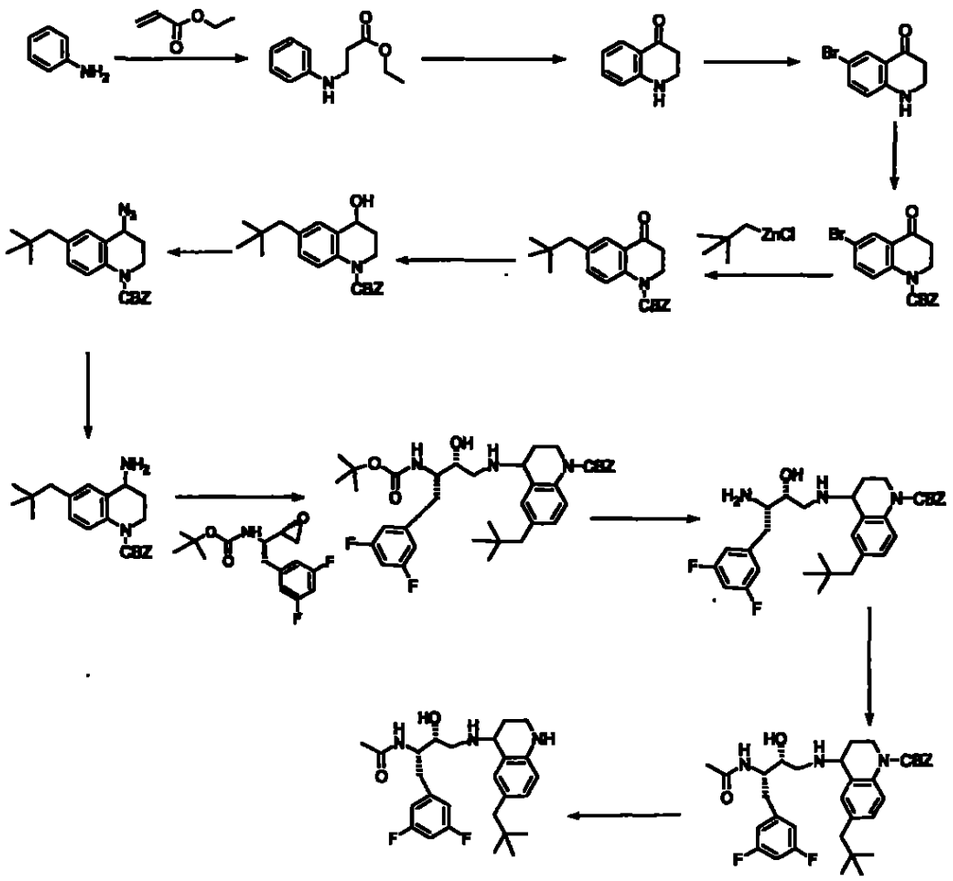
To a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]butan-2-ol (0.218g) in dichloromethane (15mL) was added 1-acetylimidazole (0.062g). The mixture was stirred overnight at room temperature. The mixture was partitioned between dichloromethane and brine, and the organic was extracted three times, dried with sodium sulfate, filtered, and concentrated. A silica gel column was run for purification using 3% MeOH in dichloromethane with 0.5% NH_4OH as the solvent solution. HPLC still showed small amounts of starting material present, so the mixture was washed one time with 1N HCl, dried with magnesium sulfate, filtered, and concentrated. 0.115g of the title product were recovered. (48% yield). MS (ESI+) for $C_{24}H_{31}F_2N_3O_2$ *m/z* 432.18 $(M+H)^+$.

A.19. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide and N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4R)-6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide

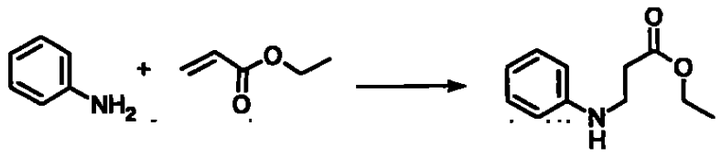


Silica gel chromatography of approximately 0.1 g of N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide using methanol/dichloromethane (8/92) with 0.1 % ammonium hydroxide gave 0.032 g of N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide [R_f ($MeOH/CH_2Cl_2/NH_4OH$) = 0.40; MS (ESI+) for $C_{24}H_{31}F_2N_3O_2$ *m/z* 432.2 $(M+H)^+$]. Re-chromatography of mixed fractions gave 0.011 g of a 9:1 mixture of the 4R isomer [R_f ($MeOH/CH_2Cl_2/NH_4OH$) = 0.35; MS (ESI+) for $C_{24}H_{31}F_2N_3O_2$ *m/z* 432.2 $(M+H)^+$] and the 4S isomer.

B. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]propyl}acetamide



B.1. Ethyl N-phenyl-beta-alaninate



The above compound was prepared essentially according to the method of Example 109, step A.1. The crude product was purified by chromatography on silica gel using 15% ethyl acetate in heptane with 0.25% TFA solvent. The purified mixture comprised the mono and di-ester products (1:1) which were used in the next step. MS (ESI+) for $C_{11}H_{15}NO_2$ m/z 193.99 $(M+H)^+$.

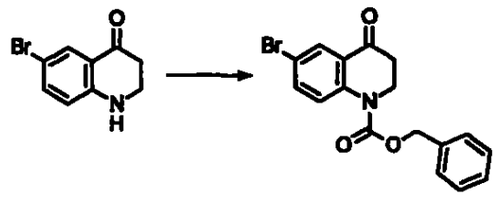
B.2. 2,3-dihydroquinolin-4(1H)-one

The above compound was prepared essentially according to the method of Example 109, step A.2. The crude product was purified by column chromatography using a 20-30% ethyl acetate in heptane gradient. MS (ESI+) for C_9H_9NO *m/z* 147.96 $(M+H)^+$.

B.3. 6-bromo-2,3-dihydroquinolin-4(1H)-one

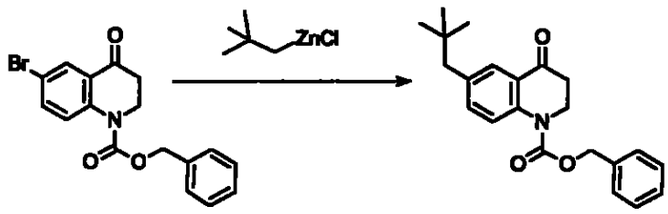
To a solution of 2,3-dihydroquinolin-4(1H)-one (2.94 g) in dichloromethane (25 mL) was added N-bromosuccinimide (3.63 g). The mixture was stirred at room temperature for 1.5 h and was partitioned between aqueous sodium bicarbonate and dichloromethane. The organic layer was washed with brine, dried with sodium sulfate, filtered, and concentrated. The concentrate was chromatographed on silica gel using a 35% ethyl acetate in heptane solvent solution and gave 4.14 g of the title compound. MS (ESI-) for C_9H_8BrNO *m/z* 225.77 $(M-H)^-$.

B.4. Benzyl 6-bromo-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate



The above compound was prepared essentially according to the method of Example 109, step A.3. ^1H NMR ($CDCl_3$) δ 2.78 (t, *J* = 7 Hz, 2 H), 4.22 (t, *J* = 6 Hz, 2 H), 5.28 (s, 2 H), 7.40 (m, 5 H), 7.58 (dd, *J* = 2, 9 Hz, 1 H), 7.75 (d, *J* = 9 Hz, 1 H), 8.10 (d, *J* = 2 Hz, 1 H).

B.5. Benzyl 6-neopentyl-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate

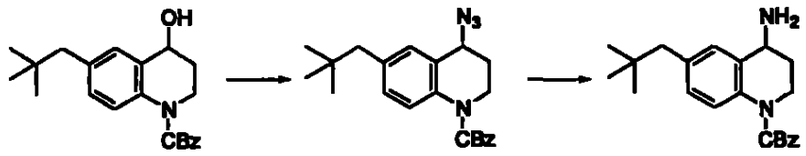


Benzyl 6-bromo-4-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (3.10 g) and dichloro[1,1'-bis(diphenylphosphino] ferrocene]palladium(II)dichloromethane adduct (0.35 g) were combined in a round bottom flask. The mixture was put under high vacuum and purged with nitrogen. A 0.5 M solution of bromo(neopentyl)zinc (55 mL) prepared using the procedure of Negishi *et al. Tet Lett.* **1983**, *24*, 3823-3824, was added to the mixture and was stirred at room temperature for two days. The reaction had not gone to completion, so an additional 10 mL of bromo(neopentyl)zinc solution was added and the mixture was stirred for one additional day. The mixture was then partitioned between ethyl acetate and aqueous ammonium chloride, dried with magnesium sulfate, filtered, and concentrated. Silica gel chromatography using a 20% ethyl acetate in heptane solvent solution gave 2.17g of the title compound. MS (ESI+) for $C_{22}H_{25}NO_3$ *m/z* 353.17 $(M+H)^+$.

B.6. Benzyl 4-hydroxy-6-neopentyl-3,4-dihydroquinoline-1(2H)-carboxylate

The above compound was prepared essentially according to the method of Example 17, step 2. The crude product was purified ^1H NMR ($CDCl_3$) δ 0.90 (s, 9 H), 1.80 (s, 1 H), 2.06 (m, 2 H), 2.45 (s, 2 H), 3.68 (m, 1 H), 4.12 (m, 1 H), 4.75 (t, *J* = 4 Hz, 1 H), 5.24 (dd, *J* = 12, 17 Hz, 2 H), 7.02 (dd, *J* = 2, 9 Hz, 1 H), 7.12 (d, *J* = 2 Hz, 1 H), 7.35 (m, 5 H), 7.76 (d, *J* = 8 Hz, 1 H).

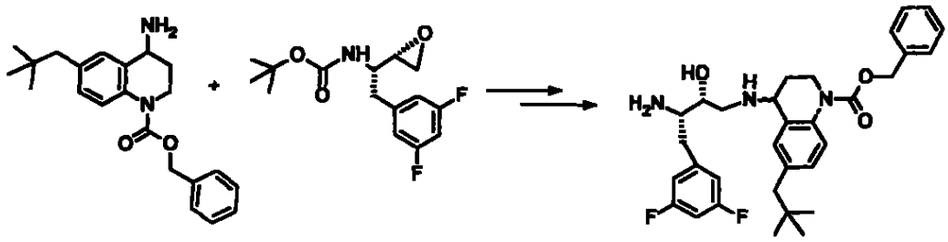
B.7. Benzyl 4-amino-6-neopentyl-3,4-dihydroquinoline-1(2H)-carboxylate



The above compound was prepared essentially according to the method of Example 17, step 2. First the azide was prepared and chromatographed on silica gel using a 15% ethyl acetate in heptane. ^{1}H NMR ($CDCl_3$) δ .091 (s, 9 H), 2.09 (m, 2 H), 2.46 (s, 2 H), 3.66 (m, 1 H), 4.14 (m, 1 H), 4.58 (t, J = 4 Hz, 1 H), 4.24 (dd, J = 12, 15 Hz, 2 H), 7.03 (d, J = 2 Hz, 1 H), 7.06 (dd, J = 2, 9 Hz, 1 H), 7.35 (m, 5 H), 7.86 (d, J = 8 Hz, 1 H);

Second, the azide was reduced using PMe_3. The resulting amine was purified by silica gel chromatography using 2.5% methanol in dichloromethane with 0.5% ammonium hydroxide. MS (ESI+) for $C_{22}H_{28}N_2O_2$ m/z 353.19 $(M+H)^+$.

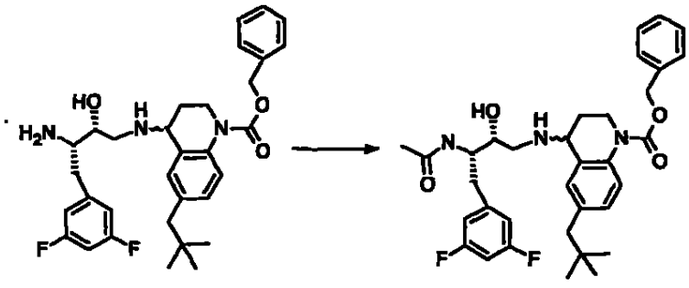
B.8. Benzyl 4-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-6-neopentyl-3,4-dihydroquinoline-1(2H)-carboxylate



To a solution of benzyl 4-amino-6-neopentyl-3,4-dihydroquinoline-1(2H)-carboxylate (1.31g) in isopropanol (25 mL) was added Example 134 (0.75 g) and the mixture was heated at 90 °C for 45 minutes. The temperature was reduced to 60 °C and the mixture was allowed to stir overnight. An additional 0.36 g of Example 134 were added to the mixture and it was

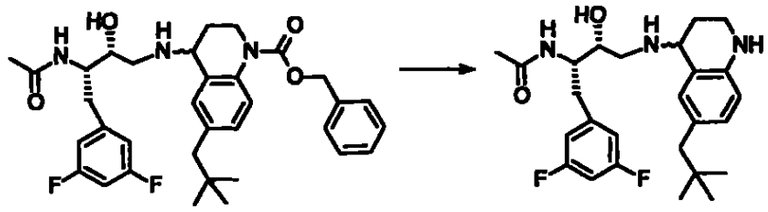
heated to 80 °C for five hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was partitioned between water and ethyl acetate and the organic layers were dried with magnesium sulfate, filtered, and concentrated. A silica gel column was run to attempt to separate the diasteriomers using a gradient of 2-4% MeOH in dichloromethane with 0.25% NH_4OH as the solvent system. The first fraction contained a 70:30 mixture of the two diasteriomers and the second fraction was a 50:50 mix of the diasteriomers. The Boc groups were removed by dissolving each fraction in a minimal amount of dichloromethane and adding 15 mL of 2N HCl in ether to each of the two mixtures. The mixtures were stirred for two hours and concentrated under reduced pressure. The mixtures were then partitioned between 1N sodium hydroxide and ethyl acetate, dried with magnesium sulfate, filtered, and concentrated to give 0.23 g of the 70:30 title compound mixture and 0.30 g of the 50:50 mixture. MS (ESI+) for $C_{32}H_{39}F_2N_3O_3$ *m/z* 552.32 $(M+H)^+$ for the 70:30 mixture and *m/z* 552.27 $(M+H)^+$ for the 50:50 mixture. Each of these mixtures was carried on separately to final product; the following procedures illustrate that for the 70:30 mixture only.

B.9. Benzyl 4-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-6-neopentyl-3,4-dihydroquinoline-1(2H)-carboxylate



To a solution of benzyl 4-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-6-neopentyl-3,4-dihydroquinoline-1(2H)-carboxylate (0.226 g) in dichloromethane (5 mL) was added N,N-diacetyl-O-methylhydroxylamine (0.064 g). The mixture was stirred over the weekend at room temperature. The solvent was then removed under reduced pressure and the residue was partitioned between 1N HCl and ethyl acetate, dried with magnesium sulfate, filtered, and concentrated to give 0.243 g of the title compound. (99% yield). MS (ESI+) for $C_{34}H_{42}F_2N_3O_4$ m/z 594.31 $(M+H)^+$.

B.10. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]propyl}acetamide



To a solution of benzyl 4-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-6-neopentyl-3,4-dihydroquinoline-1(2H)-carboxylate (0.242 g) in EtOH (30 mL) was added 1N HCl (1.0 mL) and 10% palladium on carbon (0.030 g). The mixture was degassed with N_2 for five minutes. The mixture was placed on a hydrogenation apparatus under 47 psi of H_2 and was shaken for 4.5 hours. The palladium was filtered off using Celite and the solvent was concentrated under reduced pressure. The residue was then partitioned between water and ethyl acetate and the organic layers were washed with aqueous sodium bicarbonate, dried with magnesium sulfate, filtered, and concentrated. A silica gel column using 4% MeOH in dichloromethane with 0.25% NH_4OH as the solvent solution gave 0.095 g of the title compound. MS (ESI+) for $C_{26}H_{35}F_2N_3O_2$ m/z 460.27 $(M+H)^+$.

The compounds named in **Examples 109 (C-TT)** can be made according to the methods analogous to those described above, as well as those known in the art.

Example No.	Name
C.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
D.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
E.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
F.	N-[(1S,2R)-3-{[(4S)-6-tert-butyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
G.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;
H.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-7-fluoro-6-isopropyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;
I.	N-[(1S,2R)-3-{[(4S)-6-tert-butyl-7-fluoro-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
J.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-7-fluoro-6-isobutyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;
K.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-7-fluoro-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;
L.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-1-methyl-6-neopentyl-1,2,3,4-

	tetrahydroquinolin-4-yl]amino}propyl)acetamide;
M.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
N.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
O.	N-[(1S,2R)-3-{[(4S)-6-tert-butyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
P.	N-[(1S,2R)-3-{[(4S)-6-tert-butyl-1-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
Q.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-1-(2-hydroxyethyl)-6-isopropyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
R.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-1-(2-hydroxyethyl)-6-isobutyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
S.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-1-(2-hydroxyethyl)-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
T.	N-[(1S,2R)-3-{[(4S)-1-acetyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
U.	N-[(1S,2R)-3-{[(4S)-1-acetyl-6-isobutyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
V.	N-[(1S,2R)-3-{[(4S)-1-acetyl-6-isopropyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
W.	N-[(1S,2R)-3-{[(4S)-1-acetyl-6-tert-butyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
X.	N-[(1S,2R)-3-{[(4S)-6-tert-butyl-1-

	(cyanomethyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
Y.	N-[(1S,2R)-3-{[(4S)-1-(cyanomethyl)-6-isopropyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
Z.	N-[(1S,2R)-3-{[(4S)-1-(cyanomethyl)-6-isobutyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
AA.	N-[(1S,2R)-3-{[(4S)-1-(cyanomethyl)-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
BB.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1-hydroxy-2,2-dimethylpropyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
CC.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1-hydroxy-2,2-dimethylpropyl)-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
DD.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-2,2-dimethyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;
EE.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-1,2,2-trimethyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
FF.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-1,4-dimethyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;
GG.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-4-methyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
HH.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
II.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-1,4-dimethyl-1,2,3,4-

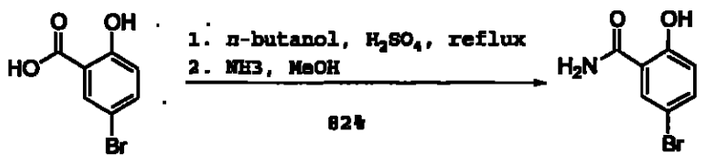
	tetrahydroquinolin-4-yl]amino}propyl)acetamide;
JJ.	N-[(1S,2R)-3-[(6-tert-butoxy-1,2,3,4-tetrahydroquinolin-4-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
KK.	N-[(1S,2R)-3-[(6-tert-butoxy-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
LL.	N-[(1S,2R)-3-[(6-tert-butoxy-4,8-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
MM.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]propyl}acetamide;
NN.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(4,8-dimethyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide;
OO.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(8-methyl-6-neopentyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]propyl}acetamide;
PP.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[6-(2-hydroxy-2-methylpropyl)-8-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
QQ.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[6-(2-hydroxy-2-methylpropyl)-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
RR.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[6-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide;
SS.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[6-(1-hydroxy-2,2-dimethylpropyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide; and
TT.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[6-(1-hydroxy-2,2-dimethylpropyl)-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}propyl)acetamide.

120

Example 111

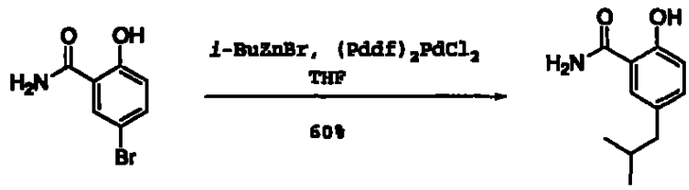
Reactions were monitored, and purity evaluated by TLC on silica gel GF, 250 μ slides obtained from Analtech, Inc., Newark, DE. Preparative low pressure (flash) chromatography was carried out on silica gel 60 (230-400 mesh ASTM) from EM Science, Gibbstown, NJ. Proton NMR spectra were collected on a Bruker Avance 400 spectrometer. Chemical shifts (δ) are in ppm, coupling constants (*J*) are in Hz. IR absorbances greater than 1200 cm^{-1} are reported. All reagents were obtained from commercial sources and were used without further purification. Unless otherwise noted, all solvents used in reaction were run under an inert atmosphere of nitrogen in over-dried glassware. Preparative flash chromatography was performed on silica gel 60 (230-240 mesh) from EM Science. HPLC analysis were carried out on a HP1100 system (Agilent) with the following a 1.0 mL/min linear gradient of 0.05% aqueous TFA (A) and 0.05% TFA in acetonitrile (B): 0% B: 5 min: 60% B, 15 min: 90% B, 2 min: 0% B. All solvents for chromatography were HPLC grade. Where not commercially available, starting materials and intermediates, including new and known compounds, were prepared by synthetic methods known in the art. HATU, which stands for *N*-[(dimethylamino)-1-*H*-1,2,3-triazolo[4,5-b]pyrindin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide, was bought from PE Biosystems. All hydrochloride salts were formed by addition of ethereal hydrochloric acid to an ethereal solution of amine, followed by concentration to dryness.

A. 5-bromo-2-hydroxybenzamide



To a stirred solution of 5-Bromosalicyclic acid (30 g, 135.5 mmol) in *n*-butylalcohol (60 mL) was added H_2SO_4 (95.6%, 289 µL, 5.42 mmol) in a 100 ml round bottom flask connected by a Dean-Stark trap/reflux condenser that was filled with 12 ml of *n*-butylalcohol. After heated to reflux for 2 days, the reaction was cooled down to R.T. and concentrated to give a pale yellow oil. The mixture was added 50 mL MeOH, followed by NH_3 in MeOH (7 N, 116 mL). The reaction was stirred at R.T. for another 2 days, monitored by HPLC. After the reaction complete, it was concentrated to give a white solid. The crude solid was washed with small amount of EtOAc and hexane to afford 24 g of the product as a white crystalline solid (82% yield). ^1H NMR ($CDCl_3$) δ 12.15 (s, 1 H), 7.54 (m, 2 H), 6.97 (d, J = 12 Hz, 1 H), 6.00 (broad, 2 H).

B. 2-hydroxy-5-isobutylbenzamide

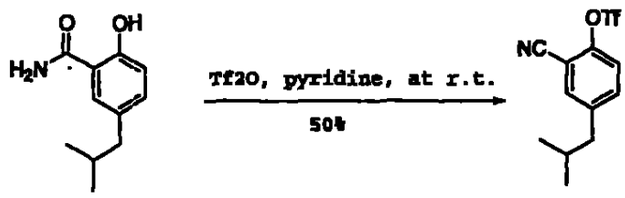


To a stirred solution of the bromobenzamide (8.64 g, 40 mmol) in THF (100 mL) under argon was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.96 g, 2.4 mmol) followed by *i*-BuZnBr (0.5 M, 200 mL). The reaction mixture was stirred at R.T. for 4 days. The reaction was quenched with 1N HCl, and then concentrated. The resulting crude was diluted with ethyl acetate, and washed with water and brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% ethyl acetate: hexane) to afford 4.63 g of the isobutylbenzamide product as an off-white solid (60% yield). ^1H NMR ($CDCl_3$) δ 12.02 (s, 1 H), 7.24 (d, J = 8 Hz, 1 H), 7.12 (s, 1 H), 6.93 (d, J = 8 Hz,

171

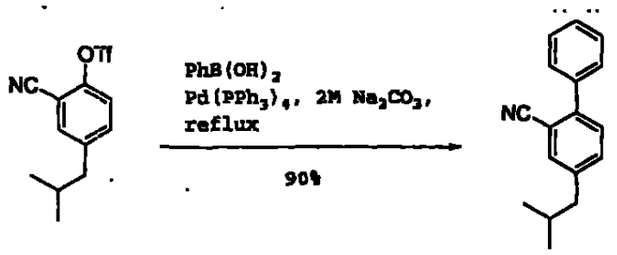
1 H), 2.44 (d, J = 8 Hz, 2 H), 1.83 (m, 1 H), 0.93 (d, J = 8 Hz, 6 H).

C. 2-cyano-4-isobutylphenyl trifluoromethanesulfonate



At 0 °C, to a stirred solution of the hydroxy-isobutylbenzamide (3.72 g, 19.3 mmol) in pyridine (15 mL) under argon was added trifluoromethanesulfonic anhydride (10.2 ml, 57.8 mmol). The reaction mixture was eventually warmed up to room temperature and stirred overnight. The reaction was diluted with ethyl acetate, and washed with 1N HCl (x2), water (x1) and brine (x1), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% ethyl acetate: hexane) to afford 2.66 g of the desired product as a clear oil (50% yield). ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.43 (d, J = 8 Hz, 1 H), 2.57 (d, J = 8 Hz, 2 H), 1.92 (m, 1 H), 0.97 (d, J = 4 Hz, 6 H).

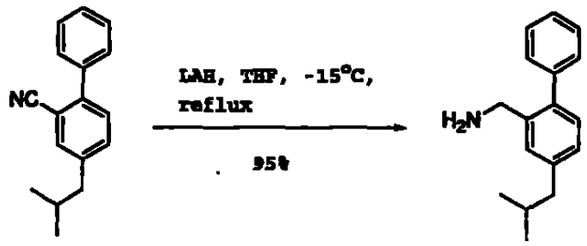
D. 4-isobutyl-1,1'-biphanyl-2-carbonitrile



To a stirred solution of the cyano compound (610 mg, 1.88 mmol), aqueous sodium carbonate (2.0 M, 3.76 mmol) in DME (6 mL) was added tetrakis(triphenylphosphine) palladium(0) (109

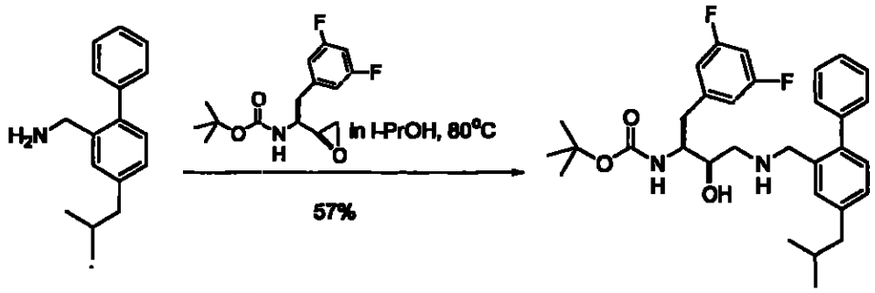
mg, 0.094 mmol) followed by phenylboronic acid (280 mg, 2.26 mmol). The reaction mixture was heated to reflux overnight, and then cooled to R.T. The reaction was diluted with ethyl acetate, and was washed with water and brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3% ethyl acetate: hexane) to afford 450 mg of the product as a white solid (90% yield). ^{1}H NMR ($CDCl_3$) δ 7.60 (m, 3 H), 7.54 (m, 2 H), 7.48 (m, 3 H), 2.60 (d, J = 8 Hz, 2 H), 1.96 (m, 1 H), 1.00 (d, J = 6 Hz, 6 H).

E. (4-isobutyl-1,1'-biphenyl-2-yl)methylamine



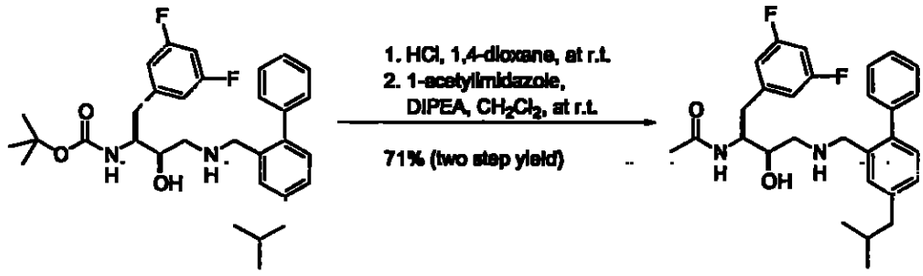
The above compound was prepared essentially according to the method of Example 10. ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 2 H), 7.44 (m, 3 H), 7.30 (s, 1 H), 7.20 (d, J = 8 Hz, 1 H), 7.14 (m, 1 H), 3.84 (s, 2 H), 2.58 (d, J = 8 Hz, 2 H), 1.93 (m, 1 H), 1.47 (s, 2 H), 1.00 (d, J = 4 Hz, 6 H); ESI-MS $[M+H^+]^+$ = 240.22.

F. tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino} propylcarbamate



To a stirred solution of the biphenyl amine (400 mg, 1.67 mmol) in i-propanol (10 mL) was added Example 134 (name generated using ACD Namepro version 5.09) (336 mg, 1.12 mmol). The reaction mixture was heated at 80 °C overnight. The reaction mixture was concentrated, and purified by flash column chromatography (2-5% MeOH: CH_2Cl_2) to afford 510 mg of product as an off-white solid (57% yield). ^1H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.38 (m, 3 H), 7.25 (s, 1 H), 7.21 (m, 1 H), 7.16 (m, 1 H), 6.76 (m, 2 H), 6.70 (m, 1 H), 4.55 (m, 1 H), 3.76 (m, 3 H), 3.34 (m, 1 H), 2.90 (m, 1 H), 2.78 (m, 2 H), 2.64 (m, 2 H), 2.55 (m, 3 H), 1.93 (m, 1 H), 1.40 (s, 9 H), 1.00 (d, 6 H); ESI-MS $[M+H^+]^+$ = 539.22.

G. **N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}propyl) acetamide**

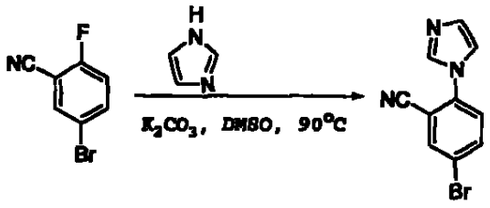


Step 1: To a stirred solution of the starting material (377 mg, 0.7 mmol) in MeOH (5 mL) was added HCl in 1,4-dioxane (4.0 M, 2 mL). After stirring at R.T. overnight, the reaction

mixture was concentrated under reduced pressure to provide an off-white solid, which was used without further purification.

Step 2: To a stirred solution of amine from step 1 in CH_2Cl_2 (8 mL) was added DIPEA (304 µL, 1.75 mmol), and then 1-acetylimidazole (86 mg, 0.77 mmol). The reaction mixture was stirred at R.T. overnight, quenched by addition of 50% ammonium hydroxide, and diluted with CH_2Cl_2. The organic layer was washed with washed with 1N HCl (x2), saturated aqueous sodium bicarbonate (x2) and brine (x1), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3-5% MeOH: CH_2Cl_2) to afford 240 mg of product as an off-white solid (71% yield, two steps). ^1H NMR ($CDCl_3$) δ 9.63 (b, 1 H), 8.48 (b, 1 H), 7.63 (s, 1 H), 7.46 (m, 3 H), 7.28 (m, 4 H), 6.74 (m, 2 H), 6.67 (m, 1 H), 4.24 (m, 1 H), 4.17 (m, 1 H), 4.05 (m, 2 H), 2.80 (m, 4 H), 2.57 (m, 3 H), 1.97 (m, 4 H), 0.97 (d, 6 H); ESI-MS $[M+H^+]^+$ = 481.35.

H. 5-bromo-2-(1H-imidazol-1-yl)benzonitrile

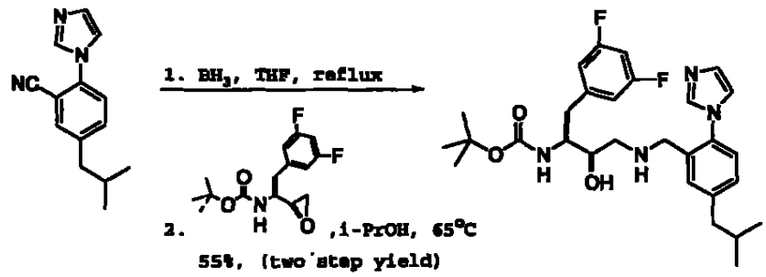


To a stirred solution 5-Bromo-2-fluorobenzonitrile (2.5 g, 12.2 mmol) in DMSO (50 mL) was added K_2CO_3 (3.337 g, 24.4 mmol), and then 1H-imidazole (996 mg, 14.64 mmol). The reaction mixture was heated to 90°C overnight, and diluted with water. The reaction mixture was extracted with EtOAC (x2). The organic layer was washed with washed with water (x1) and brine (x1), dried with sodium sulfate, filtered, and concentrated under reduced pressure to afford 2.97 g of the imidazolylbenzonitrile as an off-white solid (98% yield). ^1H NMR ($CDCl_3$) δ 7.97 (m, 2 H), 7.90 (m, 1 H), 7.41 (d, J = 8 Hz, 1 H), 7.37 (s, 1 H), 7.32 (s, 1 H).

I. 2-(1H-imidazol-1-yl)-5-isobutylbenzonitrile

The above compound was prepared essentially according to the method of Example 111, step B, but the reaction mixture was only stirred overnight. The resulting crude product was purified by flash column chromatography (50-100% ethyl acetate: hexane) to afford the product as a dark-brown oil. ^1H NMR ($CDCl_3$) δ 7.89 (s, 1 H), 7.60 (s, 1 H), 7.53 (d, J = 8 Hz, 1 H), 7.40 (m, 2 H), 7.28 (m, 1 H), 2.60 (d, J = 8 Hz, 2 H), 1.93 (m, 1 H), 0.97 (d, 6 H); ESI-MS $[M+H^+]^+$ = 226.03.

J. tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(1H-imidazol-1-yl)-5-isobutylbenzyl]amino} propylcarbamate

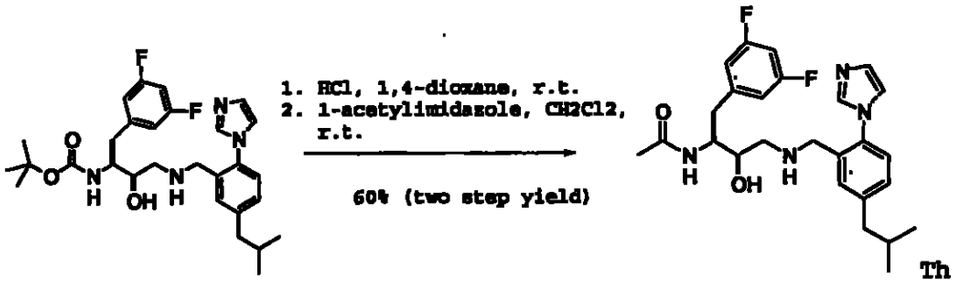


Step 1: At 0 °C, to a stirred solution of BH_3 (1.5 M in THF, 4.9 mL) was added the imidazolyl product from (I) (722 mg, 3.2 mmol) in anhydrous THF (8 mL). The reaction was eventually warmed up to R.T., and then refluxed for overnight, and then refluxed for 1 hour. The reaction mixture was cooled down to R.T, and then quenched with 5N aqueous HCl. The reaction was poured into CH_2Cl_2 (10 mL), washed with saturated aqueous sodium bicarbonate (x2) and brine (x1), dried with sodium sulfate, filtered, and concentrated under reduced pressure without further purification.

Step 2: To a stirred solution of amine from step 1 in i-propanol (14 mL) was added (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (509 mg, 1.7 mmol). The reaction mixture was heated at 65 °C overnight. The reaction

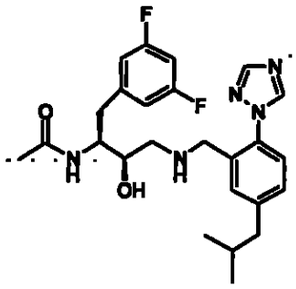
mixture was concentrated, and purified by flash column chromatography (5-20% MeOH: CH_2Cl_2) to afford 537 mg of product as an off-white solid (55% yield, two steps). ESI-MS $[M+H^+]^+$ = 529.35.

K. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(1H-imidazol-1-yl)-5-isobutylbenzyl]amino}propyl) acetamide



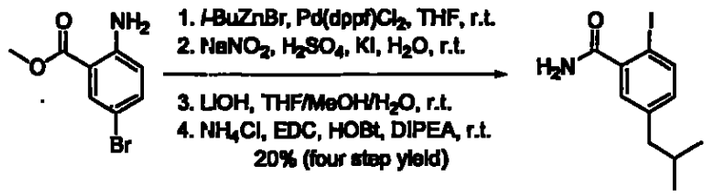
The above compound was prepared essentially according to the method of Example 111, step G. The crude acetamide was purified by flash column chromatography (5-20% MeOH: CH_2Cl_2) to afford the desired product as an off-white solid (60% yield, two steps). ESI-MS $[M+H^+]^+$ = 471.33.

L. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[5-isobutyl-2-(1H-1,2,4-triazol-1-yl)benzyl]amino}propyl) acetamide



The above compound is synthesized using procedures essentially similar to Example 111, steps J and K. ESI-MS $[M+H^+]^+$ = 472.0

M. 2-Iodo-5-isobutylbenzamide



Step 1: To a stirred solution of methyl 2-amino-5-bromobenzoate (5.77 g, 25 mmol) in THF (20 mL) under argon was added [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) (2.04 g, 2.5 mmol) followed by *i*-BuZnBr (0.5 M, 200 mL). The reaction mixture was stirred at R.T. for overnight. The reaction was quenched with 1N HCl, and then concentrated. The resulting crude was diluted with ethyl acetate, and washed with water and brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure without further purification.

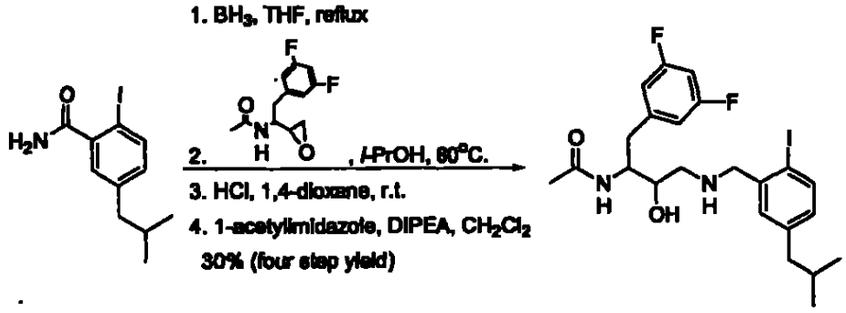
Step 2: At R.T. amine from step 1 was treated with 5% H_2SO_4 (3.2 mL), and the reaction was heated to 60 °C for 5 - 10 minutes. The reaction mixture was cooled down to ice-cold, and then was added drop-wise $NaNO_2$ (1.87 g, 27 mmol) in H_2O (10 mL). After the addition was complete, the reaction was stirred at ice-cold temperature for 15 - 20 minutes, and then KI (4.94 g, 29.7 mmol) in H_2O (20 mL) was added. The reaction was stirred at R.T. overnight. The next day, the reaction was extracted with EtOAC (x3). The organic layer was washed with washed with brine (x1), dried (sodium sulfate), filtered, and concentrated. The crude product was purified by flash column chromatography (5-10% MeOH: CH_2Cl_2) to afford 2 g of iodinated product.

Step 3: To a stirred solution of iodinated product from step 2 (6.6 g, 20.9 mmol) in a mixed solvent of MeOH (30 mL), THF (30 mL), and water (30 mL) was added $LiOH \cdot H_2O$ (4.4 mg, 104.5 mmol) at room temperature. After stirred for 12 hour at room temperature, the reaction mixture was quenched with 1N HCl, diluted with CH_2Cl_2, washed with saturated aqueous sodium

bicarbonate (x1), water (x2), and brine (x2), dried over sodium sulfate, and concentrated under reduced pressure. The crude product was used for the next step without further purification.

Step 4: Was performed essentially according to the method of Example 56. The resulting crude product was purified by flash column chromatography (10-50% EtOAC: CH_2Cl_2) to afford 900 mg of product as an off-white solid (20% yield, four steps). ^1H NMR ($CDCl_3$) δ 7.80 (d, J = 8 Hz, 1 H), 7.30 (s, 1 H), 6.95 (d, J = 8 Hz, H), 5.80 (b, 2 H), 2.47 (d, J = 6 Hz, 2 H), 1.87 (m, 1 H), 0.93 (2, H).

N. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-iodo-5-isobutylbenzyl)amino]propyl}acetamide



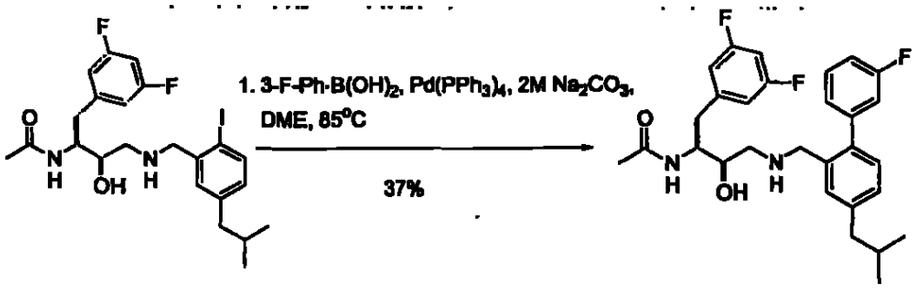
Step 1: At 0 °C, to a stirred solution of BH_3 (1.5 M in THF, 9.3 mL) was added (1.838 g, 6.1 mmol) in anhydrous THF (16 mL). The reaction was eventually warmed up to R.T., and then refluxed for overnight, and then refluxed for 1 hour. The reaction mixture was cooled down to R.T, and then quenched with 5N aqueous HCl. The reaction was poured into CH_2Cl_2 (10 mL), washed with saturated aqueous sodium bicarbonate (x2) and brine (x1), dried with sodium sulfate, filtered, and concentrated under reduced pressure without further purification.

Step 2: Was performed essentially according to the method of Example 15, step 2. The reaction mixture was concentrated under reduced pressure without further purification.

Step 3: To a stirred solution of crude form step 2 in MeOH (10 mL) was added HCl in 1,4-dioxane (4.0 M, 5.6 mL). After stirred at R.T. overnight, the reaction mixture was concentrated under reduced pressure to provide an off-white solid. The crude was re-dissolve in CH_2Cl_2, washed with saturated aqueous sodium bicarbonate (x2) and brine (x1), dried with sodium sulfate, filtered, and concentrated under reduced pressure without further purification.

Step 4: To a stirred solution of amine from step 3 in CH_2Cl_2 (60 mL) was added DIPEA (3.88 mL, 22.3 mmol), and then 1-acetylimidazole (516 mg, 4.46 mmol). The reaction mixture was stirred at R.T. overnight, quenched by addition of 50% ammonium hydroxide, and diluted with CH_2Cl_2. The organic layer was washed with washed with 1N HCl (x2), saturated aqueous sodium bicarbonate (x2) and brine (x1), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3-5% MeOH: CH_2Cl_2) to afford 1 mg of product as an off-white solid (30% yield, four steps). ^1H NMR ($CDCl_3$) δ 7.76 (d, J = 9 Hz, 1 H), 7.14 (s, 1 H), 6.76 (m, 4 H), 5.97 (d, J = 3 Hz, 1 H), 4.20 (m, 1 H), 3.84 (m, 2 H), 3.63 (m, 1 H), 2.81 (m, 4 H), 2.46 (d, J = 6 Hz, 2 H), 1.88 (m, 4 H), 0.92 (d, 6 H).

o. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(3'-fluoro-4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}-2-hydroxypropyl)acetamide



To a stirred solution of the product of step (N) (97 mg, 0.183 mmol), aqueous sodium carbonate (2.0 M, 0.403 mmol) in

DME (1 mL) was added tetrakis(triphenylphosphine) palladium(0) (21 mg, 0.0183 mmol) followed by 3-fluoro-phenylboronic acid (64 mg, 0.458 mmol): The reaction mixture was heated to reflux overnight, and then cooled to R.T. The reaction was diluted with CH_2Cl_2, and was washed with water and brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3-10% MeOH: CH_2Cl_2) to afford 36 mg of the product as a white solid (37% yield). ESI-MS $[M+H^+]^+$ = 499.32.

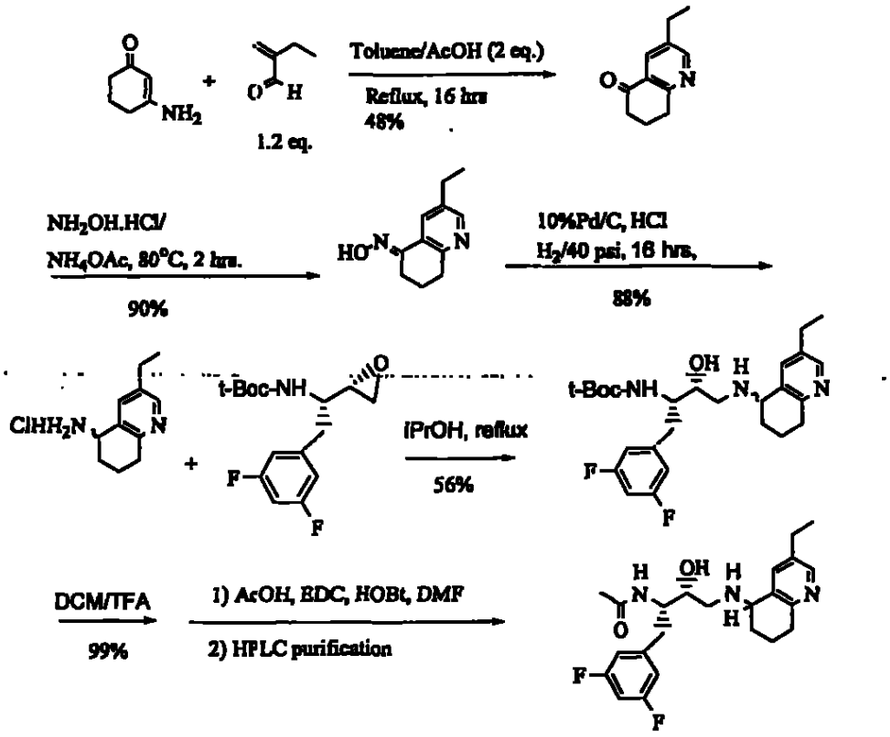
Compounds shown in Examples P-Z are synthesized using methods that are analogous to those previously described.

Example		
P.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}propyl) acetamide	ESI-MS $[M+H^+]^+$ = 481.35
Q.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-isobutyl-2-pyridin-3-ylbenzyl)amino]propyl}acetamide	ESI-MS $[M+H^+]^+$ = 482.33
R.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-isobutyl-2-pyridin-4-ylbenzyl)amino]propyl}acetamide	ESI-MS $[M+H^+]^+$ = 482.33
S.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4'-fluoro-4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}-2-hydroxypropyl)acetamide	ESI-MS $[M+H^+]^+$ = 499.31
T.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(2'-fluoro-4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}-2-hydroxypropyl)acetamide	ESI-MS $[M+H^+]^+$ = 499.32
U.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[5-isobutyl-2-(6-methoxypyridin-3-yl)benzyl]amino}propyl) acetamide	ESI-MS $[M+H^+]^+$ = 512.33
V.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3'-hydroxy-4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}propyl)acetamide	ESI-MS $[M+H^+]^+$ = 497.36

W.	N-[(1S,2R)-3-{[(3'-acetyl-4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	ESI-MS $[M+H^+]^+$ = 523.33
X.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[5-isobutyl-2-(5-methoxypyridin-3-yl)benzyl]amino}propyl) acetamide	ESI-MS $[M+H^+]^+$ = 512.30
Y.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(3-furyl)-5-isobutylbenzyl]amino}-2-hydroxypropyl)acetamide	ESI-MS $[M+H^+]^+$ = 471.32
Z.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(2-furyl)-5-isobutylbenzyl]amino}-2-hydroxypropyl)acetamide	ESI-MS $[M+H^+]^+$ = 471.32

Example 112

See Albright, J.D., *J. Heterocycl. Chem.*, 2000, *37*, 41-6 for a general reference on preparing pyridyl tetralin compounds.



STEP 1

To 5.5 g of 3-amino-2-cyclohexan-1-one (49.5 mmole) and 5 g of 2-ethyl acrolein (59.4 mmole, 1.2 eq.) was added 6 ml of acetic acid and 25 ml of toluene. The reaction mixture was heated to reflux overnight. The reaction was monitored by TLC to show formation of a new spot with Rf = 0.73 (50% MeOH/DCM + 20% EtOH/Hexane.) Solvent was removed and the residue taken up in toluene, which was removed again. The residue was extracted with DCM (2x), washed with saturated $NaHCO_3$, dried over anhydrous sodium sulfate, and concentrated to give 9.38 g crude dark tan oil. This crude oil was extracted with hot hexanes (2x of 125 ml). The extracts were concentrated and dried in vacuo to give a light tan solid. (4.13 g, 23.6 mmole, 48%). MH+ (ESI) = 176.1.

Step 2

The oxime was formed using procedures described elsewhere in the application. yield: 90%; MH+ (ESI) = 191.1.

STEP 3

Reduction of the oxime was performed essentially according to procedures described elsewhere in the application. yield: 88%; MH+ (ESI) = 177.1.

STEP 4

The amine hydrochloride salt was free based by partitioning between 1 N NaOH and EtOAc. The free base solution was then concentrated and used in the epoxide opening reaction as previously described: yield: 56%; MH+ (ESI) = 476.2.

STEP 5

Boc deprotection and acetylation was performed as previously described. Reverse phase HPLC was effective in the resolution of the two diasteromers:

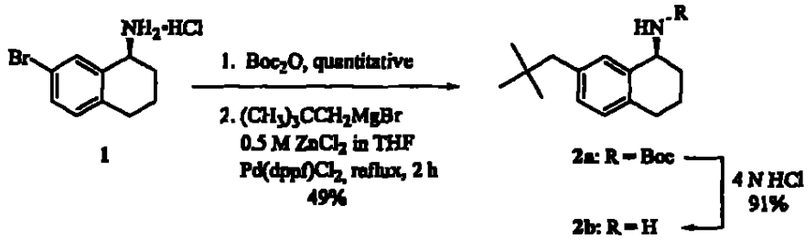
N-(1*S*, 2*R*)-[1-(3,5-Difluorobenzyl)-3-((5*S*)-3-ethyl-5,6,7,8-tetrahydroquinolin-5-ylamino)-2-hydroxypropyl]-acetamide: MH+ (ESI) = 418.2.

N-(1*S*, 2*R*)-[1-(3,5-Difluorobenzyl)-3-((5*R*)-3-ethyl-5,6,7,8-tetrahydroquinolin-5-ylamino)-2-hydroxypropyl]-acetamide: MH+ (ESI) = 418.2.

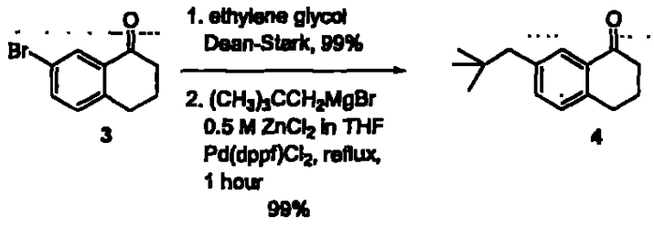
Example 113:

A. Synthesis of Chiral Amine 2b

The compound (1), which is readily available, was protected and then underwent palladium-mediated coupling with *neo*-pentylzinc chloride (generated in situ) to give *neo*-pentyl substituted tetraline 2a. Subsequent deprotection afforded intermediate amine 2b as its hydrochloride salt, which was utilized in the construction of additional targets (infra).

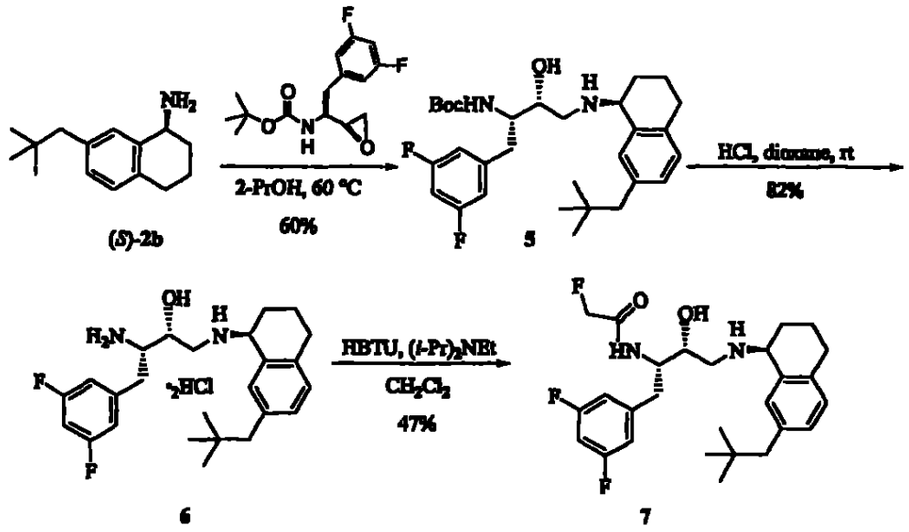


B. Synthesis of Tetralone 4



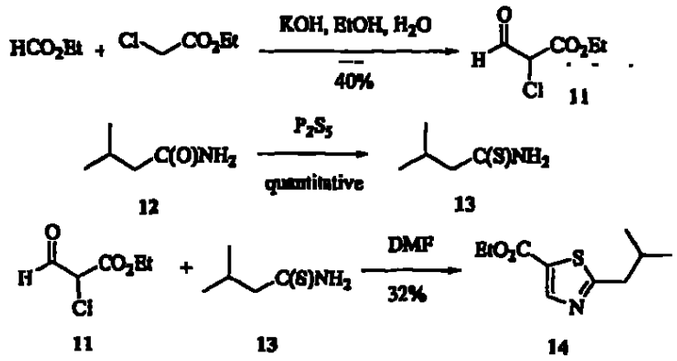
7-Bromotetralone (3) was protected as its dioxolane and then underwent palladium-mediated coupling with *neo*-pentylzinc chloride (generated in situ) to afford, after acidic work-up, *neo*-pentyl substituted tetralone 4.

C. Synthesis of Tetralin Compound 7

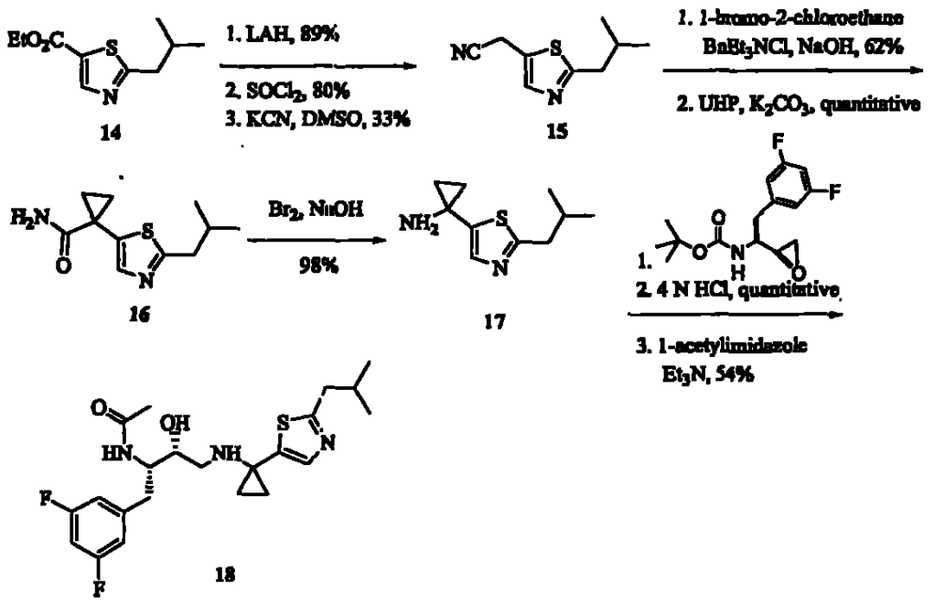


Coupling the enantiomerically pure tetralin amine of amine 2b with (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate followed by Boc-deprotection and HBTU-mediated acylation afforded the final compound (7), as predominantly one diastereoisomer.

D. Synthesis of Thiazoles 18 and 20

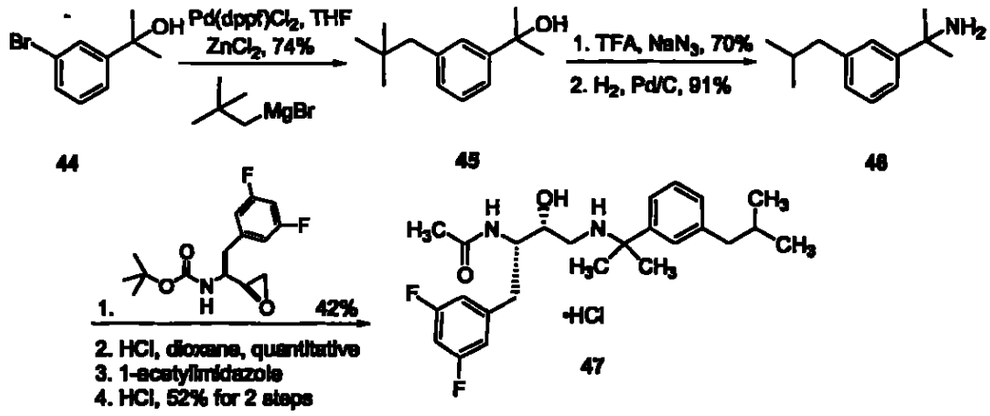


Claisen condensation of ethyl formate and ethyl chloroacetate gave ester 11. Treatment of isovaleramide (12) with phosphorus pentasulfide afforded 3-methyl-thiobutyramide (13). Cyclization of 11 and 13 afforded 5-carboethoxy-2-*iso*-butylthiazole (14).



14 15 16 17 18

Reduction of ester 14 followed by treatment of the resulting alcohol with thionyl chloride followed by nucleophilic substitution with potassium cyanide gave benzyl nitrile 15. Cyclopropanation of 15 followed by hydrolysis afforded amide 16. Hoffman rearrangement of 16 afforded amine 17. N-Alkylation of 17 followed by de-protection and N-acetylation provided (18).

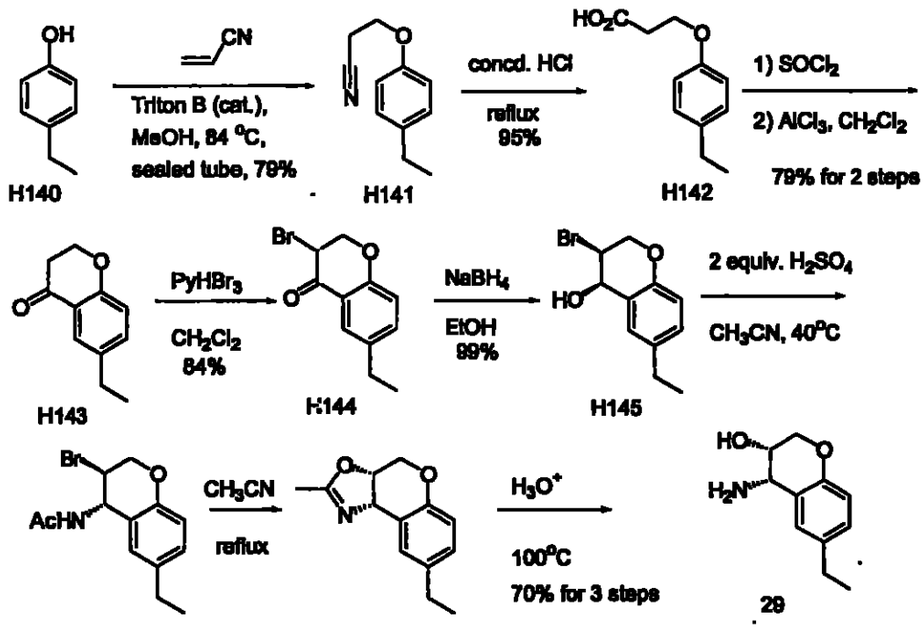


Palladium coupling of bromide 44 with neo-pentyl zinc generated in situ gave alcohol 45). Conversion of alcohol 45 to amine 46 was carried out in two steps. Epoxide opening, deprotection, and acetylation resulted in (47).

E. Synthesis of Chroman 32

The synthesis of aminochroman (29) is illustrated in scheme II . In scheme II, phenol H140 underwent Michael addition with acrylonitrile to give nitrile H141. Subsequent acid hydrolysis gave carboxylic acid H142, which was then converted to the acid chloride and cyclized intramolecularly to give chromonone H143. Alpha bromination of ketone H143 gave bromide H144, which was reduced with sodium borohydride to give bromo alcohol H145. Using Ritters reaction conditions, H145 was transformed to racemic amino alcohol 29. More specific experimental procedures follow the scheme.

Scheme II



Step 1: A mixture of 4-etylphenol (H140, 26,69 g, 0.218 mol), acrylonitrile (50 mL, 0.754 mol, 3.5 equiv), and triton B (40 wt% in methanol, 5 mL, 0.011 mol, 0.05 equiv) was stirred at 84 °C in a sealed tube overnight. The reaction mixture was diluted with ether (300 mL) and the brown precipitate was removed by suction filtration. The ether solution was washed with 2 M sodium hydroxide aqueous solution (2 x 100 mL), 1 M hydrochloric acid (100 mL) and saturated sodium chloride, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, gradient 10:1, and 6:1 hexanes/ethyl acetate) provided nitrile H141 (30.17 g, 79%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.08 (m, 2H), 6.87-6.79 (m, 2H), 4.18 (t, J=6.4 Hz, 2H), 2.80 (t, J=6.4 Hz, 2H), 2.60 (q, J=7.6 Hz, 2H), 1.20 (t, J=7.6 Hz, 3H); ESI MS m/z 176 $[C_{11}H_{13}NO + H]^+$.

Step 2: Nitrile H141 (30.17 g, 0.172 mol) was stirred with concentrated hydrochloric acid solution (100 mL, 1.20

mol, 7 equiv) at reflux overnight. White precipitate formed as the reaction proceeded. The reaction mixture was cooled to room temperature and the solid was collected by suction filtration. The filter cake was washed several times with cold water and dried in a vacuum oven at 50 °C for 14 h. Carboxylic acid H142 was obtained as a white solid (31.79g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.08 (m,2H), 6.88-6.80 (m, 2H), 4.20 (t, J=6.3 Hz, 2H), 2.85 (t, J=6.3 Hz, 2H), 2.58 (q, J-7.6 Hz, 2H), 1.18 (t, J=7.6 Hz, 3H); ESI MS m/z 193 $[C_{11}H_{14}O_3 - H]$.

Step 3: The carboxylic acid H142 (0.800 g, 4.12 mmol) was stirred with thionyl chloride (6 mL, 82.4 mmol, 20 equiv) at reflux for 2 h. Excess thionyl chloride was removed under reduced pressure. The acid chloride thus obtained was used without further purification in the next reaction.

Aluminum chloride (1.10 g, 8.24 mmol, 2 equiv) was added in one portion to a solution of acid chloride as above in dry methylene chloride (50 mL) and the resulting brown mixture was stirred at reflux for 14 h and cooled to room temperature. The mixture was poured onto crushed ice in a beaker, followed by the addition of 6 M hydrochloric acid (20 mL) and extraction with methylene chloride (3 x 40 mL). The combined organics were washed with saturated sodium chloride, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, gradient 10:1, and 6:1 hexanes/ethyl acetate) gave chromonone H143 (574 mg, 79%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J=2.2 Hz, 1H), 7.32 (dd, J=8.5, 2.2 Hz, 1H), 6.90 (d, J=8.5 Hz, 1H), 4.52 (t, J=6.5 Hz, 2H), 2,80 (t, J=6.5 Hz, 2H), 2.60 (q, J=7.6 Hz, 2H), 1.20 (t, J=7.6 Hz, 3H); ESI MS m/z 177 $[C_{11}H_{12}O_2+H]^+$.

Step 4: Pyridinium hydrobromide perbromide (743 mg, 2.32 mmol) was added to a solution of chromonone H143 (372 mg, 2.11 mmol) in dry methylene chloride (15 mL) and the reaction

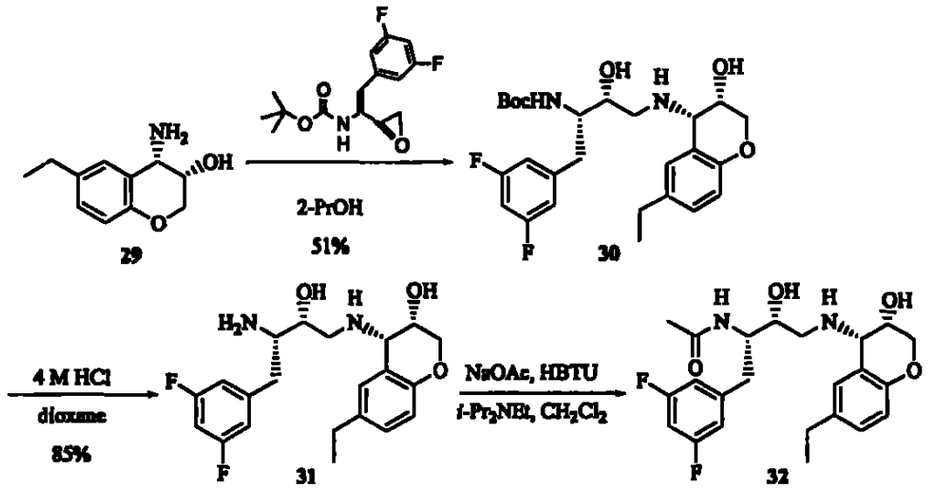
mixture was stirred at room temperature for 2 h. Water (15 mL) was added to the mixture and the layers were separated. The aqueous layer was further extracted with methylene chloride (2 x 15 mL). The combined organics were dried (magnesium sulfate) and concentrated under reduced pressure. Purification by flash column chromatography (silica, gradient 20:1, and 10:1 hexanes/ethyl acetate) provided bromo ketone H144 (450 mg, 84%) as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J=2.2 Hz, 1H), 7.39 (dd, J=8.5, 2.2 Hz, 1H), 6.97 (d, J=8.5 Hz, 1H), 4.68-4.52 (m, 3H), 2.62 (q, J=7.6 Hz, 2H), 1.22 (t, J=7.6 Hz, 3H); ESI MS m/z 255 $[C_{11}C_{11}BrO_2+H]^+$.

Step 5: Sodium borohydride (99 mg, 2.61 mmol, equiv) was added to a solution of bromo ketone H144 (444 mg, 1.74 mmol) in absolute ethanol (15 mL) and the reaction mixture was stirred at room temperature for 2 h. the reaction mixture was quenched with the addition of 1 M hydrochloric acid (4 mL) and most of ethanol was removed by rotary evaporation. The residue was partitioned between water and methylene chloride. The aqueous layer was further extracted with methylene chloride. The combined organics were dried (sodium sulfate) and concentrated under reduced pressure. Bromo alcohol H145 was obtained as a white solide (443 mg, 99%) and used in the next step without further purification: ^{1}H NMR (300 MHz, CD_3OD) δ 7.14 (d, J=1.5 Hz, 1H), 7.03 (dd, J=8.3, 1.5 Hz, 1H), 6.69 (d, J=8.3 Hz, 1H), 4.78 (d, J=3.2 Hz, 1H), 4.58-4.49 (m, 1H), 4.35-4.26 (m,2H), 2.56 (q, J=7.6 Hz, 2H), 1.16 (t, J=7.6 Hz, 2H), 1.16 (t, J=7.6 Hz, 3H).

Step 6: The bromo alcohol from step 5 H145 (443 mg, 1.72 mmol) was dissolved in anhydrous acetonitrile (10 mL) and concentrated sulfuric acid (0.19 mL, 3.47 mmol) was added via syringe. The reaction mixture was stirred at 40 °C for 5 h and then reflux for 12 h. Water (10 mL) was added and most of the acetonitrile was removed under reduced pressure. To the residue was added 6 M hydrochloric acid (10 mL) and the resulting mixture was stirred at reflux for 14 h. The

reaction mixture was cooled to room temperature, and placed in an ice bath. To this was added 6 M sodium hydroxide until pH 12, and the mixture was extracted with methylene chloride (3x 50 mL). The combined organics were washed with saturated sodium chloride, dried (sodium sulfate) and concentrated. Purification by flash column chromatography (silica, gradient 20:1, 10:1 and 1:1 methylene chloride/methanol) provided amino alcohol (29, 233 mg, 70%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J=1.5 Hz, 1H), 7.01 (dd, J=8.3, 1.5 Hz, 1H) 6.78 (d, J=8.3 Hz, 1H), 4.09 (d, J=11.5 Hz, 1H), 4.00-3.91 (m, 2H), 3.88-3.75 (m, 1H), 2.58 (q, J=7.6 Hz, 2H), 1.60 (br s, 3H) 1.20 (t, J=7.6 Hz, 3H); ESI MS m/z 194 $[C_{11}H_{15}NO_2+H]^+$; HPLC (method E) 96.7% (AUC), t_R = 9.4 min.

Scheme II-a



Subsequent coupling of racemic aminochroman 29 with Example 134, followed by Boc deprotection and HBTU-mediated acylation afforded (32), as a mixture of diastereoisomers (Scheme II-a). One possible procedure for preparing compound 32 is described below.

Synthesis of Compound (32)

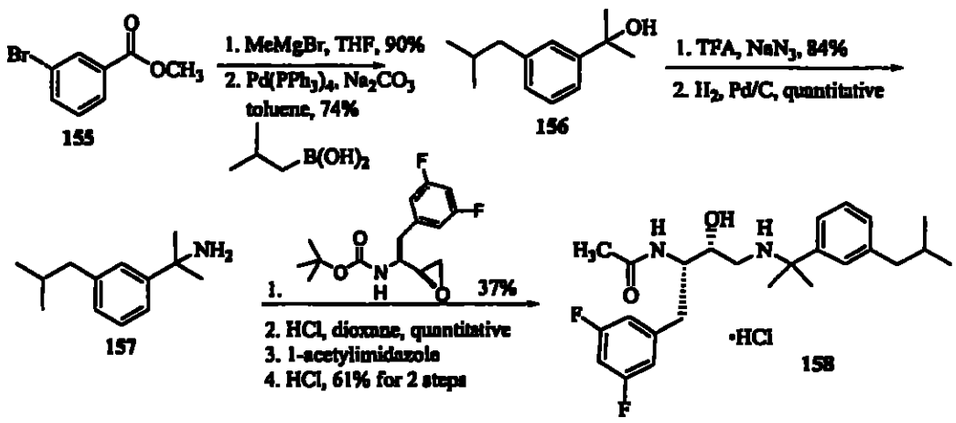
181.

Step 1: To a solution of 29 (1.00 g, 5.18 mmol) in 2-propanol (60 mL) was added Example 134 (1.40 g, 4.71 mmol) and the reaction mixture was heated to 50 °C for 17 h and then to 80 °C for 1 h. The reaction mixture was cooled to room temperature, and the solvent removed under reduced pressure. The residue was partitioned between methylene chloride (20 mL) and water (20 mL). The aqueous phase was extracted with methylene chloride (10 mL), the combined organic phase washed successively with 0.5 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL) and sodium chloride (10 mL), dried (sodium sulfate), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, 95:5 methylene chloride/methanol) to afford amino alcohol 30 (1.30 g, 51%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 1H), 7.20-6.96 (m, 1H), 6.78-6.62 (m, 5H), 4.64-4.58 (m, 1H), 4.56-4.20 (m, 1H), 4.18-4.08 (m, 2H), 3.90-3.48 (m, 4H), 3.16-2.70 (m, 5H), 2.64-2.50 (m, 2H), 1.50-1.30 (s, 9H), 1.23-1.18 (m, 3H); ESI MS m/z 493 [$C_{26}H_{34}F_2N_2O_5$ + H].

Step 2: To a solution of amino alcohol 30 (0.47 g, 0.95 mmol) in dioxane (20 mL) at room temperature was added hydrogen chloride (4.77 mL, 4 M solution in dioxane, 19.09 mmol) and the reaction mixture stirred for 17 h. The reaction mixture was concentrated under reduced pressure and the residue triturated with diethyl ether to afford amine 31 (0.38 g, 85%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.40 (s, 1H), 7.19-7.17 (m, 1H), 7.05-6.83 (m, 5H), 4.71-4.69 (m, 1H), 4.44-4.40 (m, 2H), 4.19-4.08 (m, 3H), 3.78 (br s, 1H), 3.78-3.52 (m, 1H), 3.49-3.47 (m, 1H), 3.34-3.30 (m, 1H), 3.12-3.01 (m 2H), 2.98-2.63 (m, 4H), 1.30-1.17 (m, 3H); ESI MS m/z 393 [$C_{21}H_{26}F_2N_2O_3$ + H].

Step 3: To a suspension of sodium acetate (0.67 g, 0.82 mmol), diisopropylethylamine (0.71 mL, 4.09 mmol) and HBTU (0.31 g, 0.82 mmol) in methylene chloride (5 mL) was added an additional solution of amine 31 (0.38 g, 0.82 mmol),

diisopropylethylamine (0.71 mL, 4.09 mmol) in methylene chloride (5 mL) and the combined mixture was stirred at room temperature for 24 h. Water (30 mL) was added and the aqueous phase was extracted with additional methylene chloride (5 mL). The combined organic phase was washed successively with 0.5 N hydrochloric acid (10 mL) and saturated sodium chloride (10 mL), dried (sodium sulfate), filtered and concentrated under reduced pressure. Purification by preparative HPLC (Method G) afforded ALB 15297 (32, 55 mg, 4%) as a white foam: IR (ATR) 3254, 2966, 1657, 1627, 1596 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.34-7.28 (m, 1H), 7.17-7.14 (m, 1H), 6.88-6.75 (m, 5H), 4.56-4.54 (m, 1H), 4.39-4.34 (m, 1H), 4.16-4.04 (m, 3H), 3.90-3.85 (m, 1H), 3.77-3.62 (m, 1H), 3.54-3.10 (m, 5H), 2.71-2.57 (m, 3H), 1.85-1.82 (m, 3H), 1.28-1.16 (m, 3H); ESI MS m/z 435 [$C_{23}H_{28}F_2N_2O_4$+ H]; HPLC (Method F) 94.1 (AUC), t_R=11.1, 11.5 min (3:2 mixture of diastereeoisomers).



F. Synthesis of Acetate 158

Addition of methyl Grignard to ester 155 followed by coupling with 2-methylpropyl boronic acid gave alcohol 156. Conversion of the alcohol to the azide and reduction provided amine 157. Epoxide opening, removal of the protecting group, acetalization, and formation of the hydrochloric acid salt gave (158).

182

General HPLC Methods

Method A: Phenomenex Luna C18(2) Column, 150 x 4.6 mm, 5μ
A: 0.05% TFA in 95:5 H_2O/CH_3CN; B: 0.05% TFA in 5:95 H_2O/CH_3CN
Gradient: 10-90% B over 15 min; flow 1.0 mL/min
Detection: 254 nm

Method B: Phenomenex Luna C18(2) Column, 150 x 4.6 mm, 5μ
A: 0.05% TFA in 95:5 H_2O/CH_3CN; B: 0.05% TFA in 5:95 H_2O/CH_3CN
Gradient: 30-100% B over 15 min; flow 1.0 mL/min
Detection: 254 nm

Method C: Phenomenex Synergi Max-RP Column, 150 x 4.6 mm, 4μ
A: H_2O; B: CH_3CN
Gradient: 30-100% B over 15 min; flow 1.0 mL/min
Detection: 220 nm

Method D: Phenomenex Luna C18(2) Column, 150 x 4.6 mm, 4μ
A: 95:5 H_2O/CH_3CN; B: 5:95 H_2O/CH_3CN
Gradient: 40-100% B over 15 min; flow 1.0 mL/min
Detection: 254 nm

Method E: Phenomenex Luna C18(2) Column, 150 x 4.6 mm, 4μ
A: 95:5 H_2O/CH_3CN; B: 5:95 H_2O/CH_3CN
Gradient: 1-99% B over 15 min; flow 1.0 mL/min
Detection: 254 nm

Method F: Phenomenex Luna C18(2) Column, 150 x 4.6 mm, 5μ
A: 0.05% TFA in 95:5 H_2O/CH_3CN; B: 0.05% TFA in 5:95 H_2O/CH_3CN
Gradient: 10-90% B over 15 min; flow 1.0 mL/min
Detection: 225 nm

EXAMPLE 114

A. Synthesis of *Neo*-Pentylmagnesium Bromide

A 3-necked, round-bottom flask fitted with an addition funnel, water condenser and magnetic stir bar was charged with magnesium turnings (10.0 g, 413.8 mmol), iodine (100 mg), and glass shards and then heated vigorously under vacuum with stirring for 20 min. The reaction flask was cooled to room temperature and then charged with argon and the magnesium turnings stirred for an additional 0.5 h. The flask was then charged with diethyl ether (65 mL) and the addition funnel charged with a solution of *neo*-pentyl bromide (20.0 g, 132.4 mmol) in diethyl ether (100 mL). Neat *neo*-pentyl bromide (2.5 g, 16.55 mmol) was added directly to the reaction mixture and the solution was gently warmed with a heat gun to initiate the reaction. Once the reaction was initiated, the contents of the addition funnel were added dropwise over the course of 1 h to maintain a gentle reflux. Another aliquot of neat *neo*-pentyl bromide (2.5 g, 16.55 mmol) was then added to the reaction mixture in one portion followed by dropwise addition of 1,2-dibromoethane (14.3 mL, 165.5 mmol) over the course of 1 h. Ethane gas generated was swept from the reaction flask by a steady stream of nitrogen. The reaction mixture was then heated at reflux for 24 h and cooled to room temperature to yield a black solution. The suspended solid was allowed to settle and the solution above the solid residue was *neo*-pentylmagnesium bromide (ca. 1.0 M in ether, 165.5 mmol), which was used in subsequent coupling reactions.

B. Synthesis of Amine 2b

Step 1: Di-tert-butyl dicarbonate (5.45 g, 25.0 mmol) was added in one portion at room temperature to a solution of compound (1) (5.05 g, 19.23 mmol) and *N,N*-diisopropylethylamine (10.0 mL, 57.7 mmol) in acetonitrile (32 mL) and the reaction mixture was stirred at room temperature for 36 h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and saturated sodium bicarbonate. The phases were separated and the organic

phase was washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield the desired protected amine (7.38 g, quantitative) as a waxy solid, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.28-7.24 (m, 1H), 6.94 (d, J = 8.2 Hz, 1H), 4.77 (m, 2H), 2.72-2.66 (m, 2H), 2.04-2.00 (m, 1H), 1.83-1.72 (m, 3H), 1.44 (s, 9H).

Step 2: A solution of the *neo*-pentylmagnesium bromide prepared above (115.4 mL) was added dropwise at room temperature to a solution of zinc chloride (115.4 mL, 0.5 M in tetrahydrofuran, 57.7 mmol) over 40 min. Following Grignard addition, the reaction mixture was stirred for 0.5 h to yield a white heterogenous suspension. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (1.60 g, 1.92 mmol) was added in one portion followed by dropwise addition over 20 min of a solution of the protected amine prepared in step 1 (7.38 g, 19.23 mmol) in tetrahydrofuran (20 mL) to yield a yellow reaction mixture. The reaction mixture was stirred at room temperature for 0.5 h then heated at reflux for 2 h to yield a brown solution. The reaction mixture was cooled to room temperature and carefully quenched with 10% hydrochloric acid (100 mL) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with diethyl ether and the phases separated. The organic phase was then washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a brown semisolid. Purification by flash column chromatography (silica, 19:1 hexanes/ethyl acetate) afforded protected amine **2a** (3.0 g, 49%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.98-6.90 (m, 2H), 4.82-4.75 (m, 2H), 2.76-2.69 (m, 2H), 2.43 (s, 2H), 2.04-1.97 (m, 1H), 1.84-1.80 (m, 3H), 1.47 (s, 9H), 0.88 (m, 9H); ESI MS *m/z* 318 $[C_{20}H_{31}NO_2 + H]^+$.

Step 3: To a solution of amine **2a** (3.00 g, 9.45 mmol) in 1,4-dioxane (25 mL) was added at room temperature a solution of hydrochloric acid (23.5 mL, 4 N in 1,4-dioxane, 94.5 mmol) and the reaction mixture stirred at room temperature overnight to yield a white precipitate. Vacuum filtration yielded amine **2b** (2.15 g, 91%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.21 (s, 1H), 7.08–7.02 (m, 2H), 4.43 (m, 1H), 3.01–2.76 (m, 5H), 2.48 (s, 2H), 2.19–2.12 (m, 2H), 1.96–1.87 (m, 2H), 0.90 (m, 9H); ESI MS *m/z* 201 $[C_{15}H_{20}]^+$.

C. Synthesis of Tetralone 4

Step 1: A solution of tetralone **3** (5.0 g, 22.21 mmol) in benzene (100 mL) containing ethylene glycol (5.0 mL, 88.8 mmol) and *p*-toluenesulfonic acid monohydrate (420 mg, 2.22 mmol) was heated at reflux in a Dean-Stark apparatus for 24 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the resulting residue partitioned between ethyl acetate and water. The phases were separated and the organic phase was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield the desired dioxolane (5.97 g, 99%) as a golden oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 2.0 Hz, 1H), 7.32 (dd, J = 8.2, 2.0 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 4.23–4.07 (m, 4H), 2.73–2.72 (m, 2H); 2.04–1.94 (m, 4H).

Step 2: A solution of the *neo*-pentylmagnesium bromide prepared above (60 mL) was added dropwise at room temperature over 20 min to a solution of zinc chloride (60 mL, 0.5 M in tetrahydrofuran, 30.0 mmol). Following Grignard addition, the reaction mixture was stirred for 0.5 h to yield a white heterogenous suspension. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (816 mg, 1.0 mmol) was added in one portion followed by dropwise addition of a solution of the dioxolane prepared in step 1 (2.69 g, 10.0 mmol) in

tetrahydrofuran (10 mL) to yield a yellow reaction mixture, which was then heated at reflux for 1 h to yield a brown solution. The reaction mixture was cooled to room temperature and carefully quenched with 10% hydrochloric acid (100 mL) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with diethyl ether and the phases separated. The organic phase was then washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a black oil. Purification by flash column chromatography (silica, 19:1 hexanes/ethyl acetate) afforded compound (4) (2.17 g, 99%) as a yellow oil: IR (ATR) 3359, 2957, 1762, 1686, 1521, 1236, 1126, 1076, 1053, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.26-7.22 (m, 1H), 7.15 (m, 1H), 2.96-2.92 (m, 2H), 2.67-2.62 (m, 2H), 2.50 (s, 2H), 2.17-2.08 (m, 2H), 0.89 (s, 9H); ESI MS *m/z* 217 $[C_{15}H_{20}O + H]^+$; HPLC: (Method D) >99% (AUC), t_R = 13.30 min.

D. Synthesis of Compound (7)

Step 1: To a solution of 2b (0.22 g, 1.03 mmol) in 2-propanol (10 mL) was added Example 134 (0.31 g, 1.03 mmol) and the reaction mixture was heated to 50 °C for 17 h. The reaction mixture was cooled to room temperature, and the solvent removed under reduced pressure. The resulting residue was partitioned between methylene chloride (20 mL) and water (20 mL). The aqueous phase was extracted with methylene chloride (10 mL), the combined organic phase washed successively with 0.5 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL) and sodium chloride (10 mL), dried (sodium sulfate), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, 95:5 methylene chloride/methanol) to afford amino alcohol 5 (0.32 g, 60%) which was carried on without further characterization: ESI MS *m/z* 517 $[C_{30}H_{42}F_2N_2O_3 + H]$.

Step 2: To a solution of amino alcohol 5 (0.32 g, 0.61 mmol) in dioxane (5 mL) at room temperature was added hydrogen chloride (1.50 mL, 4 M solution in dioxane, 6.18 mmol) and the reaction mixture stirred for 17 h. The reaction mixture was concentrated under reduced pressure and the resulting residue triturated with diethyl ether to afford amine 6 (0.25 g, 85%) as a white solid, which was carried on without further purification or characterization: ESI MS *m/z* 417 [$C_{25}H_{36}Cl_2F_2N_2O$ + H].

Step 3: To a suspension of sodium fluoroacetate (0.04 g, 0.82 mmol), *N,N*-diisopropylethylamine (0.23 mL, 1.41 mmol) and HBTU (0.17 g, 0.47 mmol) in methylene chloride (2 mL) was added a solution of amine 6 (0.23 g, 0.47 mmol) and *N,N*-diisopropylethylamine (0.15 mL, 0.94 mmol) in methylene chloride (2 mL) and the combined mixture was stirred at room temperature for 24 h. Water (20 mL) was added and the aqueous phase was extracted with additional methylene chloride (5 mL). The combined organic phase was washed successively with 0.5 N hydrochloric acid (10 mL) and saturated sodium chloride (10 mL), dried (sodium sulfate), filtered and concentrated under reduced pressure. Purification by preparative HPLC (Method B) afforded compound (7) (106 mg, 47%) as a white solid: IR (ATR) 3324, 2957, 1659, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.12-6.95 (m, 2H), 6.82-6.55 (m, 4H), 4.93-4.83 (m, 1H), 4.81-4.67 (m, 1H), 4.27-4.18 (m, 1H), 3.75-3.74 (m, 1H), 3.57-3.52 (m, 1H), 3.10-3.04 (m, 1H), 2.94-2.67 (m, 5H), 2.48 (s, 2H), 1.98-1.75 (m, 4H), 1.60-1.40 (br s, 2H), 0.93 (s, 9H); ESI MS *m/z* 476 [$C_{27}H_{33}F_3N_2O_2$ + H]; HPLC (Method C) >99% (AUC), t_R = 8.60 min.

E. Synthesis of 5-Carboethoxy-2-*iso*-butylthiazole (14)

Step 1: A solution of ethyl formate (38 mL, 470 mmol) and ethyl chloroacetate (44 mL, 416 mmol) in diethyl ether (200 mL) was added to an ice-cold solution of potassium ethoxide (33.5 g, 400 mmol) in 1:2 ethyl alcohol/diethyl ether (300

mL). The resulting suspension was stirred overnight at room temperature. The solid was filtered, washed with diethyl ether and dissolved in water (200 mL). The solution was cooled in an ice bath and acidified to pH 4 with concentrated hydrochloric acid. The solution was extracted with diethyl ether and the organic layer washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give formylchloroacetate (11, 24.2 g, 40%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99-4.19 (m, 2H), 4.08 (s, 1H), 3.64-3.57 (m, 1H), 1.35-1.18 (m, 3H).

Step 2: Phosphorus pentasulfide (3.8 g, 10.9 mmol) was added in portions to a solution of isovaleramide (12, 10 g, 99 mmol) in diethyl ether (400 mL). The reaction mixture was stirred at room temperature for 2 h and then filtered. The filtrate was concentrated under reduced pressure to give isovalerothioamide (13, 11.60 g, quantitative) as a yellow oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 1H), 9.12 (s, 1H), 2.33 (d, J = 7.3 Hz, 2H), 2.17-2.12 (m, 1H), 0.86 (d, J = 8.4 Hz, 6H).

Step 3: A solution of 13 (11.60 g, 98.97 mmol) and 11 (9.98 g, 66.31 mmol) in *N*,*N*-dimethylformamide (40 mL) was heated at 95 °C overnight. The reaction mixture was cooled to 0 °C and cold water (100 mL) added. The reaction mixture was adjusted to pH 8 by slow addition of solid sodium bicarbonate and extracted with diethyl ether. The organic layer was washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 90:10 hexanes/ethyl acetate) gave 5-carboethoxy-2-*iso*-butylthiazole (14, 4.53 g, 32%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (q, J = 7.2 Hz, 2H), 2.90 (d, J = 7.2 Hz, 2H), 2.15 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 6.7 Hz, 6H).

F. Synthesis of Compound (18)

Step 1: To an ice-cold solution of lithium aluminum hydride (18.7 mL, 1.0 M in tetrahydrofuran, 18.7 mmol) was added a solution of 14 (2.0 g, 9.37 mmol) in tetrahydrofuran (3 mL). The reaction mixture was stirred at 0 °C for 0.5 h and then overnight at room temperature. The reaction mixture was quenched by sequential addition of water (1 mL), 15% sodium hydroxide (1 mL) and water (1 mL). The resulting mixture was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the desired alcohol (1.43 g, 89%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 4.81 (s, 2H), 2.83 (d, J = 7.2 Hz, 2H), 2.71 (s, 1H), 2.10 (m, 1H), 0.98 (d, J = 6.7 Hz, 6 Hz).

Step 2: To an ice-cold solution of the alcohol prepared in step 1 (1.3 g, 7.6 mmol) in methylene chloride (5 mL) was added thionyl chloride (5.53 mL, 76 mmol). The reaction mixture was stirred at room temperature for 1 h and evaporated under reduced pressure. The residue was neutralized by saturated sodium bicarbonate and then partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, triethylamine was added, and the resulting solution was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the desired chloride (1.15 g, 80%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 4.78 (s, 2H), 2.85 (d, J = 7.2 Hz, 2H), 2.10 (m, 1H), 0.99 (d, J = 6.7 Hz, 6H).

Step 3: To a solution of the chloride prepared in step 2 (1.15 g, 6.1 mmol) in dimethyl sulfoxide (5 mL) was added potassium cyanide (475 mg, 7.3 mmol). The reaction mixture was stirred at room temperature overnight and then partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a black oil. Purification by flash column chromatography (silica, 66:34 hexanes/ethyl acetate) gave nitrile 15 (363 mg, 33%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H),

3.89 (s, 2H), 2.85 (d, J = 7.2 Hz, 2H), 2.10 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H).

Step 4: To a mixture of 15 (367 mg, 2.04 mmol), 1-bromo-2-chloroethane (2.5 mL, 30.5 mmol), and benzyltriethylammonium chloride (14 mg, 0.06 mmol) at 50 °C was added a solution of 50% sodium hydroxide (3.6 mL). The reaction mixture was stirred at 50 °C for 1 h, cooled to room temperature and then partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a black oil. Purification by flash column chromatography (silica, 66:34 hexanes/ethyl acetate) gave the desired cyclopropylbenzylnitrile (260 mg, 62%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 2.81 (d, J = 7.2 Hz, 2H), 2.05 (m, 1H), 1.77 (m, 2H), 1.43 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H).

Step 5: To a solution of the nitrile prepared in step 4 (250 mg, 1.21 mmol) in 1:1 acetone/water (2 mL) was added potassium carbonate (17 mg, 0.12 mmol) and urea hydrogen peroxide (456 mg, 4.85 mmol). The reaction mixture was stirred at room temperature overnight. Acetone was evaporated under reduced pressure and the residue diluted with water. Desired amide 16 (270 mg, quantitative) was collected by filtration. This compound was used in the next step without further characterization.

Step 6: To an ice-cold solution of sodium hydroxide (228 mg, 5.7 mmol) in water (2.5 mL) was added bromine (94 µL, 1.84 mmol) dropwise. After stirring for 5 min at 0 °C, amide 16 (336 mg, 1.5 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 20 min and then heated at 75 °C for 5 h. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a yellow solid. Purification by flash column

chromatography (silica, 95:5 methylene chloride/methanol) gave amine 17 (288 mg, 98%) as a light yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 1H), 2.79 (d, J = 7.2 Hz, 2H), 2.08 (m, 1H), 1.13 (m, 1H), 1.06-0.97 (m, 8H).

Step 7: A solution of amine 17 (150 mg, 0.76 mmol) and Example 134 (206 mg, 0.68 mmol) in 2-propanol (5 mL) was heated at 70 °C overnight. The reaction mixture was cooled to room temperature and then partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 95:5 methylene chloride/methanol) gave the N-alkylated amine (108 mg, 32%) as a yellow solid: ESI MS m/z 496 $[C_{25}H_{35}F_2N_3O_3S + H]^+$.

Step 8: Hydrogen chloride (2.0 mL, 4 N in 1,4-dioxane, 8 mmol) was added at room temperature to a solution of the amine prepared in step 7 (108 mg, 0.22 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure to give 19 (103 mg, quantitative) as a yellow solid: ESI MS m/z 396 $[C_{20}H_{27}F_2N_3OS + H]^+$.

Step 9: To an ice-cold solution of 19 (103 mg, 0.22 mmol) and triethylamine (129 μL, 0.92 mmol) in methylene chloride (2 mL) was added 1-acetylimidazole (24 mg, 0.22 mmol). The reaction mixture was stirred at room temperature overnight and then partitioned between methylene chloride and water. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 95:5 methylene chloride/methanol) gave compound (18) (51 mg, 54%) as an off-white solid: IR (ATR) 3330, 2960, 1647, 1595, 1529, 1458, 1112, 980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.74-6.63 (m, 3H), 5.52 (d, J = 9.1 Hz, 1H), 4.08-4.10 (m, 1H), 3.43-3.41 (m, 1H), 2.98-2.96 (m, 1H), 2.98-2.70 (m, 5H), 2.10-2.00 (m, 1H), 1.89 (s, 3H), 1.06-0.96 (m, 10H);

ESI MS *m/z* 438 $[C_{22}H_{29}F_2N_3O_2S + H]^+$; HPLC (Method E) 98.1% (AUC), t_R = 11.45 min. Anal. Calcd for $C_{22}H_{29}F_2N_3O_2S$: C, 60.39; H, 6.68; N, 9.60. Found: C, 60.10; H, 6.73; N, 9.57.

G. Synthesis of Compound (47)

Step 1: To a stirred solution of *neo*-pentyl zinc bromide (20.93 mL, 0.5 M in diethyl ether, 10.47 mmol), prepared as describe previously, was added zinc chloride (20.93 mL, 0.5 M in diethyl ether, 10.47 mmol). The reaction mixture was stirred for 1 h then $Pd(dppf)Cl_2$ (285 mg, 0.349 mmol) was added. The reaction mixture was stirred for 5 min then bromide 44 (750 mg, 3.49 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was partitioned between ethyl acetate and saturated ammonium chloride. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 5:1 hexanes/ethyl acetate) gave alcohol 45 (590 mg, 74%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 7.2 Hz, 1H), 7.25 (obs m, 2H), 6.98 (d, J = 7.2 Hz, 1H), 2.51 (s, 2H), 1.58 (s, 6H), 0.90 (s, 9H).

Step 2: To an ice-cold solution of alcohol 45 (590 mg, 2.60 mmol) and sodium azide (338 mg, 5.20 mmol) in methylene chloride (12 mL) was added trifluoroacetic acid (2.37 g, 20.80 mmol) in methylene chloride (5 mL) over 1 h. The reaction mixture was treated with water (3 mL) followed by 1:1 water/concentrated ammonium hydroxide (6 mL) and then diluted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 hexanes/ethyl acetate) gave an azide (420 mg, 70%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) □ 7.27 (obs m, 2H), 7.21-6.98 (m, 2H), 2.53 (s, 2H), 1.63 (s, 6H), 0.91 (s, 9H).

Step 3: A mixture of azide from step 2 (420 mg, 1.82 mmol) and 10% Pd/C was shaken under an atmosphere of hydrogen

for 5 h at 45 psi. The reaction mixture was filtered through diatomaceous earth and concentrated under reduced pressure to give amine 46 (340 mg, 91%) as a yellow oil. This amine was used without any further purification or characterization.

Step 4: A mixture of amine 46 (340 mg, 1.66 mmol) and Example 134 (496 mg, 1.66mmol) was heated to 60 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash column chromatography (silica, 97:3:1 methylene chloride/methanol/concentrated ammonium hydroxide) gave an amine (350 mg, 42%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.11 (m, 4H), 6.85-6.79 (m, 3H), 4.52 (m, 1H), 3.74 (m, 1H), 3.36 (m, 1H), 2.84 (m, 1H), 2.48 (m, 3H), 1.82 (m, 1H), 1.53 (s, 5H), 1.36 (s, 9H), 0.91 (d, J = 7.2 Hz, 9H).

Step 5: To a stirred solution of the amine from step 4 (350 mg, 0.694 mmol) in dioxane (3 mL) was added hydrochloric acid (0.69 mL, 4 N in dioxane, 2.78 mmol). The reaction mixture was stirred for 72 h and then concentrated under reduced pressure to give the hydrochloride salt (370 mg, quantitative), which was used without any further purification or characterization.

Step 6: To a stirred mixture of the salt from step 5 (150 mg, 0.32 mmol) and triethylamine (144 mg, 1.43 mmol) in methylene chloride (5 mL) was added 1-acetylimidazole (35 mg, 0.32 mmol). The reaction mixture was stirred overnight and then partitioned between methylene chloride and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9.5:1:1 methylene chloride/methanol/concentrated ammonium hydroxide) gave a white solid. The solid was dissolved in methanol (1 mL) and hydrochloric acid (1 mL, 1 N in diethyl ether, 1 mmol) was added. The resulting solution was concentrated under reduced pressure to provide ALB 16810 (47, 80 mg, 52%) as a white solid: IR (ATR) 3253, 2953, 1725, 1622 cm^{-1}; ^{1}H NMR (300 MHz,

DMSO-d_6) δ 9.35 (br s, 1H), 9.01 (br s, 1H), 7.92 (d, J = 7.4 Hz, 1H), 7.39–7.29 (m, 3H), 7.17 (d, J = 7.4 Hz, 1H), 7.01–6.97 (m, 1H), 6.91–6.84 (m, 2H), 5.82 (d, J = 5.9 Hz, 1H), 3.82–3.67 (m, 2H), 2.98 (m, 1H), 2.65 (m, 1H), 2.49 (d, J = 7.2 Hz, 2H), 2.48 (m, 2H), 1.87 (m, 1H), 1.74 (s, 6H), 1.61 (s, 3H), 0.86 (s, 9H); ESI MS m/z 447 $[C_{26}H_{36}F_2N_2O_2 + H]^+$; HPLC (Method B) >99% (AUC), t_R = 8.92 min.

H. Synthesis of Compound (158)

Step 1: To an ice-cold, stirred solution of ester 155 (4.64 g, 21. 57 mmol) in tetrahydrofuran (100 mL) was added methylmagnesium bromide (25.16 mL, 3.0 M solution in diethyl ether, 75.48 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched by the addition of saturated ammonium chloride and diluted with diethyl ether. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 6:1 hexanes/ethyl acetate) gave an alcohol (3.72 g, 90%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.21 (m, 1H), 1.57 (s, 6H).

Step 2: A mixture of the alcohol from step 1 (1.68 g, 7.82 mmol), 2-methylpropylboronic acid (1.19 g, 11.73 mmol), and sodium carbonate (13.69 mL, 2 M aq, 27.38 mmol) was degassed with nitrogen for 20 min. Tetrakis(triphenylphosphine)palladium(0) (450 mg, 0.391 mmol) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4:1 hexanes/ethyl acetate) gave alcohol 156 (1.11 g, 74%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.24 (m, 3H), 7.11 (d, J = 7.2 Hz, 1H), 2.48 (d, J = 6.1 Hz, 2H), 1.84 (m, 1H), 1.58 (s, 6H), 0.92 (d, J = 7.1 Hz, 3H).

Step 3: To an ice-cold, stirred solution of alcohol 156 (360 mg, 1.87 mol) and sodium azide (244 mg, 3.75 mmol) in methylene chloride (10 mL) was added trifluoroacetic acid (1,71 g, 14. 96 mmol) in methylene chloride (3 mL) dropwise over 1 h. The reaction mixture was treated with water (2 mL) and 1:1 concentrated ammonium hydroxide/water (4 mL) after 1 h. The reaction mixture was diluted with diethyl ether, the organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, hexanes) gave an azide (340 mg, 84%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.24 (m, 4H), 2.50 (d, J = 6.1 Hz, 2H), 1.84 (m, 1H), 1.63 (s, 6H), 0.92 (d, J = 7.1 Hz, 3H).

Step 4: A mixture of the azide from step 3 (340 mg, 1.57 mmol) and 10% Pd/C was shaken under an atmosphere of hydrogen for 2 h at 50 psi. The reaction mixture was filtered through diatomaceous earth and concentrated under reduced pressure to give amine 157 (300 mg, quantitative) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.24 (m, 4H), 2.49 (d, J = 6.1 Hz, 2H), 1.84 (m, 1H), 1.58 (s, 6H), 0.92 (d, J = 7.1 Hz, 3H).

Step 5: A mixture of amine 157 (150 mg, 0.79 mmol) and Example 134 (215 mg, 0.79 mmol) in 2-propanol (5 mL) was heated at reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was partitioned between methylene chloride and 1 N hydrochloric acid. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (8:1 methylene chloride/methanol) gave an alcohol (144 mg, 37%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.11 (m, 4H), 6.89-6.77 (m, 3H), 4.55 (m, 1H), 3.78 (m, 1H), 3.36 (m, 1H), 2.84 (m, 1H), 2.48 (m, 3H), 1.82 (m, 1H), 1.53 (s, 5H), 1.36 (s, 9H), 0.91 (d, J = 7.2 Hz, 3H).

Step 6: A mixture of the alcohol from step 5 (144 mg, 0.29 mmol) and hydrochloric acid (2.20 mL, 4 N solution in

dioxane, 8.81 mmol) in dioxane (1 mL) was stirred overnight. The reaction mixture was concentrated under reduced pressure to give a dihydrochloride salt (136 mg, quantitative) as a white foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.91 (br s, 1H), 9.36 (br s, 1H), 8.11 (br s, 4H), 7.54-6.98 (m, 7H), 6.28 (m, 1H), 4.12 (br s, 1H), 3.10-2.74 (m, 4H), 2.47 (d, J = 6.8 Hz, 2H), 1.91 (m, 1H), 1.72 (s, 6H), 0.87 (d, J = 7.1 Hz, 6H).

Step 7: To a stirred mixture of the salt from step 6 (136 mg, 0.29 mmol) and triethylamine (135 mg, 1.33 mmol) in methylene chloride (5 mL) was added 1-acetylimidazole (33 mg, 0.29 mmol). The reaction mixture was stirred overnight and then partitioned between methylene chloride and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9.5:1:1 methylene chloride/methanol/concentrated ammonium hydroxide) gave a white solid. The solid was dissolved in methanol (1 mL) and hydrochloric acid (1 mL, 1 N in diethyl ether, 1 mmol) was added. The resulting solution was concentrated under reduced pressure to provide compound (158) (85 mg, 61%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.45 (br s, 1H), 9.03 (br s, 1H), 7.95 (d, J = 7.4 Hz, 1H), 7.41-7.35 (m, 3H), 7.19 (d, J = 7.4 Hz, 1H), 7.01-6.97 (m, 1H), 6.91-6.84 (m, 2H), 5.82 (d, J = 5.9 Hz, 1H), 3.82-3.67 (m, 2H), 2.98 (m, 1H), 2.65 (m, 1H), 2.49 (d, J = 7.2 Hz, 2H), 2.48 (m, 2H), 1.87 (m, 1H), 1.74 (s, 6H), 1.61 (s, 3H), 0.86 (d, J = 6.5 Hz, 3H); ESI MS m/z 433 $[C_{25}H_{344}F_3N_2O_2 + H]^+$; HPLC (Method A) >99% (AUC), t_R = 10.45 min.

Example 115: The invention further comprises indole and fluorene compounds, such as the compounds contained in Tables YY and ZZ.

Table 115.YY (Fluorenes)

Example No.	Compound	MS DATA
YY1	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-7-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide	$C_{27}H_{27}F_3N_2O_2$ + H^+ requires 547, found 547
YY2	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isobutyl-9H-fluoren-9-yl)amino]propyl}acetamide	$C_{29}H_{32}F_2N_2O_2$ + H^+ requires 479, found 479
YY3	N-[(1S,2R)-3-[(2-bromo-9-methyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{26}H_{25}BrF_2N_2O_2$ + H^+ requires 557, found 557
YY4	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(1-ethylpropyl)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide	$C_{30}H_{34}F_2N_2O_2$ + H^+ requires 491, found 491
YY5	N-[(1S,2R)-3-[(2-cyclopentyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{30}H_{32}F_2N_2O_2$ + H^+ requires 493, found 493
YY6	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-9-methyl-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide	$C_{28}H_{30}F_2N_2O_2$ + H^+ requires 465, found 465
YY7	N-[(1S,2R)-3-[(2-cyclohexyl-9H-fluoren-9-yl)amino]-1-(3,5-	$C_{31}H_{34}F_2N_2O_2$ + H^+

Example No.	Compound	MS DATA
	difluorobenzyl)-2-hydroxypropyl]acetamide	requires 505, found 505
YY8	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(dimethylamino)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide	$C_{27}H_{29}F_2N_3O_2$ + H^+ requires 466, found 466
YY9	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-6-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide	$C_{27}H_{27}F_3N_2O_2$ + H^+ requires 467, found 467
YY10	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(methoxymethyl)-9H-fluoren-9-yl]amino}propyl)acetamide.	$C_{27}H_{28}F_2N_2O_3$ + H^+ requires 469, found 469
YY11	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-ethyl-5-(trifluoromethyl)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide	$C_{28}H_{27}F_5N_2O_2$ + H^+ requires 519, found 519
YY12	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(3-methylbutyl)-9H-fluoren-9-yl]amino}propyl)acetamide	$C_{30}H_{34}F_2N_2O_2$ + H^+ requires 493, found 493
YY13	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isopropyl-9H-fluoren-9-yl)amino]propyl}acetamide	$C_{28}H_{30}F_2N_2O_2$ + H^+ requires 465, found 465

Example No.	Compound	MS DATA
YY14	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-neopentyl-9H-fluoren-9-yl)amino]propyl}acetamide.	$C_{30}H_{34}F_2N_2O_2$ + H^+ requires 493, found 493
YY15	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isopropenyl-9H-fluoren-9-yl)amino]propyl}acetamide	$C_{28}H_{28}F_2N_2O_2$ + H^+ requires 463, found 463
YY16	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(isopropylamino)-9H-fluoren-9-yl]amino}propyl)acetamide	$C_{28}H_{31}F_2N_3O_2$ + H^+ requires 480, found 480
YY17	N-[(1S,2R)-3-[(2-chloro-7-ethyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{27}H_{27}ClF_2N_2O_2$ + H^+ requires 543, found 543
YY18	N-[(1S,2R)-3-{[2-(tert-butylamino)-9H-fluoren-9-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{29}H_{33}F_2N_3O_2$ + H^+ requires 494, found 494.
YY19	N-[(1S,2R)-3-{[2-(tert-butylamino)-9H-fluoren-9-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{29}H_{33}F_2N_3O_2$ + H^+ requires 494, found 494
YY20	N-[(1S,2R)-3-{[2-(tert-butylamino)-9H-fluoren-9-yl]amino}-1-	$C_{29}H_{33}F_2N_3O_2$ + H^+

Example No.	Compound	MS DATA
	(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	requires 494, found 494
YY21	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-morpholin-4-yl-9H-fluoren-9-yl)amino]propyl}acetamide	$C_{29}H_{31}F_2N_3O_3$ + H^+ requires 508, found 508
YY22	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(neopentylamino)-9H-fluoren-9-yl]amino}propyl)acetamide	$C_{30}H_{35}F_2N_3O_2$ + H^+ requires 508, found 508

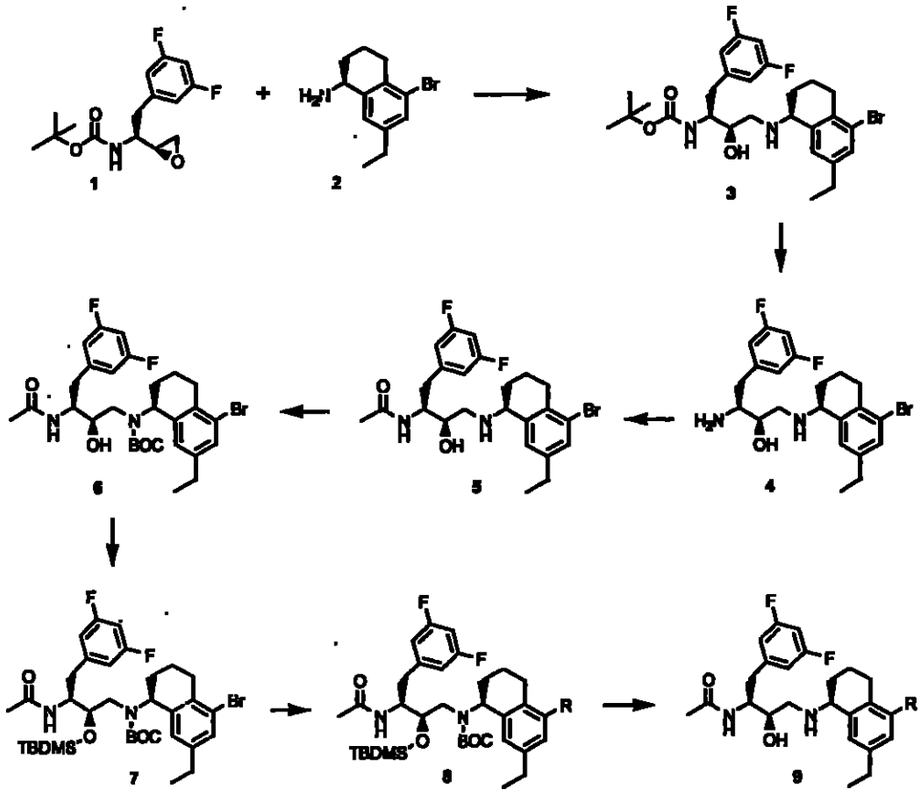
Table 115.ZZ (Indoles)

Ex. No.	Compound	MS Data
ZZ1	N-[(1S,2R)-3-{[(5-bromo-2,3-dihydro-1H-indol-7-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{21}H_{24}BrF_2N_3O_2$ + H^+ requires 468, found 468
ZZ2	N-[(1S,2R)-3-{[(5-bromo-1-ethyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{23}H_{28}BrF_2N_3O_2$ + H^+ requires 498, found 498
ZZ3	N-[(1S,2R)-3-{[(1,5-diethyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{25}H_{33}F_2N_3O_2$ + H^+ requires 446, found 446
ZZ4	N-[(1S,2R)-3-{[(1-benzyl-5-isobutyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}-1-(3,5-	$C_{32}H_{39}F_2N_3O_2$ + H^+ requires 536, found

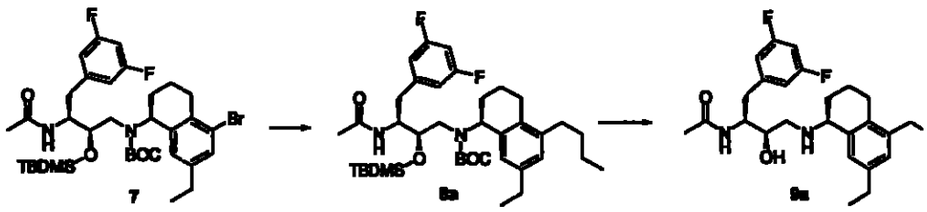
Ex. No.	Compound	MS Data
	difluorobenzyl)-2-hydroxypropyl]acetamide	536
ZZ5	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(5-isobutyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}propyl)acetamide	$C_{25}H_{33}F_2N_3O_2$ + H^+ requires 446, found 446
ZZ6	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(5-isobutyl-1-propyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}propyl)acetamide	$C_{28}H_{39}F_2N_3O_2$ + H^+ requires 488, found 488
ZZ7	N-[(1S,2R)-3-{[(1-butyl-5-isobutyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{29}H_{41}F_2N_3O_2$ + H^+ requires 502, found 502
ZZ8	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(5-isobutyl-1-isopropyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}propyl)acetamide	$C_{28}H_{39}F_2N_3O_2$ + H^+ requires 488, found 488
ZZ9	N-[(1S,2R)-3-{[(1-allyl-5-isobutyl-2,3-dihydro-1H-indol-7-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{28}H_{37}F_2N_3O_2$ + H^+ requires 486, found 486
ZZ10	N-[(1S,2R)-3-{[(1-benzyl-5-isobutyl-1H-indol-7-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{32}H_{37}F_2N_3O_2$ + H^+ requires 534, found 534
ZZ11	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(5-isobutyl-1H-indol-7-yl)methyl]amino}propyl)acetamide	$C_{25}H_{31}F_2N_3O_2$ + H^+ requires 444, found 444

Ex. No.	Compound	MS Data
ZZ12	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(5-isobutyl-1-propyl-1H-indol-7-yl)methyl]amino}propyl)acetamide	$C_{28}H_{37}F_2N_3O_2$ + H^+ requires 486, found 486
ZZ13	N-[(1S,2R)-3-{[(1-butyl-5-isobutyl-1H-indol-7-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide	$C_{29}H_{39}F_2N_3O_2$ + H^+ requires 500, found 500

Examples 116-118: The general Scheme below can be used to synthesize the compounds disclosed and described in Examples 116-118 and is not limiting to the scope of the invention.



EXAMPLE 116. Synthesis of N-[(*1S, 2R*)-3-((1*S*)-5-Butyl-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-1-(3,5-difluorobenzyl)-2-hydroxy-propyl]-acetamide



A. Preparation of [(*1S, 2R*)-3-((1*S*)-5-Bromo-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-1-(3,5-difluoro-benzyl)-2-hydroxypropyl]-carbamic acid tert-butyl ester 3

A solution of *N*-BOC-epoxide 1 (869mg, 2.91mmol) and the bromo-substituted 1-amino-tetrahydronapthalene 2 (783 mg, 2.91 mmol) in 10 mL isopropanol, is heated to 80°C for 6 hours. After completion of the reaction, the mixture is cooled and product 3 crystallizes from the crude solution, and collected by filtration. The crystals are washed with cold ethanol. After vacuum is applied to remove traces of volatiles, the reaction yields about 995 mg of 3 ($[M+H]^+$ =552.8).

B. Preparation of (3*S*, 2*R*)-3-Amino-1-((1*S*)-5-bromo-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-4-(3,5-difluoro-phenyl)-butan-2-ol 4

Compound 3 (995 mg) is dissolved in 10 mL of anhydrous CH_2Cl_2 followed by the addition of 10 mL of trifluoroacetic acid (anhydrous). The solution stands for 90 min. then the volatiles are removed with a stream of nitrogen. The compound is desalted by extraction between ethyl acetate, 10mL, and saturated aqueous sodium bicarbonate, 20 mL. The ethyl acetate phase is washed a second time with saturated sodium bicarbonate. The organic phase is then dried with $MgSO_4$

(anhydrous), filtered, and evaporated of volatiles yielding 865 mg of 4 ($[M+H]^+$ =452.8).

C. Preparation of N-[(*1S*, *2R*)-3-((1*S*)-5-Bromo-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-acetamide 5

To a solution of diamine 4 (350 mg, 0.77 mmol) in 5 mL anhydrous CH_2Cl_2, is added HOBt (125mg, 0.93mmol), *N*-methyl-morpholine (0.17mL, 1.55mmol), and glacial acetic acid (46.4mg, 0.773).

This solution is cooled to 0°C *via* ice bath and then solid EDC-HCl (1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 163 mg, 0.85 mmol) and a stir bar was added. The reaction is stirred at 0°C for 12 hours. After the warming to room temperature, the solvent is removed with a stream of N_2, and the residue washed between ethyl acetate and aqueous saturated sodium bicarbonate. The ethyl acetate phase is dried with $MgSO_4$ (anhydrous), filtered then removed of solvent by rotory evaporation and high vacuum to yield 295mg of compound 5 ($[M+H]^+$ =494.8).

D. Preparation of [(3S, 2R)-3-Acetylamino-4-(3,5-difluorophenyl)-2-hydroxybutyl]-((1*S*)-5-bromo-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-carbamic acid tert-butyl ester 6

To a solution of amine 5 (295 mg, 0.6 mmol) in 5 mL anhydrous THF is added *N,N'*-diisopropylethylamine (0.35 mL, 1.2 mmol) and di-t-butyl dicarbonate (145 mg, 0.66 mmol). The solution is stirred overnight followed by solvent removal with stream of nitrogen. The product is isolated by first washing the residue between ethyl acetate (10 mL) and 1N sodium bisulfate (20 mL). The ethyl acetate layer was then washed against aqueous saturated sodium bicarbonate (20 mL). The ethyl acetate layer was dried with $MgSO_4$ (anhydrous), filtered then removed of solvent by rotory evaporation and high vacuum to yield 354.4 mg of 6 ($[M+H]^+$ =594.5).

E. Preparation of [(*1S*, *2R*)-3-Acetylamino-2-(tert-butyl-dimethyl-silanyloxy)-4-(3,5-difluorophenyl)-butyl]-((1*S*)-5-bromo-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid tert-butyl ester 7

To a solution of *t*-butyldimethylsilyl chloride (105 mg, 0.66 mmol) and imidazole (102 mg, 1.5 mmol) in anhydrous dimethylformamide (3 mL) is added 6 (354 mg, 0.6 mmol) and the solution allowed to stir at room temperature for 16 hrs. The DMF is removed *via* rotory evaporation. The resulting residue is dissolved in ethyl acetate and washed against 1N soduim bisulfate and then saturated aqueous sodium bicarbonate. The ethyl acetate phase is dried with solid $MgSO_4$, filtered, and evaporated of volatiles *via* rotory evaporation and high vacuum. The product 7 gave M+H = 731.2, and was used in palladium-catalysed couplings without further purification.

F. Preparation of [(*1S*, *2R*)-3-Acetylamino-2-(tert-butyldimethylsilanyloxy)-4-(3,5-difluorophenyl)-butyl]-((1*S*)-5-butyl-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid tert-butyl ester 8a

The following process is performed in a nitrogen-filled glove box. To a solution of 7 (73 mg, 0.1 mmol) in 0.1 mL of anhydrous THF is added a solution of $Pd(OAc)_2$ (2.25 mg, 0.01 mmol) and 2-(di-*t*-butylphosphino)biphenyl (5.9 mg, 0.01 mmol) in 0.1 mL of anhydrous THF. The reaction is started by addition of butylzinc bromide (0.5M in THF, 0.5 mL, 0.25 mmol). The reaction is stirred for 16 hrs, after which the solvent is removed with a stream of nitrogen, and the residue is redissolved in methanol (1mL) for purification by reversed phase HPLC. The butylated product 8a ($[M+H]^+$ = 709.1) is obtained as an oil after evaporation of solvent (rotory evaporation and high vacuum).

G. Preparation of N-[(*1S, 2R*)-3-((1*S*)-5-Butyl-7-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-acetamide 9a

To a solution of 8a in 1 mL of CH_2Cl_2 is added 1mL of anhydrous trifluoroacetic acid. After 1 hr, the volatiles are removed with a stream of N_2 followed by high vacuum to yield 9a ($[M+H]^+$ = 472.8).

EXAMPLE 117. General procedure for the preparation of compounds 9

Compounds 8 were prepared from compounds 7 according to the procedure for preparing 8a (G above), except that the butylzinc bromide used in the preparation of 8a was replaced with other zinc reagents as noted in Table 117.A. The protecting groups were removed from the intermediate compounds 8 as described for the preparation of 9a from 8a.

TABLE 117.A

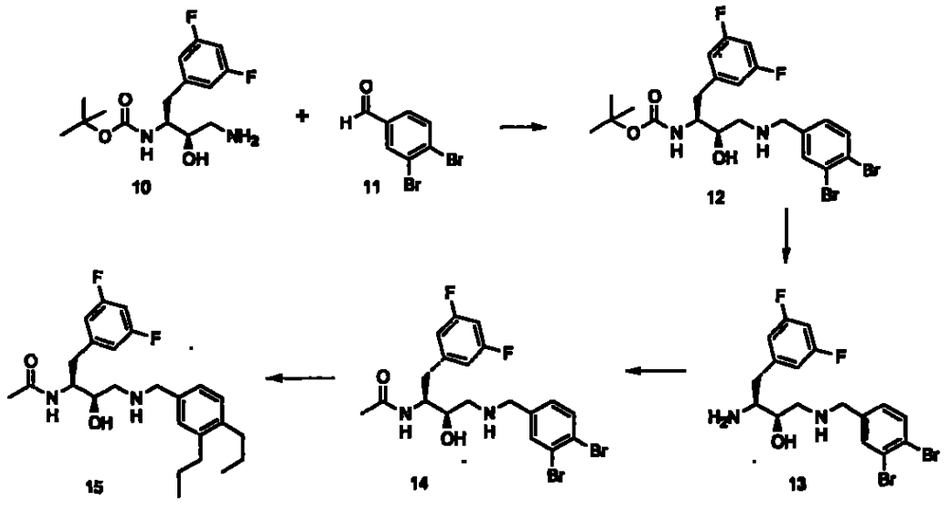
Compound	Reagent	*m/z* $(M+H)^+$
N-[(*1S, 2R*)-3-((1*S*)-5,7-Diethyl-1,2,3,4-tetrahydronaphthalen-1-ylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-acetamide	Et_2Zn (Diethylzinc)	444.8
N-[1-((*1S, 2R*)-3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-5-propyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxypropyl]-acetamide	PrZnBr (Propylzinc bromide)	458.8

Compound	Reagent	*m/z* $(M+H)^+$
N-[(1*S*, 2*R*)-1-(3,5-Difluorobenzyl)-3-((1*S*)-7-ethyl-5-isobutyl-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-hydroxypropyl]-acetamide	*i*-BuZnBr (Isobutylzinc Bromide)	472.8

EXAMPLE 118.

General scheme 118 represents a synthetic route that can be used to synthesize Compound 15.

Scheme 118



A. Preparation of [(1*S*,2*R*)-3-(3,4-Dibromobenzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl] carbamic acid tert-butyl ester 12

Commercially available 3,4-dibromobenzaldehyde (250mg, 0.95 mmol) and N-BOC-diamine 10 (250 mg, 0.79 mmol), are dissolved together in 10 mL of 10% acetic acid in THF. After the solution was allowed to stand at room temperature for 30 min., 1.7g (~3.8mmol) of MP-cyanoborohydride (a macroporous

triethylammonium methylpolystyrene cyanoborohydride, Argonaut Corporation) is added. The suspension is agitated for 3 h. using an orbit shaker (J-Kem), after which the suspension is filtered, and the solvent is removed by rotory evaporation. The residue is dissolved in methanol and divided into 10 aliquots for fractionation by reversed phase HPLC. Fractions containing pure compound 12 are combined and stripped of volatiles by rotory evaporation and/or vacuum application. Mass spectrometry of the final product 12 gave $[M+H]^+ = 564.7$.

B. Preparation of (3*S*,2*R*)-3-Amino-1-(3,4-dibromo-benzylamino)-4-(3,5-difluorophenyl)-butan-2-ol 13

Compound 13 was be prepared from compound 12 using the procedure described above for the preparation of 4 from 3. Mass spectral analysis gave m/z = 464.8.

C. Preparation of N-[(1*S*,2*R*)-3-(3,4-Dibromobenzylamino)-1-(3,5-difluorobenzyl)-2-hydroxy-propyl]-acetamide 14

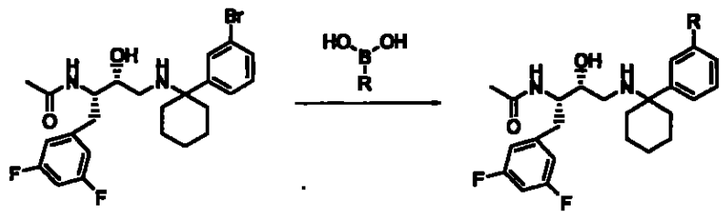
Compound 14 was prepared from compound 13 using the procedure described above for the preparation of 5 from 4. Mass spectral analysis gave m/z = 506.8

D. Preparation of N-[(1*S*,2*R*)-1-(3,5-Difluorobenzyl)-3-(3,4-dipropylbenzylamino)-2-hydroxypropyl]-acetamide 15

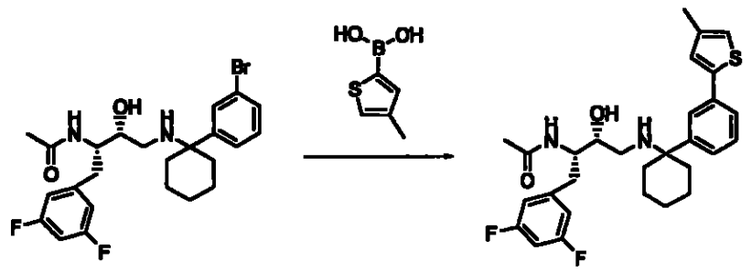
Preparation of 15 frcm 14 was performed using the procedure described above for the preparation of 8a from 7 except that propylzinc bromide is used instead of the butylzinc bromide. Mass spectral analysis of the product 13 gave $[M+H]^+ = 432.9$).

EXAMPLE 119

The compounds of the invention that comprise cyclohexyl moieties can be synthesized according the following general Scheme 119.



A. N-(*1S, 2R*)-(1-(3,5-Difluoro-benzyl)-2-hydroxy-3-{1-[3-(4-methyl-thiophen-2-yl)-phenyl]-cyclohexylamino}-propyl)-acetamide

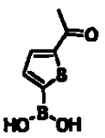
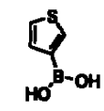
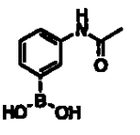


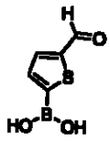
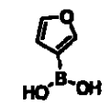
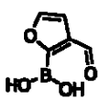
Palladium acetate ($Pd(OAc)_2$) (0.82 mgs, 10 mol. Wt. %) and Biphenyl-2-yl-di-tert-butyl-phosphane (2.16 mgs, 20 mol. Wt. %) was added to the reaction vessel (Vessel 1). N-(*1S, 2R*)-[3-[1-(3-Bromo-phenyl)-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide (0.09075 mM) was placed in a separate reaction vessel (Vessel 2) and dissolved in 200 mL DME. 4-Methylthiophene-2-boronic acid and Potassium Fluoride (KF) (3 eq., 6.33 mgs) were added to a separate reaction vessel and dissolved in 200 µL DME (Vessel 3). Solvents in Vessels 2 and 3 were added to Vessel 1 under nitrogen. Vessel 1 was stirred over night at room temperature. Reaction was then concentrated down by vacuum. Crude material purified by Prep-HPLC. Product fractions collected and concentrated down by vacuum. MS (ESI+) for $C_{29}H_{34}F_2N_2O_2S$ *m/z* 513.0 $(M+H)^+$

B. Additional Compounds.

All compounds in Table 119.A are synthesized according to the same procedure as that used for synthesizing N-(1S,2R)-(1-(3,5-Difluoro-benzyl)-2-hydroxy-3-{1-[3-(4-methyl-thiophen-2-yl)-phenyl]-cyclohexylamino}-propyl)-acetamide; however in place of 4-methylthiophene-2-boronic acid, the reagents listed next to the final products can be used.

Table 119.A

Example No.	Final Compound	Reagent	m/z $(M+H)^+$
119 C	N-(1S,2R)-[3-{1-[3-(5-Acetyl-thiophen-2-yl)-phenyl]-cyclohexylamino}-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	 5-Acetyl-2-thiophene 2-boronic acid	540.8
119 D	N-(1S,2R)-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[1-(3-thiophen-3-yl-phenyl)-cyclohexylamino]-propyl}-acetamide	 Thiophene-3-boronic	498.8
119 E	N-(1S,2R)-[3-[1-(3'-Acetylamino-biphenyl-3-yl)-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	 3-Acetamidobenzene boronic acid	549.9

Example No.	Final Compound	Reagent	m/z (M+H)+
119 F	N-(1S,2R)-(1-(3,5-Difluoro-benzyl)-3-{1-[3-(5-formyl-thiophen-2-yl)-phenyl]-cyclohexyl-amino}-2-hydroxy-propyl)-acetamide	 5-Formyl-2-thiophen boronic acid	526.8
119 G	N-(1S,2R)-{1-(3,5-Difluoro-benzyl)-3-[1-(3-furan-3-yl-phenyl)-cyclohexylamino]-2-hydroxy-propyl}-acetamide	 3-Furan-boronic acid	482.9
119 H	N-(1S,2R)-(1-(3,5-Difluoro-benzyl)-3-{1-[3-(3-formyl-furan-2-yl)-phenyl]-cyclohexyl-amino}-2-hydroxy-propyl)-acetamide	 3-Formylfuran-2-boronic acid	510.8

Example 120.

A. Step 1. 5-Bromo-2-iodobenzamide

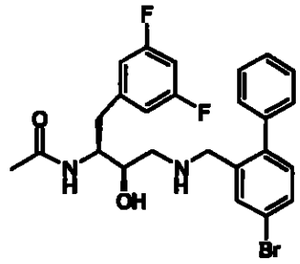
To 5-bromo-2-iodobenzoic acid (20g, 61.2 mmol) in 1:1 mixture of dichloromethane and dimethylformamide (200 mL) was added HATU (25g, 65.8 mmol), and the solution stirred 2 min. Excess ammonium chloride (20 g) was added, and the heterogeneous mixture was stirred 1 h. Ammonium hydroxide (20 mL) was added causing a white precipitate. The precipitate

was filtered and washed with ethyl acetate. The solution was diluted with ethyl acetate, washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure resulting in the formation of a white precipitate. The solid was filtered to provide the title compound (14.4 g). ESI MS *m/z* 327.0 $[M + H]^+$.

Step 2. (4-Bromo-1,1'-biphenyl-2-yl)methylamine

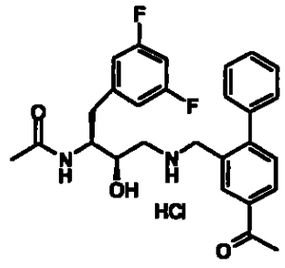
To a stirred solution of 5-bromo-2-iodobenzamide (14.1 g, 43.3 mmol), phenyl boronic acid (5.3 g, 43.3 mmol), and potassium carbonate (24.4 g, 176.8 mmol) in dimethylformamide (sparged with nitrogen, 100 mL), was added palladium(0) tetrakis(triphenylphosphine) (2.6 g, 2.2 mmol). The reaction was refluxed overnight under N_2. The brown solution was cooled and filtered through Celite. The solution was diluted in ethyl acetate and water, and then partitioned. The organic layer was washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to a tar. Flash chromatography (silica, 50% ethyl acetate/hexane) gave a tan solid (2.4 g). The biphenyl amide was dissolved in tetrahydrofuran (20 mL), and BH_3-THF (1N, 20 mL, 20 mmol) was added slowly. The reaction was refluxed overnight under N_2. The reaction was cooled to 0°C and quenched with ethyl acetate resulting in gas evolution. After gas evolution ceased, the organics were washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to give the title compound as a gray semi-solid (2.4 g). ESI MS *m/z* 262.0/264.0 $[M + H]^+$.

Step 3. N-[(1S,2R)-3-{[(4-Bromo-1,1'-biphenyl-2-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl] acetamide



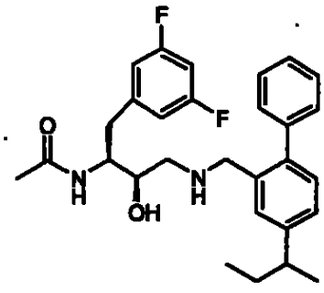
To solution of (4-bromo-1,1'-biphenyl-2-yl)methylamine (2.4 g, 9.2 mmol) in isopropanol (50 mL) was added Example 134 (1.8 g, 6.1 mmol), and the reaction was refluxed 2 h. The solution was concentrated, and the residue was redissolved in ethyl acetate, washed with 1 N hydrochloric acid and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue (3.3 g) was redissolved in methanol, and 4 N hydrochloric acid in dioxane (5 mL) was added. The reaction stirred 30 min, then concentrated to a tan foam (3.1 g). The salt was dissolved in dichloromethane (25 mL) and diisopropylethylamine (4 mL, 23 mmol), then acetylimidazole (636 mg, 5.8 mmol) was added. The reaction stirred overnight at room temperature. The organics were washed with water, 1N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography . (silica, 10% methanol/dichloromethane) provided the title compound (550 mg). ESI MS *m/z* 504.3 $[M + H]^+$. A small amount of the product was dissolved in ether, precipitated with excess 1N HCl in ether, and concentrated to provide the mono-HCl salt.

B. Step 1. N-[(1S,2R)-3-{[(4-Acetyl-1,1'-biphenyl-2-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl] acetamide hydrochloride



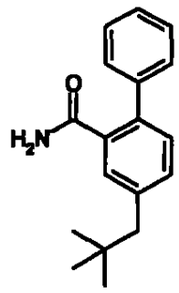
To N-[(1S,2R)-3-{[(4-bromo-1,1'-biphenyl-2-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl] acetamide (120 mg, 0.24 mmol) in toluene (1 mL) was added tributyl(1-ethoxyvinyl)tin (100 µL, 0.28 mmol) and *bis*-triphenylphoshine palladium(II) dichloride (10 mg, 0.012 mmol), and the reaction was heated at 100°C 3 h under N_2. The solution was cooled to room temperature, 1N hydrochloric acid (1 mL) was added, and the mixture was stirred 20 min. The mixture was partitioned, and the organics were washed with saturated potassium fluoride (aq). The reaction mixture was dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 8% methanol/methylene chloride) provided an oil. The residue was dissolved in ether, precipitated with excess 1N HCl in ether, and concentrated to provide the title compound (11 mg). ESI MS *m/z* 467.28 $[M + H]^+$.

C. N-[(1S,2R)-3-{[(4-sec-Butyl-1,1'-biphenyl-2-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl] acetamide



To N-[(1S,2R)-3-{[(4-bromo-1,1'-biphenyl-2-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl] acetamide (150 mg, 0.3 mmol) in THF (2 mL) was added 2M potassium phosphate (0.65 mmol), tri-*sec* butylborane (1M in THF, 330 µL, 0.33 mmol), and *bis*-triphenylphoshine palladium(II) dichloride (3 mg, 0.003 mmol), and the reaction was heated at reflux for 2 days. Tri-*sec* butylborane (1M in THF, 1.2 mL, 1.2 mmol) was added, then *bis*-triphenylphoshine palladium(II) dichloride (10 mg, 0.012 mmol), and the reaction was refluxed 16 h. The solution is diluted in ethyl acetate and washed with water, 1N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Flash chromatography (7% methanol/dichloromethane) gave the title compound. MS (ESI) $[M+H^+]$ = 481.34.

D. Step 1. 4-Neopentyl-1,1'-biphenyl-2-carboxamide



To methyl 5-bromo-2-iodobenzoate (4.41 g, 13 mmol), phenylboronic acid (1.6 g, 13 mmol), potassium carbonate (3.6 g, 26 mmol), and cesium carbonate (4.2 g, 13 mmol) in DMF (50 mL, sparged with nitrogen) was added palladium(0) tetrakis(triphenylphosphine) (751 mg, 0.65 mmol). The reaction was refluxed 16 h, cooled and washed with water, 1N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure.

199

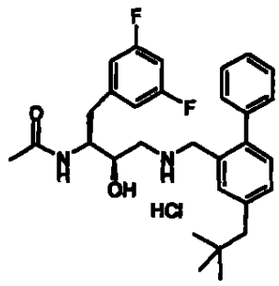
The residue was purified by flash chromatography (5% ethyl acetate/hexane) to yield methyl 4-bromo-1,1'-biphenyl-2-carboxylate (1.3 g). To methyl 4-bromo-1,1'-biphenyl-2-carboxylate (500 mg, 1.72 mmol) and $Pd(dppf)Cl_2$-CH_2Cl_2 (70 mg, 0.086 mmol) in THF (5 mL) was added 1M neopentyl magnesium chloride (5 mL, 5 mmol) slowly at room temperature. The reaction was stirred overnight and then quenched with water. The reaction was diluted in ethyl acetate, and the resulting brown solid was filtered away. The organic layer was washed with water, 1N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1% ethyl acetate/hexane) to yield a yellow solid (200 mg).

The solid was redissolved in 2:1:1 THF/methanol/water (8 mL) and lithium hydroxide monohydrate (60 mg, 1.4 mmol) was added. The reaction stirred 6 days, and the solution was concentrated to dryness. (An addition 1.7 g 4-bromo-1,1'-biphenyl-2-carboxylate was used to prepare a combined total of 1.8g residue from hydrolysis). The pooled lots were redissolved in DMF (10 mL), and diisopropylethylamine (3.7 mL, 21 mmol), HATU (4 g, 10.2 mmol), and ammonium chloride (5 g) were added. The reaction was stirred 1 h. Ammonium hydroxide was added causing a white precipitate. The liquid was diluted in ethyl acetate and was washed with water, 1N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to a black oil. The residue was purified by flash chromatography (60% ethyl acetate/hexane) to yield the title compound as a tan solid (210 mg). ESI MS *m/z* 268 $[M + H]^+$.

Step 2. (4-Neopentyl-1,1'-biphenyl-2-yl)methylamine

To borane-THF (1M, 1.7 mL, 1.7 mmol) was added 4-neopentyl-1,1'-biphenyl-2-carboxamide (200 mg, 0.75 mmol), and the reaction stirred at reflux 16 h. The solution was cooled and quenched with 1N HCl. The solution was basified with saturated sodium bicarbonate, and the product was extracted into ethyl acetate. The organics were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated *in vacuo* to give the title compound as an oil (200 mg). ESI MS *m/z* 254.22 $[M + H]^+$.

Step 3. N-((1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-{[(4-neopentyl-1,1'-biphenyl-2-yl)methyl]amino}propyl) acetamide hydrochloride



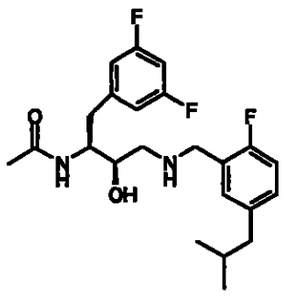
To solution of (4-Neopentyl-1,1'-biphenyl-2-yl)methylamine (200 mg, 0.8 mmol) in isopropanol (5 mL) was added Example 134 (120 mg, 0.4 mmol), and the reaction was refluxed 2 h. The solution was concentrated, and the residue was dissolved in ethyl acetate, washed with 1 N hydrochloric acid and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue was dissolved in methanol, and 4 N hydrochloric acid in dioxane (5 mL) was added. The reaction stirred 30 min, then concentrated to a white foam (100 mg). The salt was dissolved in dichloromethane (2 mL) and diisopropylethylamine (100 µL, 0.5 mmol), then acetylimidazole (30 mg, 0.3 mmol) was added. The reaction stirred 1 h at room temperature. The organics were washed with water, 1N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride,

dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 8% methanol/dichloromethane) provided the title compound (60 mg) in crude form. The material was purified by preparative RP-HPLC to give the desired compound. The product was dissolved in ether, precipitated with excess 1N HCl in ether, and concentrated to provide the mono-HCl salt (6 mg). ESI MS *m/z* 495 $[M + H]^+$.

E. Step 1. 2-Fluoro-5-isobutyl-benzonitrile

To 5-bromo-2-fluorobenzonitrile (2.3 g, 11.7 mmol) in THF (5 mL) was added 0.5 M isobutylzinc bromide (70 mL, 35 mmol), then $Pd(dppf)Cl_2$ (955 mg, 1.17 mmol), and the reaction was stirred 16 h at room temperature under N_2. The reaction was quenched with excess aqueous hydrochloric acid (1N). Ethyl acetate was added, and the solution was partitioned. The organic layer was washed with saturated sodium chloride. Flash chromatography (silica, 4% ethyl acetate/ hexane) yielded a colorless oil (1.3 g).

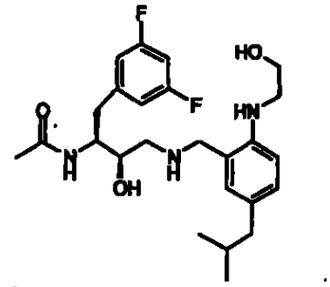
Step 2



To (product from step 1) (230 mg, 1.3 mmol) in THF (2 mL) was added borane-THF (1M, 3 mL, 3 mmol) slowly at 0°C. The reaction was stirred 16 h at room temperature. The solution was cooled and quenched with 1N HCl. The solution was basified with saturated sodium bicarbonate, and the product was extracted into ethyl acetate. The organics were washed

with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated *in vacuo* to give an oil. The residue was dissolved in isopropanol (2 mL), Example 134 (120 mg, 0.4 mmol) was added, and the reaction was refluxed 3 h. 4 N hydrochloric acid in dioxane (5 mL) was added, and the reaction stirred 1.5 h, then concentrated to a white foam. The residue was dissolved in dichloromethane (5 mL) and diisopropylethylamine (678 µL, 3.9 mmol), then acetylimidazole (66 mg, 0.6 mmol) was added. The reaction stirred 30 min at room temperature. Additional acetylimidazole (30 mg, 0.3 mmol) was added. The organics were washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 8% methanol/dichloromethane) provided the title compound as a white solid (89 mg). ESI MS m/z 423 $[M + H]^+$.

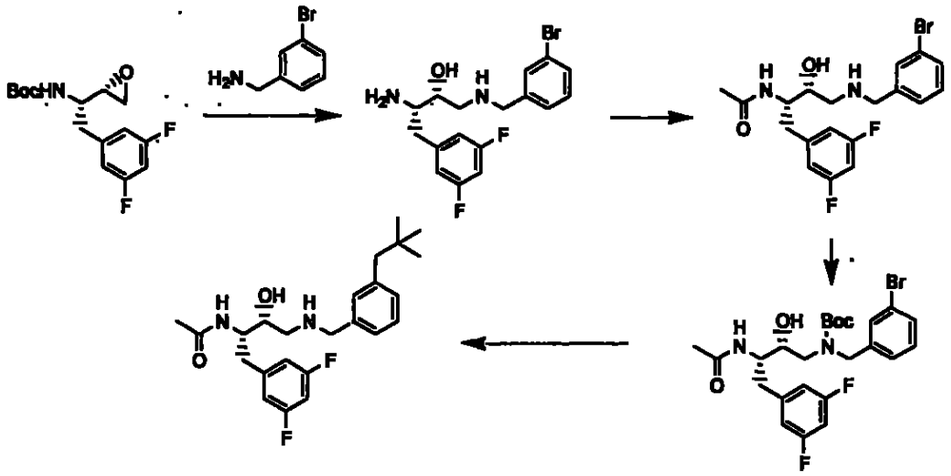
F. N-[(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-({2-[(2-hydroxyethyl)amino]-5-isobutylbenzyl}amino)propyl]acetamide



2-Fluoro-5-isobutyl-benzonitrile (533 g, 3 mmol) in ethanolamine (5 mL) was heated at 100°C 2 h in a sealed tube. The reaction was diluted in ethyl acetate, and the organic layer was washed with water and saturated sodium chloride. The solution was dried (sodium sulfate), filtered, and concentrated to an oil. The residue was redissolved in THF (3 mL), and this solution was added to borane-THF (9 mL) at 0°C. The reaction was stirred at room temperature 16 h. The solution was poured onto ice, and ethyl acetate was added.

The organic was partitioned, washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to an oil (220 mg). The residue was dissolved in isopropanol (5 mL), 2-Fluoro-5-isobutyl-benzonitrile (160 mg, 0.5 mmol) was added, and the reaction was refluxed 2 h. The reaction was cooled and concentrated. Flash chromatography (silica, 8% methanol/dichloromethane) yielded an oil (108 mg). The residue was treated with 4 N hydrochloric acid in dioxane (5 mL), and the reaction stirred 1 h, then concentrated to a white solid. The residue was dissolved in dichloromethane (5 mL) and diisopropylethylamine (108 µL, 0.6 mmol), then acetylimidazole (44 mg, 0.4 mmol) was added. The reaction stirred 30 min at room temperature. The organics were washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 8% methanol/dichloromethane) provided the title compound as an oil (18 mg). ESI MS *m/z* 464.34 $[M + H]^+$.

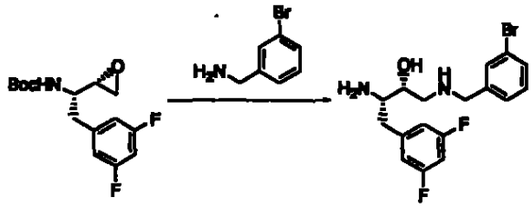
EXAMPLE 122. Synthesis of N-(*1S, 2R*)-{1-(3,5-Difluoro-benzyl)-3-[3-(2,2-dimethyl-propyl)-benzylamino]-2-hydroxy-propyl}-acetamide



A. 3-Bromo-benzylamine

3-Bromo-benzylamine HCl salt (0.75 g) was dissolved in 10 mL 15% IPA in CH_2Cl_2. 7 drops of 10N Sodium Hydroxide (NaOH) was added and stirred for 3 minutes. To the reaction mixture, 5 mL of dH_2O was added and stirred for 5 minutes. The IPA/CH_2Cl_2 layer was extracted. The aqueous layer was rinsed with 10 mL 15% IPA in CH_2Cl_2. All organic layers were added together and concentrated under vacuum. MS (ESI+) for C_7H_8BrN *m/z* 186.3 $(M+H)^+$

B. (*1S,2R*)-3-Amino-1-(3-bromobenzylamino)-4-(3,5-difluorophenyl)butan-2-ol



(*1S, 2R*)-[2-(3,5-Difluoro-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester (0.32 g, 1.075 mM) was added to a sealed tube along with 3-Bromo-benzylamine (0.2 g, 1.075 mM). 2 mL of IPA was added to the sealed tube. The reaction mixture was stirred and heated at 80°C for 2 hours. Once the reaction was complete, the reaction mixture was concentrated down by vacuum. The product was then dissolved in 750 µL of 4N HCl in dioxane. Reaction stood for 1 hour. The reaction was then concentrated down by vacuum. MS (ESI+) for $C_{17}H_{19}BrF_2N_2O$ *m/z* 387.1 $(M+H)^+$

C. N-(*1S,2R*)-[3-(3-bromobenzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide

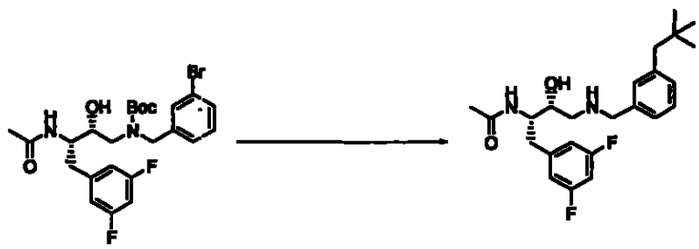
(*1S, 2R*)-3-Amino-1-(3-bromo-benzylamino)-4-(3,5-difluoro-phenyl)-butan-2-ol (0.348 g, 0.9040 mM) was dissolved in 9 mL of CH_2Cl_2. N-Methylmorpholine (NMM) (0.4114 g, 4.0679 mM) was

added to the reaction mixture. The reaction mixture was cooled to 0°C and stirred for 15 minutes. Acetic acid (0.057 g, 0.9944 mM) was added slowly to reaction mixture and stirred for 5 minutes. HOBt (0.134 g, 0.9944 mM) was then added, then EDC (0.190 g, 0.9944 mM). The reaction mixture stirred at room temperature for two days. Once reaction complete, solvent was taken off by vacuum. The crude material was purified on a Silica column using 10% Methanol in CH_2Cl_2. MS (ESI+) for $C_{19}H_{21}BrF_2N_2O_2$ *m/z* 427.2 $(M+H)^+$

D. (1S,2R)-[3-Acetylamino-4-(3,5-difluorophenyl)-2-hydroxybutyl]-(3-bromobenzyl)-carbamic acid tert-butyl ester

N-(*1s*, *2r*)-[3-(3-bromo-benzylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide (0.10 g, 0.234 mm) was dissolved in ch_2cl_2 (2.3 ml, 0.1 m). Reaction cooled to 0°c. Di-tert-butyl dicarbonate (boc_2o) (0.051 g, 0.234 mm) was added slowly to reaction. Allowed reaction to stir at room temperature over night. The reaction was concentrated down by vacuum. Ms (esi+) for $c_{24}h_{29}brf_2n_2o_4$ *m/z* 529.1 $(m+h)^+$

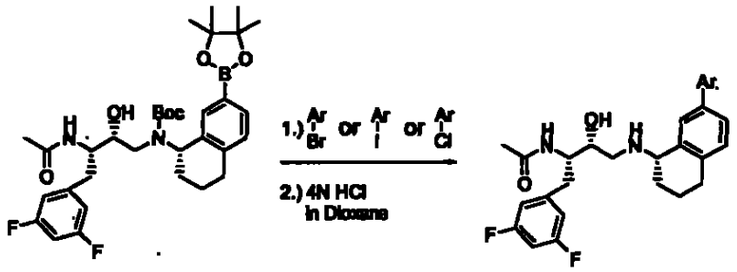
E. N-(1s,2r)-{1-(3,5-difluoro-benzyl)-3-[3-(2,2-dimethyl-propyl)-benzylamino]-2-hydroxy-propyl}-acetamide



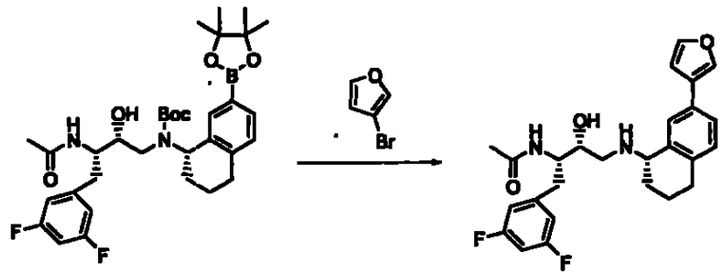
1-Iodo-2,2-dimethyl-propane (1.5 eq., 0.0579 g, 0.2926 mM) and Zinc metal (1.6 eq., 0.0204 g, 0.3122 mM) was added to an oven dried sealed tube (with rubber septa for the top). 2 mL THF was added to the sealed tube. The reaction stirred for 30 minutes under nitrogen. 1-Methyl-2-pyrrolidinone (dried with Molecular Sieves) (0.43 mL) was added to the reaction

mixture. Bis(Tri-t-butylphosphine) Palladium [0] (0.15 eq., 0.0149 g, 0.02926 mM) and N-(*1S, 2R*)-[3-Acetylamino-4-(3,5-difluoro-phenyl)-2-hydroxy-butyl]-(3-bromo-benzyl)-carbamic acid tert-butyl ester (0.1029 g, 0.1951 mM) was added to the reaction mixture. The screw cap was added to the sealed tube. The reaction was heated to 100°C over night. The reaction mixture was then cooled to room temperature and transferred to separatory funnel. The reaction mixture was diluted with 10 mL Ethyl Acetate. Organic layer washed once with 7 mL dH_2O and once with 7 mL Brine. Organic layer dried with Magnesium Sulfate, filtered, and concentrated under vacuum. Product was then dissolved in 500 µL 4N HCl and stood for 1 hour. Reaction concentrated down by vacuum and purified by Prep-HPLC. MS (ESI+) for $C_{24}H_{32}F_2N_2O_2$ m/z 419.2 $(M+H)^+$

Example 123: General synthesis for N-(*1S, 2R*)-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(*1S*)-(1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide



Example 124: General synthesis for N-(*1S, 2R*)-[1-(3,5-Difluoro-benzyl)-3-((*1S*)-7-furan-3-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-acetamide

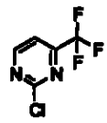
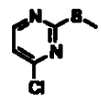


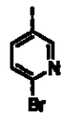
3-Bromofuran (4.85 mgs, 0.033 mM) and Tetrakis(triphenyl-phosphine)palladium [0] (3.81 mgs, 10. mol. wt %) was dissolve in 300 µL 1,2-Dimethoxyethane (glyme) (DME). 99 µL 2M Na_2CO_3 in dH_2O was added to the reaction mixture. *N*-(*1S, 2R*)-[3-Acetylamino-4-(3,5-difluoro-phenyl)-2-hydroxy-butyl]-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-(*1S*)-1,2,3,4-tetrahydro-naphthalen-1-yl]-carbamic acid tert-butyl ester (20.28 mgs, 0.033 mM) was added to the reaction mixture and stirred at 90°C over night. The reaction mixture was concentrated down under vacuum then dissolves in 1.5 mL methanol. The reaction mixture was purified by Prep-HPLC. The isolate product was concentrated down by vacuum. The product was dissolved in 500 µL 4N HCl in Dioxane and stood at room temperature for 30 minutes. The reaction mixture was then concentrated down by vacuum. MS (ESI+) for $C_{26}H_{28}F_2N_2O_3$ *m/z* 455.2 $(M+H)^+$

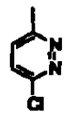
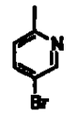
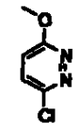
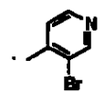
All final compounds in Table 124.A can be synthesized using the same procedure as that for N-(*1S, 2R*)-[1-(3,5-Difluoro-benzyl)-3-((*1S*)-7-furan-3-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-acetamide; however in place of 3-bromofuran, the reagents listed next to the final products were used.

Table 124.A

Example No.	Reagent	Final Compound	m/z (M+H)+

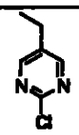
Example No.	Reagent	Final Compound	m/z (M+H)+
A	 3-Bromo-4-methyl-thiophene	N-(1S, 2R) -{1-(3,5-Difluoro-b enzyl)-2-hydroxy-3-(1S)-[7-(4-methyl-thiophen-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	485.1
B	 5-Iodo-1-methyl-1H-imidazole	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(3-methyl-3H-imidazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	469.2
C	 2-Bromo-pyrimidine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-pyrimidin-2-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	467.2
D	 2-Chloro-4-trifluoromethyl-pyrimidine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(4-trifluoromethyl-pyrimidin-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	535.2
E	 4-Chloro-2-methylsulfanyl-pyrimidine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(2-methylsulfanyl-pyrimidin-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	513.2

Example No.	Reagent	Final Compound	m/z (M+H)+
F	 5-Bromo-pyrimidine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-pyrimidin-5-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	467.2
G	 2-Iodo-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-pyridin-2-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	466.6
H	 2-Bromo-5-methyl-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(5-methyl-pyridin-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	480.2
I	 3-Iodo-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-pyridin-3-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	466.2
J	 2-Bromo-3-methyl-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(3-methyl-pyridin-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	480.3

Example No.	Reagent	Final Compound	m/z (M+H)+
K	 3-Chloro-6-methyl-pyridazine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(6-methyl-pyridazin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	481.2
L	 4-Iodo-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-pyridin-4-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	466.2
M	 5-Bromo-2-methyl-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(6-methyl-pyridin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	480.2
N	 3-Chloro-6-methoxy pyridazine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(6-methoxy-pyridazin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	497.2
O	 3-Bromo-4-methyl-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(4-methyl-pyridin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	480.2

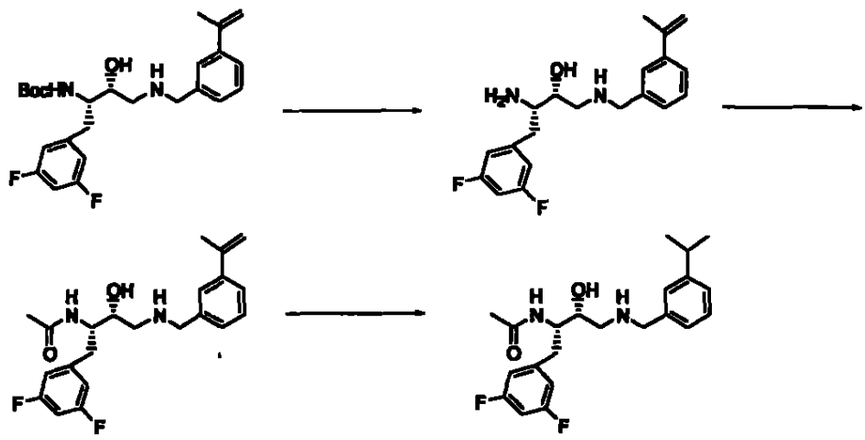
Example No.	Reagent	Final Compound	m/z (M+H)+
P	 2-Chloro-pyrazine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-pyrazin-2-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	467.2
Q	 3-Chloro-2,5-dimethyl-pyrazine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(3,6-dimethyl-pyrazin-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-2-hydroxy-propyl}-acetamide	495.3
R	 2-Bromo-5-methyl-thiophene	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(5-methyl-thiophen-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	485.2
S	 2-Bromo-furan	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)--(7-furan-2-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-2-hydroxy-propyl]-acetamide	455.2
T	 2-Bromo-thiazole	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-thiazol-2-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	472.2

Example No.	Reagent	Final Compound	m/z (M+H)+
U	 3-Bromo-thiophene	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-thiophen-3-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	471.2
V	 (2-Bromo-vinyl)-benzene	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-styryl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	491.2
W	 4-Iodo-3,5-dimethyl isoxazole	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(3,5-dimethyl-isoxazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-2-hydroxy-propyl}-acetamide	484.1
X	 2-Iodo-1-methyl-1H-imidazole	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)--[7-(1-methyl-1H-imidazol-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	469.2
Y	 2-Bromo-thiophene	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-thiophen-2-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	471.2

Example No.	Reagent	Final Compound	m/z (M+H)+
Z	 2-Bromo-3-methyl-thiophene	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(3-methyl-thiophen-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	485.2
AA	 2-Chloro-5-ethyl-pyrimidine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(5-ethyl-pyrimidin-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-2-hydroxy-propyl}-acetamide	495.2
BB	 2-Bromo-4-methyl-pyridine	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-[7-(4-methyl-pyridin-2-yl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propyl}-acetamide	480.2
CC	 2-Bromo-propene	N-(1S, 2R) -{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1S)-(7-isopropenyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide	429.1

Example 125: Synthesis of N-(*1S, 2R*)-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-isopropenyl-benzylamino)-propyl]-acetamide and

N-(*1S,2R*)-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-isopropyl-benzylamino)-propyl]-acetamide



A. (*1S,2R*)-3-Amino-4-(3,5-difluoro-phenyl)-1-(3-isopropenyl-benzylamino)-butan-2-ol

(*1S,2R*)-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-isopropenyl-benzylamino)-propyl]-carbamic acid tert-butyl ester was dissolved in 6 mL CH_2Cl_2 with 600 µL TFA. The reaction mixture stirred for 4 hours at room temperature. 15 mL of 15% IPA in Chloroform was added to reaction mixture was washed with 10 mL Saturated Sodium Bicarbonate (Sat. $NaHCO_3$) in dH_2O. The Sat. $NaHCO_3$ in dH_2O layer was rinsed with 15% IPA in Chloroform. All organic layers were combined and dried with Magnesium Carbonate, filtered and concentrated under vacuum. MS (ESI+) for $C_{20}H_{24}F_2N_2O$ *m/z* 347.4 $(M+H)^+$

B. N-(*1S,2R*)-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-isopropenyl-benzylamino)-propyl]-acetamide

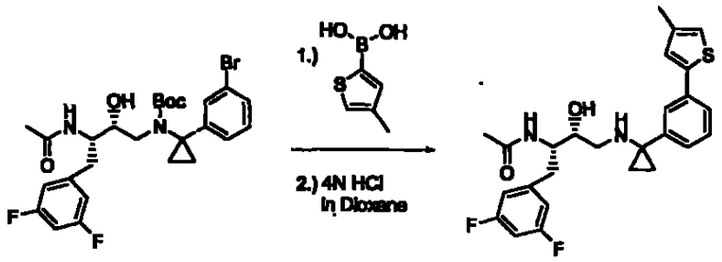
The above compound was prepared essentially according to the method of Example 56. The crude material was purified on Silica gel using 5% Methanol in CH_2Cl_2. MS (ESI+) for $C_{22}H_{26}F_2N_2O_2$ *m/z* 389.5 $(M+H)^+$

C. N-(*1S,2R*)-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-isopropyl-benzylamino)-propyl]-acetamide

The product from step B (0.036 g) was dissolved in 2 mL Methanol. 5% Pd/C (0.004 g) was added to the vial. The reaction was hydrogenated at 50 psi for 4 hours. The reaction mixture was filtered and the filtrate was concentrated. MS (ESI+) for $C_{22}H_{28}F_2N_2O_2$ m/z 391.4 $(M+H)^+$

Example 126

N-(*1S,2R*)-(1-(3,5-Difluoro-benzyl)-2-hydroxy-3-{1-[3-(4-methyl-thiophen-2-yl)-phenyl]-cyclopropylamino}-propyl)-acetamide

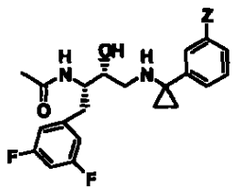


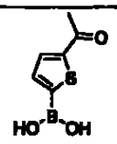
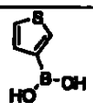
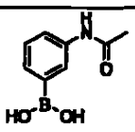
Palladium acetate ($Pd(OAc)_2$) (0.82 mgs, 10 mol. wt. %) and Biphenyl-2-yl-di-tert-butyl-phosphane (2.16 mgs, 20 mol. wt. %) was added to the reaction vessel (Vessel 1). N-(*1S, 2R*)-[3-Acetylamino-4-(3,5-difluoro-phenyl)-2-hydroxy-butyl]-[1-(3-bromo-phenyl)-cyclopropyl]-carbamic acid tert-butyl ester (13.88 mgs, 0.09075 mM) was placed in a separate reaction vessel (Vessel 2) and dissolved in 200 mL DME. 4-Methylthiophene-2-boronic acid and Potassium Fluoride (KF) (3 eq., 6.33 mgs) were added to a separate reaction vessel and dissolved in 200 µL DME (Vessel 3). Solvents in Vessels 2 and 3 were added to Vessel 1 under nitrogen. Vessel 1 was stirred over night at room temperature. Reaction was then concentrated down by vacuum. Crude material purified by Prep-HPLC. Product fracticns collected and concentrated down by vacuum. Product then dissolved in 500 µL 4N HCl in dioxane.

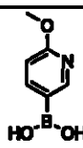
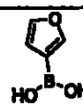
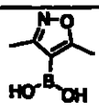
Allowed to stand for 30 minutes at room temperature. Reaction mixture then concentrated down by vacuum. MS (ESI+) for $C_{26}H_{28}F_2N_2O_2S$ *m/z* 471.2 $(M+H)^+$

All compounds in Table 126.A were synthesized using the same general procedure as used in the synthesis of Example 126. The table illustrates the boronic acid derivative that was used, the mass of the product, and the name of the product.

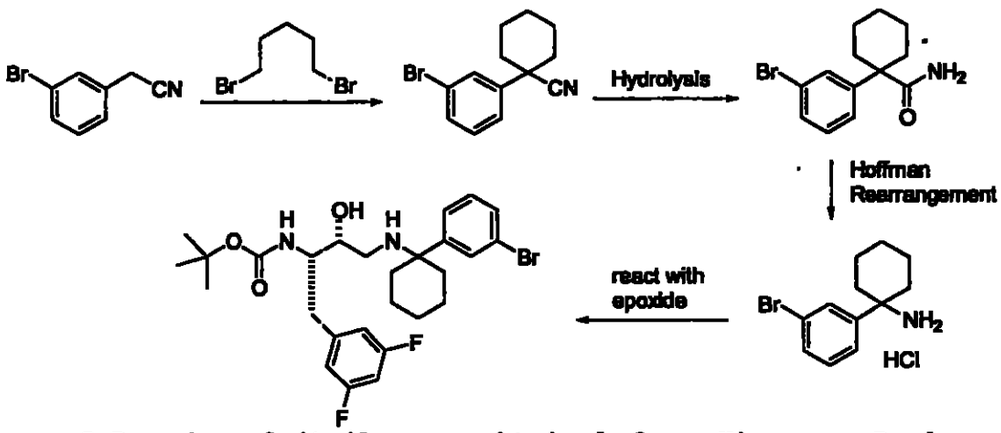
Table 126.A



Example No.	Z	*m/z* $(M+H)^+$	Product
127	 5-Acetyl-2-thiophene-2-boronic acid	499.2	N-(1S,2R)-[3-{1-[3-(5-Acetyl-thiophen-2-yl)-phenyl]-cyclopropylamino}-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide
128	 Thiophene-3-boronic acid	457.2	N-(1S,2R)-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[1-(3-thiophen-3-yl-phenyl)-cyclopropylamino]-propyl}-acetamide
129	 3-Acetamidobenzene boronic acid	508.1	N-(1S,2R)-[3-[1-(3'-Acetylamino-biphenyl-3-yl)-cyclopropylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide

Example No.	Z	m/z (M+H)+	Product
130	 2-Methoxy-5-pyridine bornonic acid	482.3	N-(1S,2R)-(1-(3,5-Difluoro-benzyl)-2-hydroxy-3-{1-[3-(6-methoxy-pyridin-3-yl)-phenyl]-cyclopropylamino}-propyl)-acetamide
131	 3-Furan-boronic acid	441.2	N-(1S,2R)-{1-(3,5-Difluoro-benzyl)-3-[1-(3-furan-3-yl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-acetamide
132	 3,5-Dimethyl isoxazole-4-boronic acid	470.2	N-(1S,2R)-(1-(3,5-Difluoro-benzyl)-3-{1-[3-(3,5-dimethyl-isoxazol-4-yl)-phenyl]-cyclopropylamino}-2-hydroxy-propyl)-acetamide

Example 133



3-Bromobenzylnitrile was obtained from Kimera. Powder KOH was obtained from Oxechem. Other reagents were from Aldrich.

Step 1: 1-(3-bromophenyl)cyclohexanecarbonitrile

To a 5 L 3-neck round bottom flask equipped with N_2 inlet, temperature probe, addition funnel, and mechanical stirrer was added 3-bromobenzylnitrile (297 g, 1.51 mol, 1.0 eq) and THF (2.75 L). The clear solution was cooled to 0-5° C via ice bath. KOtBu (374 g, 3.33 mol, 2.2 eq) was weighed out inside the glove box into a 200 mL round bottom flask and added to the cold clear solution in shots. The first shot (71.1 g) was added over 30 seconds and an immediate exotherm of 9° C was observed along with color change from clear to orange/brown solution. After waiting for 15 min for the solution to cool back down to 5.1° C, the second shot (96.0 g) was added and an exotherm of 6.5° C was observed. After another 15 min, the third shot (100.4 g) was added and an exotherm of 5° C was observed. After another 15 min, the fourth and final shot (106.5 g) was added and an exotherm of 3.8° C was observed. The orange/brown solution was stirred in ice bath for 30 min upon which the solution thickened. Carefully add 1,5-dibromopentane (365.5 g, 1.56 mol, 1.05 eq) to orange/brown mixture at such a rate to maintaining reaction temperature <15° C. The reaction will change from solution to brown slurry and the exotherm will continue to climb during addition. The addition took *ca* 2 hours. The addition funnel was rinsed with THF (250 mL) and added to the brown slurry. The ice bath was then removed and the slurry self-warmed to RT while maintaining medium agitation. Sample of the slurry was pulled after 1 hour of stirring. GC indicated completion with only excess 1,5-dibromopentane and product. The light brown slurry was then filtered over a pad of celite to remove salts. The cake was rinsed with THF (*ca* 2 L) until clear. Ice (*ca* 1 L in volume) was then added to the burgundy filtrate and stirred at RT overnight. The mixture was then concentrated to remove THF and the resultant biphasic brown mixture was extracted with EtOAc and saturated NaCl solution. The orange organic layers were dried with anhydrous Na_2SO_4, filtered and rinsed with EtOAc. The orange filtrate was then concentrated

to dryness to give red oil. EtOAc (100 mL) was added to redissolve oil. While stirring at medium speed, heptane (2 L) was added over 1-2 min upon which burgundy oil sticks to bottom and sides of flask. The yellow solution was then carefully decanted away from the sticky oil and concentrated to dryness to give light orange oil (379.7 g, 95% yield). GC of light orange oil indicated excess 1,5-dibromopentane (2.8 area%), product (95.3 area%), and 7 other peaks having less than 0.5 area% (total = 1.9 area%).

GC Conditions: 15m DB5 0.25 x 0.25 micron; Init. Temp. = 75° C, Init. Time = 5 min, Rate = 15° C/min, Final Temp. = 275° C, Final Time = 2 min, Inj. Temp. = 275° C, Det. Temp. = 250° C; 1,5-dibromopentane RT = 6.35 min, Prod. RT = 13.47 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.45 (d, 2H), 7.26 (t, 1H), 2.14 (d, 2H), 1.74-1.88 (m, 6H), 1.26-1.29 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.63, 130.98, 130.40, 128.73, 124.41, 122.94, 122.07, 44.14, 37.23, 24.82, 23.46.

Step 2: 1-(3-bromophenyl)cyclohexanecarboxamide

With overhead stirrer, a mixture of crude product from step 1, above, (380 g, 1207 mmol), powdered KOH (720 g) and t-BuOH (2.5 L) was heated at reflux overnight. See Hall, J. H.; Gisler, M. A simple method for converting nitriles to amides. Hydrolysis with potassium hydroxide in tert-butyl alcohol. *J. Org. Chem.* 1976, *41*, 3769-3770. If deemed complete by GC analysis, it was cooled with ice-water (cool slowly to avoid shock to the glass), quenched with ice-water (1500 mL). The quenched mixture was then extracted with MTBE (3.5 L + 1.5 L). MTBE layers were concentrated to a yellow solid, 390 g.

GC Conditions: 15m DB5 0.25 x 0.25 micron; Init. Temp. = 75° C, Init. Time = 5 min, Rate = 15° C/min, Final Temp. =

275° C, Final Time = 2 min, Inj. Temp. = 275° C, Det. Temp. = 250° C; Product RT = 15.3 min.

Step 3: 1-(3-bromophenyl)cyclohexanamine hydrochloride,

The product from step 2, above (189 g, 603 mmol) was suspended in warmed t-BuOH (1140 mL) at ~35°C, 3N NaOH (570 mL, 2.8 equiv) was added. The reaction cooled to 30°C. NaOCl (380 mL, 13.6wt%, 1.4 equiv.) was added in one portion. The reaction mixture was cooled to 26°C, and then started to warm up. Ice was directly added to the mixture to controlled the temperature <35°C. A total of 300 g of ice was used. The heat generation stopped after 15 min. All solids dissolved at that point. Assayed organic layer at 30 min, GC indicated completion. The mixture was extracted with 1100 mL of MTBE. The organic layer was combined with the organic layer of a parallel run of the same scale, and filtered to remove some white ppt (likely urea side product). The aqueous layers were extracted with 300 mL of MTBE. The combined MTBE layers (ca. 5 L) was treated with 150 mL of conc. HCl (1.8 mol), stirred for 4h, cooled to 0°C and filtered. The white solid was dried at 50°C to give 1st crop 180 g (52%) of material. The filtrate was treated with NaOH and $NaHSO_3$ to pH>12. The organic layer was concentrated to an oil. This oil was dissolved in 1 L of MTBE and treated with 75 mL of conc. HCl, cooled, filtered and dried to give 140 g (40%) of the desired product .Anal. Calcd for $C_{12}H_{16}BrN.HCl$: C, 49.59; H, 5.90; N, 4.82; Br, 27.49; Cl, 12.20; Found: C, 50.34; H, 6.23; N, 4.70; HRMS calcd for $C_{12}H_{16}BrN^{+}$ 253.0467, found 253.0470.

GC Conditions: 15m DB5 0.25 x 0.25 micron; Init. Temp. = 75° C, Init. Time = 5 min, Rate = 15° C/min, Final Temp. = 275° C, Final Time = 2 min, Inj. Temp. = 275° C, Det. Temp. = 250° C; Product RT = 12.9 min.

Step 4: tert-butyl-(1S,2R)-3-{[1-(3-bromophenyl)cyclohexyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate,

The product from step 3, above (90 g, 310 mmol, 1.5 eq) was converted into a free base in 1000 mL of MTBE/400 mL of 2N NaOH. MTBE layer was separated, washed with brine. Aqueous layers were back extracted with 400 mL of MTBE. Combined MTBE layer was concentrated (thereotical 78.3 g) to afford the free base.

61.7 g the epoxide (206 mmol, 1 eq., FW 299.3) and the above free base were suspended in 320 ml t-BuOH (warm). A mantle and thermo/probe was used to heat the stirring mixture to 80°C at 5°C/hour ramp overnight. The mixture was concentrated on rotovap with 20°C condenser. The resulting oil was dissolved in MTBE (1L), washed with 1N HCl (200ml, then 100 mL x 5) (contain the product from step 3, the first wash was quickly separated to avoid crash out). Aqueous layer was sequentially back-extracted with MTBE (200 mL). The MTBE layer was stirred with 1N NaOH (500 mL) for 30 min, then separated. MTBE layer was washed with brine and then concentrated to dryness. Recrystallized in MTBE/Heptane (150/900 mL). Filtered at 0°C and washed with heptane (150 mL x 2), dried at 45°C, 95.3 g (83.5%).

The HCl washes (suspension) were basified with 50% NaOH (ca. 50 g), extracted with MTBE (400 mL + 200 mL). The MTBE layer was treated with conc. HCl (15 mL). The resulting suspension was cooled and filtered to give the unreacted starting amine, the product from step 3, above, 31.3 g (52%).

HPLC conditions: Luna C18(2), 3 micron, min, 80:20 0.1%TFA in MeOH/0.1%TFA in water; 10 min, Product, RT= 2.0 min.

Example 134

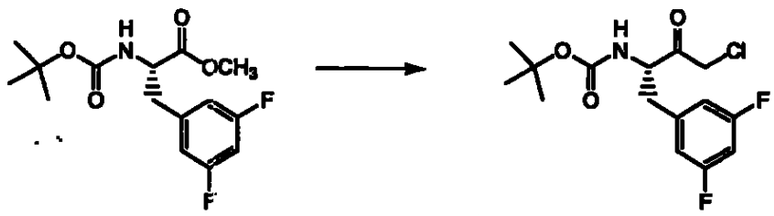
tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate

Step 1: (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid methyl ester



To a 1-L 3-neck round bottom flask equipped with a magnetic stirrer, nitrogen inlet and thermocouple is added (2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid (I, 40 g, 0.133 moles, 1 equivalent) followed by THF (240 mL). Lithium hydroxide monohydrate (5.6 g, 0.133 moles, 1 equivalent) is added in a single portion and is allowed to stir for 30 min at which time, the contents are cooled to 0°. Once cooled, dimethyl sulfate (12.6 mL, 0.133 moles, 1 equivalent) is added dropwise *via* syringe and then stirred for 30 min. The mixture is then heated to about 50° and monitored (by HPLC) until 90% conversion had been achieved. At that time, the mixture is cooled to below 20° (solids form). The mixture is then poured into sodium bicarbonate (200 mL), stirred for 15 min then extracted with methyl *t*-butyl ether (200 mL). The phases are separated and the aqueous layer is extracted with methyl t-butyl ether (2 x 200 mL). The combined organic phases are washed with water (400 mL) dried over sodium sulfate, filtered and concentrated under reduced pressure to give a solid. This material is then recrystallized from hexanes to give the title compound, NMR (DMSO-d_6) δ 7.51, 7.15-7.25, 4.43, 3.81, 3.00-3.26 and 1.49; CMR (DMSO-d_6) δ 172.43, 163.74, 161.20, 155.67, 142.58, 112.70, 120.23, 78.69, 54.71, 52.24, 39.25 and 28.37.

Step 2: tert-butyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III)



To a 1-L 3-neck round bottom flask equipped with a magnetic stirrer, nitrogen inlet, thermocouple and additional funnel is added (2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid methyl ester (II, Step 1, 10.0 g, 0.0317 moles, 1 equivalent) followed by THF (175 mL) then cooled to -78°. Once the mixture is cooled, iodochloromethane (9.25 mL, 0.127 moles, 4 equivalents) is added in one portion *via* syringe. The addition funnel is charged with LDA (79 mL, 0.158 moles, 5 equivalents, 2.0 M in heptane/THF) and is subsequently added dropwise to the mixture keeping the internal temperature below -70°. Once the addition is complete, the contents are stirred for 15 min at which time acetic acid (47.2 mL, 0.824 moles, 26 equivalents) is added dropwise *via* the addition funnel keeping the internal temperature below -65°. Once this addition is complete, the mixture is stirred for 15 min then warmed to 0° and poured into water (500 mL), saline (500 mL) and methyl t-butyl ether (500 mL) then transferred to a separatory funnel. The phases are separated and the aqueous phase is extracted with methyl t-butyl ether (2 x 250 mL). The combined organic phases are washed with saturated sodium bicarbonate (500 mL), sodium sulfite (500 mL) and water (500 mL). The organic phase is then dried over sodium sulfate, filtered and concentrated under reduced pressure to give a solid. The solid is recrystallized from heptane/i-propyl alcohol (10/1) to give the title compound, NMR (DMSO-d_6) δ 7.47, 7.06-7.14, 4.78, 4.49,

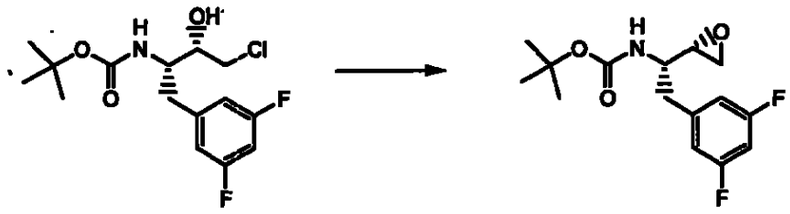
3.20, 2.82 and 1.40; CMR (DMSO-d_6) δ 200.87, 163.74, 161.20, 142.74, 112.80, 102.13, 79.04, 58.97, 47.72, 34.95 and 28.30.

Step 3: tert-butyl (1S,2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV)



To a 250 mL 3-neck round bottom flask equipped with magnetic stir bar, nitrogen inlet and thermocouple, is added tert-butyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III, Step 2, 4.4 g, 0.0132 moles, 1 equivalent) followed by THF (20 mL) and ethanol (30 mL) then cooled to -78°. Once the mixture is cooled, sodium borohydride (2.0 g, 0.0527 moles, 4 equivalents) is added as a solid portion wise over 30 min keeping the internal temperature below -70°. Once this addition is complete, the contents are stirred for 2 hr at -78° then warmed to 0° and stirred an additional 1 hr. The mixture is quenched by the addition of saturated potassium bisulfate (15 mL) and water (15 mL). This slurry is stirred for 30 min at 20-25° then concentrated under reduced pressure to half its volume. The mixture is then cooled to 0° and stirred for 30 min. After this time, the resultant solids are collected by filtration and washed with water (2 x 50 mL) then dried under reduced pressure at 50° to give crude product. A syn/anti ratio of 4-9:1 has been observed. The desired product is recrystallized from hexanes/ethanol (25/1) to give the title compound, NMR (DMSO-d_6) δ 6.89-7.16, 5.61, 3.64-3.83, 3.19, 2.69 and 1.41; CMR (DMSO-d_6) δ 163.67, 161.24, 155.44, 112.70, 101.55, 78.04, 72.99, 54.29, 48.24, 35.97 and 28.37.

Step 4: tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate



To a 250 mL 3-neck round bottom flask equipped with magnetic stir bar, nitrogen inlet and thermocouple, is added tert-butyl (1S,2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV, Step 3, 3.5 g, 0.010 moles, 1 equivalent) followed by absolute ethanol (60 mL) and cooled to 0°. To this mixture is added potassium hydroxide (0.73 g, 0.013 moles, 1.25 equivalents) dissolved in absolute ethanol (10 mL) over 1 hr and the resulting suspension is warmed to 15-20° and stirred for 1 hr. At this time, water (100 mL) is added and the reaction contents are cooled to -5° and stirred for 30 min. The solids are collected by filtration and washed with cold water (2 x 25 mL) then dried under reduced pressure at 45° to give the title compound; NMR (DMSO-d_6) δ 7.03, 3.61, 2.68-2.98 and 1.33; CMR (DMSO-d_6) δ 163.72, 161.29, 155.55, 143.35, 112.65, 101.80, 78.17, 53.42, 52.71, 44.90, 36.98 and 28.36.

Example 135

The following compounds are prepared essentially according to the procedures set forth in the above examples and schemes.

Ex. No.	Compound Name
A1.	N-[(1S,2R)-3-{[(1R)-5-(3-aminophenyl)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
A2.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-5-(1,3-thiazol-2-yl)-1,2,3,4-tetrahydronaphthalen-1-

yl]amino}-2-hydroxypropyl)acetamide;

A3. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-5-pyridin-2-yl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

A4. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-5-(3-methylpyridin-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

A5. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-5-(4-methylpyridin-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

A6. N-[(1S,2R)-3-{[1-acetyl-4-(3-isopropylphenyl)piperidin-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A7. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[4-(3-isopropylphenyl)-1-(methylsulfonyl)piperidin-4-yl]amino}propyl)acetamide;

A8. N-((1R,2S)-1-[4-(benzyloxy)-3-fluorobenzyl]-3-{[(1S)-7-(2,2-dimethylpropyl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

A9. N-[(1R,2S)-3-{[4-(3-tert-butylphenyl)tetrahydro-2H-pyran-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A10. N-[(1R,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(trifluoromethyl)phenyl]cyclohexyl}amino)propyl]acetamide;

A11. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4R)-6-(2,2-dimethylpropyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)-2-fluoroacetamide;

A12. N-((1R,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[4-(3-isopropoxyphenyl)tetrahydro-2H-pyran-4-yl]amino}propyl)-N'-phenylurea;

A13. phenyl {(1R,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropoxy-1,1-dimethyl-3,4-dihydro-1H-isochromen-4-

yl)amino]propyl}carbamate;

A14. N-((1R,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(2-isobutyl-1,3-thiazol-5-yl)-1-methylethyl]amino}propyl)acetamide;

A15. N-[(1S,2R)-3-({1-[3-(2-adamantyl)phenyl]cyclohexyl}amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A16. N-[(1S,2R)-3-{[1-(3-cyclopentylphenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A17. N-[(1S,2R)-3-{[1-(3-bicyclo[2.2.1]hept-2-ylphenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A18. Ethyl 3-[3-(1-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}cyclohexyl)phenyl]propanoate;

A19. N-[(1S,2R)-3-{[1-(3-sec-butylphenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A20. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3',5'-difluorobiphenyl-3-yl)cyclopropyl]amino}-2-hydroxypropyl)acetamide;

A21. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[5-(2,2-dimethylpropyl)-2-(2-propyl-1H-imidazol-1-yl)benzyl]amino}-2-hydroxypropyl)acetamide;

A22. N-[(1S,2R)-3-{[1-(3-sec-butylphenyl)cyclohexyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A23. N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(3-methylbutyl)phenyl]cyclohexyl}amino)propyl]acetamide;

A24. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(1-ethylpropyl)phenyl]cyclohexyl}amino)-2-hydroxypropyl]acetamide;

A25. N-[(1S,2R)-3-{[1-(3-

cyclopentylphenyl)cyclohexyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A26. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-pent-4-en-1-ylphenyl)cyclohexyl]amino}propyl)acetamide;

B1. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-pyridin-2-ylphenyl)cyclohexyl]amino}propyl)acetamide;

B2. N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(3-methylpyridin-2-yl)phenyl]cyclohexyl}amino)propyl]acetamide;

B3. N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(1,3-thiazol-2-yl)phenyl]cyclohexyl}amino)propyl]acetamide;

B4. N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(3-methyl-2-thienyl)phenyl]cyclohexyl}amino)propyl]acetamide;

B5. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(2-fluorobenzyl)phenyl]cyclohexyl}amino)-2-hydroxypropyl]acetamide;

B6. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(4-fluorobenzyl)phenyl]cyclohexyl}amino)-2-hydroxypropyl]acetamide;

B7. N-[(1R,2S)-3-{[(1S)-7-(2,2-dimethylpropyl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-1-(3-fluoro-4-hydroxybenzyl)-2-hydroxypropyl]acetamide; and

B8. N-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(3-isopropylphenyl)tetrahydro-2H-pyran-3-yl]amino}propyl)acetamide.

Example 136

The following compounds are prepared essentially according to the procedures set forth in the above examples and schemes.

Ex. No.	Compound

A1. (1S,2R)-N-[3-[1-(3-tert-Butyl-phenyl)-4-oxo-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A2. (1S,2R)-N-[3-[5-(3-tert-Butyl-phenyl)-2-oxo-[1,3]oxazinan-5-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A3. (1S, 2R)-N-[3-[5-(3-tert-Butyl-phenyl)-2-oxo-hexahydro-pyrimidin-5-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A4. (1S,2R)-N-[3-[1-(3-Bromo-5-tert-butyl-phenyl)-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A5. (1S,2R)-N-[3-[1-(3-tert-Butyl-5-ethyl-phenyl)-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A6. (1S,2R)-N-[3-[4-(3-tert-Butyl-5-ethyl-phenyl)-tetrahydropyran-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxypropyl]-acetamide;

A7. (1S,2R)-N-[3-[4-(3-Bromo-5-tert-butyl-phenyl)-tetrahydropyran-4-ylamino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-acetamide;

A8. (1S,2R)-N-[3-[1-(3-tert-Butyl-5-ethylphenyl)cyclopropylamino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-acetamide;

A9. (1S,2R)-N-[3-{1-[3-Bromo-5-(2,2-dimethyl-propyl)-phenyl]-cyclopropylamino}-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A10. (1S,2R)-N-(1-(3,5-Difluorobenzyl)-3-{1-[5-(2,2-dimethylpropyl)-2-imidazol-1-yl-phenyl]-cyclopropylamino}-2-hydroxy-propyl)-acetamide;

A11. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethylpropyl)-2-(5-ethyl-imidazol-1-yl)-benzylamino]-2-hydroxypropyl}-acetamide;

A12. (1S,2R)-N-[3-[3-Chloro-5-(2,2-dimethyl-propyl)-2-imidazol-1-yl-benzylamino]-1-(3,5-difluoro-benzyl)-2-

hydroxy-propyl]-acetamide;

A13. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-tetrazol-1-yl-benzylamino]-2-hydroxy-propyl}-acetamide;

A14. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-oxazol-5-yl-benzylamino]-2-hydroxy-propyl}-acetamide;

A15. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-oxazol-2-yl-benzylamino]-2-hydroxy-propyl}-acetamide;

A16. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-1-methyl-1,2,3,4-tetrahydro-quinolin-4-ylamino]-2-hydroxy-propyl}-acetamide;

A17. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-thiochroman-4-ylamino]-2-hydroxy-propyl}-acetamide;

A18. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-8-ethyl-chroman-4-ylamino]-2-hydroxy-propyl}-acetamide;

A19. (1S,2R)-N-[3-[8-Bromo-6-(2,2-dimethylpropyl)-chroman-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxypropyl]-acetamide;

A20. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-2-oxo-chroman-4-ylamino]-2-hydroxy-propyl}-acetamide;

A21. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[7-(2,2-dimethyl-propyl)-4-oxo-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-2-hydroxy-propyl}-acetamide;

A22. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-1-oxo-1λ^4-thiochroman-4-ylamino]-2-hydroxypropyl}-acetamide;

A23. (1S,2R)-N-{1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-1,1-dioxo-1λ^6-thiochroman-4-ylamino]-2-hydroxy-propyl}-acetamide;

A24. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[7-(2,2-dimethylpropyl)-5-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

A25. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4R)-6-(2,2-dimethylpropyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

A26. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-(2,2-dimethylpropyl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

B1. N-[(1S,2R)-3-{[1-(3-tert-butylphenyl)cyclohexyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

B2. N-[(1S,2R)-3-{[4-(3-tert-butylphenyl)tetrahydro-2H-pyran-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

B3. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[6-(2,2-dimethylpropyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;

B4. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)-4-oxocyclohexyl]amino}propyl)acetamide;

B5. N-[(1S,2R)-3-{[(4S)-6-(2,2-dimethylpropyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3-fluorobenzyl)-2-hydroxypropyl]acetamide;

B6. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[5-(2,2-dimethylpropyl)-2-(1H-imidazol-1-yl)benzyl]amino}-2-hydroxypropyl)acetamide;

B7. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[7-(2,2-dimethylpropyl)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

B8. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[6-(2,2-dimethylpropyl)-4-methyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

B9. N-((1S,2R)-1-(3-fluoro-4-hydroxybenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide;

B10. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)-2-fluoroacetamide;

B11. N-((1S,2R)-1-[3-(allyloxy)-5-fluorobenzyl]-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide;

B12. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(2,2-dimethylpropyl)phenyl]-1-methylethyl}amino)-2-hydroxypropyl]-2-fluoroacetamide;

B13. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-(2,2-dimethylpropyl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2-fluoroacetamide;

B14. N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(3-thienyl)phenyl]cyclohexyl}amino)propyl]acetamide;

B15 N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[4-(2,2-dimethylpropyl)pyridin-2-yl]cyclopropyl}amino)-2-hydroxypropyl]acetamide

B16 N-((1R,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-7-propyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)acetamide

B17 N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylphenyl)cyclohexyl]amino}propyl)acetamide

B18 N-((1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide

B19 N-((1R,2S)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2-ethoxyacetamide

B20 N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2,2-difluoroacetamide

Example 137

The following compounds are prepared essentially according to the procedures set forth in the above examples and schemes.

Ex. No.	Compound
A1.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[1-(3-isopropyl-phenyl)-cyclobutylamino]-propyl}-acetamide;
A2.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[1-(3-isopropyl phenyl)-cyclopentylamino]-propyl}-acetamide;
A3.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-(3-isopropyl-phenyl)-bicyclo[3.1.0]hex-3-ylamino]-propyl}-acetamide;
A4.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-(3-isopropyl-phenyl)-6-aza-bicyclo[3.1.0]hex-3-ylamino]-propyl}-acetamide;
A5.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-(3-isopropyl-phenyl)-6-methyl-6-aza-bicyclo[3.1.0]hex-3-ylamino]-propyl}-acetamide;
A6.	N-[3-[6-Acetyl-3-(3-isopropyl-phenyl)-6-aza-bicyclo[3.1.0]hex-3-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;
A7.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-(3-isopropyl-phenyl)-6-methanesulfonyl-6-aza-bicyclo[3.1.0]hex-3-ylamino]-propyl}-acetamide;
A8.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[1-(3-isopropyl-phenyl)-2,2,4,4-tetramethyl-3-oxo-cyclobutylamino]-propyl}-acetamide;
A9.	N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-hydroxy-1-(3-isopropyl-phenyl)-2,2,4,4-tetramethyl-cyclobutylamino]-propyl}-acetamide;

A10. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-(3-isopropyl-phenyl)-octahydro-cyclopenta[c]pyrrol-5-ylamino]-propyl}-acetamide;

A11. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-(3-isopropyl-phenyl)-2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylamino]-propyl}-acetamide;

A12. N-[3-[2-Acetyl-5-(3-isopropyl-phenyl)-octahydro-cyclopenta[c]pyrrol-5-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A13. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-(3-isopropyl-phenyl)-2-methanesulfonyl-octahydro-cyclopenta[c]pyrrol-5-ylamino]-propyl}-acetamide;

A14. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-5-oxo-octahydro-pentalen-2-ylamino]-propyl}-acetamide;

A15. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-hydroxy-2-(3-isopropyl-phenyl)-octahydro-pentalen-2-ylamino]-propyl}-acetamide;

A16. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-3a,6a-dimethyl-5-oxo-octahydro-pentalen-2-ylamino]-propyl}-acetamide;

A17. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-hydroxy-2-(3-isopropyl-phenyl)-3a,6a-dimethyl-octahydro-pentalen-2-ylamino]-propyl}-acetamide;

A18. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-5-oxo-cyclohexylamino]-propyl}-acetamide;

A19. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-hydroxy-2-(3-isopropyl-phenyl)-5-methyl-cyclohexylamino]-propyl}-acetamide;

A20. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-5-methanesulfonylamino-cyclohexylamino]-propyl}-acetamide;

A21. N-[3-[5-Acetylamino-2-(3-isopropyl-phenyl)-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A22. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-4-oxo-cyclohexylamino]-propyl}-acetamide;

A23. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-hydroxy-2-(3-isopropyl-phenyl)-4-methyl-cyclohexylamino]-propyl}-acetamide;

A24. N-[3-[4-Acetylamino-2-(3-isopropyl-phenyl)-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

A25. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-4-methanesulfonylamino-cyclohexylamino]-propyl}-acetamide;

A26. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-4-oxo-cyclopentylamino]-propyl}-acetamide;

B1. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-hydroxy-2-(3-isopropyl-phenyl)-4-methyl-cyclopentylamino]-propyl}-acetamide;

B2. N-[3-[4-Acetylamino-2-(3-isopropyl-phenyl)-cyclopentylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

B3. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[2-(3-isopropyl-phenyl)-4-methanesulfonylamino-cyclopentylamino]-propyl}-acetamide;

B4. N-{1-(3,5-Difluoro-benzyl)-3-[4-(2,2-dimethyl-propyl)-pyridin-3-ylamino]-2-hydroxy-propyl}-acetamide;

B5. N-(1-(3,5-Difluoro-benzyl)-3-{[4-(2,2-dimethyl-propyl)-pyridin-3-ylmethyl]-amino}-2-hydroxy-propyl)-acetamide;

B6. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(5-isobutyl-2-piperazin-1-yl-benzylamino)-propyl]-acetamide;

B7. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-isobutyl-2-(4-methyl-piperazin-1-yl)-benzylamino]-propyl}-acetamide;

B8. N-[3-[2-(4-Acetyl-piperazin-1-yl)-5-isobutyl-benzylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

B9. N-{1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[5-isobutyl-2-(4-methanesulfonyl-piperazin-1-yl)-benzylamino]-propyl}-

acetamide;

B10. N-{1-(3,5-Difluoro-benzyl)-3-[4-(2,2-dimethyl-propyl)-piperidin-3-ylamino]-2-hydroxy-propyl}-acetamide;

B11. N-(1-(3,5-Difluoro-benzyl)-3-{[4-(2,2-dimethyl-propyl)-piperidin-3-ylmethyl]-amino}-2-hydroxy-propyl)-acetamide;

B12. N-[3-[1-Acetyl-4-(2,2-dimethyl-propyl)-piperidin-3-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

B13. N-[3-{[1-Acetyl-4-(2,2-dimethyl-propyl)-piperidin-3-ylmethyl]-amino}-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

B14. N-{1-(3,5-Difluoro-benzyl)-3-[4-(2,2-dimethyl-propyl)-1-methanesulfonyl-piperidin-3-ylamino]-2-hydroxy-propyl}-acetamide;

B15. N-(1-(3,5-Difluoro-benzyl)-3-{[4-(2,2-dimethyl-propyl)-1-methanesulfonyl-piperidin-3-ylmethyl]-amino}-2-hydroxy-propyl)-acetamide;

B16. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(6-isopropyl-2-oxo-1,2,3,4-tetrahydro-quinolin-4-ylamino)-propyl]-acetamide;

B17. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(5-isopropyl-2-oxo-2,3-dihydro-1H-indol-3-ylamino)-propyl]-acetamide;

B18. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(7-isopropyl-3-oxo-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide;

B19. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(3-hydroxy-7-isopropyl-3-methyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide;

B20. N-[3-(3-Acetylamino-7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

B21. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(7-isopropyl-3-methanesulfonylamino-1,2,3,4-tetrahydro-naphthalen-1-ylamino)-propyl]-acetamide;

B22. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(6-isopropyl-2-oxo-indan-1-ylamino)-propyl]-acetamide;

B23. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(2-hydroxy-6-isopropyl-2-methyl-indan-1-ylamino)-propyl]-acetamide;

B24. N-[3-(2-Acetylamino-6-isopropyl-indan-1-ylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

B25. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(6-isopropyl-2-methanesulfonylamino-indan-1-ylamino)-propyl]-acetamide;

B26. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(5-isobutyl-2-piperidin-4-yl-benzylamino)-propyl]-acetamide;

C1. N-[3-[2-(1-Acetyl-piperidin-4-yl)-5-isobutyl-benzylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

C2. N-{1-(3,5-Diflucro-benzyl)-2-hydroxy-3-[5-isobutyl-2-(1-methanesulfonyl-piperidin-4-yl)-benzylamino]-propyl}-acetamide;

C3. N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-piperidin-4-yl-benzylamino]-2-hydroxy-propyl}-acetamide;

C4. N-[3-[2-(1-Acetyl-piperidin-4-yl)-5-(2,2-dimethyl-propyl)-benzylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide

C5. N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-(1-methanesulfonyl-piperidin-4-yl)-benzylamino]-2-hydroxy-propyl}-acetamide;

C6. N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(6-isobutyl-2,2-dioxo-1,2,3,4-tetrahydro-2λ^6-benzo[c][1,2]thiazin-4-ylamino)-propyl]-acetamide;

C7. N-{1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-1-methyl-2,2-dioxo-1,2,3,4-tetrahydro-2λ^6-benzo[c][1,2]thiazin-4-ylamino]-2-hydroxy-propyl}-acetamide;

C8. N-[3-[6-(2,2-Dimethyl-propyl)-2,2-dioxo-1,2,3,4-tetrahydro-2λ^6-benzo[c][1,2]thiazin-4-ylamino]-1-(3-fluoro-4-hydroxy-benzyl)-2-hydroxy-propyl]-acetamide;

C9. N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-

methanesulfonylamino-benzylamino]-2-hydroxy-propyl}-acetamide;

C10. N-[3-[2-Benzenesulfonylamino-5-(2,2-dimethyl-propyl)-benzylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

C11. N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-phenylsulfamoyl-benzylamino]-2-hydroxy-propyl}-acetamide;

C12. N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-methylsulfamoyl-benzylamino]-2-hydroxy-propyl}-acetamide;

C13. N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-(2-oxo-piperidin-4-yl)-benzylamino]-2-hydroxy-propyl}-acetamide;

C14. N-{1-(3,5-Difluoro-benzyl)-3-[5-(2,2-dimethyl-propyl)-2-(1-methyl-2-oxo-piperidin-4-yl)-benzylamino]-2-hydroxy-propyl}-acetamide;

C15. N-[3-[6-(2,2-Dimethyl-propyl)-chroman-4-ylamino]-1-(3-fluoro-4-hydroxy-benzyl)-2-hydroxy-propyl]-acetamide;

C16. N-[3-[7-(2,2-Dimethyl-propyl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-1-(3-fluoro-4-hydroxy-benzyl)-2-hydroxy-propyl]-acetamide;

C17. N-[3-[7-(2,2-Dimethyl-propyl)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-2-hydroxy-1-(5-hydroxy-pyridin-2-ylmethyl)-propyl]-acetamide;

C18. N-[3-[6-(2,2-Dimethyl-propyl)-chroman-4-ylamino]-2-hydroxy-1-(5-hydroxy-pyridin-2-ylmethyl)-propyl]-acetamide;

C19. N-[3-[4-(3-tert-Butyl-phenyl)-tetrahydro-pyran-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-butyl]-acetamide;

C20. N-[3-[4-(3-tert-Butyl-phenyl)-tetrahydro-pyran-4-ylamino]-1-(3,5-difluoro-benzyl)-2,4-dihydroxy-butyl]-acetamide;

C21. N-[3-(5-tert-Butyl-2-imidazol-1-yl-benzylamino)-1-(3,5-

difluoro-benzyl)-2-hydroxy-butyl]-acetamide;

C22. N-[3-(5-tert-Butyl-2-imidazol-1-yl-benzylamino)-1-(3,5-difluoro-benzyl)-2,4-dihydroxy-butyl]-acetamide;

C23. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-tetrahydro-thiopyran-4-ylamino]-propyl}-acetamide;

C24. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-1,1-dioxo-tetrahydro-thiopyran-4-ylamino]-propyl}-acetamide;

C25. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-1-oxo-tetrahydro-thiopyran-4-ylamino]-propyl}-acetamide;

C26. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-1-methanesulfonyl-piperidin-4-ylamino]-propyl}-acetamide;

D1. N-[(1S,2R)-3-[1-Acetyl-4-(3-isopropyl-phenyl)-piperidin-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

D2. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-piperidin-4-ylamino]-propyl}-acetamide;

D3. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-1-trifluoroacetyl-piperidin-4-ylamino]-propyl}-acetamide;

D4. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropoxy-phenyl)-tetrahydro-pyran-4-ylamino]-propyl}-acetamide;

D5. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-1,1-dimethyl-piperidin-4-ylamino]-propyl}-acetamide;

D6. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-[1-formyl-4-(3-isopropyl-phenyl)-piperidin-4-ylamino]-2-hydroxy-propyl}-acetamide;

D7. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-[1-ethyl-4-(3-isopropyl-phenyl)-piperidin-4-ylamino]-2-hydroxy-

propyl}-acetamide;

D8. N-[3-[4-(3-tert-Butyl-phenyl)-tetrahydro-pyran-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

D9. N-{(1S,2R)-1-(3,5-Difluoro-4-hydroxy-benzyl)-2-hydroxy-3-[1-(3-isopropyl-phenyl)-cyclohexylamino]-propyl}-acetamide;

D10. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[1-(2-isobutyl-thiazol-5-yl)-1-methyl-ethylamino]-propyl}-acetamide;

D11. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-(3-isopropoxy-phenyl)-tetrahydro-pyran-3-ylamino]-propyl}-acetamide;

D12. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[3-(3-isopropyl-phenyl)-tetrahydro-pyran-3-ylamino]-propyl}-acetamide;

D13. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropoxy-phenyl)-tetrahydro-pyran-4-ylamino]-propyl}-2-fluoro-acetamide;

D14. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-[6-(2,2-dimethyl-propyl)-chroman-4-ylamino]-2-hydroxy-propyl}-2-fluoro-acetamide;

D15. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-{1-[2-(2,2-dimethyl-propyl)-thiazol-5-yl]-1-methyl-ethylamino}-2-hydroxy-propyl)-acetamide;

D16. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-{1-[3-(2,2-dimethyl-propyl)-phenyl]-1-methyl-ethylamino}-2-hydroxy-propyl)-2-fluoro-acetamide;

D17. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-tetrahydro-pyran-4-ylamino]-propyl}-acetamide;

D18. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[4-(3-isopropyl-phenyl)-1-methyl-piperidin-4-ylamino]-propyl}-acetamide;

D19. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-[1-ethanesulfonyl-

4-(3-isopropyl-phenyl)-piperidin-4-ylamino]-2-hydroxy-propyl}-acetamide;

D20. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-[1-propanesulfonyl-4-(3-isopropyl-phenyl)-piperidin-4-ylamino]-2-hydroxy-propyl}-acetamide;

D21. N-{(1S,2R)-1-(3,5-Difluoro-benzyl)-3-[2-propanesulfonyl-4-(3-isopropyl-phenyl)-piperidin-4-ylamino]-2-hydroxy-propyl}-acetamide;

D22. N-[(1S,2R)-3-[4-(3-tert-Butyl-phenyl)-1-ethanesulfonyl-piperidin-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

D23. N-[(1S,2R)-3-[4-(3-tert-Butyl-phenyl)-1-methanesulfonyl-piperidin-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

D24. 4-[(2R,3S)-3-Acetylamino-4-(3,5-difluoro-phenyl)-2-hydroxy-butylamino]-4-(3-tert-butyl-phenyl)-piperidine-1-carboxylic acid amide;

D25. 4-[(2R,3S)-3-Acetylamino-4-(3,5-difluoro-phenyl)-2-hydroxy-butylamino]-4-(3-tert-butyl-phenyl)-piperidine-1-carboxylic acid methylamide;

D26. 4-[(2R,3S)-3-Acetylamino-4-(3,5-difluoro-phenyl)-2-hydroxy-butylamino]-4-(3-tert-butyl-phenyl)-piperidine-1-carboxylic acid methyl ester;

E1. N-[(1S,2R)-3-[(4S)-4-(3-tert-Butyl-phenyl)-1-methanesulfonyl-azepan-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

E2. N-[(1S,2R)-3-[(4R)-4-(3-tert-Butyl-phenyl)-1-methanesulfonyl-azepan-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide;

E3. N-[(1S,2R)-3-[(4R)-4-(3-tert-Butyl-phenyl)-azepan-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide; and

E4. N-[(1S,2R)-3-[(4S)-4-(3-tert-Butyl-phenyl)-azepan-4-ylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide.

Example 138

The following compounds are prepared essentially according to the procedures set forth in the above examples and schemes.

Ex. No.	Compound
A1.	N-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;
A2.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4R)-6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}propyl)acetamide;
A3.	N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}propyl)acetamide;
A4.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;
A5.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;
A6.	N-[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide hydrochloride;
A7.	methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-bromophenyl)propanoate;
A8.	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide;
A9.	methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoate;
A10.	3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoic acid;
A11.	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-

3-hydroxypropyl]amino}-2-hydroxypropyl)acetamide;

A12. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino]propyl}acetamide;

A13. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

A14. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-methylamino-acetamide;

A15. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}acetamide;

A16. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-iodophenyl)propanoate;

A17. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(3-hydroxyprop-1-ynyl)phenyl]propanoate;

A18. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-hydroxy-1-(3-iodophenyl)propyl]amino}propyl)acetamide;

A19. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(3-hydroxypropyl)phenyl]propanoate;

A20. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl}acetamide;

A21. 2-Amino-N-[1-(3,5-difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-acetamide;

A22. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[6-ethyl-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;

A23. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

A24. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-

1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

A25. N-[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

A26. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(5-formylthien-2-yl)phenyl]propanoate;

B1. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(2'-acetyl-1,1'-biphenyl-3-yl)propanoate;

B2. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-methyl-butyramide;

B3. N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3'-(hydroxymethyl)-1,1'-biphenyl-3-yl]cyclopropyl}amino)propyl]acetamide;

B4. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(5-formylthien-2-yl)phenyl]cyclopropyl}amino)-2-hydroxypropyl]acetamide;

B5. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(9H-fluoren-9-ylamino)-2-hydroxypropyl]acetamide;

B6. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(trifluoromethyl)phenyl]propanoate;

B7. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-cyanophenyl)propanoate;

B8. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-2,2-dimethyl-propionamide;

B9. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)acetamide;

B10. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-

bromophenyl)propanoate;

B11. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)acetamide;

B12. N-[(1S,2R)-3-[(2-bromo-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

B13. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

B14. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}acetamide;

B15. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide;

B16. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

B17. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4R)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

B18. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-propionamide;

B19. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}acetamide;

B20. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}acetamide;

B21. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[4-(3-ethylphenyl)tetrahydro-2H-pyran-4-yl]amino}-2-hydroxypropyl)acetamide;

B22. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)butyl]amino}-2-hydroxypropyl)acetamide;

B23. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

B24. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4R)-6-ethyl-3,4-

dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

B25. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)amino]-2-hydroxypropyl}acetamide;

B26. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-butyramide;

C1. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclohexyl]amino}-2-hydroxypropyl)acetamide;

C2. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopentyl]amino}-2-hydroxypropyl)acetamide;

C3. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

C4. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-5-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

C5. methyl (3S)-3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)butanoate;

C6. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl)acetamide;

C7. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-phenyl-acetamide;

C8. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-7-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

C9. methyl (3R)-3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)butanoate;

C10. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,5-dipropylbenzyl)amino]-2-hydroxypropyl}acetamide;

C11. {[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-

isothiochroman-4-ylamino)-2-hydroxy-propylcarbamoyl]-methyl}-methyl-carbamic acid tert-butyl ester;

C12. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isobutyl-9H-fluoren-9-yl)amino]propyl}acetamide;

C13. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-6-ethyl-2,3-dihydro-1H-inden-1-yl]amino}-2-hydroxypropyl)acetamide;

C14. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-methyl-2-methylamino-propionamide;

C15. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-ethyl-1-(3-ethylphenyl)propyl]amino}-2-hydroxypropyl)acetamide;

C16. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl)amino]-2-hydroxypropyl}acetamide;

C17. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl)amino]-2-hydroxypropyl}acetamide;

C18. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-3-methyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

C19. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-3-methyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

C20. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide;

C21. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoate;

C22. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-(1H-imidazol-4-yl)-acetamide;

C23. methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoate;

C24. N-[(1S,2R)-3-[(2-bromo-9-methyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

C25. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(1-ethylpropyl)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide;

C26. N-[(1S,2R)-3-[(2-cyclopentyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

D1. N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-propionamide;

D2. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-9-methyl-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

D3. N-[(1S,2R)-3-[(2-cyclohexyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

D4. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(4-ethylpyridin-2-yl)cyclopropyl]amino}-2-hydroxypropyl)acetamide;

D5. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1H-pyrrol-3-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

D6. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(5R)-3-ethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl]amino}-2-hydroxypropyl)acetamide;

D7. N-[(1S,2R)-3-{[1-(3-bromophenyl)-1-methylethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

D8. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(dimethylamino)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide;

D9. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-7-propyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)acetamide;

D10. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({(1S)-7-[(dimethylamino)methyl]-1,2,3,4-tetrahydronaphthalen-1-yl}amino)-2-hydroxypropyl]acetamide;

D11. N-[(1S,2R)-3-{[(1S)-7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

D12. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-

propylphenyl)cyclopropyl]amino}propyl)acetamide;

D13. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cycloheptyl]amino}-2-hydroxypropyl)acetamide;

D14. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide;

D15. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino]-2-hydroxypropyl}acetamide;

D16. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-6-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

D17. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(methoxymethyl)-9H-fluoren-9-yl]amino}propyl)acetamide;

D18. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-2-(5-methyl-1,3-oxazol-2-yl)ethyl]amino}-2-hydroxypropyl)acetamide hydrochloride;

D19. N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-2H-chromen-4-ylamino)-2-hydroxypropyl]acetamide;

D20. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-ethyl-5-(trifluoromethyl)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide;

D21. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(3-methylbutyl)-9H-fluoren-9-yl]amino}propyl)acetamide;

D22. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isopropyl-9H-fluoren-9-yl)amino]propyl}acetamide;

D23. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-neopentyl-9H-fluoren-9-yl)amino]propyl}acetamide;

D24. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isopropenyl-9H-fluoren-9-yl)amino]propyl}acetamide;

D25. N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)acetamide hydrochloride;

D26. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-3,4-dihydro-2H-chromen-4-

yl]amino}propyl)acetamide;

E1. N-[(1S,2R)-3-{[(4S)-6-cyano-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

E2. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

E3. N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide;

E4. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(isopropylamino)-9H-fluoren-9-yl]amino}propyl)acetamide;

E5. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylphenyl)cyclopropyl]amino}propyl)acetamide; and

E6. N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}propyl)acetamide.

Generally, the protection of amines is conducted, where appropriate, by methods known to those skilled in the art. Amino protecting groups are known to those skilled in the art. See for example, "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Chapter 7; "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. When the amino protecting group is no longer needed, it is removed by methods known to those skilled in the art. By definition the amino protecting group must be readily removable. A variety of suitable methodologies are known to those skilled in the art; see also T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 3rd edition, 1999. Suitable amino protecting groups include t-butoxycarbonyl, benzyl-oxycarbonyl, formyl, trityl, phthalimido, trichloro-acetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-

phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxy-carbonyl, cyclopentanyloxycarbonyl, 1-methylcyclo-pentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methyl-cyclohexanyloxycabonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)-ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxy-carbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, 9-fluoroenylmethyl carbonate, -CH-CH=CH_2 and phenyl-C(=N-)-H.

It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and/or benzyloxycarbonyl (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One skilled in the art will recognize suitable methods of introducing a t-butoxycarbonyl or benzyloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 3rd edition, 1999 for guidance.

The compounds of the invention may contain geometric or optical isomers as tautomers. Thus, the invention includes all tautomers and pure geometric isomers, such as the *E* and *Z* geometric isomers, as mixtures thereof. Further, the invention includes pure enantiomers, diastereomers and/or

mixtures thereof, including racemic mixtures. The individual geometric isomers, enantiomers or diastereomers may be prepared or isolated by methods known to those in the art, including but not limited to chiral chromatography; preparing diastereomers, separating the diastereomers and then converting the diastereomers into enantiomers.

Compounds of the invention with designated stereochemistry can be included in mixtures, including racemic mixtures, with other enantiomers, diastereomers, geometric isomers or tautomers. In a preferred aspect, compounds of the invention are typically present in these mixtures in diastereomeric and/or enantiomeric excess of at least 50 percent. Preferably, compounds of the invention are present in these mixtures in diastereomeric and/or enantiomeric excess of at least 80 percent. More preferably, compounds of the invention with the desired stereochemistry are present in diastereomeric and/or enantiomeric excess of at least 90 percent. Even more preferably, compounds of the invention with the desired stereochemistry are present in diastereomeric and/or enantiomeric excess of at least 99 percent. Preferably the compounds of the invention have the "S" configuration at position 1. Also preferred are compounds that have the "R" configuration at position 2. Most preferred are compounds that have the "1S,2R" configuration.

All compound names were generated using ACD Namepro version 5.09, Chemdraw v. 6.02, or were derived therefrom.

Several of the compounds of formula (I) are amines, and as such form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding amines since they produce compounds which are more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic

acids. The preferred pharmaceutically acceptable salts include salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J. Pharm. Sci.*, 66(1), 1, (1977).

The invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

Methods of the Invention

The compounds of the invention, and pharmaceutically acceptable salts thereof, are useful for treating humans or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such a condition. For example, the compounds are useful for treating Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from

MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobal hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type Alzheimer's disease. The compounds and compositions of the invention are particularly useful for treating or preventing Alzheimer's disease. When treating or preventing these diseases, the compounds of the invention can either be used individually or in combination, as is best for the patient.

As used herein, the term "treating" means that the compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

The term "preventing" means that the compounds of the invention are useful when administered to a patient who has not been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the individual from developing the disease at all. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

In treating a patient displaying any of the diagnosed above conditions a physician may administer a compound of the invention immediately and continue administration indefinitely, as needed. In treating patients who are not diagnosed as having Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should preferably start treatment when the patient first experiences early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some patients who may be determined to be at risk for developing Alzheimer's through the detection of a genetic marker such as APOE4 or other biological indicators that are predictive for Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, administration of the compounds of the invention may be started before symptoms appear, and treatment may be continued indefinitely to prevent or delay the onset of the disease.

Dosage Forms and Amounts

The compounds of the invention can be administered orally, parenterally, (IV, IM, depo-IM, SQ, and depo SQ), sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable

pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

About .1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 2 to about 100 mg, more preferably about 10 to about 30 mg of the active ingredient. The term "unit dosage from" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion, or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, or have another action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

Where the compcunds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least cne symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration. The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampoules, vials, and the like for parenteral administration; and patches, medipads, creams, and the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the

professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and

other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. Parenteral preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for preparation of such formulations are known to those in the art.

The compounds of the invention can be administered orally, parenterally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the invention can be administered in usual dosage forms for oral administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions, and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each

coated to protect from the acidic stomach, are also well known to those skilled in the art.

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A beta production, to inhibit A beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes.

Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in U.S. Patent No. 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depot formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, the appropriate

dosage forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the invention for intranasal administration is the amount described above for IM administration.

The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art. The dosage of the compounds of the invention for intrathecal administration is the amount described above for IM administration.

The compounds of the invention can be administered topically. When given by this route, the appropriate dosage form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those skilled in the art. When administered by suppository, the therapeutically effective amount is from about 0.5 mg to about 500 mg.

The compounds of the invention can be administered by implants as is known to those skilled in the art. When administering a compound of the invention by implant, the therapeutically effective amount is the amount described above for depot administration.

Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule

as described above, for preventing disease or treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and ginkolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454), and other neurotropic agents of the future.

In addition, the compounds of formula (I) can also be used with inhibitors of P-glycoprotein (P-gp). P-gp inhibitors and the use of such compounds are known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), International Publications

WO99/64001 and WO01/10387. The important thing is that the blood level of the P-gp inhibitor be such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of formula (A). To that end the P-gp inhibitor and the compounds of formula (A) can be administered at the same time, by the same or different route of administration, or at different times. The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is to be understood that additional agents will be found that have the same function and therefore achieve the same outcome; such compounds are also considered to be useful.

The P-gp inhibitors can be administered orally, parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

The therapeutically effective amount of the P-gp inhibitors is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the P-gp inhibitors need to be administered only

once or twice daily. The oral dosage forms are administered to the patient one thru four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release form which permits once or twice daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ.

The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art.

The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a

patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

The P-gp inhibitors can be administered rectally by suppository or by implants, both of which are known to those skilled in the art.

There is nothing novel about the route of administration nor the dosage forms for administering the P-gp inhibitors. Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compounds of the invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the individual may be taking as is well known to administering physicians who are skilled in this art.

Inhibition of APP Cleavage

The compounds of the invention inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site"). While not wishing to be bound by a particular theory, inhibition of beta-secretase activity is thought to inhibit production of beta amyloid peptide (A beta). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a beta-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in

cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate efficacy of the compound inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as well as in the Examples below.

The enzymatic activity of beta-secretase and the production of A beta can be analyzed *in vitro* or *in vivo*, using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, animal models expressing native APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, fluorometric or chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

Beta-Secretase

Various forms of beta-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and WO00/17369, as well as in literature publications (Hussain et

al., 1999, *Mol. Cell. Neurosci.* 14:419-427; Vassar et al., 1999, *Science* 286:735-741; Yan et al., 1999, *Nature* 402:533-537; Sinha et al., 1999, *Nature* 40:537-540; and Lin et al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

Preferred compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than 50 micromolar, preferably at a concentration of 10 micromolar or less, more preferably 1 micromolar or less, and most preferably 10 nanomolar or less.

APP Substrate

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the beta-secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a

peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other detection moiety, a binding substrate, and the like.

Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et al., 1999, *Neuro. Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A beta peptide; antibodies 162 and 164 (New York State Institute for Basic Research, Staten Island, NY) that are specific for human A beta 1-40 and 1-42, respectively; and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

Assay Systems

Assays for determining APP cleavage at the beta-secretase cleavage site are well known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

Cell Free Assays

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S.

Patents No. 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beta-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the beta-secretase cleavage site of APP, under incubation conditions suitable for the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Useful modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at approximately 37 degrees C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and

the like. . Such optimization is routine and will not require undue experimentation.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of the substrate at the beta-secretase cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

Cellular Assay

Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A beta. Contact of an APP substrate with a beta-secretase enzyme within the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate beta-secretase inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least about 30%, most preferably at least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to express a recombinant beta-secretase or synthetic variant enzyme as discussed above. The APP substrate may be added to the culture medium and is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or synthetic APP peptide or fusion protein containing the beta-

secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic cleavage activity can be analyzed.

Human cell lines that normally process A beta from APP provide a useful means to assay inhibitory activities of the compounds of the invention. Production and release of A beta and/or other cleavage products into the culture medium can be measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as compared with a control. Activity of beta-secretase can be measured by analysis of one or more cleavage products of the APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced APP cleavage products such as A beta.

Although both neural and non-neural cells process and release A beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced processing of APP to A beta, and/or enhanced production of A beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced beta-secretase activity and producing amounts of A beta that can be readily measured.

In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the cells to the compound inhibitor, the amount of A beta released into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The

cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

Preferred cells for analysis of beta-secretase activity include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW.

In vivo Assays: Animal Models

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A beta, as described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for example, in U.S. Patent Nos.: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5,811,633, and in Ganes et al., 1995, *Nature* 373:523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at the beta-secretase cleavage site and of A beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues. Analysis of brain tissues for A beta deposits or plaques is preferred.

On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the

invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of A beta from the substrate, the compounds of the invention are effective to reduce beta-secretase-mediated cleavage of APP at the beta-secretase cleavage site and/or effective to reduce released amounts of A beta. Where such contacting is the administration of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are effective to reduce A beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A beta, to slow the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are hereby incorporated by reference for all purposes.

Definitions

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims:

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

Where multiple substituents are indicated as being attached to a structure, it is to be understood that the substituents can be the same or different. Thus for example "R_m optionally substituted with 1, 2 or 3 R_q groups" indicates that R_m is substituted with 1, 2, or 3 R_q groups where the R_q groups can be the same or different.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A beta. Human beta-secretase is described, for example, in WO00/17369.

Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

By "alkyl" and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or

longer than 6 carbons, it will be so indicated in the second "C" as, for example, "C_1-C_{10}" indicates a maximum of 10 carbons.

By "alkoxy" and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

"Alkenyl" and "C_2-C_6 alkenyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

"Alkynyl" and "C_2-C_6 alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, a polycyclic fused system, or a bi or polycyclic bridged system, such as adamantyl or bicyclo[2.2.1] heptyl. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Preferred cycloalkyl groups are cyclopentyl, cyclohexyl, and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl) or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl groups of the present invention are phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, fluorenyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

By "heteroaryl" is mean at least one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heteroaryl groups of the present invention include pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl,

imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide,, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide, tetrahydrocarbazole, tetrahydrobetacarboline. The heteroaryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heteroaryl groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

By "heterocycle", "heterocycloalkyl" or "heterocyclyl" is meant one or more carbocyclic ring systems of 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl,

homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. The heterocycle groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl or =O.

All patents and publications referred to herein are hereby incorporated by reference for all purposes.

Structures were named using Name Pro IUPAC Naming Software, version 5.09, available from Advanced Chemical Development, Inc., 90 Adelaide Street West, Toronto, Ontario, M5H 3V9, Canada.

The present invention may be better understood with reference to the following examples. These examples are intended to be representative of specific embodiments of the invention, and are not intended as limiting the scope of the invention.

The following abbreviations may be used in the Examples:

EDC stands for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or the hydrochloride salt;

DIEA stands for diisopropylethylamine;

PyBOP stands for benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate;

HATU stands for O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate;

THF stands for tetrahydrofuran;

EtBz stands for ethylbenzene;

DCM stands for dichloromethane.

BIOLOGY EXAMPLES

Example A

Enzyme Inhibition Assay

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as described in Sinha et al, 1999, *Nature* 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

Specific Assay Procedure:

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30 microliters of ice-cold enzyme-substrate mixture (2.5 microliters MBP-C12SSW substrate, 0.03 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaOAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme reaction. After 90 minutes at 37 degrees C, 200 microliters/well cold specimen diluent is added to stop the reaction and 20 microliters/well was transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/well specimen diluent. This reaction is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hour incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and fluorescent substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty percent reduction in detected signal (IC_{50}) compared to the enzyme reaction signal in the control wells with no added

compound. In this assay, preferred compounds of the invention exhibit an IC_{50} of less than 50 micromolar.

Example B

Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by the covalent attachment of Oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Useful substrates include the following:

Biotin-SEVNL-DAEFRC[oregon green]KK [SEQ ID NO: 1]

Biotin-SEVKM-DAEFRC[oregon green]KK [SEQ ID NO: 2]

Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK [SEQ ID NO: 3]

Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEFRC [oregon green]KK [SEQ ID NO: 4]

Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC [oregon green]KK [SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001-100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per well. The final assay conditions are: 0.001-100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37

degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example, using a LJL Acquest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate. In this assay, preferred compounds of the invention exhibit an IC_{50} of less than 50 micromolar. More preferred compounds of the invention exhibit an IC_{50} of less than 10 micromolar. Even more preferred compounds of the invention exhibit an IC_{50} of less than 5 micromolar.

Example C

Beta-Secretase Inhibition: P26-P4'SW Assay

Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity, using the methods described, for example, in published PCT application WO00/47618. The P26-P4'SW substrate is a peptide of the sequence:

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF [SEQ ID NO: 6]

The P26-P1 standard has the sequence:

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7].

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is preferred. Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The

concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range of the ELISA assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

Cleavage products can be assayed by ELISA. Diluted samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), the samples are incubated with streptavidin-AP according to the manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of beta-secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

Example D

Assays using Synthetic Oligopeptide-Substrates

Synthetic oligopeptides are prepared that incorporate the known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties. Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be

detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art.

By way of example, one such peptide has the sequence SEVNL-DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the compound inhibitor to control results provides a measure of the compound's inhibitory activity.

Example E

Inhibition of Beta-Secretase Activity - Cellular Assay

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta (Citron et al., 1992, *Nature* 360:672-674), as described in U.S. Patent No. 5,604,102.

The cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A beta can be analyzed by immunoassay, using specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound

inhibitors to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

Example F

Inhibition of Beta-Secretase in Animal Models of AD

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

PDAPP mice, prepared as described in Games et al., 1995, *Nature* 373:523-527 are useful to analyze *in vivo* suppression of A beta release in the presence of putative inhibitory compounds. As described in U.S. Patent No. 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or multiple doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including A beta, for example, by immunoassay using specific antibodies for A beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed

for the presence of A beta and/or beta-amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors of the invention are expected to demonstrate reduced A beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

Example G

Inhibition of A Beta Production in Human Patients

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A beta in the brain. AD patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; A beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

Example H

Prevention of A Beta Production in Patients at Risk for AD

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration.

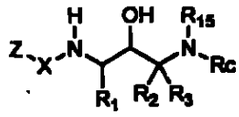
Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of the formula I:



(I)

or pharmaceutically acceptable salts thereof, wherein

Z is hydrogen, or

Z is $(C_3-C_7$ cycloalkyl$)_{0-1}(C_1-C_6$ alkyl$)$-, $(C_3-C_7$ cycloalkyl$)_{0-1}(C_2-C_6$ alkenyl$)$-, $(C_3-C_7$ cycloalkyl$)_{0-1}(C_2-C_6$ alkynyl$)$- or $(C_3-C_7$ cycloalkyl$)$-, wherein each of said groups is optionally substituted with 1, 2, or 3 R_8 groups, wherein 1 or 2 methylene groups within said $(C_3-C_7$ cycloalkyl$)_{0-1}(C_1-C_6$ alkyl$)$-, $(C_3-C_7$ cycloalkyl$)_{0-1}(C_2-C_6$ alkenyl$)$-, $(C_3-C_7$ cycloalkyl$)_{0-1}(C_2-C_6$ alkynyl$)$- or $(C_3-C_7$ cycloalkyl$)$- groups are optionally replaced with -(C=O)-;

R_8 at each occurrence is independently halogen (in one aspect, F or Cl), -OH, -SH, -CN, $-CF_3$, $-OCF_3$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy or $-NR_{100}R_{101}$;

R_{100} and R_{101} at each occurrence are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1-C_6$ alkyl$)$ or $SO_2C_1-C_6$ alkyl;

X is -(C=O)- or $-(SO_2)$-;

R_1 is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -CN, $-CF_3$, $-OCF_3$, $-C_{3-7}$ cycloalkyl, $-C_1-C_4$ alkoxy, amino, mono- or dialkylamino, aryl, heteroaryl, and heterocycloalkyl, wherein each aryl group is optionally substituted with 1, 2 or 3 R_{50} groups; each heteroaryl is optionally substituted with 1 or 2 R_{50} groups; and each heterocycloalkyl group is optionally substituted with 1 or 2 groups that are independently R_{50} or =O;

R_{50} is selected from halogen, OH, SH, CN, -CO-(C_1-C_4 alkyl), $-NR_7R_8$, $-S(O)_{0-2}$-(C_1-C_4 alkyl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl; wherein

the alkyl, alkenyl, alkynyl, alkoxy and cycloalkyl groups are optionally substituted with 1 or 2 substituents independently selected from C_1-C_4 alkyl, halogen, OH, $-NR_5R_6$, CN, C_1-C_4 haloalkoxy, NR_7R_8, and C_1-C_4 alkoxy; wherein

R_5 and R_6 are independently H or C_1-C_6 alkyl; or

R_5 and R_6 and the nitrogen to which they are attached form a 5 or 6 membered heterocycloalkyl ring;

R_7 and R_8 are independently selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, $-NH_2$, and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl;

R_2 and R_3 are independently selected from H; F; -C_1-C_6 alkyl optionally substituted with -F, -OH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, or $-NR_5R_6$; $-(CH_2)_{0-2}-R_{17}$; $-(CH_2)_{0-2}-R_{18}$; -C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl and alkynyl groups are optionally substituted with 1 or 2 groups that are independently -F, -OH, -C≡N, $-CF_3$ or C_1-C_3 alkoxy; $-(CH_2)_{0-2}$-C_3-C_7 cycloalkyl, which is optionally substituted with 1 or 2 groups that are independently -F, -OH, -C≡N, $-CF_3$, C_1-C_3 alkoxy and $-NR_5R_6$;

R_{17} at each occurrence is an aryl group (preferably selected from phenyl, 1-naphthyl, 2-naphthyl , indanyl, indenyl, dihydronaphthyl and tetralinyl,) wherein said aryl group is optionally substituted with one or two groups that are independently -C_1-C_3 alkyl; -C_1-C_4 alkoxy; CF_3; -C_2-C_6 alkenyl or -C_2-C_6 alkynyl each of which is optionally substituted with

one substituent selected from F, OH, C_1-C_3 alkoxy; halogen; OH; -C≡N; -C_3-C_7 cycloalkyl; -CO-(C_1-C_4 alkyl); or -SO_2-(C_1-C_4 alkyl);

R_{18} is a heteroaryl group (preferably selected from pyridinyl, pyrimidinyl, quinolinyl, indolyl, pryidazinyl, pyrazinyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrrolyl, oxadiazolyl or thiadiazolyl,) wherein said heteroaryl groups are optionally substituted with one or two groups that are independently -C_1-C_6 alkyl optionally substituted with one substituent selected from OH, C≡N, CF_3, C_1-C_3 alkoxy, and -NR_5R_6;

R_{15} is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, halo C_1-C_6 alkyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, and NH_2, and -R_{26}-R_{27}; wherein

R_{26} is selected from a bond, -C(O)-, -SO_2-, -CO_2-, -C(O)NR_5-, and -NR_5C(O)-,

R_{27} is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl C_1-C_6 alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, haloalkyl, hydroxyalkyl, -NR_5R_6, or -C(O)NR_5R_6; or

R_2, R_3 and the carbon to which they are attached form a C_3-C_7 carbocycle, wherein 1, 2, or 3 carbon atoms are optionally replaced by groups that are independently selected from -O-, -S-, -SO_2-, -C(O)-, or -NR_7-;

R_C is selected from -$(CH_2)_{0-3}$-(C_3-C_8) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from -R_{205}; and -CO_2-(C_1-C_4 alkyl); -$(CR_{245}R_{250})_{0-4}$-aryl; -$(CR_{245}R_{250})_{0-4}$-heteroaryl; -$(CR_{245}R_{250})_{0-4}$-heterocycloalkyl; -$(CR_{245}R_{250})_{0-4}$-aryl-

heteroaryl; $-(CR_{245}R_{250})_{0-4}$-aryl-heterocycloalkyl; $-(CR_{245}R_{250})_{0-4}$-aryl-aryl; $-(CR_{245}R_{250})_{0-4}$-heteroaryl-aryl; $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heterocycloalkyl; $-(CR_{245}R_{250})_{0-4}$-heteroaryl-heteroaryl; $-CHR_{245}-CHR_{250}$-aryl; $-(CR_{245}R_{250})_{0-4}$-heterocycloalkyl-heteroaryl; $-(CR_{245}R_{250})_{0-4}$-heterocycloalkyl-heterocycloalkyl; $-(CR_{245}R_{250})_{0-4}$-heterocycloalkyl-aryl; a monocyclic or bicyclic ring of 5, 6, 7 8, 9, or 10 carbons fused to 1 or 2 aryl (preferably phenyl), heteroaryl (preferably pyridyl, imidazolyl, thienyl, thiazolyl, or pyrimidyl), or heterocycloalkyl (preferably piperidinyl or piperazinyl) groups;

wherein 1, 2 or 3 carbons of the monocyclic or bicyclic ring are optionally replaced with -NH-, $-N(CO)_{0-1}R_{215}$-, $-N(CO)_{0-1}R_{220}$-, -O-, or $-S(=O)_{0-2}$-, and wherein the monocyclic or bicyclic ring is optionally substituted with 1, 2 or 3 groups that are independently $-R_{205}$, $-R_{245}$, $-R_{250}$ or =O;

and $-C_2-C_6$ alkenyl optionally substituted with 1, 2, or 3 R_{205} groups;

wherein each aryl or heteroaryl group attached directly or indirectly to the $-(CR_{245}R_{250})_{0-4}$ group is optionally substituted with 1, 2, 3 or 4 R_{200} groups;

wherein each heterocycloalkyl attached directly or indirectly to the $-(CR_{245}R_{250})_{0-4}$ group is optionally substituted with 1, 2, 3, or 4 R_{210};

R_{200} at each occurrence is independently selected from $-C_1-C_6$ alkyl optionally substituted with 1, 2, or 3 R_{205} groups; -OH; $-NO_2$; -halogen; -C≡N; $-(CH_2)_{0-4}$-CO-$NR_{220}R_{225}$; $-(CH_2)_{0-4}$-CO-(C_1-C_8 alkyl); $-(CH_2)_{0-4}$-CO-(C_2-C_8 alkenyl); $-(CH_2)_{0-4}$-CO-(C_2-C_8 alkynyl); $-(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl); $-(CH_2)_{0-4}-(CO)_{0-1}$-aryl (preferably phenyl); $-(CH_2)_{0-4}-(CO)_{0-1}$-heteroaryl (preferably pyridyl, pyrimidyl, furanyl, imidazolyl, thienyl, oxazolyl, thiazolyl, or pyrazinyl); $-(CH_2)_{0-4}-(CO)_{0-1}$-

heterocycloalkyl (preferably imidazolidinyl, piperazinyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl); $-(CH_2)_{0-4}-CO_2R_{215}$; $-(CH_2)_{0-4}-SO_2-NR_{220}R_{225}$; $-(CH_2)_{0-4}-S(O)_{0-2}-(C_1-C_8$ alkyl); $-(CH_2)_{0-4}-S(O)_{0-2}-(C_3-C_7$ cycloalkyl); $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO_2R_{215}$; $-(CH_2)_{0-4}-N(H$ or $R_{215})-SO_2-R_{220}$; $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO-N(R_{215})_2$; $-(CH_2)_{0-4}-N(-H$ or $R_{215})-CO-R_{220}$; $-(CH_2)_{0-4}-NR_{220}R_{225}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl); $-(CH_2)_{0-4}-O-(R_{215})$; $-(CH_2)_{0-4}-S-(R_{215})$; $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with 1, 2, 3, or 5 -F); $-C_2-C_6$ alkenyl optionally substituted with 1 or 2 R_{205} groups; $-C_2-C_6$ alkynyl optionally substituted with 1 or 2 R_{205} groups; adamantly, and $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl;

each aryl and heteroaryl group included within R_{200} is optionally substituted with 1, 2, or 3 groups that are independently $-R_{205}$, $-R_{210}$ or $-C_1-C_6$ alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210};

each heterocycloalkyl group included within R_{200} is optionally substituted with 1, 2, or 3 groups that are independently R_{210};

R_{205} at each occurrence is independently selected from $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_1-C_6$ haloalkoxy, $-(CH_2)_{0-3}(C_3-C_7$ cycloalkyl), -halogen, $-(CH_2)_{0-6}-OH$, -O-phenyl, OH, SH, $-(CH_2)_{0-6}-C\equiv N$, $-(CH_2)_{0-6}-C(=O)NR_{235}R_{240}$, $-CF_3$, $-C_1-C_6$ alkoxy, C_1-C_6 alkoxycarbonyl, and $-NR_{235}R_{240}$;

R_{210} at each occurrence is independently selected from $-C_1-C_6$ alkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-C_2-C_6$ alkenyl optionally substituted with 1, 2, or 3 R_{205} groups; C_1-C_6 alkanoyl; $-SO_2-(C_1-C_6$ alkyl); $-C_2-C_6$ alkynyl optionally substituted with 1, 2, or 3 R_{205}

groups; -halogen; -C_1-C_6 alkoxy; -C_1-C_6 haloalkoxy; -$NR_{220}R_{225}$; -OH; -C≡N; -C_3-C_7 cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; -CO-(C_1-C_4 alkyl); -SO_2-$NR_{235}R_{240}$; -CO-$NR_{235}R_{240}$; -SO_2-(C_1-C_4 alkyl); and =O;

R_{215} at each occurrence is independently selected from -C_1-C_6 alkyl, -$(CH_2)_{0-2}$-(aryl), -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_7 cycloalkyl, -$(CH_2)_{0-2}$-(heteroaryl), and -$(CH_2)_{0-2}$-(heterocycloalkyl); wherein the aryl group included within R_{215} is optionally substituted with 1, 2, or 3 groups that are independently -R_{205} or -R_{210}; wherein the heterocycloalkyl and heteroaryl groups included within R_{215} are optionally substituted with 1, 2, or 3 R_{210};

R_{220} and R_{225} at each occurrence are independently H, -C_1-C_6 alkyl, -CHO, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, -amino C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, C_1-C_6 alkanoyl optionally substituted with up to three halogens, -$C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -halo C_1-C_6 alkyl, -$(CH_2)_{0-2}$-(C_3-C_7 cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -aryl (preferably phenyl), -heteroaryl, or -heterocycloalkyl; wherein the aryl, heteroaryl and heterocycloalkyl groups included within R_{220} and R_{225} is optionally substituted with 1, 2, or 3 R_{270} groups,

R_{270} at each occurrence is independently -R_{205}, -C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; -C_2-C_6 alkenyl optionally substituted with 1, 2, or 3 R_{205} groups; -C_2-C_6 alkynyl optionally substituted with 1, 2, or 3 R_{205} groups; -phenyl; -halogen; -C_1-C_6 alkoxy; -C_1-C_6

haloalkoxy; -$NR_{235}R_{240}$; -OH; -C≡N; -C_3-C_7 cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; -CO-(C_1-C_4 alkyl); -SO_2-$NR_{235}R_{240}$; -CO-$NR_{235}R_{240}$; -SO_2-(C_1-C_4 alkyl); and =O;

R_{235} and R_{240} at each occurrence are independently -H, -C_1-C_6 alkyl, C_2-C_6 alkanoyl, -SO_2-(C_1-C_6 alkyl), or -phenyl;

R_{245} and R_{250} at each occurrence are independently selected from H, -$(CH_2)_{0-4}CO_2C_1$-C_4 alkyl, -$(CH_2)_{0-4}C(=O)C_1$-C_4 alkyl, -C_1-C_6 alkyl, -C_1-C_4 hydroxyalkyl, -C_1-C_4 alkoxy, -C_1-C_4 haloalkoxy, -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -$(CH_2)_{0-4}$ aryl, -$(CH_2)_{0-4}$ heteroaryl, and -$(CH_2)_{0-4}$ heterocycloalkyl, or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a monocycle or bicycle of 3, 4, 5, 6, 7 or 8 carbon atoms, where 1, 2, or 3 carbon atoms are optionally replaced by 1, 2, or 3 groups that are independently -O-, -S-, -SO_2-, -C(O)-, -NR_{220}-, or -$NR_{220}R_{220}$- wherein both R_{220} groups are alkyl; and wherein the ring is optionally substituted with 1, 2, 3, 4, 5, or 6 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH-C(O)C_1-C_3 alkyl, -NH-SO_2-(C_1-C_6 alkyl), or halogen;

wherein the aryl, heteroaryl or heterocycloalkyl groups included within R_{245} and R_{250} are optionally substituted with 1, 2, or 3 groups that are independenly halogen, C_{1-6} alkyl, CN or OH.

2. A compound according to claim 1, wherein Z is (C_3-C_7 cycloalkyl)$_{0-1}$(C_1-C_6 alkyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkenyl)-, (C_3-C_7 cycloalkyl)$_{0-1}$(C_2-C_6 alkynyl)- or (C_3-C_7 cycloalkyl)-, wherein each of said groups is optionally substituted with 1, 2, or 3 R_z groups;

wherein, R_g at each occurrence is independently halogen, -OH, -CN, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy, $-NR_{100}R_{101}$;

where R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, $CO(C_1$-C_6 alkyl) or SO_2C_1-C_6 alkyl.

3. A compound according to claim 1, wherein X is -(C=O)-.

4. A compound according to claim 3, wherein Z is H.

5. A compound according to claim 1, wherein R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, $-CF_3$, $-OCF_3$, $-C_{3-7}$ cycloalkyl, -C_1-C_4 alkoxy, amino or aryl, wherein the aryl group is optionally substituted with 1 or 2 R_{50} groups;

wherein R_{50} is selected from halogen, OH, $-CO-(C_1$-C_4 alkyl), $-NR_7R_8$, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl;

wherein the alkyl, alkoxy and cycloalkyl groups are optionally substituted with 1 or 2 substituents independently selected from C_1-C_4 alkyl, halogen, OH, $-NR_5R_6$, NR_7R_8, and C_1-C_4 alkoxy;

wherein R_5 and R_6 at are independently H or C_1-C_6 alkyl; or

wherein R_5 and R_6 and the nitrogen to which they are attached form a 5 or 6 membered heterocycloalkyl ring; and

wherein R_7 and R_8 are independently selected from -H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups independently selected from -OH, $-NH_2$, and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl).

6. A compound according to claim 5, wherein R_1 is $-CH_2$-phenyl where the phenyl ring is optionally substituted with 1

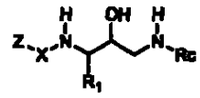
or 2 groups independently selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy and hydroxy.

7. A compound according to claim 6, wherein R_1 is benzyl, 3-fluorobenzyl or 3,5-difluorobenzyl.

8. A compound according to claim 1, wherein R_{15} is H.

9. A compound according to claim 7, wherein R_{15} is H.

10. A compound according to claim 1 of the formula II:



(II)

wherein Z is hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl, where each of said groups is optionally substituted with 1 or 2 R_8 groups, wherein 1 or 2 methylene groups within said -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl or -C_3-C_7 cycloalkyl groups are optionally replaced with -(C=O)-;

wherein R_8 at each occurrence is independently halogen, -OH, -CN, -CF_3, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkoxy or -$NR_{100}R_{101}$;

where R_{100} and R_{101} are independently H, C_1-C_6 alkyl, phenyl, CO(C_1-C_6 alkyl) or SO_2C_1-C_6 alkyl;

wherein X is -C(=O)-;

wherein R_1 is C_1-C_{10} alkyl optionally substituted with 1 or 2 groups independently selected from halogen, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cycloalkyl, -C_1-C_4 alkoxy, amino, mono- dialkylamino, aryl, heteroaryl or heterocycloalkyl, wherein the aryl group is optionally substituted with 1 or 2 R_{50} groups;

where R_{50} is halogen, OH, CN, -CO-(C_1-C_4 alkyl), -NR_7R_8, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl;

where R_7 and R_8 are selected from H; -C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups selected from -OH, -NH_2 and halogen; -C_3-C_6 cycloalkyl; -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl); -C_2-C_4 alkenyl; and -C_2-C_4 alkynyl;

wherein R_C is selected from

-$(CR_{245}R_{250})_{0-4}$-aryl;

-$(CR_{245}R_{250})_{0-4}$-heteroaryl;

-$(CR_{245}R_{250})_{0-4}$-heterocycloalkyl;

where the aryl group attached to the -$(CR_{245}R_{250})_{0-4}$- group is optionally substituted with 1, 2, 3 or 4 R_{200} groups;

where the heteroaryl group attached to the -$(CR_{245}R_{250})_{0-4}$- group is optionally substituted with 1, 2, 3, or 4 R_{200} groups;

where the heterocycloalkyl group attached to the -$(CR_{245}R_{250})_{0-4}$- group is optionally substituted with 1, 2, 3, or 4 R_{210} groups.

11. A compound according to claim 10, wherein

Z is -C_1-C_6 alkyl;

R_1 is C_1-C_{10} alkyl substituted with 1 phenyl group, where the phenyl group attached to the alkyl is optionally substituted with 1 or 2 R_{50} groups, where each R_{50} is independently halogen, OH, CN, or C_1-C_6 alkyl; and

R_C is -$(CR_{245}R_{250})_{0-4}$-aryl or -$(CR_{245}R_{250})_{0-4}$-heteroaryl, where the aryl and heteroaryl groups are optionally substituted with 1 or 2 R_{200} groups.

12. A compound according to claim 1 which is

N-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4R)-6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}propyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

N-[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide hydrochloride;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-bromophenyl)propanoate;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoate;

3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoic acid;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-3-hydroxypropyl]amino}-2-hydroxypropyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino]propyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-methylamino-acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-iodophenyl)propanoate;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(3-hydroxyprop-1-ynyl)phenyl]propanoate;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-hydroxy-1-(3-iodophenyl)propyl]amino}propyl)acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(3-hydroxypropyl)phenyl]propanoate;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl}acetamide;

2-Amino-N-[1-(3,5-difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ^6-isothiochroman-4-ylamino)-2-hydroxy-propyl]-acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[6-ethyl-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

N-[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(5-formylthien-2-yl)phenyl]propanoate;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(2'-acetyl-1,1'-biphenyl-3-yl)propanoate;

N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-methyl-butyramide;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3'-(hydroxymethyl)-1,1'-biphenyl-3-yl]cyclopropyl}amino)propyl]acetamide;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(5-formylthien-2-yl)phenyl]cyclopropyl}amino)-2-hydroxypropyl]acetamide;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(9H-fluoren-9-ylamino)-2-hydroxypropyl]acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-[3-(trifluoromethyl)phenyl]propanoate;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-cyanophenyl)propanoate;

N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-2,2-dimethyl-propionamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-bromophenyl)propanoate;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)acetamide;

N-[(1S,2R)-3-[(2-bromo-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-iodo-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4R)-6-iodo-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-propionamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[4-(3-ethylphenyl)tetrahydro-2H-pyran-4-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)butyl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4R)-6-ethyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)amino]-2-hydroxypropyl}acetamide;

N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-3-hydroxy-butyramide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclohexyl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopentyl]amino}-2-hydroxypropyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-5-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

methyl (3S)-3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)butanoate;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl)acetamide;

N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-phenyl-acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-7-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

methyl (3R)-3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)butanoate;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,5-dipropylbenzyl)amino]-2-hydroxypropyl}acetamide;

{[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propylcarbamoyl]-methyl}-methyl-carbamic acid tert-butyl ester;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isobutyl-9H-fluoren-9-yl)amino]propyl}acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-6-ethyl-2,3-dihydro-1H-inden-1-yl]amino}-2-hydroxypropyl)acetamide;

N-[1-(3,5-Difluoro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-methyl-2-methylamino-propionamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-ethyl-1-(3-ethylphenyl)propyl]amino}-2-hydroxypropyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-3-methyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-3-methyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]-2-hydroxypropyl}acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoate;

N-[1-(3,5-Diflucro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-2-(1H-imidazol-4-yl)-acetamide;

methyl 3-{[(2R,3S)-3-(acetylamino)-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-3-(3-ethylphenyl)propanoate;

N-[(1S,2R)-3-[(2-bromo-9-methyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(1-ethylpropyl)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide;

N-[(1S,2R)-3-[(2-cyclopentyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-[1-(3,5-Diflucro-benzyl)-3-(6-ethyl-2,2-dioxo-2λ⁶-isothiochroman-4-ylamino)-2-hydroxy-propyl]-propionamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-9-methyl-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

N-[(1S,2R)-3-[(2-cyclohexyl-9H-fluoren-9-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(4-ethylpyridin-2-yl)cyclopropyl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-(1H-pyrrol-3-yl)-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(5R)-3-ethyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl]amino}-2-hydroxypropyl)acetamide;

N-[(1S,2R)-3-{[1-(3-bromophenyl)-1-methylethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(dimethylamino)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-7-propyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)acetamide;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({(1S)-7-[(dimethylamino)methyl]-1,2,3,4-tetrahydronaphthalen-1-yl}amino)-2-hydroxypropyl]acetamide;

N-[(1S,2R)-3-{[(1S)-7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-propylphenyl)cyclopropyl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cycloheptyl]amino}-2-hydroxypropyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(6-ethyl-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino]-2-hydroxypropyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-ethyl-6-fluoro-9H-fluoren-9-yl)amino]-2-hydroxypropyl}acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(methoxymethyl)-9H-fluoren-9-yl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-2-(5-methyl-1,3-oxazol-2-yl)ethyl]amino}-2-hydroxypropyl)acetamide hydrochloride;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,4-dihydro-2H-chromen-4-ylamino)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-ethyl-5-(trifluoromethyl)-9H-fluoren-9-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(3-methylbutyl)-9H-fluoren-9-yl]amino}propyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isopropyl-9H-fluoren-9-yl)amino]propyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-neopentyl-9H-fluoren-9-yl)amino]propyl}acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-isopropenyl-9H-fluoren-9-yl)amino]propyl}acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)acetamide hydrochloride;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-isobutyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

N-[(1S,2R)-3-{[(4S)-6-cyano-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4S)-6-neopentyl-3,4-dihydro-2H-chromen-4-yl]amino}propyl)acetamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-neopentyl-3,4-dihydro-2H-chromen-4-yl)amino]propyl}acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[2-(isopropylamino)-9H-fluoren-9-yl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylphenyl)cyclopropyl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4-isobutyl-1,1'-biphenyl-2-yl)methyl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[7-(2,2-dimethylpropyl)-5-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4R)-6-(2,2-dimethylpropyl)-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-(2,2-dimethylpropyl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

N-[(1S,2R)-3-{[1-(3-tert-butylphenyl)cyclohexyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-[(1S,2R)-3-{[4-(3-tert-butylphenyl)tetrahydro-2H-pyran-4-yl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[6-(2,2-dimethylpropyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)-4-oxocyclohexyl]amino}propyl)acetamide;

N-[(1S,2R)-3-{[(4S)-6-(2,2-dimethylpropyl)-3,4-dihydro-2H-chromen-4-yl]amino}-1-(3-fluorobenzyl)-2-hydroxypropyl]acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[5-(2,2-dimethylpropyl)-2-(1H-imidazol-1-yl)benzyl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[7-(2,2-dimethylpropyl)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[6-(2,2-dimethylpropyl)-4-methyl-3,4-dihydro-2H-chromen-4-yl]amino}-2-hydroxypropyl)acetamide;

N-((1S,2R)-1-(3-fluoro-4-hydroxybenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)-2-fluoroacetamide;

N-((1S,2R)-1-[3-(allyloxy)-5-fluorobenzyl]-2-hydroxy-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(2,2-dimethylpropyl)phenyl]-1-methylethyl}amino)-2-hydroxypropyl]-2-fluoroacetamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-(2,2-dimethylpropyl)-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2-fluoroacetamide;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(3-thienyl)phenyl]cyclohexyl}amino)propyl]acetamide;

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[4-(2,2-dimethylpropyl)pyridin-2-yl]cyclopropyl}amino)-2-hydroxypropyl]acetamide;

N-((1R,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-7-propyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)acetamide;

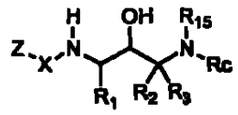
N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylphenyl)cyclohexyl]amino}propyl)acetamide;

N-((1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-{[1-(3-isopropylphenyl)cyclohexyl]amino}propyl)acetamide;

N-((1R,2S)-1-(3,5-difluorobenzyl)-3-{[(1S)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2-ethoxyacetamide; or

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(1R)-7-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl]amino}-2-hydroxypropyl)-2,2-difluoroacetamide; or a pharmaceutically acceptable salt thereof.

13. A method for preparing a compound of the formula



or a pharmaceutically acceptable salt thereof, wherein Z, X, R_1, R_2, R_3, R_{15} and R_c are as defined in claim 1.

14. The method of treating a subject who has, or in preventing a subject from developing Alzheimer's disease (AD); preventing or delaying the onset of Alzheimer's disease; treating subjects with mild cognitive impairment (MCI); preventing or delaying the onset of Alzheimer's disease in subjects who would progress from MCI to AD; treating Down's syndrome; treating subjects who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type; treating cerebral amyloid angiopathy and preventing its potential

consequences; treating other degenerative dementias; treating dementia associated with Parkinson's disease, progressive supranuclear palsy, or cortical basal degeneration; treating diffuse Lewy body type AD; and treating frontotemporal dementias with parkinsonism (FTDP), comprising administering a pharmaceutically acceptable amount of a compound according to claim 1 to a patient in need of such treatment.

255

DOCKETED

MAY 26 2004

PCT DUE DATE: 7-21-04 BY: DC 5-21-04

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
STEVEN J. SARUSSI
MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, IL 60606

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 02-793-D	Date of Mailing (day/month/year) FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US03/28503	International filing date (day/month/year) 10 September 2003 (10.09.2003)
Applicant ELAN PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

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

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

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

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

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

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

4. Reminders

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

   Within 19 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 19 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 ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer: J. Roberts for SHAILENDRA KUMAR Telephone No. (571)272-1600

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 02-793-D	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/28503	International filing date (*day/month/year*) 10 September 2003 (10.09.2003)	(Earliest) Priority Date (*day/month/year*) 10 September 2002 (10.09.2002)
Applicant ELAN PHARMACEUTICALS, INC.		

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 2 sheets.

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

1. Basis of the Report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

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

6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.
   ☒ None of the figures

257

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/28503

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 215/38, 311/04, 335/04; C07C 233/05; A61K 31/35, 31/38, 31/16
US CL : 546/159; 549/404, 23; 564/218, 220; 514/313, 456, 432, 629, 630
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)
U.S. : 546/159; 549/404, 23; 564/218, 220; 514/313, 456, 432, 629, 630

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,150,416 A (KICK et al) 21 November 2000 (21.11.2000), claim 1.	1-14
A	XU, PING et al. The Study on HCMV Protease Inhibitors (I) Design and Liquid-phase Combinatorial Building Block Synthesis of Peptidomimetic Inhibitors. Chinese Journal of Medicinal Chemistry. February 2001, Vol. 11, N, 1, pages 32-36, especially page 33.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family 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 application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 May 2004 (07.05.2004)	21 MAY 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer SHAILENDRA - KUMAR Telephone No. (571)272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the International application may be amended ?

Under Article 19, only the claims may be amended.

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

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

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

Where not to file the amendments ?

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

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

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

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

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

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

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

NOTES TO FORM PCT/ISA/220 (continued)

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

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

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

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

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

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

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

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

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

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

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

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

The applicant's attention is drawn to the fact that, 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 the *PCT Applicant's Guide*, Volume II.

Agent's reference: 02-793-D

IN THE INTERNATIONAL BUREAU OF WIPO

International application No. PCT/US2003/028503	International filing date *(day/month/year)* 10 September 2003 (10.09.03)	(Earliest) Priority date *(day/month/year)* 10 September 2002 (10.09.02)
Title of invention ACETYL 2-HYDROXY-1,3-DIAMINOALKANES		
Applicant(s) ELAN PHARMACEUTICALS, INC. et al.		

REQUEST FOR RECORDING CHANGES UNDER RULE 92bis

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

Dear Sir:

The applicants hereby request the following changes be recorded in the above-identified application filed on 10 September 2003:

1. The co-applicant in the above-mentioned world published application (WO 2004/024081) is incorrect. Please delete the below listed applicant from the cover page of the publication.

Pfizer, Inc.
235 East 42nd Street
20th Floor
New York, New York 10017
US

2. Please add the applicant listed below to this publication. A corrected page one of the Request (PCT/RO/101) is attached to indicate this change. This change does not alter the subject matter of the originally filed international application.

Pharmacia & Upjohn Company LLC
301 Henrietta Street
Kalamazoo, Michigan 49007
US

3. A copy of the papers filed herewith will be sent to the United States Receiving Office via facsimile on the date indicated below.

PCT/US2003/028503 Agent's Reference: 02-793-D

Respectfully submitted,

By _____
Steven J. Sarussi
Attorney for the Applicants

Date: 01 March 2005

261

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SARUSSI, Steven, J.
McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606
United States of America

Date of mailing (day/month/year) 18 March 2005 (18.03.2005)	
Applicant's or agent's file reference 02-793-D	IMPORTANT NOTIFICATION
International application No. PCT/US2003/028603	International filing date (day/month/year) 10 September 2003 (10.09.2003)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
PFIZER, INC. 235 E. 42nd Street 20th Floor New York, NY 10017 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The applicant identified in Box 1 should be deleted from the record.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[X] other: PFIZER, INC.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer El Mostafa MOUSSAID (Fax 338-87-20)
Facsimile No. (41-22) 338.87.20	Telephone No. (41-22) 338 8242

Form PCT/IB/306 (March 1994) 008639492

262

File copy

PATENT COOPERATION TREATY

22

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

SARUSSI, Steven, J.
McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606
United States of America

Date of mailing (day/month/year)	
08 March 2005 (08.03.2005)	
Applicant's or agent's file reference: 02-783-D	IMPORTANT NOTIFICATION
International application No.: PCT/US2003/028503	International filing date (day/month/year): 10 September 2003 (10.09.2003)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
PHARMACIA & UPJOHN COMPANY LLC 301 Henrietta Street Kalamazoo, Michigan 49007 United States of America	US	US
	Telephone No.: —	
	Facsimile No.: ---	
	Teleprinter No.	

3. Further observations, if necessary:
The person identified in Box 2 is now recorded as applicant for all designated States except the United States of America.

4. A copy of this notification has been sent to:

- [X] the receiving Office
- [X] the International Searching Authority
- [ ] the International Preliminary Examining Authority
- [ ] the designated Offices concerned
- [X] the elected Offices concerned
- [ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Bernard THORAX (Fax 338-87-20
Facsimile No. (41-22) 338.87.20	Telephone No. (41-22) 338 8213

Form PCT/IB/306 (March 1994) 008626992

263

DNA NO.01317.PCT1
ELN No. 00447-PCT-NEW

PATENT COOPERATION TREATY

DOCKETED

JUL 12 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
BRADLEY W. CRAWFORD
MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE, SUITE 3200
CHICAGO, ILLINOIS 60606

PCT

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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

Date of mailing *(day/month/year)*	07 JUL 2004
Applicant's or agent's file reference: 02-793-D	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/28503	10 Sep 2003	10 Sep 2002

Applicant
ELAN PHARMACEUTICALS, INC.

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

12 Apr 2004

2. That date of receipt is:

[X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

[ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(c)).

[ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

[ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer
Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Catherine Williams
Facsimile No. 703-305-3230	Telephone No. 703-305-3677

Form PCT/IPEA/402 (July 1998)

703-308-9290

264

PATENT COOPERATION TREATY

DOCKETED

AUG 30 2004

DUE DATE:
BY:

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
STEVEN J. SARUSSI
MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, IL 60606

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	26 AUG 2004
Applicant's or agent's file reference: 02-793-D	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US03/28503	10 September 2003 (10.09.2003)	10 September 2002 (10.09.2002)

Applicant

ELAN PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

DHA NO, 01317.PCT1
ELN. NO. 00447-PCT-NEW
PC No. 27693

Name and mailing address of the IPEA/US	Authorized officer:
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	SHAILENDRA - KUMAR
Facsimile No. (703) 305-3230	Telephone No. (571)272-1600

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 02-793-D	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/28503	International filing date (day/month/year) 10 September 2003 (10.09.2003)	Priority date (day/month/year) 10 September 2002 (10.09.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 215/38, 311/04, 335/04; C07C 233/05; A61K 31/147, 31/35, 31/38, 31/16 and US Cl.: 546/159; 549/404, 23; 564/218, 220; 514/313, 456, 432, 629, 630		
Applicant ELAN PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 April 2004 (12.04.2004)	09 August 2004 (09.08.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer SHAILENDRA - KUMAR Telephone No. (571)272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

266

PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 02-793-D

Box No. I TITLE OF INVENTION

Acetyl 2-Hydroxy-1,3-Diaminoalkanes

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ELAN PHARMACEUTICALS, INC.
800 Gateway Boulevard
South San Francisco, California 94080
US

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PHARMACIA & UPJOHN COMPANY LLC
301 Henrietta Street
Kalamazoo, Michigan 49007
US

This person is:
☒ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SARUSSI, Steven J.
McDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
US

Telephone No.
(312) 913-0001

Facsimile No.
(312) 913-0002

Teleprinter No.

Agent's registration No. with the Office
32,784

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

267

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/28503

I. Basis of the report

1. With regard to the elements of the international application:*

- [x] the international application as originally filed.
- [x] the description:
  - pages 1-437 as originally filed
  - pages NONE, filed with the demand
  - pages NONE, filed with the letter of _____.
- [x] the claims:
  - pages 438-459, as originally filed
  - pages NONE, as amended (together with any statement) under Article 19
  - pages NONE, filed with the demand
  - pages NONE, filed with the letter of _____.
- [ ] the drawings:
  - pages NONE, as originally filed
  - pages NONE, filed with the demand
  - pages NONE, filed with the letter of _____.
- [ ] the sequence listing part of the description:
  - pages NONE, as originally filed
  - pages NONE, filed with the demand
  - pages NONE, filed with the letter of _____.

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

- [ ] the language of a translation furnished for the purposes of international search (under Rule23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

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

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

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages NONE
   - [ ] the claims, Nos. NONE
   - [ ] the drawings, sheets/fig NONE

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/28503

268

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-14	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-14	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-14 the meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the instant claimed compounds.

The closest prior arts are Kick et al(US 6,150,416) and Xu, Ping et al(J. Med. Chem). Kick et al in claim 1, teach structurally similar compounds as claimed herein. However the claim differ from the reference in the definition of R15 and Rc. Xu, Ping et al likewise teach structurally similar compounds as claimed herein, see for example on page 33, Fig 3. However, the reference has many more carbonamide groups than claimed herein. There is no motivation to arrive at the claimed compounds using the prior art references.

Claims 1-14 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

269
270

Sheet No. . . . 2. . . .

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
MAILLARD, Michel
219 Shorebird Circle
Redwood Shores, California 94065
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
BALDWIN, Eric T.
5163 Sue Drive
Carmel, Indiana 46035
US

This person is:
☐ applicant only .
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
BECK, James P.
1372 Robert Court
Zionsville, Indiana 46077
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
HUGHES, Robert
1020 Stone Spring Court
Eureka, Missouri 63025
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

270

Sheet No. ...3....

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not to be included in the request.

Name and address: *(Family name followed by given names for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below).)*

JOHN, Varghese
1722 18th Avenue
San Francisco, California 94122
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given names for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below).)*

PULLEY, Shon R.
2243 East 151st Street
Carmel, Indiana 46033
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given names for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below).)*

TENBRINK, Ruth
125 Skyview Lane
Labadie, Missouri 63055
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given names for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence (if no State of residence is indicated below).)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

271

Sheet No. ...4...

Box No.V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

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

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of

☒ **EP** **European Patent:** AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, HU Hungary, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, RO Romania, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line* .....

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

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

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

☐ ..... ☐ ..... ☐ .....

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

272

Sheet No. ....5...

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 10 September 2002 (10.09.02)	60/409,453	US		
item (2) 05 March 2003 (05.03.03)	60/452,231	US		
item (3) 01 August 2003 (01.08.03)		US		
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* .....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA/ . US.....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Sheet No. ....6..

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) In paper form, the following number of sheets:

request (including declaration sheets)	:	6
description (excluding sequence listings and/or tables related thereto)	:	437
claims	:	21
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	485
sequence listings	:	
tables related thereto	:	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)	:	
Total number of sheets	:	485

(b) ☐ only in computer readable form (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ also in computer readable form (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

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

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☐ original separate power of attorney	:	
3. ☐ original general power of attorney	:	
4. ☐ copy of general power of attorney; reference number, if any:	:	
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listings in computer readable form *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column	:	
10. ☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:	
11. ☒ other *(specify)*: Transmittal letter	:	1

Figure of the drawings which should accompany the abstract:	**Language of filing of the international application:** English

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

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

Steven F. Sarussi

For receiving Office use only

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

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

274

ACETIL 2-HIDROXI-1, 3-DIAMINOALCANOS

Antecedentes del invento

Área del invento

El invento se refiere a los acetil 2-hidroxi-1,3-diaminoalcanos y a aquellos compuestos que resultan útiles para el tratamiento del mal de Alzheimer y enfermedades relacionadas. Más específicamente, se refiere a aquellos compuestos que son capaces de inhibir la secretasa beta, una enzima que disocia la proteína precursora de amiloide para producir péptido amiloide beta (A beta), un componente principal de las placas amiloides que se encuentran en el cerebro de los enfermos de Alzheimer.

Contexto del invento

El mal de Alzheimer (AD, en inglés) es una enfermedad degenerativa progresiva del cerebro que se relaciona mayormente con el envejecimiento. La presentación clínica del AD se caracteriza por la pérdida de la memoria, el conocimiento, el razonamiento, el juicio y la orientación. A medida que avanza la enfermedad, también se ven afectadas las capacidades motrices, sensoriales y lingüísticas hasta que se produce un deterioro global de las múltiples funciones cognitivas. Estas pérdidas cognitivas se producen en forma gradual, pero en general llevan a un deterioro severo y finalmente a la muerte en un plazo de cuatro a doce años.

El mal de Alzheimer se caracteriza por dos principales observaciones patológicas en el cerebro: nudos neurofibrilares y placas amiloides beta (o neuríticas), principalmente compuestas por una acumulación de un fragmento péptido conocido como beta. Las personas con AD presentan depósitos de amiloide beta en el cerebro (placas amiloides beta) y en los vasos sanguíneos cerebrales (angiopatía amiloide beta) además de nudos neurofibrilares. Los nudos neurofibrilares no sólo existen en el mal de Alzheimer sino también en otras alteraciones que llevan a la demencia. En estudios de autopsia, suelen encontrarse grandes cantidades de estas lesiones en áreas del cerebro humano importantes para la memoria y el conocimiento.

En el cerebro de personas de edad avanzada que no poseen manifestación clínica de AD se encuentran menores cantidades de estas lesiones con una distribución anatómica más limitada. Las placas amiloidogénicas y la angiopatía amiloide vascular también son características de los cerebros de personas con Trisomía 21 (Síndrome de Down), Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés (HCHWA-D) y otras alteraciones neurodegenerativas. El amiloide beta es una característica definitoria del AD, a la que actualmente se le atribuye ser precursora o factor causal del desarrollo de la enfermedad. El depósito de A beta en zonas del cerebro encargadas de las actividades cognitivas es un factor principal en el desarrollo de AD. Las placas amiloides beta están principalmente compuestas por péptido amiloide beta (A beta, a veces

275

también denominado betaA4). Un péptido beta resulta de la proteolisis de la proteína precursora de amiloide (PPA) y se compone de 39-42 aminoácidos. Varias proteasas llamadas secretasas están involucradas en el procesamiento de PPA.

La división de PPA en el extremo N-terminal del péptido A beta por parte de la secretasa beta y en el extremo C-terminal por parte de una o más secretasas gamma constituye la vía de acceso beta-amiloidogénica, es decir, la vía de acceso a través de la cual se forma A beta. La división de PPA por parte de la secretasa alfa produce alfa-sPPA, una forma de PPA secretada que no deriva en la formación de placas amiloides beta. Esta vía de acceso alternativa impide la formación del péptido A beta. Una descripción de los fragmentos de PPA de procesamiento proteolítico puede encontrarse, por ejemplo, en las patentes de EE.UU. números 5.441.870; 5.721.130; y 5.942.400.

Se ha identificado una proteasa de aspartilo como la enzima responsable del procesamiento de PPA en el lugar donde se produce la división por parte de la secretasa beta. La enzima secretasa beta se ha conocido mediante distintas denominaciones, incluidas BACE, Asp, i Memapsin. Ver, por ejemplo, Sinha et al., 1999, *Nature* 402:537-554 (p501) y la aplicación WO00/17369 de PCT publicada.

Existen distintas evidencias de que el depósito gradual de péptido amiloide beta (A beta) en el cerebro cumple una función seminal en la patogénesis de AD y puede anteceder a los síntomas cognitivos en años o décadas. Ver, por ejemplo, Selkoe, 1991, *Neuron* 6:487. Ha quedado demostrada la liberación de A beta a partir de células neuronales desarrolladas en cultivo y la presencia de A beta en el fluido cerebroespinal (FCE) tanto en personas normales como en enfermos de AD. Ver, por ejemplo, Seubert et al., 1992, *Nature* 359:325-327.

Se ha sugerido que el péptido A beta se acumula como resultado del procesamiento de PPA por parte de la secretasa beta, por lo que la inhibición de la actividad de esta enzima resulta deseable para el tratamiento de AD. Se cree que el procesamiento *in vivo* de PPA en el lugar donde se produce la división por parte de la secretasa beta es un paso que limita la velocidad de producción de A beta y por lo tanto resulta ser un objetivo terapéutico para el tratamiento de AD. Ver, por ejemplo, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

Los ratones que no expresan (o que no manifiestan) BACE1 no generan A beta y presentan un fenotipo normal. Cuando se los cruza con ratones transgénicos que presentan exceso de PPA, la proteína muestra cantidades reducidas de A beta en extractos cerebrales en comparación con los animales de control (Luo et al., 2001 *Nature Neuroscience* 4:231-232). Esta evidencia avala aún más la creencia de que la inhibición de la actividad de la secretasa beta y la reducción de A beta en el cerebro proporciona un método terapéutico para el tratamiento de AD y otras alteraciones del amiloide beta.

276

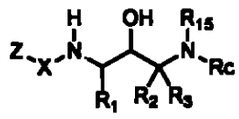
En la actualidad no existen tratamientos eficaces para detener, prevenir o revertir el avance del mal de Alzheimer. Por consiguiente, existe una necesidad urgente de contar con agentes farmacológicos capaces de retardar el avance del mal de Alzheimer y/o de prevenirlo directamente.

Para el tratamiento y la prevención de las enfermedades caracterizadas por depósitos o placas amiloides beta, como es el caso de AD, se requieren compuestos que sean inhibidores eficaces de la secretasa beta, que inhiban la división de PPA por medio de la secretasa beta, que sean inhibidores eficaces de la producción de A beta y/o que sean eficaces para reducir los depósitos o placas amiloides beta.

RESUMEN DEL INVENTO

El invento comprende los compuestos de la fórmula (I) que aparece abajo, los preparados farmacéuticos que contengan esos compuestos y los métodos que utilicen esos compuestos o preparados para el tratamiento del mal de Alzheimer y más específicamente los compuestos capaces de inhibir la secretasa beta, una enzima que divide la proteína precursora de amiloide para producir péptido A-beta, un componente principal de las placas amiloides que se encuentran en el cerebro de quienes padecen Alzheimer.

En líneas generales, el invento proporciona compuestos de la fórmula I



(I)

y sales aceptables desde un punto de vista farmacológico, donde

Eliminado: ¶

Z es hidrógeno o

Z es $(C_3-C_7$ cicloalquilo$)_{0-1}(C_1-C_6$ alquilo$)$-, $(C_3-C_7$ cicloalquilo$)_{0-1}(C_2-C_6$ alquenilo$)$-, $(C_3-C_7$ cicloalquilo$)_{0-1}(C_2-C_6$ alquinilo$)$- o $(C_3-C_7$ cicloalquilo$)$-, donde cada uno de dichos grupos se reemplaza opcionalmente por 1, 2 ó 3 grupos R_Z, donde 1 ó 2 grupos de *metileno dentro de dichos grupos* $(C_3-C_7$ cicloalquilo$)_{0-1}(C_1-C_6$ alquilo$)$-, $(C_3-C_7$ cicloalquilo$)_{0-1}(C_2-C_6$ alquenilo$)$-, $(C_3-C_7$ cicloalquilo$)_{0-1}(C_2-C_6$ alquinilo$)$- o $(C_3-C_7$ cicloalquilo$)$ se reemplazan opcionalmente por -(C=O)-;

en cada aparición R_Z es independientemente halógeno, -OH, -SH, -CN, $-CF_3$, $-OCF_3$, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o $-NR_{100}R_{101}$;

en cada aparición R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, $CO(C_1-C_6$ alquilo$)$ o $SO_2C_1-C_6$ alquilo;

277

X es -(C=O)- o -(SO_2)-;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -SH, -CN, -CF_3, -OCF_3, -C_{3-7} cicloalquilo, -C_1-C_4 alcoxi, amino, mono- o dialquilamino, arilo, heteroarilo y heterocicloalquilo, donde cada grupo de arilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{50}; cada heteroarilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50}; y cada grupo de heterocicloalquilo se reemplaza opcionalmente por 1 ó 2 grupos que son independientemente R_{50} o =O;

R_{50} se selecciona a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -NR_7R_8, -$S(O)_{0-2}$-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi y C_3-C_8 cicloalquilo; donde

los grupos de alquilo, alquenilo, alquinilo, alcoxi y cicloalquilo se reemplazan opcionalmente por 1 ó 2 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, -NR_5R_6, CN, C_1-C_4 haloalcoxi, NR_7R_8 y C_1-C_4 alcoxi; donde

R_5 y R_6 son independientemente H o C_1-C_6 alquilo; o

R_5 y R_6 y el nitrógeno al que están ligados forman un anillo de heterocicloalquilo de 5 ó 6 componentes;

R_7 y R_8 se seleccionan independientemente a partir de H; -C_1-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; -C_3-C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; y -C_2-C_4 alquinilo;

R_2 y R_3 se seleccionan independientemente a partir de H; F; -C_1-C_6 alquilo opcionalmente reemplazado por -F, -OH, -C≡N, -CF_3, C_1-C_3 alcoxi o -NR_5R_6; -$(CH_2)_{0-2}$-R_{17}; -$(CH_2)_{0-2}$-R_{18}; -C_2-C_6 alquenilo o C_2-C_6 alquinilo, donde los grupos de alquenilo y alquinilo se reemplazan opcionalmente por 1 ó 2 grupos que son independientemente -F, -OH, -C≡N, -CF_3 o C_1-C_3 alcoxi; -$(CH_2)_{0-2}$-C_3-C_7 cicloalquilo, que se reemplaza opcionalmente por 1 ó 2 grupos que son independientemente -F, -OH, -C≡N, -CF_3, C_1-C_3 alcoxi y –NR_5R_6;

en cada aparición R_{17} es un grupo de arilo (preferentemente seleccionado a partir de fenilo, 1-naftilo, 2-naftilo , indanilo, indenilo, dihidronaftilo y tetralinilo), donde cada grupo de arilo se reemplaza opcionalmente por uno o dos grupos que son independientemente -C_1-C_3 alquilo; -C_1-C_4 alcoxi; CF_3; -C_2-C_6 alquenilo o -C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por un sustituto

278

seleccionado a partir de F, OH, C_1-C_3 alcoxi; halógeno; OH; -C≡N; -C_3-C_7 cicloalquilo; -CO-(C_1-C_4 alquilo); o -SO_2-(C_1-C_6 alquilo);

R_{18} es un grupo de heteroarilo (preferentemente seleccionado a partir de piridinilo, pirimidinilo, quinolinilo, indolilo, pridazinilo, pirazinilo, isoquinolilo, quinazolinilo, quinoxalinilo, ftalazinilo, imidazolilo, isoxazolilo, oxazolilo, tiazolilo, furanilo, tienilo, pirrolilo, oxadiazolilo o tiadiazolilo), donde dichos grupos de heteroarilo se reemplazan opcionalmente por uno o dos grupos que son independientemente -C_1-C_6 alquilo opcionalmente reemplazado por un sustituto seleccionado a partir de OH, C≡N, CF_3, C_1-C_3 alcoxi y -NR_5R_6;

R_{19} se selecciona a partir de hidrógeno, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 alcoxi C_1-C_6 alquilo, hidroxi C_1-C_6 alquilo, halo C_1-C_6 alquilo, cada uno de los cuales se reemplaza o no por 1, 2, 3 ó 4 grupos independientemente seleccionados a partir de halógeno, C_1-C_6 alquilo, hidroxi, C_1-C_6 alcoxi, NH_2 y -R_{26}-R_{27}; donde

R_{26} se selecciona a partir de un enlace, –C(O)-, -SO_2-, -CO_2-, -C(O)NR_5- y -NR_5C(O)-,

R_{27} se selecciona a partir de C_1-C_6 alquilo, C_1-C_6 alcoxi, arilo C_1-C_6 alquilo, heterocicloalquilo y heteroarilo, donde cada uno de los elementos precedentes se reemplaza o no por 1, 2, 3, 4 ó 5 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno, haloalquilo, hidroxialquilo, -NR_5R_6 o -C(O)NR_5R_6; o

R_2, R_3 y el carbono al que están ligados forman un carbociclo C_3-C_7, donde 1, 2 ó 3 átomos de carbono son opcionalmente reemplazados por grupos que se seleccionan independientemente a partir de –O-, -S-, -SO_2-, -C(O)- o -NR_7-;

R_C se selecciona a partir de -(CH_2)$_{0-3}$-(C_3-C_6) cicloalquilo, donde el cicloalquilo se reemplaza opcionalmente por 1, 2 ó 3 grupos independientemente seleccionados a partir de -R_{205}; y -CO_2-(C_1-C_4 alquilo); -($CR_{245}R_{250}$)$_{0-4}$-arilo; -($CR_{245}R_{250}$)$_{0-4}$-heteroarilo; -($CR_{245}R_{250}$)$_{0-4}$-heterocicloalquilo; -($CR_{245}R_{250}$)$_{0-4}$-arilo-heteroarilo; -($CR_{245}R_{250}$)$_{0-4}$-arilo-heterocicloalquilo; -($CR_{245}R_{250}$)$_{0-4}$-arilo-arilo; -($CR_{245}R_{250}$)$_{0-4}$-heteroarilo-arilo; -($CR_{245}R_{250}$)$_{0-4}$-heteroarilo-heterocicloalquilo; -($CR_{245}R_{250}$)$_{0-4}$-heteroarilo-heteroarilo; -CHR_{245}-CHR_{250}-arilo; -($CR_{245}R_{250}$)$_{0-4}$-heterocicloalquilo-heteroarilo; -($CR_{245}R_{250}$)$_{0-4}$-heterocicloalquilo-heterocicloalquilo; -($CR_{245}R_{250}$)$_{0-4}$-heterocicloalquilo-arilo; un anillo monocíclico o bicíclico de 5, 6, 7 8, 9 ó 10 carbonos fusionados con 1 ó 2 grupos de arilo (preferentemente fenilo), heteroarilo (preferentemente piridilo, imidazolilo, tienilo o pirimidilo) o heterocicloalquilo (preferentemente piperidinilo o piperazinilo);

donde 1, 2 ó 3 carbonos del ciclo monocíclico o bicíclico se reemplazan opcionalmente por -NH-, $-N(CO)_{0-1}R_{215}$-, $-N(CO)_{0-1}R_{220}$-, -O- o $-S(=O)_{0-2}$- y donde el ciclo monocíclico o bicíclico se reemplaza opcionalmente por 1, 2 ó 3 grupos que son independientemente $-R_{205}$, $-R_{245}$, $-R_{250}$ o =O;

y $-C_2$-C_6 alquenilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205};

donde cada grupo de arilo o heteroarilo ligado directa o indirectamente al grupo $-(CR_{245}R_{250})_{0-4}$ se reemplaza opcionalmente por 1, 2, 3 ó 4 grupos R_{200};

donde cada heterocicloalquilo ligado directa o indirectamente al grupo $-(CR_{245}R_{250})_{0-4}$ se reemplaza opcionalmente por 1, 2, 3 ó 4 R_{210};

en cada aparición R_{200} se selecciona independientemente a partir de $-C_1$-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; -OH; $-NO_2$; -halógeno; -C≡N; $-(CH_2)_{0-4}$-CO-$NR_{220}R_{225}$; $-(CH_2)_{0-4}$-CO-(C_1-C_8 alquilo); $-(CH_2)_{0-4}$-CO-(C_2-C_8 alquenilo); $-(CH_2)_{0-4}$-CO-(C_2-C_8 alquinilo); $-(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo); $-(CH_2)_{0-4}$-$(CO)_{0-1}$-arilo (preferentemente fenilo); $-(CH_2)_{0-4}$-$(CO)_{0-1}$-heteroarilo (preferentemente piridilo, pirimidilo, furanilo, imidazolilo, tienilo, oxazolilo, tiazolilo o pirazinilo); $-(CH_2)_{1-4}$-$(CO)_{0-1}$-heterocicloalquilo (preferentemente imidazolidinilo, piperazinilo, pirrolidinilo, piperidinilo o tetrahidropiranilo); $-(CH_2)_{0-4}$-CO_2R_{215}; $-(CH_2)_{0-4}$-SO_2-$NR_{220}R_{225}$; $-(CH_2)_{0-4}$-$S(O)_{0-2}$-(C_1-C_8 alquilo); $-(CH_2)_{0-4}$-$S(O)_{0-2}$-(C_3-C_7 cicloalquilo); $-(CH_2)_{0-4}$-N(H o R_{215})-CO_2R_{215}; $-(CH_2)_{0-4}$-N(H o R_{215})-SO_2-R_{220}; $-(CH_2)_{0-4}$-N(H o R_{215})-CO-$N(R_{215})_2$; $-(CH_2)_{0-4}$-N(-H o R_{215})-CO-R_{220}; $-(CH_2)_{0-4}$-$NR_{220}R_{225}$; $-(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); $-(CH_2)_{0-4}$-O-(R_{215}); $-(CH_2)_{0-4}$-S-(R_{215}); $-(CH_2)_{0-4}$-O-(C_1-C_6 alquilo opcionalmente reemplazado por 1, 2, 3 ó 5 -F); $-C_2$-C_6 alquenilo opcionalmente reemplazado por 1 ó 2 grupos R_{205}; $-C_2$-C_6 alquinilo opcionalmente reemplazado por 1 ó 2 grupos R_{205}; en forma categórica, y $-(CH_2)_{0-4}$- C_3-C_7 cicloalquilo;

cada grupo de arilo y heteroarilo incluido en R_{200} se reemplaza opcionalmente por 1, 2 ó 3 grupos que son independientemente $-R_{205}$, $-R_{210}$ o $-C_1$-C_6 alquilo reemplazado por 1, 2 ó 3 grupos que son independientemente R_{205} o R_{210};

cada grupo de heterocicloalquilo incluido en R_{200} se reemplaza opcionalmente por 1, 2 ó 3 grupos que son independientemente R_{210};

en cada aparición R_{205} se selecciona independientemente a partir de $-C_1$-C_6 alquilo, $-C_2$-C_6 alquenilo, $-C_2$-C_6 alquinilo, $-C_1$-C_6 haloalcoxi, $-(CH_2)_{0-3}$(C_3-C_7 cicloalquilo), -halógeno, $-(CH_2)_{0-4}$-OH, -O-fenilo, OH, SH, -

286

$(CH_2)_{0-6}$-C≡N, -$(CH_2)_{1-6}$-C(=O)$NR_{235}R_{240}$, -CF_3, -C_1-C_6 alcoxi, C_1-C_6 alcoxicarbonilo y -$NR_{235}R_{240}$;

en cada aparición R_{210} se selecciona independientemente a partir de -C_1-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; -C_2-C_6 alquenilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; C_1-C_6 alcanoilo; -SO_2-(C_1-C_6 alquilo); -C_2-C_6 alquinilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; -halógeno; -C_1-C_6 alcoxi; -C_1-C_6 haloalcoxi; -$NR_{220}R_{225}$; -OH; -C≡N; -C_3-C_7 cicloalquilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; -CO-(C_1-C_4 alquilo); -SO_2-$NR_{235}R_{240}$; -CO-$NR_{235}R_{240}$; -SO_2-(C_1-C_4 alquilo); y =O;

en cada aparición R_{215} se selecciona independientemente a partir de -C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(arilo), -C_2-C_6 alquenilo, -C_2-C_6 alquinilo, -C_3-C_7 cicloalquilo, -$(CH_2)_{0-2}$-(heteroarilo) y -$(CH_2)_{0-2}$-(heterocicloalquilo); donde el grupo de arilo incluido en R_{215} se reemplaza opcionalmente por 1, 2 ó 3 grupos que son independientemente -R_{205} o -R_{210}; donde los grupos de heterocicloalquilo y heteroarilo incluidos en R_{215} son opcionalmente reemplazados por 1, 2 ó 3 R_{210};

en cada aparición R_{220} y R_{225} son independientemente H, -C_1-C_6 alquilo, hidroxi C_1-C_6 alquilo, C_1-C_6 alcoxicarbonilo, -amino C_1-C_6 alquilo, -SO_2-C_1-C_6 alquilo, C_1-C_6 alcanoilo opcionalmente reemplazado por hasta tres halógenos, -C(O)NH_2, -C(O)NH(C_1-C_6 alquilo), -C(O)N(C_1-C_6 alquilo)(C_1-C_6 alquilo), -halo C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(C_3-C_7 cicloalquilo), -(C_1-C_6 alquilo)-O-(C_1-C_3 alquilo), -C_2-C_6 alquenilo, -C_2-C_6 alquinilo, -arilo (preferentemente fenilo), -heteroarilo o -heterocicloalquilo; donde los grupos de arilo, heteroarilo y heterocicloalquilo incluidos en R_{220} y R_{225} se reemplazan opcionalmente por 1, 2 ó 3 grupos R_{270}.

En cada aparición R_{270} es *independientemente* -R_{205}, -C_1-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; -C_2-C_6 alquenilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; -C_2-C_6 alquinilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{205}; -fenilo; -halógeno; -C_1-C_6 alcoxi; -C_1-C_6 haloalcoxi; -$NR_{215}R_{240}$; -OH; -C≡N; -C_3-C_7 cicloalquilo opcionalmente

281

reemplazado por 1, 2 ó 3 grupos R_{235}; -CO-(C_1-C_4 alquilo); -SO_2-$NR_{235}R_{240}$; -CO-$NR_{235}R_{240}$; -SO_2-(C_1-C_4 alquilo); y =O;

en cada aparición R_{235} y R_{240} son independientemente -H, -C_1-C_6 alquilo, C_2-C_6 alcanoilo, -SO_2-(C_1-C_6 alquilo) o -fenilo;

En cada aparición R_{245} y R_{250} se seleccionan independientemente a partir de H, -$(CH_2)_{0-4}CO_2C_1$-C_4 alquilo, -$(CH_2)_{0-4}C(=O)C_1$-C_4 alquilo, -C_1-C_4 alquilo, -C_1-C_4 hidroxialquilo, -C_1-C_4 alcoxi, -C_1-C_4 haloalcoxi, -$(CH_2)_{0-4}$-C_3-C_7 cicloalquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo, -$(CH_2)_{0-4}$ arilo, -$(CH_2)_{0-4}$ heteroarilo y -$(CH_2)_{0-4}$ heterocicloalquilo o

R_{245} y R_{250} se juntan con el carbono con el cual se unen para formar un monociclo o biciclo de 3, 4, 5, 6, 7 u 8 átomos de carbono, donde 1, 2 ó 3 átomos de carbono se reemplazan opcionalmente por 1, 2 ó 3 grupos que son independientemente -O-, -S-, -SO_2-, -C(O)-, -NR_{220}- o -$NR_{220}R_{220}$- donde ambos grupos R_{220} son alquilo; y donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxilo, NH_2, NH(C_1-C_6 alquilo), N(C_1-C_6 alquilo)(C_1-C_6 alquilo), -NH-C(O)C_1-C_3 alquilo, -NH-SO_2-(C_1-C_6 alquilo) o halógeno;

donde los grupos de arilo, heteroarilo o heterocicloalquilo incluidos en R_{245} y R_{250} son opcionalmente reemplazados por 1, 2 ó 3 grupos que son independientemente halógeno, C_{1-6} alquilo, CN o OH.

El invento también proporciona métodos para el tratamiento o la prevención del mal de Alzheimer, el deterioro cognitivo leve, el síndrome de Down, la Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés, la angiopatía amiloide cerebral, otras demencias degenerativas, demencias de origen vascular y degenerativo combinado, demencia asociada con mal de Parkinson, demencia asociada con parálisis supranuclear progresiva, demencia asociada con degeneración cortico-basal, tipo de mal de Alzheimer con cuerpos de Lewy difusos, que implican la administración al paciente que lo requiera de una dosis terapéuticamente eficaz de un compuesto o sal con la fórmula I.

Preferentemente, el paciente es un ser humano.

Más preferentemente, la enfermedad es el mal de Alzheimer.

Más preferentemente, la enfermedad es la demencia.

282

El invento también proporciona preparados farmacológicos que incluyen un compuesto o sal con la fórmula I y por lo menos un vehículo, solvente, adyuvante o diluyente farmacológicamente aceptable.

El invento también permite la utilización de un compuesto o sal según la fórmula I para la fabricación de un medicamento.

El invento también permite la utilización de un compuesto o sal con la fórmula I para el tratamiento o la prevención del mal de Alzheimer, el deterioro cognitivo leve, el síndrome de Down, la Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés, la angiopatía amiloide cerebral, otras demencias degenerativas, demencias de origen vascular y degenerativo combinado, demencia asociada con mal de Parkinson, demencia asociada con parálisis supranuclear progresiva, demencia asociada con degeneración cortico-basal o tipo de mal de Alzheimer con cuerpos de Lewy difusos.

El invento también proporciona compuestos, preparados farmacológicos, conjuntos y métodos para inhibir la división de la proteína precursora de amiloide (PPA) por medio de la secretasa beta. Más específicamente, los compuestos, preparados y métodos del invento son eficaces para inhibir la producción del péptido A-beta y para tratar o prevenir cualquier enfermedad o estado humano o animal vinculados con una forma patológica del péptido A-beta.

Los compuestos, preparados y métodos del invento son útiles para tratar a personas que sufren mal de Alzheimer (AD), para contribuir a evitar o demorar el comienzo de AD, para tratar a pacientes con deterioro cognitivo leve (MCI, en inglés) y prevenir o demorar el comienzo de AD en aquellos pacientes en los que de otro modo se esperaría que MCI evolucione hacia AD, para tratar el síndrome de Down, para tratar la Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés, para tratar la angiopatía amiloide beta cerebral y evitar sus potenciales consecuencias como las hemorragias lobulares de episodio único o recurrentes, para tratar otras demencias degenerativas, incluidas las demencias de origen vascular y degenerativo combinado, para tratar la demencia asociada con el mal de Parkinson, la demencia asociada con la parálisis supranuclear progresiva, la demencia asociada con la degeneración cortico-basal y el tipo de AD con cuerpos de Lewy difusos, y para tratar las demencias frontotemporales con parkinsonismo (DFTP).

Los compuestos del invento poseen una acción inhibitoria de la secretasa beta. La acción inhibitoria de los compuestos del invento puede demostrarse con facilidad utilizando, por ejemplo, uno o más de los ensayos aquí descriptos o conocidos dentro de esta disciplina.

283

A menos que se definan expresamente los sustitutos de una fórmula en particular, se entiende que les son aplicables las definiciones establecidas para la fórmula precedente a la que se refiere la fórmula en particular.

El invento también proporciona métodos para preparar los compuestos del invento y los medios utilizados en esos métodos.

El invento también permite la utilización de compuestos y sales farmacológicamente aceptables según la fórmula I para la fabricación de un medicamento que pueda aplicarse para: tratar a una persona que padezca, o prevenir que una persona desarrolle el mal de Alzheimer (AD); evitar o demorar el comienzo de AD; tratar a pacientes con deterioro cognitivo leve (MCI); prevenir o demorar el comienzo de AD en personas que evolucionarían de MCI a AD; tratar el síndrome de Down; tratar a personas que sufren Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés; tratar la angiopatía amiloide cerebral y evitar sus potenciales consecuencias; tratar otras demencias degenerativas; tratar la demencia asociada con el mal de Parkinson, la parálisis supranuclear progresiva o la degeneración cortico-basal; tratar el tipo de AD con cuerpos de Lewy difusos; y tratar las demencias frontotemporales con parkinsonismo (DFTP).

DESCRIPCIÓN DETALLADA DEL INVENTO

Tal como se ha señalado precedentemente, el invento proporciona compuestos de la fórmula I. De acuerdo con los compuestos de la fórmula I y otras fórmulas aplicables a continuación, cuando Z es $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_1\text{-}C_6$ alquilo$)$-, $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_2\text{-}C_6$ alquenilo$)$-, $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_2\text{-}C_6$ alquinilo$)$- o $(C_3\text{-}C_7$ cicloalquilo$)$-, 1 ó 2 grupos de metileno dentro de esos grupos $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_1\text{-}C_6$ alquilo$)$-, $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_2\text{-}C_6$ alquenilo$)$-, $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_2\text{-}C_6$ alquinilo$)$- o $(C_3\text{-}C_7$ cicloalquilo$)$- son opcionalmente reemplazados por -(C=O)-. Este reemplazo opcional puede ser alfa con respecto a X, por ejemplo, están considerados en el invento los compuestos K,2-dicetónicos. Además, dicho reemplazo por carbonilos comprende compuestos, por ejemplo, donde un grupo de metileno es reemplazado en la porción cíclica del grupo de cicloalquilo (para formar una fracción cetónica cíclica) y/o donde un grupo de metileno es reemplazado en la porción de alquilo, alquenilo o alquinilo de dichos grupos.

Los compuestos preferidos de la fórmula I incluyen aquéllos donde Z es $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_1\text{-}C_6$ alquilo$)$-, $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_2\text{-}C_6$ alquenilo$)$-, $(C_3\text{-}C_7$ cicloalquilo$)_{0\text{-}1}(C_2\text{-}C_6$ alquinilo$)$- o $(C_3\text{-}C_7$ cicloalquilo$)$-, donde cada uno de esos grupos se reemplaza opcionalmente por 1, 2 ó 3 grupos R_Z;

284

en cada aparición R_Z es independientemente halógeno, -OH, -CN, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o $-NR_{100}R_{101}$;

R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, $CO(C_1$-C_6 alquilo) o SO_2C_1-C_6 alquilo.

En otra forma de presentación preferida, el invento incluye compuestos de la fórmula I donde Z es tal como se define más arriba y X es –(C=O)-. En una forma de presentación alternativa, X es –(C=O)- y Z es H. En otra forma de presentación preferida, X es –(C=O)- y Z es C_1-C_4 alquilo, más preferentemente C_1-C_3 alquilo, y aún más preferentemente metilo.

Los compuestos preferidos de la fórmula I también incluyen aquéllos donde R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, -OH, =O, $-CF_3$, $-OCF_3$, $-C_{3-7}$ cicloalquilo, $-C_1$-C_4 alcoxi, amino y arilo, donde el grupo de arilo (preferentemente fenilo) se reemplaza opcionalmente por 1 ó 2 grupos R_{50};

R_{50} se selecciona a partir de halógeno, OH, $-CO-(C_1$-C_4 alquilo), $-NR_7R_8$, C_1-C_6 alquilo, C_1-C_6 alcoxi y C_3-C_8 cicloalquilo; donde los grupos de alquilo, alcoxi y cicloalquilo son opcionalmente reemplazados por 1 ó 2 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, $-NR_5R_6$, NR_7R_8 y C_1-C_4 alcoxi;

R_5 y R_6 son independientemente H o C_1-C_6 alquilo; o

R_5 y R_6 y el nitrógeno al que están ligados forman un anillo de heterocicloalquilo de 5 ó 6 componentes; y

R_7 y R_8 se seleccionan independientemente a partir de -H; $-C_1$-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, $-NH_2$ y halógeno; $-C_3$-C_6 cicloalquilo; y $-(C_1$-C_4 alquilo)-O-(C_1-C_4 alquilo).

Los compuestos preferidos de la fórmula I también incluyen aquéllos donde R_1 es $-CH_2$-fenilo, donde el anillo de fenilo se reemplaza opcionalmente por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, C_1-C_2 alquilo, C_1-C_2 alcoxi e hidroxi. Más preferentemente, R_1 es bencilo, 3-fluorbencilo ó 3,5-difluorbencilo.

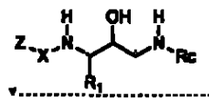
Los compuestos preferidos de la fórmula I incluyen aquéllos donde R_2 y R_3 son independientemente –H o $-C_1$-C_6 alquilo.

Otros compuestos igualmente preferidos de la fórmula I incluyen aquéllos donde R_{15} es H.

Por otro lado, el invento proporciona compuestos de la fórmula II:

Eliminado: ¶

285



(II)

y sales farmacológicamente aceptables de la misma, donde

Z es hidrógeno, -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo, donde cada uno de dichos grupos se reemplaza opcionalmente por 1 ó 2 grupos R_Z, donde 1 ó 2 grupos de metileno dentro de dichos grupos -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo son opcionalmente reemplazados por -(C=O)-;

en cada aparición R_Z es independientemente halógeno, -OH, -CN, -CF_3, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o -$NR_{100}R_{101}$;

R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, CO(C_1-C_6 alquilo) o SO_2C_1-C_6 alquilo;

X es -C(=O)-;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cicloalquilo, -C_1-C_4 alcoxi, amino, mono- dialquiloamino, arilo, heteroarilo o heterocicloalquilo, donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50};

R_{50} es halógeno, OH, CN, -CO-(C_1-C_4 alquilo), -NR_7R_8, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi y C_3-C_8 cicloalquilo;

R_7 y R_8 se seleccionan a partir de H; -C_1-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos seleccionados a partir de -OH, -NH_2 y halógeno; -C_3-C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; y -C_2-C_4 alquinilo;

R_C se selecciona a partir de -$(CR_{245}R_{250})_{0-4}$-arilo; -$(CR_{245}R_{250})_{0-4}$-heteroarilo; -$(CR_{245}R_{250})_{0-4}$-heterocicloalquilo; donde los grupos de arilo y heteroarilo ligados al grupo -$(CR_{245}R_{250})_{0-4}$- son opcionalmente reemplazados por 1, 2, 3 ó 4 grupos R_{200}; donde el grupo de heterocicloalquilo ligado al grupo -$(CR_{245}R_{250})_{0-4}$- se reemplaza opcionalmente por 1, 2, 3 ó 4 grupos R_{210}; y

R_{245} R_{250}, R_{200} y R_{210} son como se los define más arriba.

Por otro lado, el invento proporciona compuestos donde

R_C es -$(CR_{245}R_{250})_{0-4}$-heterocicloalquilo (preferentemente piperidinilo, piperazinilo, pirrolidinilo, 2-oxo-tetrahidroquinolinilo, 2-oxo-dihidro-1H-indolilo o imidazolidinilo); donde el grupo

286

de heterocicloalquilo ligado al grupo -$(CR_{245}R_{250})_{0-4}$- se reemplaza opcionalmente por 1, 2, 3 ó 4 grupos R_{210}.

En otra forma de presentación preferida de los compuestos de la fórmula II, Z es -C_1-C_6 alquilo;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos de arilo, que son opcionalmente reemplazados por 1 ó 2 grupos R_{50},

cada R_{50} es independientemente halógeno, OH, CN, -NR_7R_8 o C_1-C_6 alquilo,

R_7 y R_8 son independientemente -H; -C_1-C_4 alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; o -C_3-C_6 cicloalquilo; y

R_C es -$(CR_{245}R_{250})_{0-4}$-arilo o -$(CR_{245}R_{250})_{0-4}$-heteroarilo (preferentemente el heteroarilo es piridilo, pirimidilo, quinolinilo, isoquinolinilo, más preferentemente piridilo), donde los grupos de arilo y heteroarilo son opcionalmente reemplazados por 1 ó 2 grupos R_{200}, donde R_{200} es como se lo define más arriba.

Existen asimismo otros compuestos preferidos de la fórmula II que incluyen aquéllos donde

Eliminado: ¶

R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo, donde el grupo de arilo (preferentemente fenilo o naftilo, aún más preferentemente fenilo) se reemplaza opcionalmente por 1 ó 2 grupos R_{50};

R_C es -$(CR_{245}R_{250})_{1-4}$-arilo o -$(CR_{245}R_{250})_{1-4}$-heteroarilo,

R_{245} y R_{250} se seleccionan independientemente a partir de H, -$(CH_2)_{0-4}CO_2C_1$-C_4 alquilo, -$(CH_2)_{0-4}CO_2H$, -C_1-C_4 alquilo, -(C_1-C_4 alquilo)OH o

R_{245}, R_{250} y el carbono al que están ligados forman un monociclo o biciclo de 3, 4, 5, 6, 7 u 8 átomos de carbono, donde 1 ó 2 átomos de carbono se reemplazan opcionalmente por -O-, -S-, -SO_2- o -NR_{220}-, donde R_{220} es tal como se lo define precedentemente; y

donde los grupos de arilo y heteroarilo ligados a los grupos -$(CR_{245}R_{250})_{1-4}$- son opcionalmente reemplazados por 1 ó 2 grupos R_{300}.

En otra forma de presentación preferida de los compuestos de la fórmula II,

R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo (preferentemente fenilo o naftilo), que se reemplaza opcionalmente por 1 ó 2 grupos R_{50},

R_{50} es independientemente halógeno, OH o C_1-C_6 alquilo;

R_C es -$(CR_{245}R_{250})$-arilo o -$(CR_{245}R_{250})$-heteroarilo, donde los grupos de arilo y heteroarilo ligados a los grupos -$(CR_{245}R_{250})_{1-4}$- son opcionalmente reemplazados por 1 ó 2 sustitutos seleccionados a partir de -Cl, -Br, -I, -C_1-C_3 alquilo, -(C_1-C_3 alquilo)OH, -CN, -C≡CH, -C≡C-CH_2-OH, -CF_3, -tienilo opcionalmente reemplazado por un grupo -C(=O)H, -fenilo

287

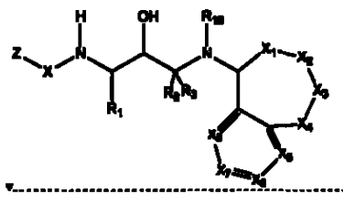
opcionalmente reemplazado por 1 ó 2 grupos C_1-C_3 alquilo, grupo -(C_1-C_3 alquilo)OH o grupo -CO(C_1-C_3 alquilo), -isoxazolilo opcionalmente reemplazado por un grupo C_1-C_4 alquilo o -(C_1-C_2 alquilo)oxazolilo donde el anillo oxazólico se reemplaza opcionalmente por un grupo -C_1-C_2 alquilo;

en cada aparición R_{245} y R_{250} son independientemente -H, -C_1-C_3 alquilo, -(C_1-C_3 alquilo)CO_2H, -(C_1-C_3 alquilo)CO_2(C_1-C_3 alquilo) o -(C_1-C_3 alquilo)OH o

R_{245} y R_{250} se juntan con el carbono al que están ligados para formar un monociclo o biciclo de 3, 4, 5, 6, 7 u 8 átomos de carbono, donde 1 ó 2 átomos de carbono se reemplazan opcionalmente por -O-, -S-, -SO_2- o -NR_{220}- y

R_{220} es tal como se lo define precedentemente.

Por otro lado, el invento proporciona compuestos de la fórmula III:



(III)

y sales farmacológicamente aceptables de la misma; donde

Z, X, R_1, R_2, R_3 y R_{15} son como se define más arriba;

X_1 es CH_2, CHR_{200}, $C(R_{200})_2$ o -(C=O)-;

X_2 y X_3 son independientemente CH_2, CHR_{200}, $C(R_{200})_2$, O, C=O, S, SO_2, NH o NR_7;

X_4 es un enlace, CH_2, CHR_{200}, $C(R_{200})_2$ O, C=O, S, SO_2, NH o NR_7;

siempre que cuando X_1 es -(C=O)-, X_2 sea CH_2, CHR_{200}, $C(R_{200})_2$, O, NH o NR_7 y el grupo X_3 ligado a X_2 sea CH_2, CHR_{200}, $C(R_{200})_2$ o SO_2 cuando X_2 es NH o NR_7 y X_4 es CH_2, CHR_{200} o $C(R_{200})_2$ o un enlace; o

-X_3-X_4- es -(C=O)O-, -O(C=O)-, -(C=O)NH-, -NH(C=O)-, -(C=O)NR_7- o -NR_7(C=O)-, con la condición de que X_1 no sea -(C=O)- y con la condición de que X_4 sea CH_2, CHR_{200} o $C(R_{200})_2$ o un enlace; o

-X_3-X_4- es -(C=O)O-, -O(C=O)-, -(C=O)NH-, -NH(C=O)-, -(C=O)NR_7- o -NR_7(C=O)-, con la condición de que X_2 sea CH_2, CHR_{200} o $C(R_{200})_2$; o

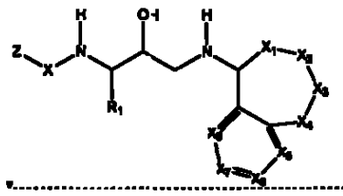
-X_2-X_3-X_4- es -(C=O)NH-SO_2- o -SO_2-NH(C=O)-, -(C=O)NR_7-SO_2- o -SO_2-NR_7(C=O)-, con la condición de que X_1 no sea -(C=O)-; y

X_5, X_6, X_7 y X_8 son CH o CR_{200}, donde 1 ó 2 de X_5, X_6, X_7 y X_8 son opcionalmente reemplazados por N y donde R_{200} y R_7 son como se define más arriba.

288

En una forma de presentación preferida de los compuestos de la fórmula III, el invento también ofrece compuestos de la fórmula IV:

Eliminado: ¶



(IV)

donde

Z es hidrógeno, -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo, donde cada uno se reemplaza opcionalmente por 1 ó 2 grupos R_Z y donde 1 ó 2 grupos de metileno dentro de dichos grupos -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo son opcionalmente reemplazados por -(C=O)-;

en cada aparición R_Z es independientemente halógeno, -OH, -CN, -CF_3, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o -$NR_{100}R_{101}$;

R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, CO(C_1-C_6 alquilo) o SO_2C_1-C_6 alquilo;

X es -C(=O)-;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cicloalquilo, -C_1-C_4 alcoxi, amino, mono- dialquiloamino, arilo opcionalmente reemplazado por 1 ó 2 grupos R_{50}, heteroarilo o heterocicloalquilo;

R_{50} es halógeno, OH, CN, -CO-(C_1-C_4 alquilo), -NR_7R_8, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo; y

R_7 y R_8 se seleccionan a partir de H; -C_1-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos seleccionados a partir de -OH, -NH_2 y halógeno; -C_3-C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; y -C_2-C_4 alquinilo.

En otros compuestos preferidos de la fórmula IV,

Z es -C_1-C_6 alquilo;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos de arilo (preferentemente fenilo o naftilo), que son opcionalmente reemplazados por 1 ó 2 grupos R_{50},

290
289

R_{50} es independientemente halógeno, OH, CN, $-NR_7R_8$ o C_1-C_6 alquilo, R_7 y R_8 son independientemente H; $-C_1$-C_4 alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de -OH, $-NH_2$ y halógeno; o $-C_3$-C_6 cicloalquilo; y

X_1, X_2 o X_3 son CH_2 o CHR_{200}, donde uno entre X_2 y X_3 es opcionalmente reemplazado por O, C=O, SO_2, NH, NR_7,

X_4 es un enlace; y

X_5, X_6, X_7 y X_8 son CH o CR_{200}, donde uno entre X_5, X_6, X_7 y X_8 es opcionalmente reemplazado por N y

R_{200} es como se define más arriba.

En otra forma preferida del invento relacionada con compuestos de la fórmula VI, R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo, donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50};

X_1, X_2 y X_3 son CH_2, CHR_{200} o $C(R_{200})_2$, donde uno entre X_2 y X_3 es opcionalmente reemplazado por O, NH o NR_7 y donde X_4 es un enlace; y

X_5, X_6, X_7 y X_8 son CH o CR_{200}, donde uno entre X_5, X_6, X_7 y X_8 es opcionalmente reemplazado por N, donde R_{50}, R_{200} y R_7 son como se define más arriba.

En otra forma de presentación preferida de compuestos de la fórmula IV,

R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo (preferentemente fenilo o naftilo, más preferentemente fenilo), donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50},

R_{50} es independientemente halógeno, OH o C_1-C_6 alquilo;

X_1, X_2 y X_3 son CH_2 o CHR_{200}, donde uno entre X_2 y X_3 es opcionalmente reemplazado por O, NH o NR_7;

X_4 es un enlace;

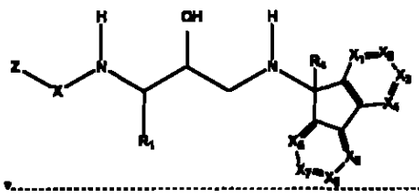
X_5, X_6, X_7 y X_8 son CH o CR_{200}, donde uno entre X_5, X_6, X_7 y X_8 es opcionalmente reemplazado por N; y

R_{200} es $-C_{1-4}$ alquilo, -halógeno; $-O-C_{1-3}$ alquilo; -pirrolilo o $-(CH_2)_{1-3}-N(R_7)_2$, donde R_7 es como se define más arriba.

Por otro lado, el invento proporciona compuestos de la fórmula V:

Eliminado: ¶

290



(V)

y una sal farmacológicamente aceptable de la misma, donde

Z es hidrógeno, -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo, donde cada uno de dichos grupos se reemplaza opcionalmente por 1 ó 2 grupos R_Z, donde 1 ó 2 grupos de metileno dentro de dichos grupos -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo son opcionalmente reemplazados por -(C=O)-;

en cada aparición R_Z es independientemente halógeno, -OH, -CN, -CF_3, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o -$NR_{100}R_{101}$;

R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, CO(C_1-C_6 alquilo) o SO_2C_1-C_6 alquilo;

X es -C(=O)-;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cicloalquilo, -C_1-C_4 alcoxi, amino, mono- dialquiloamino, arilo opcionalmente reemplazado por 1 ó 2 grupos R_{30}, heteroarilo o heterocicloalquilo;

R_{30} es halógeno, OH, CN, -CO-(C_1-C_4 alquilo), -NR_7R_8, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi y C_3-C_8 cicloalquilo;

R_7 y R_8 se seleccionan a partir de H; -C_1-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos seleccionados a partir de -OH, -NH_2 y halógeno; -C_3-C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; y -C_2-C_4 alquinilo;

X_1–X_5 son independientemente CH o CR_{200}, donde 1, 2, 3 ó 4 de X_1 – X_5 son opcionalmente reemplazados por N (más preferentemente, 1, 2 ó 3 se remplazan por N);

donde R_{200} es tal como se define más arriba.

En otra forma de presentación preferida de compuestos de la fórmula V,

Z es -C_1-C_6 alquilo;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos de arilo, donde cada grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{30},

R_{30} es independientemente halógeno, OH, CN, -NR_7R_8 ó C_1-C_6 alquilo,

291

R_7 y R_8 son independientemente H; -C_1-C_4 alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; o -C_3-C_6 cicloalquilo; y

$X_1 - X_8$ son CH o CR_{200}, donde uno o dos de $X_1 - X_8$ son opcionalmente reemplazados por N y R_{50} y R_{200} son como se define más arriba.

En otra forma de presentación preferida de compuestos de la fórmula V,

R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo, donde el grupo de arilo (preferentemente fenilo) se reemplaza opcionalmente por 1 ó 2 grupos R_{50},

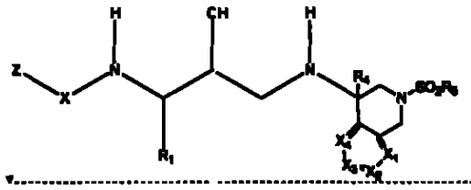
R_{50} se selecciona independientemente a partir de halógeno, OH o C_1-C_6 alquilo;

$X_1 - X_8$ son CH o CR_{200}, donde uno entre X_1–X_8 es opcionalmente reemplazado por N.

En otra forma de presentación preferida de compuestos de la fórmula V,

R_{200} es -C_1-C_5 alquilo, -C_2-C_5 alquenilo, -C_3-C_6 cicloalquilo, halógeno, -CF_3, -O-C_1-C_3 alquilo, -(C_1-C_3 alquilo)-O-(C_1-C_3 alquilo), pirrolilo o -$(CH_2)_{1-3}$-$N(R_7)_2$.

Un aspecto adicional del invento proporciona compuestos de la fórmula VI:



(VI)

y una sal farmacológicamente aceptable de la misma, donde

Z es hidrógeno, -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo, donde cada uno de dichos grupos se reemplaza opcionalmente por 1 ó 2 grupos R_Z, donde 1 ó 2 grupos de metileno dentro de dichos grupos -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo son opcionalmente reemplazados por -(C=O)-;

en cada aparición R_Z es independientemente halógeno, -OH, -CN, -CF_3, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o -$NR_{100}R_{101}$;

R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, CO(C_1-C_6 alquilo) o SO_2C_1-C_6 alquilo;

X es -C(=O)-;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cicloalquilo, -C_1-C_4 alcoxi, amino, mono- dialquilamino, arilo, heteroarilo y heterocicloalquilo, donde los grupos de arilo, heterocicloalquilo y heteroarilo son opcionalmente reemplazados por 1 ó

292

2 grupos R_{50}, donde el grupo de heterocicloalquilo también se reemplaza opcionalmente por =O;

R_{50} es halógeno, OH, CN, -CO-(C_1-C_4 alquilo), -NR_7R_8, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi y C_3-C_8 cicloalquilo;

R_7 y R_8 se seleccionan a partir de H; -C_1-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos seleccionados a partir de -OH, -NH_2 y halógeno; -C_3-C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; y -C_2-C_4 alquinilo;

R_4 es H o -C_1-C_4 alquilo;

R_5 es -C_1-C_4 alquilo;

X_1 – X_4 son independientemente CH o CR_{200}, donde 1 ó 2 de X_1 – X_4 son opcionalmente reemplazados por N; y donde

R_{200} es como se define más arriba.

En una forma de presentación preferida de los compuestos de la fórmula VI,

Eliminado: .

Z es -C_1-C_6 alquilo;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos de arilo, donde cada grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50},

cada R_{50} es independientemente halógeno, OH, CN, -NR_7R_8 o C_1-C_6 alquilo,

R_7 y R_8 son independientemente H; -C_1-C_4 alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; o -C_3-C_6 cicloalquilo; y

X_1 – X_4 son CH o CR_{200}, donde uno o dos de X_1 – X_4 son opcionalmente reemplazados por N,

R_{200} es como se define más arriba.

En otra forma de presentación preferida de compuestos de la fórmula VI,

R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo (preferentemente fenilo), donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50},

R_{50} se selecciona independientemente a partir de halógeno, OH o C_1-C_6 alquilo;

X_1–X_4 son CH o CR_{200}, donde uno entre X_1 – X_4 es opcionalmente reemplazado por N y donde

R_{50} y R_{200} son como se define más arriba.

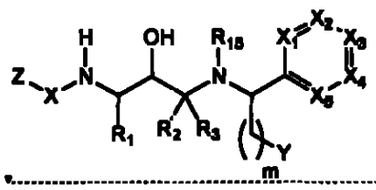
En otra forma de presentación preferida de compuestos de la fórmula VI,

R_{200} es -C_1-C_5 alquilo, -C_1-C_5 alquenilo, -C_3-C_6 cicloalquilo, halógeno, -CF_3, -O-C_1-C_3 alquilo, -(C_1-C_3 alquilo)-O-(C_1-C_3 alquilo), pirrolilo o -$(CH_2)_{1-3}$-$N(R_7)_2$.

Otro aspecto del invento proporciona compuestos de la fórmula VII:

Eliminado: ¶

293



(VII)

y las sales farmacológicamente aceptables de la misma, donde

Z, X, R_1, R_2 y R_3 son como se define más arriba;

m es 0 o un número entero entre 1-6;

Y es H, CN, OH, C_1-C_6 alcoxi, CO_2H, CO_2R_{215}, NH_2, arilo o heteroarilo; y

X_1–X_5 son independientemente CH o CR_{200}, donde 1 ó 2 de X_1–X_5 son opcionalmente reemplazados por N y

R_{200} es tal como se define más arriba.

En una forma de presentación preferida de compuestos de la fórmula VII, R_2, R_3 y R_{15} son H;

Z es hidrógeno, -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo, donde cada uno de dichos grupos se reemplaza opcionalmente por 1 ó 2 grupos R_Z, donde 1 ó 2 grupos de metileno dentro de dichos grupos -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo son opcionalmente reemplazados por -(C=O)-;

en cada aparición R_Z es independientemente halógeno, -OH, -CN, -CF_3, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o -$NR_{100}R_{101}$;

R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, CO(C_1-C_6 alquilo) o SO_2C_1-C_6 alquilo;

X es -C(=O)-;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cicloalquilo, -C_1-C_4 alcoxi, amino, mono- dialquiloamino, arilo, heteroarilo o heterocicloalquilo, donde los grupos de arilo, heterocicloalquilo y heteroarilo son opcionalmente reemplazados por 1 ó 2 grupos R_{50} y donde el grupo de heterocicloalquilo también se reemplaza adicionalmente por =O;

R_{50} es halógeno, OH, CN, -CO-(C_1-C_4 alquilo), -NR_7R_8, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

R_7 y R_8 son independientemente H; -C_1-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos seleccionados a partir de -OH, -NH_2 y halógeno; -C_3-

294

C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; o -C_2-C_4 alquinilo;

Y es como se define más arriba;

X_1–X_5 son independientemente CH o CR_{200}, donde 1 ó 2 de X_1–X_5 son opcionalmente reemplazados por N; y

R_{200} es tal como se define más arriba.

En otra forma de presentación preferida de compuestos de la fórmula VII,

Z es -C_1-C_6 alquilo;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos de arilo, donde cada grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50},

R_{50} es independientemente halógeno, OH, CN, -NR_7R_8 o C_1-C_6 alquilo, R_7 y R_8 son independientemente -H; -C_1-C_4 alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; o -C_3-C_6 cicloalquilo;

X_1–X_5 son CH o CR_{200}, donde uno o dos de X_1–X_5 son opcionalmente reemplazados por N.

Más preferentemente para compuestos de la fórmula VII,

R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo, donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50}, donde R_{50} se selecciona independientemente a partir de halógeno, OH o C_1-C_6 alquilo;

donde X_1 – X_5 son CH o CR_{200}, donde uno entre X_1 – X_5 es opcionalmente reemplazado por N, donde R_{50} y R_{200} son tal como se define más arriba.

En otra forma de presentación preferida de compuestos de la fórmula VII,

R_{200} es -C_1-C_5 alquilo, -C_1-C_3 alquenilo, -C_3-C_6 cicloalquilo, halógeno, -CF_3, -O-C_1-C_3 alquilo, -(C_1-C_3 alquilo)-O-(C_1-C_3 alquilo), pirrolilo o -$(CH_2)_{1-3}$-$N(R_7)_2$, donde R_7 es como se define más arriba.

Por otro lado, el invento proporciona compuestos de la fórmula II, es decir, compuestos de la fórmula II-a, donde

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -CF_3, -OCF_3, -C_{3-7} cicloalquilo, -C_1-C_4 alcoxi, amino y arilo, donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50};

donde

R_{50} se selecciona a partir de halógeno, OH, -CO-(C_1-C_3 alquilo), -NR_7R_8, C_1-C_6 alquilo, C_1-C_6 alcoxi y C_1-C_3 cicloalquilo; y

295

R_7 y R_8 son independientemente -H; -C_1-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; -C_3-C_6 cicloalquilo; o -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo).

Los compuestos preferidos de la fórmula II-a incluyen los de la fórmula II-b, es decir, compuestos donde

R_C es $(CR_{245}R_{250})_1$-arilo, donde el arilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{200}; y

R_{245} es H y R_{250} es H o C_1-C_6 alquilo; o

$CR_{245}R_{250}$ representa un grupo C_3-C_7 cicloalquilo.

Los compuestos preferidos de la fórmula II-b incluyen los de la fórmula II-c, es decir, compuestos donde

el $(CR_{245}R_{250})_1$-arilo es $(CR_{245}R_{250})_1$-fenilo, donde el fenilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{200}.

Los compuestos preferidos de la fórmula II-c incluyen los de la fórmula II-d, es decir, compuestos donde

el fenilo en $(CR_{245}R_{250})_1$-fenilo se reemplaza por

1-3 grupos R_{200} independientemente seleccionados ó

1 ó 2 grupos R_{200} independientemente seleccionados y

1 grupo de heteroarilo opcionalmente reemplazado por 1 grupo R_{200} ó 1 grupo de fenilo opcionalmente reemplazado por 1 grupo R_{200}.

Otros compuestos preferidos incluyen aquellos donde el fenilo se reemplaza por un grupo de heterocicloalquilo, que se reemplaza opcionalmente por 1 ó 2 grupos R_{200} y/o =O.

Los compuestos preferidos de la fórmula II-d incluyen los de la fórmula II-e, es decir, compuestos donde

R_{245} es hidrógeno y R_{250} es C_1-C_3 alquilo.

Los compuestos preferidos de la fórmula II-d incluyen los de la fórmula II-f, es decir, compuestos donde

R_{245} y R_{250} son ambos hidrógeno.

Los compuestos preferidos de la fórmula II-f incluyen los de la fórmula II-g, es decir, compuestos donde

el fenilo en $(CR_{245}R_{250})_1$-fenilo se reemplaza por

1 grupo R_{200} y

1 grupo de heteroarilo opcionalmente reemplazado por 1 grupo R_{200} ó

1 grupo R_{200} y 1 grupo de fenilo opcionalmente reemplazado por 1 grupo R_{200}; ó

296

1 grupo R_{200} y 1 heterocicloalquilo, que se reemplaza opcionalmente por un R_{200} o =O.

Los compuestos preferidos de la fórmula II-g incluyen los de la fórmula II-h, es decir, compuestos donde

R_{200} es C_1-C_6 alquilo, C_2-C_6 alquenilo, C_1-C_6 alcoxi, hidroxi(C_1-C_6)alquilo, C_1-C_6 alcoxi(C_1-C_6)alquilo, heterocicloalquilo, heteroarilo, halógeno, hidroxi, ciano o $-NR_{220}R_{225}$, donde R_{220} y R_{225} son independientemente hidrógeno o alquilo,

Los compuestos preferidos de las fórmulas II-g y II-h incluyen los de la fórmula II-i, es decir, compuestos donde

R_1 es bencilo donde la porción de fenilo se reemplaza opcionalmente por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, C_1-C_2 alquilo, C_1-C_2 alcoxi e hidroxi,

Los compuestos preferidos de la fórmula II-i incluyen los de la fórmula II-j, es decir, compuestos donde

Z es hidrógeno o C_1-C_3 alquilo,

Los compuestos preferidos de la fórmula II-i incluyen los de la fórmula II-k, es decir, compuestos donde

el fenilo en $(CR_{245}R_{250})_1$-fenilo se reemplaza por

1 grupo R_{200} y 1 grupo de heteroarilo, donde

el heteroarilo es un anillo heteroaromático de 5-6 componentes que contiene 0 ó 1-3 átomos de nitrógeno y 0 ó 1 átomo de oxígeno con la condición de que el anillo contiene por lo menos un átomo de nitrógeno u oxígeno y donde el anillo se reemplaza opcionalmente por uno o dos grupos que son independientemente C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxi(C_1-C_6)alquilo, hidroxi, halógeno, ciano, nitro, trifluorometilo, amino, mono(C_1-C_6)alquilamino o di(C_1-C_6)alquilamino.

Otros compuestos preferidos incluyen los de la fórmula II-i, es decir, compuestos de la fórmula II-K-1, donde

el fenilo en $(CR_{245}R_{250})_1$-fenilo se reemplaza por 1 grupo R_{200} y 1 grupo de heterocicloalquilo, que es piperazinilo, piperidinilo o pirrolidinilo y donde el anillo se reemplaza opcionalmente por uno o dos grupos que son independientemente C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxi(C_1-C_6)alquilo, hidroxi, halógeno, ciano, nitro, trifluorometilo, $-SO_2$-(C_1-C_4 alquilo), -C_1-C_6 alcanoilo, amino, mono(C_1-C_6)alquilamino o di(C_1-C_6)alquilamino.

Los compuestos preferidos de la fórmula II-k incluyen los de la fórmula II-l, es decir, compuestos

297

de heteroarilo como piridinilo, pirimidinilo, imidazolilo, pirazolilo, furanilo o oxazolilo, cada uno de los cuales se reemplaza opcionalmente por uno o dos grupos que son independientemente C_1-C_6 alquilo, C_1-C_6 alcoxi, hidroxi(C_1-C_6)alquilo, hidroxi, halógeno, ciano, nitro, trifluormetilo, amino, mono(C_1-C_6)alquilamino o di(C_1-C_6)alquilamino.

Los compuestos preferidos de la fórmula II-l incluyen los de la fórmula II-m, es decir, compuestos donde R_{200} es C_1-C_6 alquilo o C_2-C_6 alquenilo.

Los compuestos preferidos de la fórmula II-d incluyen los de la fórmula II-n, es decir, compuestos donde $CR_{245}R_{250}$ representa un grupo C_3-C_7 cicloalquilo.

Los compuestos preferidos de la fórmula II-n incluyen los de la fórmula II-o, es decir, compuestos donde $CR_{245}R_{250}$ representa un grupo C_5-C_7 cicloalquilo.

Los compuestos preferidos de la fórmula II-n incluyen los de la fórmula II-p, es decir, compuestos donde $CR_{245}R_{250}$ representa un grupo C_5-C_6 cicloalquilo.

Los compuestos preferidos de la fórmula II-p incluyen los de la fórmula II-q, es decir, compuestos donde $CR_{245}R_{250}$ representa un C_6 cicloalquilo.

Los compuestos preferidos de la fórmula II-q incluyen los de la fórmula II-r, es decir, compuestos donde el fenilo en $(CR_{245}R_{250})_1$-fenilo se reemplaza por

1 grupo R_{200}; ó

1 grupo R_{200} y un grupo de heteroarilo opcionalmente reemplazado por un grupo R_{210} ó

1 grupo R_{200} y un grupo de fenilo opcionalmente reemplazado por un grupo R_{270}.

Los compuestos preferidos de la fórmula II-r incluyen los de la fórmula II-s, es decir, compuestos donde

el fenilo en $(CR_{245}R_{250})_1$-fenilo se reemplaza por 1 grupo R_{200}.

Los compuestos preferidos de la fórmula II-s incluyen los de la fórmula II-t, es decir, compuestos donde

R_{200} es C_1-C_6 alquilo, C_2-C_6 alquenilo, C_1-C_6 alcoxi, hidroxi(C_1-C_6)alquilo, C_1-C_6 alcoxi(C_1-C_6)alquilo, halógeno, hidroxi, ciano o $-NR_{220}R_{225}$ donde

R_{220} y R_{225} son independientemente hidrógeno o alquilo.

Los compuestos preferidos de la fórmula II-t incluyen los de la fórmula II-u, es decir, compuestos donde

R_1 es bencilo donde la porción de fenilo del grupo bencilo se reemplaza opcionalmente por 1 ó 2 grupos independientemente seleccionados a partir de halógeno, C_1-C_2 alquilo, C_1-C_2 alcoxi e hidroxi.

298

Los compuestos preferidos de la fórmula II-u incluyen los de la fórmula II-v, es decir, compuestos donde

Z es hidrógeno o C_1-C_3 alquilo.

Los compuestos preferidos de la fórmula II-v incluyen los de la fórmula II-w, es decir, compuestos donde

R_{200} es C_1-C_6 alquilo o C_2-C_6 alquenilo.

Los compuestos preferidos de la fórmula II-w incluyen los de la fórmula II-x, es decir, compuestos donde

Z es C_1-C_3 alquilo y

R_1 es bencilo, 3-fluorbencilo ó 3,5-difluorbencilo.

Los compuestos preferidos de la fórmula II-m incluyen los de la fórmula II-y, es decir, compuestos donde

Z es C_1-C_3 alquilo y R_1 es bencilo, 3-fluorbencilo ó 3,5-difluorbencilo.

Los compuestos preferidos de la fórmula II-w incluyen los de la fórmula II-z, es decir, compuestos donde

R_{200} es C_1-C_3 alquilo.

Los compuestos preferidos de la fórmula II-m incluyen los de la fórmula II-aa, es decir, compuestos donde

R_{200} es C_3-C_5 alquilo.

Por otro lado, el invento proporciona compuestos de la fórmula II-bb, es decir, compuestos de las fórmulas II a II-aa, donde

R_2 es H, metilo o hidroximetilo y R_3 es H.

Otros compuestos preferidos de la fórmula II incluyen los de la fórmula II-cc, donde R_c es un anillo monocíclico o bicíclico de 5, 6, 7 8, 9 ó 10 carbonos fusionados con 1 grupo de arilo (preferentemente fenilo), heteroarilo (preferentemente piridilo, imidazolilo, tienilo o pirimidilo) o heterocicloalquilo (preferentemente piperidinilo o piperazinilo);

donde 1, 2 ó 3 carbonos del anillo monocíclico o bicíclico son opcionalmente reemplazados por -NH-, $-N(CO)_{0-1}R_{215}$-, $-N(CO)_{0-1}R_{220}$-, -O- o $-S(=O)_{0-2}$- y donde el anillo monocíclico o bicíclico se reemplaza opcionalmente por 1, 2 ó 3 grupos que son independientemente $-R_{205}$, $-R_{245}$, $-R_{250}$ o =O. Más preferentemente, R_c es como se define más arriba y R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo (preferentemente fenilo), donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50}. Más preferentemente, Z también es $-CH_2$-halógeno o $-CH_3$.

300
299

Otros compuestos preferidos de la fórmula II incluyen los de la fórmula II-dd, donde Rc es -CHR_{245}-CHR_{250}-fenilo; donde el fenilo se reemplaza opcionalmente por 1, 2, 3 ó 4 grupos R_{200}; y

R_{245} y R_{250} se juntan con el carbono con el que se ligan para forman un monociclo o biciclo de 5, 6, 7 u 8 átomos de carbono, donde 1 ó 2 átomos de carbono se reemplazan opcionalmente por 1 ó 2 grupos que son independientemente -O-, -S-, -SO_2-, -C(O)- o -NR_{220}- y donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo, NH_2, NH(C_1-C_6 alquilo), N(C_1-C_6 alquilo)(C_1-C_6 alquilo), -NH-C(O)C_1-C_5 alquilo, -NH-SO_2-(C_1-C_6 alquilo) o halógeno; y

R_1 es C_1-C_{10} alquilo reemplazado por un grupo de arilo (preferentemente fenilo), donde el grupo de arilo se reemplaza opcionalmente por 1 ó 2 grupos R_{50}. Más preferentemente, Z también es –CH_2-halógeno o –CH_3.

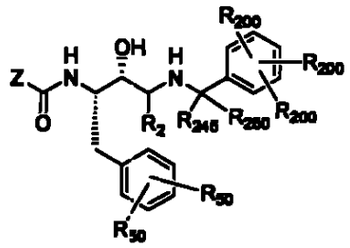
Los compuestos preferidos de la fórmula II-cc incluyen los de la fórmula II-dd, es decir compuestos de la fórmula II-cc, donde

R_{245} y R_{250} se juntan con los carbonos con los cuales se ligan para formar un monociclo o un biciclo de 5, 6, 7 u 8 átomos de carbono y donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo, NH_2, NH(C_1-C_6 alquilo), N(C_1-C_6 alquilo)(C_1-C_6 alquilo), -NH-C(O)C_1-C_5 alquilo, -NH-SO_2-(C_1-C_6 alquilo) o halógeno.

Los compuestos preferidos de la fórmula II-dd incluyen los de la fórmula II-ee, es decir compuestos de la fórmula II-dd, donde

R_{245} y R_{250} se juntan con los carbonos con los cuales se ligan para formar un monociclo o un biciclo de 5 ó 6, átomos de carbono y donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo, NH_2, NH(C_1-C_6 alquilo), N(C_1-C_6 alquilo)(C_1-C_6 alquilo), -NH-C(O)C_1-C_5 alquilo, -NH-SO_2-(C_1-C_6 alquilo) o halógeno.

Por otro lado, el invento proporciona compuestos de la fórmula VIII:



300

(VIII)

y sales farmacológicamente aceptables de la misma, donde

R_{245} y R_{250} se juntan con el carbono con el que se ligan para formar un monociclo o biciclo de 3, 4, 5, 6, 7 u 8 átomos de carbono, donde 1, 2 ó 3 átomos de carbono se reemplazan opcionalmente por 1, 2 ó 3 grupos que son independientemente -O-, -S-, $-SO_2-$, -C(O)- o $-NR_{220}-$; y donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo y halógeno;

Z, R_2, R_{50}, R_{200} y R_{220} son como se define para la fórmula I.

Los compuestos preferidos de la fórmula VIII incluyen compuestos de la fórmula VIII-a, es decir, compuestos de la fórmula VIII, donde al menos uno de los grupos R_{50} es halógeno.

Los compuestos preferidos de la fórmula VIII-a incluyen compuestos de la fórmula VIII-b, es decir, compuestos donde Z es $-CH_2$-halógeno o CH_3.

Los compuestos preferidos de la fórmula VIII-b incluyen compuestos de la fórmula VIII-c, es decir, compuestos de la fórmula VIII-b, donde ambos grupos R_{50} son halógenos y, más preferentemente, F o Cl. Aún más preferentemente, ambos grupos R_{50} son F.

Los compuestos preferidos de las fórmulas VIII, VIII-a, VIII-b y VIII-c incluyen compuestos de la fórmula VIII-d, donde

R_{245} y R_{250} se juntan con el carbono con el que se ligan para formar un monociclo de 3, 4, 5, 6 ó 7 átomos de carbono, donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo, =O y halógeno.

Los compuestos preferidos de las fórmulas VIII, VIII-a, VIII-b y VIII-c incluyen compuestos de la fórmula VIII-e, donde

R_{245} y R_{250} se juntan con el carbono con el que se ligan para formar un biciclo de 5, 6, 7 u 8 átomos de carbono, donde 1 átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de -O-, -S-, $-SO_2-$, -C(O)- y $-NR_{220}-$; y donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo y halógeno. Preferentemente el biciclo es biciclo[3.1.0]hexilo, 6-aza-biciclo[3.1.0]hexano, donde el nitrógeno se reemplaza opcionalmente por $-C(O)CH_3$ o CH_3, octahidro-ciclopenta[c]pirrolilo, 5-oxo-octahidro-pentalenilo, ro5-hidroxi-octahidro-pentalenilo, cada uno de los cuales se reemplaza opcionalmente por 1, 2, 3, 4, 5 ó 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo y halógeno.

Los compuestos preferidos de las fórmulas VIII-c, VIII-d y VIII-e incluyen compuestos donde un R_{200} es imidazolilo, tiazolilo, oxazolilo, tetrazolilo, tienilo, furanilo, bencilo,

301

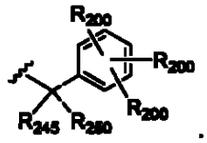
piperidinonilo o piridilo, donde cada elemento se reemplaza opcionalmente por halógeno o C_1-C_4 alquilo. También son preferidos los compuestos donde existe un segundo R_{200} de C_1-C_6 alquilo.

Los compuestos preferidos de las fórmulas VIII, VIII-a, VIII-b y VIII-c incluyen compuestos de la fórmula VIII-f, es decir, compuestos donde

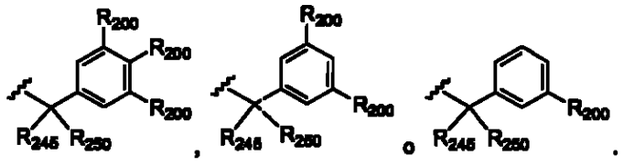
R_{245} y R_{250} se juntan con el carbono con el que se ligan para formar un monociclo de 3, 4, 5, 6 6 7 átomos de carbono, donde por lo menos 1 pero no más de 3 átomos de carbono son reemplazados por grupos que son independientemente -O-, -S-, -SO_2-, -C(O)- o -NR_{225}-; y donde el anillo se reemplaza opcionalmente por 1, 2, 3, 4, 5 6 6 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxilo y halógeno. Preferentemente el monociclo es tetrahidropiranilo, 2-oxo-tetrahidropirimidinonilo, piperidinilo, 2-oxo(1,3)oxazinonilo o ciclohexanonilo. Preferentemente, R_{220} es H, -C_1-C_6 alquilo, hidroxi C_1-C_6 alquilo, C_1-C_6 alcoxicarbonilo, -amino C_1-C_6 alquilo, -SO_2-C_1-C_6 alquilo, C_1-C_6 alcanoilo opcionalmente reemplazado por hasta tres halógenos, -C(O)NH_2, -C(O)NH(C_1-C_6 alquilo), -C(O)N(C_1-C_6 alquilo)(C_1-C_6 alquilo), -halo C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(C_3-C_7 cicloalquilo). Más preferentemente, R_{220} es H, -C_1-C_6 alquilo, C_1-C_6 alcoxicarbonilo, -SO_2-C_1-C_6 alquilo, -C(O)CF_3, -C(O)NH_2, -C(O)NH(C_1-C_6 alquilo) o -C(O)N(C_1-C_6 alquilo)(C_1-C_6 alquilo).

Los compuestos preferidos de las fórmulas VIII-d y VIII-e incluyen compuestos de la fórmula VIII-g, es decir, compuestos donde por lo menos un R_{200} es C_1-C_6 alquilo.

Los compuestos preferidos de las fórmulas VIIIa-VIIIg incluyen compuestos de la fórmula VIII-h, es decir, compuestos donde R_c posee la siguiente fórmula:



Más preferentemente, Rc posee la fórmula:

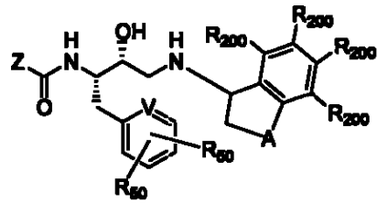


302

Por otro lado, el invento proporciona compuestos con las fórmulas VIII-VIII-h, donde R_2 es H.

Por otro lado, el invento proporciona compuestos con las fórmulas VIII-VIII-h, donde R_2 es C_1-C_4 alquilo o hidroxi C_1-C_4 alquilo.

Por otro lado, el invento proporciona compuestos de la fórmula IX:



(IX)

donde

A es $-CH_2-CR_{100}R_{101}-$, $-CH_2-S-$, $-CH_2-S(O)-$, $-CH_2-S(O)_2-$, $-CH_2-NR_{100}-$, $-CH_2-C(O)-$, $-CH_2-O-$, $-O-C-CR_{100}R_{101}-$, $-SO_2-NR_{100}$ o $-C(O)-O-$;

V es CH, CR_{50} o N; y

Z, R_{50} y R_{200} son tal como se los define para la fórmula I.

Los compuestos preferidos de la fórmula IX incluyen compuestos de la fórmula IX-a, es decir, compuestos de la fórmula IX, donde como mínimo uno de los grupos R_{50} es halógeno. Los compuestos preferidos de la fórmula IX-a incluyen compuestos de la fórmula IX-b, es decir, compuestos donde Z es $-CH_2$-halógeno o CH_3. Los compuestos preferidos de la fórmula IX-b incluyen compuestos de la fórmula IX-c, es decir, compuestos de la fórmula IX-b, donde ambos grupos R_{50} son halógenos y más preferentemente, F o Cl. Aún más preferentemente, ambos grupos R_{50} son F. En otros compuestos preferidos, por lo menos un R_{50} es OH o –O-bencilo. Más preferentemente, existe un segundo R_{50} que es un halógeno.

Los compuestos preferidos de las fórmulas IX, IX-a, IX-b y IX-c incluyen los de la fórmula IX-d, es decir, aquellos donde por lo menos un R_{200} es C_1-C_6 alquilo. Por un lado, R_{200} es C_3-C_6 alquilo. Por otro lado, R_{200} es C_1-C_4 alquilo.

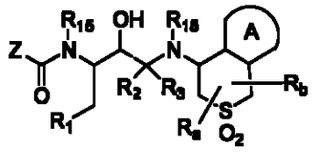
Los compuestos preferidos de la fórmula IX-d incluyen aquellos donde A es $-CH_2-O-$. También son preferidos los compuestos donde A es –C(O)-O-. Otros compuestos preferidos son aquellos donde A es $-CH_2-NR_{100}-$. También son preferidos los compuestos donde A es $-CH_2-S-$, $-CH_2-S(O)-$ o $-CH_2-S(O)_2-$.

Los compuestos preferidos de la fórmula IX incluyen compuestos donde un R_{200} es C_1-C_6 alquilo. Otros compuestos preferidos son aquellos donde existe un segundo R_{200} que es un

303

imidazolilo, tiazolilo, oxazolilo, tetrazolilo, tienilo, furanilo, bencilo o piridilo, donde cada grupo cíclico se reemplaza opcionalmente por -R_{205}, halógeno o C_1-C_4 alquilo. Por otro lado, son reemplazados por halógeno y/o C_1-C_4 alquilo. También son preferidos los compuestos donde un segundo R_{200} es C_1-C_6 alquilo.

Por un lado, el invento ofrece compuestos de la fórmula A-I:



y una sal farmacológicamente aceptable de la misma, donde

el anillo A es un grupo de heteroarilo, seleccionado a partir de piridinilo, pirimidinilo, imidazolilo, oxazolilo, tiazolilo, furanilo, tienilo, pirrolilo, donde dichos grupos de heteroarilo son opcionalmente reemplazados por uno, dos, tres o cuatro grupos R_c y/o R_d, donde

en cada aparición R_c y R_d son independientemente

C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y -NR_5R_6; o OH; NO_2; halógeno; CO_2H; C≡N; -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$ donde

R_{21} y R_{22} son iguales o diferentes y se seleccionan a partir de H; -C_1-C_6 alquilo opcionalmente reemplazado por un sustituto seleccionado a partir de OH y -NH_2; -C_1-C_6 alquilo reemplazado opcionalmente por entre uno y tres grupos que son independientemente -F, -Cl, -Br o –I; -C_3-C_7 cicloalquilo; -(C_1-C_2 alquilo)-(C_3-C_7 cicloalquilo); -(C_1-C_6 alquilo)-O-(C_1-C_3 alquilo); -C_2-C_6 alquenilo; -C_2-C_6 alquinilo; una cadena -C_1-C_6 alquilo con un enlace doble y uno triple; R_{17}; y R_{18}; o

-$(CH_2)_{0-4}$-CO-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alquenilo); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alquinilo); -$(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-CO-R_{17}; -$(CH_2)_{0-4}$-CO-R_{18}; -$(CH_2)_{0-4}$-CO-R_{19}; o -$(CH_2)_{0-4}$-CO-R_{11} donde

en cada aparición R_{17} es un grupo de arilo seleccionado a partir de fenilo, 1-naftilo, 2-naftilo y indanilo, indenilo, dihidronaftilo o tetralinilo, donde dichos grupos de arilo son opcionalmente reemplazados por uno, dos, tres o cuatro grupos que son independientemente

304

C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, F, Cl, Br, I, OH, SH y -NR_5R_6, C≡N, CF_3 y C_1-C_3 alcoxi; o

C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por uno, dos o tres sustitutos seleccionados a partir de F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y -NR_5R_6; o

halógeno; -C_1-C_6 alcoxi opcionalmente reemplazado por uno, dos o tres F; -$NR_{21}R_{22}$; OH; C≡N; C_3-C_7 cicloalquilo, opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y -NR_5R_6; o

-CO-(C_1-C_4 alquilo); -SO_2-NR_5R_6; -CO-NR_5R_6; o -SO_2-(C_1-C_4 alquilo);

en cada aparición R_{18} es un grupo de heteroarilo seleccionado a partir de piridinilo, pirimidinilo, quinolinilo, benzotienilo, indolilo, indolinilo, pridazinilo, pirazinilo, isoindolilo, isoquinolilo, quinazolinilo, quinoxalinilo, ftalazinilo, imidazolilo, isoxazolilo, pirazolilo, oxazolilo, tiazolilo, indolizinilo, indazolilo, benzotiazolilo, bencimidazolilo, benzofuranilo, furanilo, tienilo, pirrolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, oxazolopiridinilo, imidazopiridinilo, isotiazolilo, naftiridinilo, cinnolinilo, carbazolilo, beta-carbolinilo, isocromanilo, cromanilo, tetrahidroisoquinolinilo, isoindolinilo, isobenzotetrahidrofuranilo, isobenzotetrahidrotienilo, isobenzotienilo, benzoxazolilo, pyridopiridinilo, benzotetrahidrofuranilo, benzotetrahidrotienilo, purinilo, benzodioxolilo, triazinilo, fenoxazinilo, fenotiazinilo, teridinilo, benzotiazolilo, imidazopiridinilo, imidazotiazolilo, dihidrobencisoxazinilo, bencisoxazinilo, benzoxazinilo, dihidrobencisotiazinilo, benzopiranilo, benzotiopiranilo, cumarinilo, isocumarinilo, cromonilo, cromanonilo, piridinilo-N-óxido, tetrahidroquinolinilo, dihidroquinolinilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidrocumarinilo, dihidroisocumarinilo, isoindolinonilo, benzodioxanilo, benzoxazolinonilo, pirrolilo N-óxido, pirimidinilo N-óxido, piridazinilo N-óxido, pirazinilo N-óxido, quinolinilo N-óxido, indolilo N-óxido, indolinilo N-óxido, isoquinolilo N-óxido, quinazolinilo N-óxido, quinoxalinilo N-óxido, ftalazinilo N-óxido, imidazolilo N-óxido, isoxazolilo N-óxido, oxazolilo N-óxido, tiazolilo N-óxido, indolizinilo N-óxido, indazolilo N-óxido, benzotiazolilo N-óxido, bencimidazolilo N-óxido, pirrolilo N-óxido, oxadiazolilo N-óxido, tiadiazolilo N-

305

óxido, triazolilo N-óxido, tetrazolilo N-óxido, benzotiopiranilo S-óxido y benzotiopiranilo S,S-dióxido, donde dicho grupo de heteroarilo se reemplaza opcionalmente por uno, dos, tres o cuatro grupos que son independientemente

C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y $-NR_5R_6$; o

C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por uno, dos o tres sustitutos seleccionados a partir de -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alcoxi y $-NR_5R_6$; o

halógeno; $-C_1$-C_6 alcoxi opcionalmente reemplazado por uno, dos o tres -F; $-NR_{21}R_{22}$; -OH; -C≡N; C_3-C_7 cicloalquilo opcionalmente reemplazado por uno, dos o tres sustitutos independientemente seleccionados a partir de F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y $-NR_5R_6$; $-CO-(C_1$-C_4 alquilo); $-SO_2-NR_5R_6$; $-CO-NR_5R_6$; o $-SO_2-(C_1$-C_4 alquilo);

en cada aparición R_{19} es independientemente morfolinilo, tiomorfolinilo, tiomorfolinilo S-óxido, tiomorfolinilo S,S-dióxido, piperazinilo, homopiperazinilo, pirrolidinilo, pirrolinilo, tetrahidropiranilo, piperidinilo, tetrahidrofuranilo, tetrahidrotienilo, homopiperidinilo, homomorfolinilo, homotiomorfolinilo, homotiomorfolinilo S,S-dióxido, oxazolidinonilo, dihidropirazolilo, dihidropirrolilo, dihidropirazinilo, dihidropiridinilo, dihidropirimidinilo, dihidrofurilo, dihidropiranilo, tetrahidrotienilo S-óxido, tetrahidrotienilo S,S-dióxido u homotiomorfolinilo S-óxido; donde dicho grupo R_{19} se reemplaza opcionalmente por uno, dos, tres o cuatro grupos que son independientemente

C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y $-NR_5R_6$;

C_2-C_6 alquenilo o C_2-C_6 alquinilo, donde cada uno se reemplaza opcionalmente por uno, dos o tres sustitutos seleccionados a partir de F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y $-NR_5R_6$;

halógeno; C_1-C_6 alcoxi; C_1-C_6 alcoxi opcionalmente reemplazado por uno, dos o tres F; OH; C≡N; $-NR_{21}R_{22}$; C_3-C_7 cicloalquilo opcionalmente reemplazado por uno, dos o tres sustitutos independientemente seleccionados a partir de F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y -

306

NR_5R_6; -CO-(C_1-C_4 alquilo); $-SO_2-NR_5R_6$; -CO-NR_5R_6; $-SO_2-(C_1-C_4$ alquilo); o =O;

R_{11} se selecciona a partir de morfolinilo, tiomorfolinilo, piperazinilo, piperidinilo, homomorfolinilo, homotiomorfolinilo, homomorfolinilo S-óxido, homotiomorfolinilo S,S-dióxido, pirrolinilo y pirrolidinilo, donde cada grupo se reemplaza opcionalmente por uno, dos, tres o cuatro grupos que son independientemente C_1-C_6 alquilo, C_1-C_4 alcoxi y halógeno; o

En cada aparición R_c y R_d son independientemente $-(CH_2)_{0-4}-CO_2R_{20}$; $-(CH_2)_{0-4}-SO_2-NR_{21}R_{22}$; $-(CH_2)_{0-4}$-SO-(C_1-C_8 alquilo); $-(CH_2)_{0-4}-SO_2$-(C_1-C_{12} alquilo), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cicloalquilo); $-(CH_2)_{0-4}$-N(H o R_{20})-CO-O-R_{20}; $-(CH_2)_{0-4}$-N(H o R_{20})-CO-$N(R_{20})_2$; $-(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; $-(CH_2)_{0-4}$-N(-H o R_{20})-CO-R_{21}; $-(CH_2)_{0-4}-NR_{21}R_{22}$; $-(CH_2)_{0-4}-R_{11}$; $-(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); $-(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; $-(CH_2)_{0-4}$-O-CO-$N(R_{20})_2$; $-(CH_2)_{0-4}$-O-CS-$N(R_{20})_2$; $-(CH_2)_{0-4}$-O-$(R_{20})_2$; $-(CH_2)_{0-4}$-O-(R_{20})-CO_2H; $-(CH_2)_{0-4}$-S-(R_{20}); $-(CH_2)_{0-4}$-O-(C_1-C_6 alquilo opcionalmente reemplazado por uno, dos, tres, cuatro o cinco halógenos); C_3-C_7 cicloalquilo; $-(CH_2)_{0-4}$-N(-H o R_{20})-SO_2-R_{21}; o $-(CH_2)_{0-4}$- C_3-C_7 cicloalquilo; donde

R_{20} se selecciona a partir de C_1-C_6 alquilo, $-(CH_2)_{0-3}-(R_{17})$, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_3-C_7 cicloalquilo y $-(CH_2)_{0-3}-(R_{18})$; o

En cada aparición R_c y R_d son independientemente C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por C_1-C_3 alquilo, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi o $-NR_5R_6$;

o

el anillo A es un hidrocarburo aromático seleccionado a partir de fenilo, naftilo, tetralinilo, indanilo, dihidronaftilo ó 6,7,8,9-tetrahidro-5H-benzo[a]cicloheptenilo, donde cada hidrocarburo aromático se reemplaza opcionalmente por uno, dos, tres o cuatro grupos R_c y/o R_d que en cada aparición pueden ser iguales o diferentes y son:

C_1-C_6 alquilo, opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y $-NR_5R_6$; o

-OH; $-NO_2$; halógeno; $-CO_2H$; -C≡N; $-(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$; $-(CH_2)_{0-4}$-CO-(C_1-C_{12} alquilo), $-(CH_2)_{0-4}$-CO-(C_2-C_{12} alquenilo), $-(CH_2)_{0-4}$-CO-(C_2-C_{12} alquinilo), $-(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo), $-(CH_2)_{0-4}$-CO-R_{17}; $-(CH_2)_{0-4}$-CO-R_{18}; $-(CH_2)_{0-4}$-CO-R_{19}; $-(CH_2)_{0-4}$-CO-R_{11}; $-(CH_2)_{0-4}-CO_2R_{20}$; $-(CH_2)_{0-4}-SO_2-NR_{21}R_{22}$; $-(CH_2)_{0-4}$-SO-(C_1-C_8 alquilo); $-(CH_2)_{0-4}-SO_2$-(C_1-C_{12} alquilo), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cicloalquilo); $-(CH_2)_{0-4}$-N(H o R_{20})-CO_2R_{20}; $-(CH_2)_{0-4}$-N(H o R_{20})-CO-$N(R_{20})_2$; -

307

$(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N(-H o R_{20})-CO-R_{21}; -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-R_{11}; -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); -$(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; -$(CH_2)_{0-4}$-O-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-$(R_{20})_2$; -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-(C_1-C_6 alquilo opcionalmente reemplazado por uno, dos, tres, cuatro o cinco -F); C_3-C_7 cicloalquilo; -$(CH_2)_{0-4}$-N(-H o R_{20})-SO_2-R_{21}; -$(CH_2)_{0-4}$- C_3-C_7 cicloalquilo; o

C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por C_1-C_3 alquilo, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi o -NR_5R_6;

R_a y R_b se seleccionan independientemente a partir de C_1-C_3 alquilo, F, OH, SH, C≡N, CF_3, C_1-C_6 alcoxi, =O y -NR_5R_6; o

R_a y R_b y el carbono con el que se ligan forman un ciclo espiral C_3-C_7 que se reemplaza opcionalmente por 1 ó 2 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno, CF_3 o CN;

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -SH, -CN, -CF_3, -C_1-C_4 alcoxi, amino, mono- o dialquiloamino, -N(R)C(O)R', -OC(=O)-amino y -OC(=O)-mono- o dialquiloamino; o

R_1 es C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alcoxi, amino y mono- o dialquiloamino; o

R_1 es arilo, heteroarilo, heterociclilo, arilo C_1-C_6 alquilo, heteroarilo C_1-C_6 alquilo o heterocicloalquilo C_1-C_6 alquilo, donde

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos *que son independientemente* R_{50} o =O;

R_1 es G-L-A-E-W-, donde

W es un enlace, ausente, -S-, -S(O)-, -SO_2-, -O-, -NH- o -N(C_1-C_4 alquilo);

E es un enlace, ausente o C_1-C_3 alquileno;

A está ausente, alquilo, arilo o cicloalquilo, donde cada arilo o cicloalquilo se reemplaza opcionalmente por uno, dos o tres grupos R_{100}; heteroarilo opcionalmente

308

reemplazado por 1 ó 2 grupos R_{100}; o heterocicloalquilo opcionalmente reemplazado por 1 ó 2 grupos R_{200}, donde

en cada aparición R_{100} se selecciona independientemente a partir de NO_2, C≡N, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, -N(R)CO(R')R,-CO_2-R_{25}, -NH-CO_2-R_{25}, -O-(C_1-C_6 alquilo)-CO_2H, –NRR', –SR, CH_2OH, –C(O)-(C_1-C_6)alquilo, –C(O)NRR',-SO_2NRR', CO_2H, CF_3, halógeno, C_1-C_3 alcoxi, -OCF_3, -NH_2, OH, CN, halógeno y -$(CH_2)_{0-2}$-O-$(CH_2)_{0-2}$-OH;

donde

R_{25} se selecciona a partir de C_1-C_6 alquilo, -$(CH_2)_{0-2}$-cicloalquilo, -$(CH_2)_{0-2}$-arilo, donde el arilo se reemplaza opcionalmente por halógeno, hidroxi, C_1-C_6 alquilo, C_1-C_6 alquilo, amino, mono(C_1-C_6)alquiloamino o di(C_1-C_6)alquiloamino e hidrógeno y

En cada aparición R y R' son independientemente hidrógeno, C_1-C_6 alquilo, -$(CH_2)_{0-2}$-arilo o -$(CH_2)_{0-2}$-cicloalquilo, donde cada arilo o cicloalquilo se reemplaza opcionalmente por halógeno, hidroxi, C_1-C_6 alquilo, C_1-C_6 alquilo, amino, mono(C_1-C_6)alquiloamino o di(C_1-C_6)alquiloamino;

en cada aparición R_{200} se selecciona independientemente a partir de =O, C_1-C_3 alquilo, CF_3, F, Cl, Br, I, C_1-C_3 alcoxi, OCF_3, NH_2, OH y C≡N;

con la condición de que L es un enlace o está ausente cuando G está ausente,

o

L es –C(O)-, -S(O)-, -SO_2-, -O-, -C(R_{110})(R_{112})O-, -OC(R_{110})(R_{112})-, -N(R_{110})-, -CON(R_{110})-, -N(R_{110})CO-, -C(R_{110})(R')-,-C(OH)R_{110}-, -SO_2NR_{110}-, -N(R_{110})SO_2-, -N(R_{110})CON(R_{112})-, N(R_{110})CSN(R_{112})-, -OCO_2-, -NCO_2- o -OCON(R_{110})-, donde

R_{110} y R_{112} son independientemente hidrógeno, C_1-C_4 alquilo, C_1-C_4 hidroxialquilo, C_1-C_4 alcoxi C_1-C_4 alquilo o C_1-C_4 fluoralquilo; y

G está ausente o es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -CO_2H, -CO_2(C_1-C_4 alquilo), C_1-C_6 alcoxi, -OH, -NRR', -C_1-C_6 haloalquilo, -(C_1-C_{10} alquilo)-O-(C_1-C_3 alquilo), -C_2-C_{10} alquenilo, -C_2-C_{10} alquinilo, cadena -C_6-C_{10} alquilo con un enlace doble y uno triple, arilo opcionalmente reemplazado por 1, 2 ó 3 R_{100}, heteroarilo opcionalmente reemplazado por 1, 2 ó 3 R_{100} y C_1-C_6 alquilo; o

310
309

G es -$(CH_2)_{0-3}$-(C_3-C_7) cicloalquilo, donde el cicloalquilo se reemplaza opcionalmente por uno, dos o tres sustitutos independientemente seleccionados a partir de –CO_2H, -CO_2-(C_1-C_4 alquilo), C_1-C_6 alcoxi, OH, -NH_2, -C_1-C_6 haloalquilo, -(C_1-C_{10} alquilo)-O-(C_1-C_3 alquilo), -C_2-C_{10} alquenilo con 1 ó 2 enlaces dobles, C_2-C_{10} alquinilo con 1 ó 2 enlaces triples, cadena -C_4-C_{10} alquilo con un enlace doble y uno triple, arilo opcionalmente reemplazado por R_{100}, heteroarilo opcionalmente reemplazado por R_{100}, mono(C_1-C_6 alquilo)amino, di(C_1-C_6 alquilo) amino y C_1-C_6 alquilo,

o

G es -$(CH_2)_{0-4}$-arilo, -$(CH_2)_{0-4}$-heteroarilo o -$(CH_2)_{0-4}$-heterociclo, donde los grupos de arilo, heteroarilo -$(CH_2)_{0-4}$-heterociclo son opcionalmente reemplazados por 1, 2 ó 3 R_{100}, donde el grupo heterocíclico se reemplaza opcionalmente por 1 ó 2 grupos R_{200};

o

G es -$C(R_{10})(R_{12})$-CO-NH-R_{14}, donde

R_{10} y R_{12} son iguales o diferentes y se seleccionan a partir de H, -C_1-C_6 alquilo, -(C_1-C_4 alquilo)-arilo, donde el arilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{100}; -(C_1-C_4 alquilo)-heteroarilo, donde el heteroarilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{100}; -(C_1-C_4 alquilo)-heterociclo, donde el heterociclo se reemplaza opcionalmente por 1 ó 2 grupos R_{200}; heteroarilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{100}; heterociclo opcionalmente reemplazado por 1 ó 2 grupos R_{200}; -$(CH_2)_{1-4}$-OH, -$(CH_2)_{1-4}$-Y-$(CH_2)_{1-4}$-arilo, donde el arilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{100}; -$(CH_2)_{1-4}$-Y-$(CH_2)_{1-4}$-heteroarilo, donde el heteroarilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{100}; -arilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{100}, -heteroarilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{100} y -heterociclo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{200}, donde
Y es –O–, -S—, -NH- o -NH(C_1-C_6 alquilo); y

R_{14} es H, -C_1-C_6 alquilo, -arilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{100}, -heteroarilo opcionalmente reemplazado por 1, 2 ó 3 grupos R_{100}, -heterociclo opcionalmente reemplazado por 1 ó 2 grupos R_{200}, -(C_1-C_4 alquilo)-arilo, donde el arilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{100}; -(C_1-C_4 alquilo)-heteroarilo, donde el heteroarilo se reemplaza opcionalmente por 1, 2 ó 3 grupos R_{100}; -(C_1-C_4 alquilo)-heterociclo, donde

310

el heterociclo se reemplaza opcionalmente por 1 ó 2 grupos R_{200} o $-(CH_2)_{0-2}-O-(CH_2)_{1-2}-OH$;

R_2 Y R_3 SE SELECCIONAN INDEPENDIENTEMENTE A PARTIR DE -H, C_1-C_6 ALQUILO, OPCIONALMENTE REEMPLAZADO POR UNO, DOS O TRES SUSTITUTOS SELECCIONADOS A PARTIR DE C_1-C_3 ALQUILO, -F, -CL, -BR, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 ALCOXI Y $-NR_5R_6$; $-(CH_2)_{0-4}-R_{17}$; $-(CH_2)_{0-4}-R_{18}$; C_2-C_6 ALQUENILO O C_2-C_6 ALQUINILO, DONDE CADA ELEMENTO SE REEMPLAZA OPCIONALMENTE POR UNO, DOS O TRES SUSTITUTOS SELECCIONADOS A PARTIR DE -F, -CL, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 ALCOXI Y $-NR_5R_6$; $-(CH_2)_{0-4}-C_3$-C_7 CICLOALQUILO, OPCIONALMENTE REEMPLAZADO POR UNO, DOS O TRES SUSTITUTOS SELECCIONADOS A PARTIR DE -F, -CL, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 ALCOXI Y $-NR_5R_6$; DONDE

en cada aparición R_5 y R_6 son independientemente H o C_1-C_6 alquilo; o

R_5 y R_6 y el nitrógeno al que están ligados forman en cada aparición un anillo de heterocicloalquilo de 5 ó 6 componentes; o

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a siete átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, $-SO_2-$ o $-NR_7-$;

en cada aparición R_{15} se selecciona independientemente a partir de hidrógeno, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 alcoxi C_1-C_6 alquilo, hidroxi C_1-C_6 alquilo, halo C_1-C_6 alquilo, C_1-C_6 alcanoilo, cada uno de los cuales se reemplaza o no por 1, 2, 3 ó 4 grupos independientemente seleccionados a partir de halógeno, alquilo, hidroxi, alcoxi, NH_2 y $-R_{26}-R_{27}$; y

$-R_{26}-R_{27}$; donde

R_{26} se selecciona a partir de un enlace, –C(O)-, $-SO_2-$, $-CO_2-$, $-C(O)NR_5-$ y $-NR_5C(O)-$,

R_{27} se selecciona a partir de C_1-C_6 alquilo, C_1-C_6 alcoxi, arilo C_1-C_6 alquilo, heterocicloalquilo y heteroarilo, donde cada uno de los elementos precedentes se reemplaza o no por 1, 2, 3, 4 ó 5 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno, haloalquilo, hidroxialquilo, $-NR_5R_6$, $-C(O)NR_5R_6$;

Z se selecciona a partir de H; C_1-C_6 alcoxi; C_1-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos que son independientemente OH, halógeno, C_1-C_4 alcoxi, CF_3, OCF_3, NO_2, CN y NR_5R_6; arilo; heteroarilo; arilcalquilo; y heteroarilcalquilo; y donde cada grupo de arilo, heteroarilo, arilcalquilo y heteroarilcalquilo se reemplaza opcionalmente por 1 ó 2 grupos que son independientemente C_1-C_4 alquilo, halógeno, haloalquilo y C_1-C_4 alcoxi.

Los compuestos preferidos de la fórmula A-I incluyen aquellos donde

311

R_2 y R_3 se seleccionan independientemente a partir de H; C_1-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 sustitutos que se seleccionan independientemente a partir de C_1-C_4 alquilo, halógeno, $-CF_3$ y C_1-C_4 alcoxi; y C_2-C_6 alquenilo o C_2-C_6 alquinilo, donde cada elemento se reemplaza opcionalmente por uno, dos o tres sustitutos seleccionados a partir de -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alcoxi y $-NR_5R_6$; o

R_2, R_3 y el carbono al que se ligan forman un carbociclo de tres a siete átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, $-SO_2-$ o $-NR_7-$; donde

R_7 se selecciona a partir de H, $-C_1$-C_8 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, $-NH_2$, fenilo y halógeno; C_3-C_8 cicloalquilo; $-(C_1$-C_2 alquilo)-(C_3-C_8 cicloalquilo); $-(C_1$-C_6 alquilo)-O-(C_1-C_4 alquilo); C_2-C_6 alquenilo; C_2-C_6 alquinilo; fenilo; naftilo; heteroarilo; heterocicloalquilo.

Otros compuestos igualmente preferidos de la fórmula A-I incluyen aquéllos donde en cada aparición R_{15} se selecciona independientemente a partir de hidrógeno, C_1-C_4 alquilo, C_1-C_4 alcoxi, C_1-C_4 alcanoilo, cada uno de los cuales se reemplaza o no por 1, 2, 3 ó 4 grupos independientemente seleccionados a partir de halógeno, alquilo, hidroxi, C_1-C_4 alcoxi y NH_2; y $-R_{26}$-R_{27}; donde

R_{26} se selecciona a partir de un enlace, –C(O)-, $-SO_2-$, $-CO_2-$, $-C(O)NR_5-$ y $-NR_5C(O)-$; y

R_{27} se selecciona a partir de C_1-C_6 alquilo, C_1-C_6 alcoxi y bencilo, donde cada uno de los elementos precedentes se reemplaza o no por 1, 2, 3, 4 ó 5 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno, halo C_1-C_4 alquilo, hidroxialquilo, $-C(O)NR_5R_6$ o $-NR_5R_6$.

Otros compuestos igualmente preferidos de la fórmula A-I incluyen aquéllos donde R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -SH, -CN, $-CF_3$, $-C_1$-C_4 alcoxi, amino, mono- o dialquiloamino, –N(R)C(O)R', -OC(=O)-amino y -OC(=O)-mono- o dialquiloamino; o

R_1 es C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alcoxi, amino y mono- o dialquiloamino; o

R_1 es arilo, heteroarilo, heterociclilo, arilo C_1-C_6 alquilo, heteroarilo C_1-C_6 alquilo o heterocicloalquilo C_1-C_6 alquilo; donde

312

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O; y

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_6 haloalquilo, C_1-C_4 haloalcoxi, fenilo, NR_7R_8 y C_1-C_6 alcoxi.

Otros compuestos igualmente preferidos de la fórmula A-I incluyen los de la fórmula A-I-1, es decir, compuestos de la fórmula A-I donde

R_c y R_d se seleccionan independientemente a partir de C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, CN, CF_3, C_1-C_3 alcoxi y -NR_5R_6; hidroxi; nitro; halógeno; -CO_2H; ciano; y -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$; donde

R_{21} y R_{22} independientemente representan hidrógeno, C_1-C_6 alquilo, hidroxilo(C_1-C_6)alquilo, amino(C_1-C_6)alquilo, haloalquilo, C_3-C_7 cicloalquilo, -(C_1-C_2 alquilo)-(C_3-C_7 cicloalquilo), -(C_1-C_6 alquilo)-O-(C_1-C_3 alquilo), -C_2-C_6 alquenilo, -C_2-C_6 alquinilo, cadena -C_1-C_6 alquilo con un enlace doble y uno triple, fenilo, naftilo, heteroarilo; o

R_c y R_d se seleccionan independientemente a partir de -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alquenilo); $CH_2)_{0-4}$-CO-(C_2-C_{12})alquinilo; -$(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-CO-fenilo; -$(CH_2)_{0-4}$-CO-naftilo; -$(CH_2)_{0-4}$-CO-heteroarilo; -$(CH_2)_{0-4}$-CO-heterocicloalquilo; -$(CH_2)_{0-4}$-CO_2R_{20}; donde

R_{20} se selecciona a partir de C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(fenilo), -$(CH_2)_{0-2}$-(naftilo), C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_3-C_7 cicloalquilo y -$(CH_2)_{0-2}$-(heteroarilo) o

R_c y R_d se seleccionan independientemente a partir de -$(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-SO-(C_1-C_8 alquilo); -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-

313

N(H o R_{20})-CO_2R_{20}; -$(CH_2)_{0-4}$-N(H o R_{20})-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N(-H o R_{20})-CO-R_{21}; -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-heterocicloalquilo; -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); -$(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; -$(CH_2)_{0-4}$-O-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-(R_{20}); -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-halo(C_1-C_6)alquilo; -$(CH_2)_{0-4}$-O-(C_1-C_6)alquilo; C_3-C_8 cicloalquilo; y -$(CH_2)_{0-4}$-N(-H o R_{20})-SO_2-R_{21}; o

R_c y R_d son independientemente C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por C_1-C_4 alquilo, halógeno, hidroxi, SH, ciano, CF_3, C_1-C_4 alcoxi o NR_5R_6; donde

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

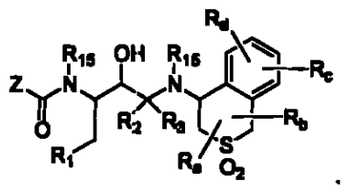
cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O;

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, fenilo, NR_7R_8 y C_1-C_6 alcoxi.

Los compuestos preferidos de la fórmula A-I-1 incluyen los de la fórmula A-II:



Los compuestos preferidos de la fórmula II incluyen aquéllos donde

R_2 y R_3 se seleccionan independientemente a partir de H; C_1-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 sustitutos que se seleccionan independientemente a partir de C_1-C_4 alquilo, halógeno, -CF_3 y C_1-C_4 alcoxi; C_2-C_6 alquenilo o C_2-C_6 alquinilo, donde cada

314

elemento se reemplaza opcionalmente por uno, dos o tres sustitutos seleccionados a partir de -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alcoxi y $-NR_5R_6$;

en cada aparición R_5 y R_6 son independientemente H o C_1-C_6 alquilo; o

R_5 y R_6 y el nitrógeno al que están ligados forman en cada aparición un anillo de heterocicloalquilo de 5 ó 6 componentes;

o

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, $-SO_2-$ o $-NR_7-$; donde

R_7 se selecciona a partir de H; $-C_1$-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, $-NH_2$ y halógeno; $-C_3$-C_6 cicloalquilo; $-(C_1$-C_4 alquilo$)$-O-$(C_1$-C_4 alquilo); $-C_2$-C_4 alquenilo; y $-C_2$-C_4 alquinilo.

Otros compuestos preferidos de la fórmula A-II incluyen aquéllos donde en cada aparición R_{15} se selecciona independientemente a partir de hidrógeno, C_1-C_4 alquilo, C_1-C_6 alcanoilo, bencilo opcionalmente reemplazado por OCH_3, -C(O)-butilo terciario y -CO_2-bencilo.

Otros compuestos preferidos de la fórmula A-II incluyen aquéllos donde

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -SH, -CN, $-CF_3$, $-C_1$-C_4 alcoxi, amino, mono- o dialquiloamino, –N(R)C(O)R', -OC(=O)-amino OC(=O)-mono- y dialquiloamino; o

R_1 es C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alcoxi, amino y mono- o dialquiloamino; o

R_1 es arilo, heteroarilo, heterociclilo, arilo C_1-C_6 alquilo, heteroarilo C_1-C_6 alquilo o heterocicloalquilo C_1-C_6 alquilo;

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O;

315

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

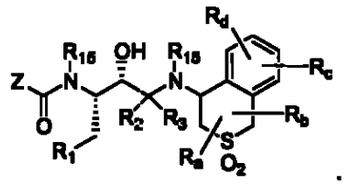
donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_4 haloalquilo, C_1-C_4 haloalcoxi, fenilo, NR_7R_8 y C_1-C_4 alcoxi.

Además, otros compuestos preferidos de la fórmula A-II incluyen los de la fórmula A-II-1, es decir, los compuestos de la fórmula A-II donde

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, -NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_4 haloalquilo, C_1-C_4 haloalcoxi, fenilo, NR_7R_8 y C_1-C_4 alcoxi.

Los compuestos preferidos de la fórmula A-II-1 incluyen los de la fórmula A-III:



Otros compuestos preferidos de la fórmula A-III incluyen los de la fórmula A-III-1, es decir, compuestos de la fórmula A-III donde

R_1 es fenilo, fenilo C_1-C_6 alquilo, naftilo o naftilo C_1-C_6 alquilo, donde el grupo de fenilo o naftilo se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50}.

Otros compuestos preferidos de la fórmula A-III-1 incluyen los de la fórmula A-III-2, es decir, compuestos de la fórmula A-III-1 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, -SO_2- o -NR_7-; donde

316

R_7 es H, -C_1-C_8 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; -C_2-C_4 alquenilo; o -C_2-C_4 alquinilo.

Los compuestos preferidos de la fórmula A-III-2 incluyen los de la fórmula A-III-3, es decir, compuestos de la fórmula A-III-2 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive.

Compuestos igualmente preferidos de la fórmula A-III-2 incluyen los de la fórmula A-III-4, es decir, compuestos de la fórmula A-III-2 compuestos donde

R_2, R_3 y el carbono al que están ligados forman un grupo de heterocicloalquilo que contiene de 2 a 5 átomos de carbono y un grupo seleccionado a partir de –O-, -S-, -SO_2- y -NR_7-; donde

R_7 es H, -C_1-C_8 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, -NH_2 y halógeno; -C_2-C_4 alquenilo; o -C_2-C_4 alquinilo.

Otros compuestos igualmente preferidos de la fórmula A-III-1 incluyen los compuestos de la fórmula A-III-5, es decir, compuestos de la fórmula A-III-1 donde

R_2 y R_3 se seleccionan independientemente a partir de H; C_1-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 sustitutos que se seleccionan independientemente a partir de C_1-C_4 alquilo, halógeno, -CF_3 y C_1-C_4 alcoxi; C_2-C_6 alquenilo; y C_2-C_6 alquinilo.

Otros compuestos preferidos de las fórmulas A-III-3, A-III-4 y A-III-5 incluyen los de la fórmula A-III-6, es decir, compuestos de las fórmulas A-III-3, A-III-4 y A-III-5 donde

R_a y R_b se seleccionan independientemente a partir de C_1-C_6 alquilo, C_1-C_6 alcoxi, halógeno, CN, OH, hidroxialquilo, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi y -C_1-C_6 alquilo-NR_5R_6; o

R_a y R_b se ligan al mismo carbono y forman un ciclo espiral C_3-C_7; y

en cada aparición R_{13} es independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-III-6 incluyen los de la fórmula A-III-6a, es decir, compuestos de la fórmula A-III-6 donde

R_c y R_d se seleccionan independientemente a partir de C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y -NR_5R_6; hidroxi; halógeno; C_3-C_6 alquenilo o C_2-C_6 alquinilo, donde

el grupo de alquenilo o alquinilo se reemplaza opcionalmente por C_1-C_4 alquilo, halógeno, hidroxi, SH, ciano, CF_3, C_1-C_4 alcoxi o NR_5R_6.

Otros compuestos preferidos de la fórmula A-III-6 incluyen aquéllos donde

317

R_c y R_d son -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$, -$(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-SO-(C_1-C_6 alquilo); -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-N(H o R_{20})-CO-O-R_{20}; -$(CH_2)_{0-4}$-N(H o R_{20})-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N(-H o R_{20})-CO-R_{21}; o -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; donde

R_{21} y R_{22} independientemente representan hidrógeno, C_1-C_6 alquilo, hidroxilo(C_1-C_6)alquilo, amino(C_1-C_6)alquilo, haloalquilo, C_3-C_7 cicloalquilo, -(C_1-C_2 alquilo)-(C_3-C_7 cicloalquilo), -(C_1-C_6 alquilo)-O-(C_1-C_3 alquilo), -C_2-C_6 alquenilo, -C_2-C_6 alquinilo, fenilo, naftilo o heteroarilo;

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Asimismo otros compuestos preferidos de la fórmula A-III-6 incluyen aquéllos donde

R_c y R_d son -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alquenilo); $CH_2)_{0-4}$-CO-(C_2-C_{12})alquinilo; -$(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-CO-fenilo; -$(CH_2)_{0-4}$-CO-naftilo; -$(CH_2)_{0-4}$-CO-heteroarilo; -$(CH_2)_{0-4}$-CO-heterocicloalquilo; -$(CH_2)_{0-4}$-CO_2R_{20}; donde

R_{20} se selecciona a partir de C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(fenilo), -$(CH_2)_{0-2}$-(naftilo), C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_3-C_7 cicloalquilo y -$(CH_2)_{0-2}$-(heteroarilo);

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Otros compuestos preferidos de la fórmula A-III-6 incluyen aquéllos donde

R_c y R_d son -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); -$(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; -$(CH_2)_{0-4}$-O-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-(R_{20}); -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-halo(C_1-C_6)alquilo; -$(CH_2)_{0-4}$-O-(C_1-C_6)alquilo; C_3-C_8 cicloalquilo; o -$(CH_2)_{0-4}$-N(-H o R_{20})-SO_2-R_{21}; donde

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

318

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O;

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, fenilo, NR_7R_8 y C_1-C_6 alcoxi.

Otros compuestos preferidos de la fórmula A-III incluyen los de la fórmula A-III-7, es decir, compuestos de la fórmula A-III donde

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -SH, -CN, -CF_3, -C_1-C_4 alcoxi, amino, mono- o dialquiloamino, –N(R)C(O)R', -OC(=O)-amino y -OC(=O)-mono- o dialquiloamino; o

R_1 es C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alcoxi, amino y mono- o dialquiloamino.

Otros compuestos preferidos de la fórmula A-III-7 incluyen los compuestos de la fórmula A-III-8, es decir, compuestos de la fórmula A-III-7 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, -SO_2- o -NR_7-; donde

R_7 se selecciona a partir de H o -C_1-C_4 alquilo opcionalmente reemplazado por 1 grupo seleccionado a partir de -OH, -NH_2 y halógeno.

Los compuestos preferidos de la fórmula A-III-8 incluyen los compuestos de la fórmula A-III-9, es decir, compuestos de la fórmula A-III-8 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive.

320

319

Otros compuestos preferidos de la fórmula A-III-8 incluyen los compuestos de la fórmula A-III-10, es decir, compuestos de la fórmula A-III-8 donde

R_2, R_3 y el carbono al que están ligados forman un grupo de heterocicloalquilo que contiene de 2 a 5 átomos de carbono y un grupo seleccionado a partir de –O–, -S–, $-SO_2-$ y $-NR_7-$; donde

R_7 se selecciona a partir de H o $-C_1-C_4$ alquilo opcionalmente reemplazado por 1 grupo seleccionado a partir de -OH, $-NH_2$ y halógeno.

Asimismo, otros compuestos preferidos de la fórmula A-III-8 incluyen los compuestos de la fórmula A-III-11, es decir, compuestos de la fórmula A-III-8 donde

R_2 y R_3 se seleccionan independientemente a partir de H; C_1-C_6 alquilo opcionalmente reemplazado por 1 ó 2 sustitutos que se seleccionan independientemente a partir de C_1-C_4 alquilo, halógeno, $-CF_3$ y C_1-C_4 alcoxi; C_2-C_6 alquenilo; y C_2-C_6 alquinilo.

Otros compuestos preferidos de las fórmulas A-III-9, A-III-10 y A-III-11 incluyen los de la fórmula A-III-12, es decir, compuestos de las fórmulas A-III-9, A-III-10 y A-III-11 donde

R_a y R_b se seleccionan independientemente a partir de C_1-C_3 alquilo, F, OH, C≡N, CF_3, C_1-C_6 alcoxi y $-NR_5R_6$; y

en cada aparición R_{13} es independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-III-12 incluyen aquellos compuestos donde

R_c y R_d se seleccionan independientemente a partir de C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y $-NR_5R_6$; hidroxi; halógeno;

C_2-C_6 alquenilo y C_2-C_6 alquinilo; donde

el grupo de alquenilo o alquinilo se reemplaza opcionalmente por C_1-C_4 alquilo, halógeno, hidroxi, SH, ciano, CF_3, C_1-C_4 alcoxi o NR_5R_6.

Otros compuestos preferidos de la fórmula A-III-12 incluyen aquellos compuestos donde

R_c y R_d son $-(CH_2)_{0-4}-CO-NR_{21}R_{22}$, $-(CH_2)_{0-4}-SO_2-NR_{21}R_{22}$; $-(CH_2)_{0-4}-SO-(C_1-C_8$ alquilo); $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alquilo); $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cicloalquilo); $-(CH_2)_{0-4}-N(H$ o $R_{20})-CO-O-R_{20}$; $-(CH_2)_{0-4}-N(H$ o $R_{20})-CO-N(R_{20})_2$; $-(CH_2)_{0-4}-N-CS-N(R_{20})_2$; $-(CH_2)_{0-4}-N(-H$ o $R_{20})-CO-R_{21}$; o $-(CH_2)_{0-4}-NR_{21}R_{22}$; donde

R_{21} y R_{22} independientemente representan hidrógeno, C_1-C_6 alquilo, hidroxilo(C_1-C_6)alquilo, amino(C_1-C_6)alquilo, haloalquilo, C_3-C_7 cicloalquilo, $-(C_1-C_2$ alquilo)-(C_3-C_7 cicloalquilo), $-(C_1-C_6$ alquilo)-O-(C_1-C_3 alquilo), $-C_2-C_6$ alquenilo, $-C_2-C_6$ alquinilo, fenilo, naftilo o heteroarilo;

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

320

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Además, otros compuestos preferidos de la fórmula A-III-12 incluyen aquellos compuestos donde R_c y R_d son -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alquenilo); $CH_2)_{0-4}$-CO-(C_2-C_{12})alquinilo; -$(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-CO-fenilo; -$(CH_2)_{0-4}$-CO-naftilo; -$(CH_2)_{0-4}$-CO-heteroarilo; -$(CH_2)_{0-4}$-CO-heterocicloalquilo; -$(CH_2)_{0-4}$-CO_2R_{20}; donde

R_{20} se selecciona a partir de C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(fenilo), -$(CH_2)_{0-2}$-(naftilo), C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_3-C_7 cicloalquilo, -$(CH_2)_{0-2}$-(heterocicloalquilo) y -$(CH_2)_{0-2}$-(heteroarilo);

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Asimismo, otros compuestos preferidos de la fórmula A-III-12 incluyen aquellos compuestos donde

R_c y R_d son -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); -$(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; -$(CH_2)_{0-4}$-O-CO-N$(R_{20})_2$; -$(CH_2)_{0-4}$-O-CS-N$(R_{20})_2$; -$(CH_2)_{0-4}$-O-(R_{20}); -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-halo(C_1-C_6)alquilo; -$(CH_2)_{0-4}$-O-(C_1-C_6)alquilo; C_3-C_8 cicloalquilo; o -$(CH_2)_{0-4}$-N(-H o R_{20})-SO_2-R_{21}; donde

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

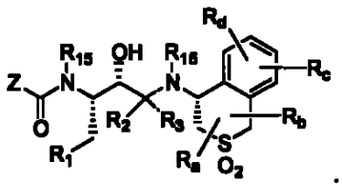
cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O;

R_{20} en cada aparición se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

321

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos *independientemente* seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, fenilo, NR_7R_8 y C_1-C_6 alcoxi.

Los compuestos preferidos de la fórmula A-III-6a incluyen los de la fórmula A-IV



Los compuestos preferidos de la fórmula A-IV incluyen aquéllos donde

R_2 y R_3 son independientemente H o C_1-C_4 alquilo.

Otros compuestos preferidos de la fórmula A-IV incluyen los de la fórmula A-IV-1, es decir, compuestos de la fórmula A-IV donde

R_a y R_b son independientemente H o C_1-C_3 alquilo; y

R_1 es fenilo, opcionalmente reemplazado por 1, 2 ó 3 grupos R_{50}; y

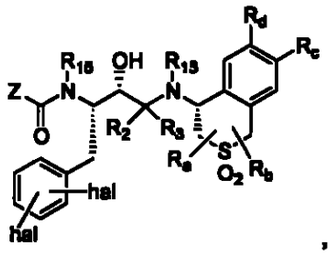
en cada aparición R_{15} es independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-IV-1 incluyen los de la fórmula A-IV-2, es decir, compuestos de la fórmula A-IV-1 donde

R_1 es un dihalofenilo; y

R_2 y R_3 son independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-IV-2 incluyen compuestos de la fórmula A-V



donde

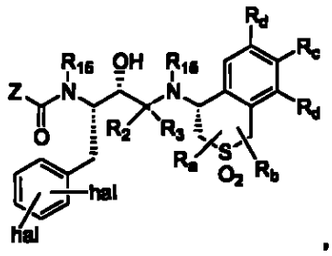
hal en cada aparición se selecciona independientemente a partir de F, Cl, Br y I.

Otros compuestos preferidos de la fórmula A-V incluyen aquellos compuestos donde

R_c es un C_1-C_4 grupo de alquilo.

322

Otros compuestos preferidos de la fórmula A-IV-2 incluyen compuestos de la fórmula A-VI

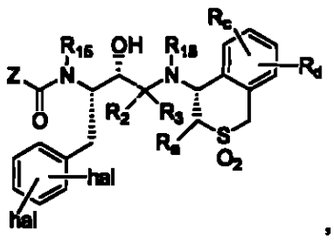


donde

hal en cada aparición se selecciona independientemente a partir de F, Cl, Br y I.

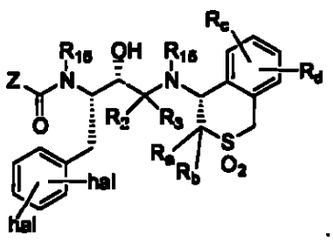
Los compuestos preferidos de la fórmula A-VI incluyen aquellos compuestos donde R_c es un grupo C_1-C_4 alquilo.

Otros compuestos preferidos de la fórmula A-IV-2 incluyen compuestos de la fórmula A-VII



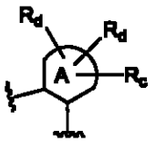
donde R_b es H.

Además, otros compuestos preferidos de la fórmula A-IV-2 incluyen compuestos de la fórmula A-VIII



Otros compuestos preferidos de la fórmula A-I-1 incluyen los compuestos de la fórmula A-IX, es decir, compuestos de la fórmula A-I-1 donde

323



es un grupo de heteroarilo de 5 ó 6 componentes.

Los compuestos preferidos de la fórmula A-IX incluyen compuestos de la fórmula A-IX-1, es decir, compuestos de la fórmula A-IX donde

R_2 Y R_3 SE SELECCIONAN INDEPENDIENTEMENTE A PARTIR DE H; C_1-C_6 ALQUILO OPCIONALMENTE REEMPLAZADO POR 1, 2 Ó 3 SUSTITUTOS QUE SE SELECCIONAN INDEPENDIENTEMENTE A PARTIR DE C_1-C_4 ALQUILO, HALÓGENO, $-CF_3$ Y C_1-C_4 ALCOXI; C_2-C_6 ALQUENILO O C_2-C_6 ALQUINILO DONDE CADA ELEMENTO SE REEMPLAZA OPCIONALMENTE POR UNO, DOS O TRES SUSTITUTOS SELECCIONADOS A PARTIR DE -F, -CL, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 ALCOXI Y $-NR_5R_6$; O

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, $-SO_2-$ o $-NR_7-$; donde

R_7 se selecciona a partir de H; $-C_1$-C_4 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, $-NH_2$ y halógeno; $-C_3$-C_8 cicloalquilo; $-(C_1$-C_4 alquilo$)$-O-$(C_1$-C_4 alquilo$)$; $-C_2$-C_4 alquenilo; y $-C_2$-C_4 alquinilo.

Los compuestos preferidos de la fórmula A-IX-1 incluyen los de la fórmula A-IX-2, es decir, compuestos de la fórmula A-IX-1, donde

en cada aparición R_{15} se selecciona independientemente a partir de hidrógeno, C_1-C_4 alquilo, C_1-C_6 alcanoilo, bencilo opcionalmente reemplazado por OCH_3, -C(O)-butilo terciario y -CO_2-bencilo.

Los compuestos preferidos de la fórmula A-IX-2 incluyen los de la fórmula A-IX-3, es decir, compuestos de la fórmula A-IX-2, donde

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -SH, -CN, $-CF_3$, $-C_1$-C_4 alcoxi, amino, mono- o dialquiloamino, –N(R)C(O)R', -OC(=O)-amino OC(=O)-mono- y dialquiloamino; o

R_1 es C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alcoxi, amino y mono- o dialquiloamino; o

R_1 es arilo, heteroarilo, heterociclilo, arilo C_1-C_6 alquilo, heteroarilo C_1-C_6 alquilo o heterocicloalquilo C_1-C_6 alquilo;

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O;

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

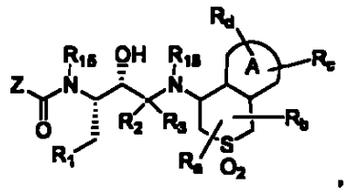
donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_4 haloalquilo, C_1-C_4 haloalcoxi, fenilo, NR_7R_8 y C_1-C_4 alcoxi.

Los compuestos preferidos de la fórmula A-IX-3 incluyen los de la fórmula A-IX-4, es decir, compuestos de la fórmula A-IX-3 donde

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, -NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_4 haloalquilo, C_1-C_4 haloalcoxi, fenilo, NR_7R_8 y C_1-C_4 alcoxi.

Los compuestos preferidos de la fórmula A-IX-4 incluyen los de la fórmula A-IX-5, es decir, compuestos de la fórmula A-X-4, según la fórmula



donde

325



se selecciona a partir de piridinilo, pirimidinilo, imidazolilo, oxazolilo, tiazolilo, furanilo, tienilo, pirazolo, isoxazolo y pirrolilo.

Los compuestos preferidos de la fórmula A-IX-5 incluyen compuestos de la fórmula A-IX-6, es decir, compuestos de la fórmula A-IX-5

donde,

R_1 es fenilo C_1-C_6 alquilo o naftilo C_1-C_6 alquilo, donde el grupo de fenilo o naftilo se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50}.

Los compuestos preferidos de la fórmula A-IX-6 incluyen compuestos de la fórmula A-IX-7, es decir, compuestos de la fórmula A-IX-6 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, $-SO_2-$ o $-NR_7-$; donde

R_7 ES H, $-C_1$-C_6 ALQUILO OPCIONALMENTE REEMPLAZADO POR 1, 2 Ó 3 GRUPOS INDEPENDIENTEMENTE SELECCIONADOS A PARTIR DE -OH, $-NH_2$ Y HALÓGENO; $-C_2$-C_4 ALQUENILO; O $-C_2$-C_4 ALQUINILO.

Los compuestos preferidos de la fórmula A-IX-7 incluyen compuestos de la fórmula A-IX-8, es decir, compuestos de la fórmula A-IX-7 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive.

Otros compuestos preferidos de la fórmula A-IX-7 incluyen compuestos de la fórmula A-IX-9, es decir, compuestos de la fórmula A-IX-7 donde

R_2, R_3 y el carbono al que están ligados forman un grupo de heterocicloalquilo que contiene de 2 a 5 átomos de carbono y un grupo seleccionado a partir de –O-, -S-, $-SO_2-$ y $-NR_7-$; donde

R_7 es H, $-C_1$-C_6 alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de -OH, $-NH_2$ y halógeno; $-C_2$-C_4 alquenilo; o $-C_2$-C_4 alquinilo.

Otros compuestos preferidos de la fórmula A-IX-6 incluyen compuestos de la fórmula A-IX-10, es decir, compuestos de la fórmula A-IX-6 donde

R_2 Y R_3 SE SELECCIONAN INDEPENDIENTEMENTE A PARTIR DE H; C_1-C_4 ALQUILO OPCIONALMENTE REEMPLAZADO POR 1 SUSTITUTO QUE SE SELECCIONA A PARTIR DE HALÓGENO, $-CF_3$ Y C_1-C_4 ALCOXI; C_2-C_4 ALQUENILO; C_2-C_4 ALQUINILO; Y $-CO_2$-(C_1-C_4 ALQUILO); DONDE

R_5 y R_6 son en cada aparición independientemente H o C_1-C_6 alquilo; o

326

R_5 y R_6 y el nitrógeno al que están ligados forman en cada aparición un anillo de heterocicloalquilo de 5 ó 6 componentes.

Los compuestos preferidos de las fórmulas A-IX-8, A-IX-9 o A-IX-10 incluyen los de la fórmula A-IX-11, es decir, compuestos de las fórmulas A-IX-8, A-IX-9 o A-IX-10 donde

R_a y R_b se seleccionan independientemente a partir de C_1-C_6 alquilo, C_1-C_6 alcoxi, halógeno, CN, OH, hidroxialquilo, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi y -C_1-C_6 alquilo-NR_5R_6; o

R_a y R_b se ligan al mismo carbono y forman un ciclo espiral C_3-C_7; y

en cada aparición R_{15} es independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-IX-11 incluyen aquéllos donde

R_c y R_d se seleccionan independientemente a partir de C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y -NR_5R_6; hidroxi; halógeno; C_2-C_6 alquenilo o C_2-C_6 alquinilo, donde

el grupo de alquenilo o alquinilo se reemplaza opcionalmente por C_1-C_4 alquilo, halógeno, hidroxi, SH, ciano, CF_3, C_1-C_4 alcoxi o NR_5R_6.

Otros compuestos preferidos de la fórmula A-IX-11 incluyen aquéllos donde

R_c y R_d son -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$, -$(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-SO-(C_1-C_8 alquilo); -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-N(H o R_{20})-CO-O-R_{20}; -$(CH_2)_{0-4}$-N(H o R_{20})-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N(-H o R_{20})-CO-R_{21}; o -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; donde

R_{21} y R_{22} independientemente representan hidrógeno, C_1-C_6 alquilo, hidroxilo(C_1-C_6)alquilo, amino(C_1-C_6)alquilo, haloalquilo, C_3-C_7 cicloalquilo, -(C_1-C_3 alquilo)-(C_3-C_7 cicloalquilo), -(C_1-C_6 alquilo)-O-(C_1-C_3 alquilo), -C_2-C_6 alquenilo, -C_2-C_6 alquinilo, fenilo, naftilo o heteroarilo;

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Asimismo, otros compuestos preferidos de la fórmula A-IX-11 incluyen aquéllos donde

R_c y R_d son -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alquenilo); $CH_2)_{0-4}$-CO-(C_2-C_{12})alquinilo; -$(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-CO-fenilo; -$(CH_2)_{0-4}$-CO-

327

naftilo; -$(CH_2)_{0-4}$-CO-heteroarilo; -$(CH_2)_{0-4}$-CO-heterocicloalquilo; -$(CH_2)_{0-4}$-CO_2R_{20}; donde

R_{20} se selecciona a partir de C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(fenilo), -$(CH_2)_{0-2}$-(naftilo), C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_3-C_7 cicloalquilo, -$(CH_2)_{0-2}$-(heterocicloalquilo) y -$(CH_2)_{0-2}$-(heteroarilo);

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Además, otros compuestos preferidos de la fórmula A-IX-11 incluyen aquéllos donde R_c y R_d son -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); -$(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; -$(CH_2)_{0-4}$-O-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-(R_{20}); -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-halo(C_1-C_6)alquilo; -$(CH_2)_{0-4}$-O-(C_1-C_6)alquilo; C_3-C_8 cicloalquilo; o -$(CH_2)_{0-4}$-N(-H o R_{20})-SO_2-R_{21}; donde

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O;

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, fenilo, NR_7R_8 y C_1-C_6 alcoxi.

Otros compuestos preferidos de la fórmula A-IX-5 incluyen los de la fórmula A-IX-12, es decir, compuestos de la fórmula A-IX-5 donde

328

R_1 es C_1-C_{10} alquilo opcionalmente reemplazado por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, -OH, =O, -SH, -CN, -CF_3, -C_1-C_4 alcoxi, amino, *mono-* o dialquiloamino, -N(R)C(O)R', -OC(=O)-amino y -OC(=O)-mono- o dialquiloamino; o

R_1 es C_2-C_6 alquenilo o C_2-C_6 alquinilo, cada uno de los cuales se reemplaza opcionalmente por 1, 2 ó 3 grupos independientemente seleccionados a partir de halógeno, OH, SH, C≡N, CF_3, OCF_3, C_1-C_4 alcoxi, amino y mono- o dialquiloamino.

Los compuestos preferidos de la fórmula A-IX-12 incluyen los de la fórmula A-IX-13, es decir, compuestos de la fórmula A-IX-12 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive, donde un átomo de carbono se reemplaza opcionalmente por un grupo seleccionado a partir de –O-, -S-, -SO_2- o -NR_7-; donde

R_7 se selecciona a partir de H o -C_1-C_4 alquilo opcionalmente reemplazado por 1 grupo seleccionado a partir de -OH, -NH_2 y halógeno.

Los compuestos preferidos de la fórmula A-IX-13 incluyen los de la fórmula A-IX-14, es decir, compuestos de la fórmula A-IX-13 donde

R_2, R_3 y el carbono al que están ligados forman un carbociclo de tres a seis átomos de carbono inclusive.

Otros compuestos preferidos de la fórmula A-IX-13 incluyen los de la fórmula A-IX-15, es decir, compuestos de la fórmula A-IX-13 donde

R_2, R_3 y el carbono al que están ligados forman un grupo de heterocicloalquilo que contiene de 2 a 5 átomos de carbono y un grupo seleccionado a partir de –O-, -S-, -SO_2- y -NR_7-; donde

R_7 se selecciona a partir de H y -C_1-C_4 alquilo opcionalmente reemplazado por 1 grupo seleccionado a partir de -OH, -NH_2 y halógeno.

Otros compuestos preferidos de la fórmula A-IX-13 incluyen los de la fórmula A-IX-16, es decir, compuestos de la fórmula A-IX-13 donde

R_3 Y R_9 SE SELECCIONAN INDEPENDIENTEMENTE A PARTIR DE H; C_1-C_4 ALQUILO OPCIONALMENTE REEMPLAZADO POR 1 SUSTITUTO QUE SE SELECCIONA A PARTIR DE HALÓGENO, -CF_3 Y C_1-C_4 ALCOXI; C_2-C_4 ALQUENILO; Y C_2-C_4 ALQUINILO; DONDE

R_5 y R_6 son en cada aparición independientemente -H o C_1-C_6 alquilo; o

R_5 y R_6 y el nitrógeno al que están ligados forman en cada aparición un anillo de heterocicloalquilo de 5 ó 6 componentes.

330
329

Los compuestos preferidos de las fórmulas A-IX-14, A-IX-15, A-IX-16 incluyen compuestos de la fórmula A-IX-17, es decir, compuestos de las fórmulas A-IX-14, A-IX-15, A-IX-16 donde

R_a y R_b se seleccionan independientemente a partir de C_1-C_3 alquilo, F, OH, SH, C≡N, CF_3, C_1-C_6 alcoxi y -NR_5R_6; y

en cada aparición R_{15} es independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-IX-17 incluyen aquellos compuestos donde R_c y R_d se seleccionan independientemente a partir de C_1-C_6 alquilo opcionalmente reemplazado por uno, dos o tres sustitutos seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_3 alcoxi y -NR_5R_6; hidroxi; halógeno;

C_2 -C_6 alquenilo o C_2-C_6 alquinilo, donde

el grupo de alquenilo o alquinilo se reemplaza opcionalmente por C_1-C_4 alquilo, halógeno, hidroxi, SH, ciano, CF_3, C_1-C_4 alcoxi o NR_5R_6.

Otros compuestos preferidos de la fórmula A-IX-17 incluyen aquellos compuestos donde R_c y R_d son -$(CH_2)_{0-4}$-CO-$NR_{21}R_{22}$, -$(CH_2)_{0-4}$-SO_2-$NR_{21}R_{22}$; -$(CH_2)_{0-4}$-SO-(C_1-C_8 alquilo); -$(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-SO_2-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-N(H o R_{20})-CO_2R_{20}; -$(CH_2)_{0-4}$-N(H o R_{20})-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-N(-H o R_{20})-CO-R_{21}; o -$(CH_2)_{0-4}$-$NR_{21}R_{22}$; donde

R_{21} y R_{22} independientemente representan hidrógeno, C_1-C_6 alquilo, hidroxilo(C_1-C_6)alquilo, amino(C_1-C_6)alquilo, haloalquilo, C_3-C_7 cicloalquilo, -(C_1-C_2 alquilo)-(C_3-C_7 cicloalquilo), -(C_1-C_6 alquilo)-O-(C_1-C_3 alquilo), -C_2-C_6 alquenilo, -C_2-C_6 alquinilo, fenilo, naftilo o heteroarilo;

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Asimismo, otros compuestos preferidos de la fórmula A-IX-17 incluyen aquellos compuestos donde

R_c y R_d son -$(CH_2)_{0-4}$-CO-(C_1-C_{12} alquilo); -$(CH_2)_{0-4}$-CO-(C_2-C_{12} alquenilo); $CH_2)_{0-4}$-CO-(C_2-C_{12})alquinilo; -$(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo); -$(CH_2)_{0-4}$-CO-fenilo; -$(CH_2)_{0-4}$-CO-naftilo; -$(CH_2)_{0-4}$-CO-heteroarilo; -$(CH_2)_{0-4}$-CO-heterocicloalquilo; -$(CH_2)_{0-4}$-CO_2R_{20}; donde

330

R_{20} se selecciona a partir de C_1-C_6 alquilo, -$(CH_2)_{0-2}$-(fenilo), -$(CH_2)_{0-2}$-(naftilo), C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_3-C_7 cicloalquilo, -$(CH_2)_{0-2}$-(heterocicloalquilo) y -$(CH_2)_{0-2}$-(heteroarilo);

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O.

Además, otros compuestos preferidos de la fórmula A-IX-17 incluyen aquellos compuestos donde

R_c y R_d son -$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo); -$(CH_2)_{0-4}$-O-P(O)-$(OR_5)_2$; -$(CH_2)_{0-4}$-O-CO-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-CS-$N(R_{20})_2$; -$(CH_2)_{0-4}$-O-(R_{20}); -$(CH_2)_{0-4}$-O-(R_{20})-CO_2H; -$(CH_2)_{0-4}$-S-(R_{20}); -$(CH_2)_{0-4}$-O-halo(C_1-C_6)alquilo; -$(CH_2)_{0-4}$-O-(C_1-C_6)alquilo; C_3-C_8 cicloalquilo; o -$(CH_2)_{0-4}$-N(-H o R_{20})-SO_2-R_{21}; donde

cada grupo de arilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

cada heteroarilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50};

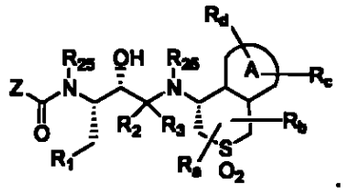
cada grupo de heterocicloalquilo en cada aparición se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos que son independientemente R_{50} o =O;

en cada aparición R_{50} se selecciona independientemente a partir de halógeno, OH, SH, CN, -CO-(C_1-C_4 alquilo), -CO_2-(C_1-C_4 alquilo), -SO_2-NR_5R_6, -NR_7R_8, -CO-NR_5R_6, -CO-NR_7R_8, -SO_2-(C_1-C_4 alquilo), C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi o C_3-C_8 cicloalquilo;

donde los grupos de alquilo, alquenilo, alquinilo, alcoxi o cicloalquilo son opcionalmente reemplazados por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_4 alquilo, halógeno, OH, SH, -NR_5R_6, CN, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, fenilo, NR_7R_8 y C_1-C_6 alcoxi.

Otros compuestos preferidos de la fórmula A-IX-4 incluyen los de la fórmula A-X

331



Los compuestos preferidos de la fórmula A-X incluyen compuestos de la fórmula A-X-1, es decir, compuestos de la fórmula A-X donde

R_1 es fenilo C_1-C_6 alquilo o naftilo C_1-C_6 alquilo, donde el grupo de fenilo o naftilo se reemplaza opcionalmente por 1, 2, 3, 4 ó 5 grupos R_{50}; y

R_2 y R_3 son independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-X-1 incluyen compuestos de la fórmula A-X-2, es decir, compuestos de la fórmula A-X-1 donde

R_a y R_b son independientemente H o C_1-C_4 alquilo; o

R_a y R_b están ligados al mismo carbono y forman un carbociclo C_3-C_6;

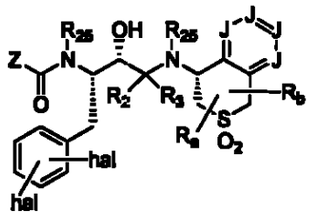
R_1 es fenilo, opcionalmente reemplazado por 1, 2 ó 3 grupos R_{50}; y

en cada aparición R_{15} es independientemente H o C_1-C_4 alquilo.

Los compuestos preferidos de la fórmula A-X-2 incluyen compuestos de la fórmula A-X-3, es decir, compuestos de la fórmula A-X-2 donde

R_1 es a dihalofenilo.

Los compuestos preferidos de las fórmulas A-IX-5, A-X y A-X-3 incluyen compuestos de la fórmula A-X-4, es decir, compuestos de las fórmulas A-IX-5, A-X y A-X-3 con la siguiente estructura:



donde

J en cada aparición se selecciona independientemente a partir de N o CR_c, donde

en cada aparición R_c se selecciona independientemente a partir de C_1-C_6 alquilo, opcionalmente reemplazado por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_6

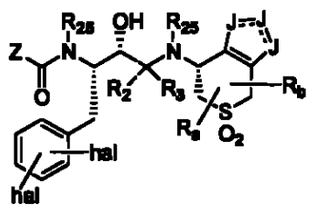
332

alcoxi, C_3-C_8 cicloalquilo y NR_5R_6; hidroxi; halógeno; C_2-C_6 alquenilo o C_2-C_6 alquinilo, donde

el grupo de alquenilo o alquinilo se reemplaza opcionalmente por C_1-C_4 alquilo, halógeno, hidroxi, SH, ciano, CF_3, C_1-C_4 alcoxi o NR_5R_6;

siempre que por lo menos dos J sean CR_c.

Otros compuestos preferidos de las fórmulas A-IX-5, A-X y A-X-3 incluyen compuestos de la fórmula A-X-5, es decir, compuestos de las fórmulas A-IX-5, A-X y A-X-3 con la siguiente estructura:



donde

--- representa un enlace simple o doble, siempre que sólo uno de los guiones de enlace sea un enlace doble;

J se selecciona a partir de N, S, O y CR_c, donde

en cada aparición R_c se selecciona independientemente a partir de C_1-C_6 alquilo, opcionalmente reemplazado por 1, 2 ó 3 sustitutos independientemente seleccionados a partir de C_1-C_3 alquilo, halógeno, OH, SH, C≡N, CF_3, C_1-C_6 alcoxi, C_3-C_8 cicloalquilo y NR_5R_6; hidroxi; halógeno; C_2-C_6 alquenilo o C_2-C_6 alquinilo, donde

el grupo de alquenilo o alquinilo se reemplaza opcionalmente por C_1-C_4 alquilo, halógeno, hidroxi, SH, ciano, CF_3, C_1-C_4 alcoxi o NR_5R_6;

siempre que por lo menos una J sea CR_c.

Otros compuestos preferidos incluyen los compuestos de acuerdo con cualquiera de las formas de presentación de A-I a A-X-5, donde

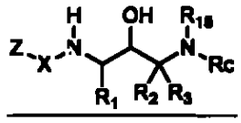
Z es C_1-C_6 alquilo, opcionalmente reemplazado por 1 ó 2 grupos que son independientemente OH, halógeno, C_1-C_4 alcoxi, CF_3, OCF_3, NO_2, CN y NR_5R_6. Más preferentemente, Z es C_1-C_4 alquilo. En otra forma de presentación preferida, Z es fenilo, bencilo, imidazolilo o –C_1-C_4-imidazolilo.

Asimismo, otros compuestos preferidos incluyen los compuestos de acuerdo con cualquiera de las formas de presentación de A-I a A-X-5, donde

333

en cada aparición R_5 y R_6 son independientemente H o C_1-C_4 alquilo. Preferentemente, Z es C_1-C_4 alquilo.

Por otro lado, el *invento* proporciona un *método* para preparar compuestos de la fórmula (I)



(I)

y una sal farmacológicamente aceptable de la misma, donde Z, X, R_1, R_2, R_3, R_{15} y R_c son como se define más arriba.

Por otra parte, el invento proporciona los medios útiles para la preparación de los compuestos de interés.

Eliminado: ¶

El invento también proporciona métodos para tratar a enfermos que padezcan, o para evitar que las personas contraigan enfermedades o estados derivados del mal de Alzheimer, para contribuir a evitar o demorar el comienzo del mal de Alzheimer, para tratar a pacientes con deterioro cognitivo leve (MCI) y evitar o demorar el comienzo del mal de Alzheimer en aquéllos que evolucionarían de MCI a AD, para tratar el síndrome de Down, para tratar a personas con Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés, para tratar la angiopatía amiloide cerebral y evitar sus consecuencias potenciales, es decir, las hemorragias lobulares de episodio único y recurrentes, para tratar otras demencias degenerativas, incluidas las demencias de origen vascular y degenerativo combinado, la demencia asociada al mal de Parkinson, la demencia asociada a la parálisis supranuclear progresiva, la demencia asociada a la degeneración cortico-basal o el tipo de mal de Alzheimer con cuerpos de Lewy difusos y todo aquél que requiera dicho tratamiento, incluida la administración de una dosis terapéuticamente eficaz de un compuesto de la fórmula (I) y las sales farmacológicamente aceptables de la misma.

En una de las realizaciones, este método de tratamiento puede utilizarse cuando la enfermedad es el mal de Alzheimer.

En una de las realizaciones, este método de tratamiento puede ayudar a prevenir o demorar el comienzo del mal de Alzheimer.

En una de las realizaciones, este método de tratamiento puede utilizarse cuando la enfermedad es un deterioro cognitivo leve.

En una de las realizaciones, este método de tratamiento puede utilizarse cuando la enfermedad es el síndrome de Down.

En una de las realizaciones, este método de tratamiento puede utilizarse cuando la enfermedad es Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés.

334

En una de las realizaciones, este método de tratamiento puede utilizarse cuando la enfermedad es angiopatía amiloide cerebral.

En una de las realizaciones, este método de tratamiento puede utilizarse cuando la enfermedad es una demencia degenerativa.

En una de las realizaciones, este método de tratamiento puede utilizarse cuando la enfermedad es un tipo de mal de Alzheimer con cuerpos de Lewy difusos.

En una de las realizaciones, este método de tratamiento puede tratar una enfermedad existente.

En una de las realizaciones, este método de tratamiento puede impedir el desarrollo de una enfermedad.

En una de las realizaciones, este método de tratamiento puede utilizar dosis terapéuticamente eficaces: para administración por vía oral, de aprox. 0,1 mg/día a aprox. 1.000 mg/día; para administración por vía parenteral, sublingual, nasal o intratecal, de aprox. 0,5 a aprox. 100 mg/día; para uso intramuscular e implantes, de aprox. 0,5 mg/día a aprox. 50 mg/día; para administración tópica, de aprox. 0,5 mg/día a aprox. 200 mg/día; para administración rectal, de aprox. 0,5 mg a aprox. 500 mg.

En una de las realizaciones, este método de tratamiento puede utilizar dosis terapéuticamente eficaces: para administración por vía oral, de aprox. 1 mg/día a aprox. 100 mg/día; y para administración parenteral, de aprox. 5 a aprox. 50 mg por día.

En una de las realizaciones, este método de tratamiento puede utilizar dosis terapéuticamente eficaces: para administración por vía oral, de aprox. 5 mg/día a aprox. 50 mg/día.

El invento también incluye preparados farmacológicos que incluyen un compuesto de la fórmula (I) y sales farmacológicamente aceptables de la misma.

El invento también incluye el uso de un compuesto de la fórmula (I) o sales farmacológicamente aceptables de la misma para la fabricación de un medicamento destinado a tratar a un enfermo que padezca, o a impedir que un paciente contraiga una enfermedad o estado derivado del mal de Alzheimer, a contribuir a prevenir o demorar el inicio del mal de Alzheimer, a tratar a pacientes con deterioro cognitivo leve (MCI) como asimismo prevenir o demorar el comienzo del mal de Alzheimer en aquellas personas que evolucionarían de MCI a AD, a tratar el síndrome de Down, a tratar a personas que sufren de Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés, a tratar la angiopatía amiloide cerebral y evitar sus consecuencias potenciales, es decir, las hemorragias lobulares de episodio único y recurrentes, a tratar otras demencias degenerativas, incluidas las de origen vascular y degenerativo combinado, la demencia asociada al mal de Parkinson, la demencia asociada a la parálisis supranuclear progresiva, la demencia asociada a la

335

degeneración cortico-basal, el tipo de mal de Alzheimer con cuerpos de Lewy difusos, y a quienes requieran dicho tratamiento.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede aplicarse cuando la enfermedad es el mal de Alzheimer.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede contribuir a evitar o demorar el comienzo del mal de Alzheimer.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede aplicarse cuando la enfermedad es un deterioro cognitivo leve.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede aplicarse cuando la enfermedad es el síndrome de Down.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede aplicarse cuando la enfermedad es Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede aplicarse cuando la enfermedad es angiopatía amiloide cerebral.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede aplicarse cuando la enfermedad es una demencia degenerativa.

En una de las realizaciones, esta utilización de un compuesto de la fórmula (I) puede aplicarse cuando la enfermedad es un tipo de mal de Alzheimer con cuerpos de Lewy difusos.

En una de las realizaciones, esta aplicación de un compuesto utiliza una sal farmacológicamente aceptable seleccionada a partir de sales de los siguientes ácidos: hidroclórico, hidrobrómico, hidroyódico, nítrico, sulfúrico, fosfórico, cítrico, metanesulfónico, CH_3-$(CH_2)_n$-COOH donde n es un valor de 0 a 4 inclusive, HOOC-(CH_2)n-COOH donde n es como se define más arriba, HOOC-CH=CH-COOH y fenilo-COOH.

El invento también incluye métodos para inhibir la actividad de la secretasa beta, para inhibir la división de la proteína precursora de amiloide (PPA), en una mezcla reactiva, en un lugar entre Met596 y Asp597, numerado para el isotipo de aminoácido PPA-695 o en un lugar correspondiente a un isotipo o mutante del mismo; para inhibir la producción de péptido amiloide beta (A beta) en una célula; para inhibir la formación de placas amiloides beta en animales; y para tratar o prevenir enfermedades caracterizadas por depósitos de amiloide beta en el cerebro. Cada uno de estos métodos incluye la administración de una dosis terapéuticamente eficaz de un compuesto de la fórmula (I) y las sales farmacológicamente aceptables de la misma.

El invento también incluye un método para inhibir la actividad de la secretasa beta, incluida la exposición de dicha secretasa beta a una dosis inhibitoria eficaz de un compuesto de la fórmula (I) y sales farmacológicamente aceptables de la misma.

336

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración inferior a 50 micromolar.

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración igual o inferior a 10 micromolar.

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración igual o inferior a 1 micromolar.

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración igual o inferior a 10 nanomolar.

En una de las realizaciones, este método incluye la exposición de dicha secretasa beta a ese compuesto *in vitro*.

En una de las realizaciones, este método incluye la exposición de dicha secretasa beta a ese compuesto en una célula.

En una de las realizaciones, este método incluye la exposición de dicha secretasa beta a ese compuesto en un animal.

En una de las realizaciones, este método incluye la exposición de dicha secretasa beta a ese compuesto en un ser humano.

El invento también incluye un método para inhibir la proteína precursora de amiloide (PPA), en una mezcla reactiva, en un lugar entre Met596 y Asp597, numerado para el isotipo de aminoácido PPA-695; o en un lugar correspondiente a un isotipo o mutante del mismo, incluida la exposición de dicha mezcla reactiva a una dosis inhibitoria eficaz de un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma.

En una de las realizaciones, este método utiliza un lugar de división: entre Met652 y Asp653, numerado para el isotipo PPA-751; entre Met 671 y Asp 672, numerado para el isotipo PPA-770; entre Leu596 y Asp597 de la Mutación Sueca PPA-695; entre Leu652 y Asp653 de la Mutación Sueca PPA-751; o entre Leu671 y Asp672 de la Mutación Sueca PPA-770.

En una de las realizaciones, este método expone esa mezcla reactiva *in vitro*.

En una de las realizaciones, este método expone esa mezcla reactiva en una célula.

En una de las realizaciones, este método expone esa mezcla reactiva en una célula animal.

En una de las realizaciones, este método expone esa mezcla reactiva en una célula humana.

El invento también incluye un método para inhibir la producción de péptido amiloide beta (A beta) en una célula, incluida la administración a esa célula de una dosis inhibitoria eficaz de un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma.

En una de las realizaciones, este método incluye la administración a un animal.

En una de las realizaciones, este método incluye la administración a un ser humano.

337

El invento también incluye un método para inhibir la producción de placas amiloides beta en animales, incluida la administración a esos animales de una dosis inhibitoria eficaz de un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma.

En una de las realizaciones, este método incluye la administración a un ser humano.

El invento también incluye un método para tratar o prevenir una enfermedad caracterizada por acumulaciones de amiloide beta en el cerebro, incluida la administración a un paciente de una dosis terapéutica eficaz de un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma.

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración inferior a 50 micromolar.

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración igual o inferior a 10 micromolar.

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración igual o inferior a 1 micromolar.

En una de las realizaciones, este método utiliza un compuesto que inhibe 50% de la actividad de la enzima en una concentración igual o inferior a 10 nanomolar.

En una de las realizaciones, este método utiliza un compuesto en una dosis terapéutica en un rango entre aprox. 0,1 y aprox. 1.000 mg/día.

En una de las realizaciones, este método utiliza un compuesto en una dosis terapéutica en un rango entre aprox. 15 y aprox. 1.500 mg/día.

En una de las realizaciones, este método utiliza un compuesto en una dosis terapéutica en un rango entre aprox. 1 y aprox. 100 mg/día.

En una de las realizaciones, este método utiliza un compuesto en una dosis terapéutica en un rango entre aprox. 5 y aprox. 50 mg/día.

En una de las realizaciones, este método puede utilizarse cuando la enfermedad mencionada es mal de Alzheimer.

En una de las realizaciones, este método puede utilizarse cuando la enfermedad mencionada es Deterioro Cognitivo Leve, Síndrome de Down o Hemorragia Cerebral Hereditaria con Amiloidosis de tipo holandés.

El invento también incluye un preparado que incluye secretasa beta combinada con un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma.

El invento también incluye un método para producir un complejo de secretasa beta que incluye la exposición de la secretasa beta a un compuesto de la fórmula (I) y una sal farmacológicamente

338

aceptable de la misma, en una mezcla reactiva bajo condiciones propicias para la generación de ese complejo.

En una de las realizaciones, este método utiliza la exposición *in vitro*.

En una de las realizaciones, este método utiliza una mezcla reactiva que es una célula.

El invento también incluye un conjunto de componentes que pueden combinarse, entre los cuales por lo menos un componente incluye un compuesto de la fórmula I contenido en un envase.

En una de las realizaciones, este conjunto de envase incluye un compuesto liofilizado y por lo menos otro componente incluye un diluyente.

El invento también incluye un conjunto de envase que incluye una serie de envases, cada uno de ellos con una o más dosis de un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma.

En una de las realizaciones, este conjunto de envase incluye cada envase adaptado para administración por vía oral e incluye una tableta, gel o cápsula.

En una de las realizaciones, este conjunto de envase incluye cada envase adaptado para administración parenteral e incluye un producto inyectable por vía intramuscular, jeringa, ampolla o frasco.

En una de las realizaciones, este conjunto de envase incluye cada envase adaptado para administración tópica e incluye un emplasto, un parche de uso médico, ungüento o crema.

El invento también incluye un conjunto de agente activo que incluye un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma; y uno o más agentes terapéuticos seleccionados entre un antioxidante, un antiinflamatorio, un inhibidor de secretasa gamma, un agente neurotrófico, un inhibidor de acetilcolinesterasa, una estatina, un péptido A beta y un anticuerpo anti-A beta.

El invento también incluye un preparado que incluye un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma; y un diluyente inerte o vehículo comestible.

En una de las realizaciones, este preparado incluye un vehículo que es un aceite.

El invento también incluye un preparado que incluye: un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma; y un aglutinante, excipiente, agente desintegrador, lubricante o cobertor.

El invento también incluye un preparado que incluye un compuesto de la fórmula (I) y una sal farmacológicamente aceptable de la misma, en forma de crema, ungüento o emplasto.

El invento proporciona compuestos de la fórmula (I) y de las demás fórmulas aquí contenidas, que son útiles para el tratamiento y la prevención del mal de Alzheimer. Los compuestos del invento pueden ser preparados por alguien con conocimiento del arte, sobre la sola base del

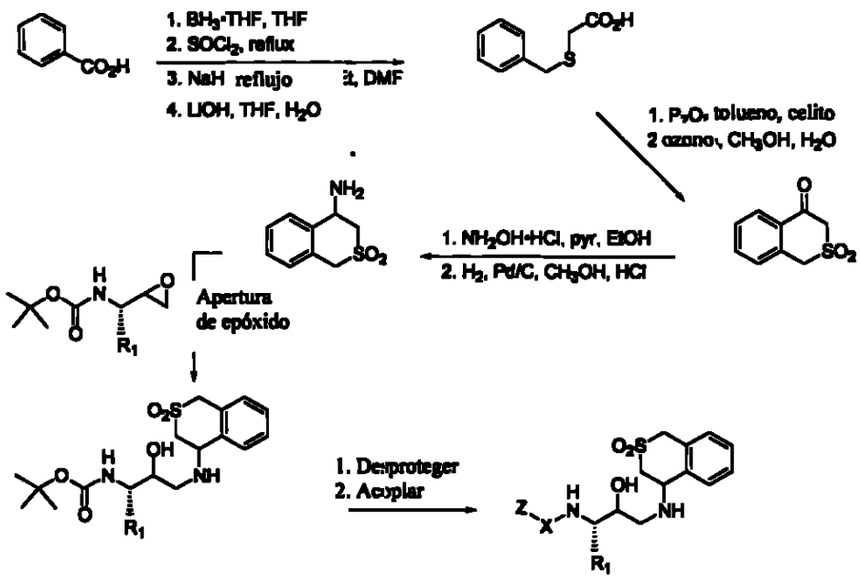
340
339

conocimiento de la estructura química del compuesto. La química para la preparación de los compuestos de este invento es familiar para los conocedores del arte. En efecto, existe más de un proceso para preparar los compuestos del invento. En la literatura del arte pueden encontrarse ejemplos específicos de métodos de preparación. Ver, por ejemplo, *J. Org. Chem.* 1998, *63*, 4898-4906; *J. Org. Chem.* 1997, *62*, 9348-9353; *J. Org. Chem.* 1996, *61*, 5528-5531; *J. Med. Chem.* 1993, *36*, 320-330; *J. Am. Chem. Soc.* 1999, *121*, 1145-1155; y las referencias allí citadas. Ver también Patentes de EE.UU. números 6.150.530, 5.892.052, 5.696.270 y 5.362.912, aquí incorporadas como referencia, y las referencias allí mencionadas.

El Esquema I presenta como ejemplo uno de los numerosos procesos que pueden emplearse para preparar los compuestos del invento.

Eliminado: ¶

Esquema I



donde R_1 y Z son como se define más arriba o más abajo.

El Esquema I ilustra la preparación de compuestos donde R_c es un isociocromano 2,2-dióxido que utiliza ácido benzoico opcionalmente sustituido como material de arranque. Alguien que conozca el arte reconocerá que también se pueden utilizar como materiales arranque haluros de bencilo o alcoholes de bencilo opcionalmente sustituidos.

En el Esquema I, el ácido benzoico se reduce a alcohol de bencilo, que luego se convierte en haluro de bencilo. Alternativamente, el alcohol de bencilo puede modificarse para incluir un

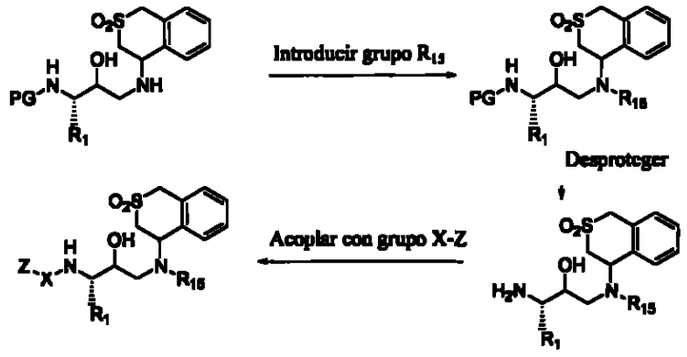
340

grupo final formado, por ejemplo, por tosilato, brosilato, nosilato, triflato o mesilato. El compuesto de bencilo luego reacciona con un sulfuro para generar el tioéter. Luego el éster carboxílico es hidrolizado para formar un ácido carboxílico, posteriormente sometido a condiciones de reacción de anulación para formar el sistema de anillo bicíclico deseado. La anulación puede efectuarse utilizando un ácido de Lewis, ácido polifosfórico o P_2O_5. En el arte se conocen otros reactivos apropiados que realizan la ciclización.

El sulfuro bicíclico resultante se oxida para formar el sulfono. El grupo cetónico se convierte directamente en una amina a través de una aminación reductiva o indirectamente por la generación de una oxima, que luego se reduce para formar la amina. Para realizar la reducción pueden utilizarse catalizadores metálicos de transición e hidrógeno u otros agentes reductores, como $NaBH_4$, $LiAlH_4$ o $NaCNBH_3$.

La amina resultante permite abrir el epóxido para formar una amina libre, que luego se acilata o sulfoniza para generar el producto final deseado. El Esquema I ilustra la utilización de un grupo de protección BOC, pero alguien conocedor del arte entenderá que también pueden utilizarse otros grupos de protección, tales como CBz, bencilo u otros.

Esquema II



El esquema II ilustra la introducción de un grupo R_{15} sin hidrógeno en el átomo de nitrógeno de 3 posiciones en la porción 1,3-diaminopropano de la molécula.

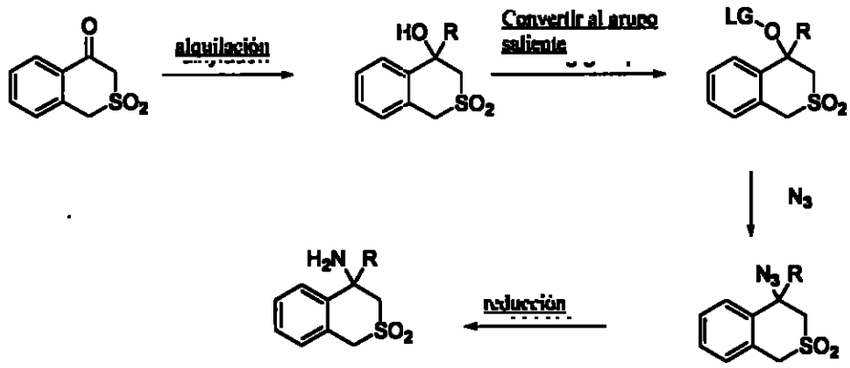
El nitrógeno libre reacciona con un electrófilo, un aldehído o cetona y un agente reductor, un cloruro de ácido, un anhídrido de ácido o un ácido con un agente acoplante, como por ejemplo DCC (carbodiimida de diciclohexilo), DIC (1,3 carbodiimida de diisopropilo), EDCI (1-etil-3-(3'-dimetilaminopropilo)hidrocloruro de carbodiimida), BBC (1-benzotriazol-1-iloxi-bis(pirrolidino)hexafluorofosfato de uronio), BDMP (5-(1*H*-benzotriazol-1-iloxi)-3,4-dihidro-1-

341

metilo 2*H*-hexacloroantimonato de pirrol), BOMI (benzotriazol-1-iloxi-*N*,*N*-dimetilmetaniminio hexacloroantimonato), HATU (*O*-(7-azabenzotriazol-1-il)-1,1,3,3-hexafluorofosfato de tetrametilouronio), HAPyU = *O*-(7-azabenzotriazol-1-il)- 1,1,3,3-bis(tetrametileno)hexafluorofosfato de uronio, HBTU que es *O*-(benzotriazol-1-il)-1,1,3,3-hexafluorofosfato de tetrametiluronio, TAPipU que es *O*-(7-azabenzotriazol-1-il)- 1,1,3,3-bis(pentametileno)etrafluoroborato de uronio, AOP (*O*-(7-azabenzotriazol-1-il)-tris(dimetilamino)hexafluorofosfato de fosfonio), BDP (benzotriazol-1-il dietilfosfato), BOP (1-benzotriazol-i-oxi-tris(dimetilamino) hexafluorofosfato de fosfonio), PyAOP (7-azobenzotriazol-i-oxi-tris(pirrolidino)hexafluorofosfato de fosfonio), PyBOP (1-benzotriazol-i-oxi-tris(pirrolidino)hexafluorofosfato de fosfonio), TDBTU (2-(3,4-dihidro-4-oxo-1,2,3-benzotriazina-3-il)-1,1,3,3-tetrametiluronio tetrafluoroborato), TNTU (2-(5-norborneno-2,3-dicarboximido)- 1,1,3,3-tetrametiluronio tetrafluoroborato), TPTU (2-(2-oxo-1(2*H*)-piridil-1,1,3,3-tetrametiluronio tetrafluoroborato), TSTU (2-succinimida-1,1,3,3-tetrafluoroborato de tetrametiluronio), BEMT (2-bromo-3-etil-4-metilo tiazolio tetrafluoroborato), BOP-Cl (bis(2-oxo-3-oxazolidinil)cloruro fosfínico), BroP (bromotris(dimetilamino)hexafluorofosfato de fosfonio), BTFFH (bis(tetrametilenofluoroformamidina) hexafluorofosfato), ClP (2-cloro-1,3-dimetilimidazolidino hexafluorofosfato), DEPBT (3-(dietoxifosforiloxi)-1,2,3-benzotriazina-4(3*H*)-uno), Dpp-Cl (cloruro difenilfosfínico), EEDQ (2-etoxi-1-etoxicarbonil-1,2-dihidroquinolina), FDPP (pentafluorofenil difenilfosfinato), HOTT (*S*-(1-oxido-2-piridinil)-1,1,3,3-tetrametiltiouronio hexafluorofosfato), PyBroP (bromotris(pirrolidino)hexafluorofosfato de fosfonio), PyCloP (clorotris(pirrolidino)hexafluorofosfato de fosfonio), TFFH (hexafluorofosfato de tetrametilfluoroformamidina) y TOTT (*S*-(1-óxido-2-piridinil)-1,1,3,3-tetrafluoroborato de tetrametiltiorouronio) para generar el producto monosustituido, que después puede desprotegerse y acoplarse al grupo "X-Y". A la inversa, el producto monosustituido puede desprotegerse y hacer reaccionar al nitrógeno libre con un electrófilo, un aldehído o cetona y un agente reductor, un cloruro de ácido o un ácido con un agente acoplante, tales como los anteriormente ejemplificados, para generar el producto disustituido que, después, se acoplará al grupo "X-Z".

342

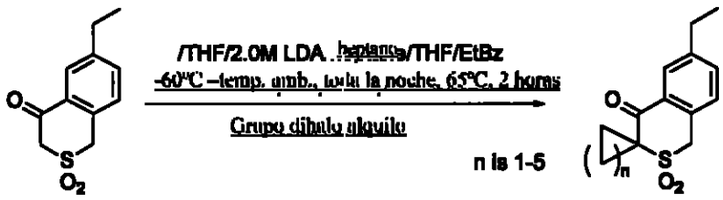
Esquema III



El Esquema III ilustra la introducción de una amina terciaria (R no es hidrógeno) o de una amina secundaria (R es hidrógeno) en la estructura base isotiocromano 2, 2-dióxido. En primer lugar, la sulfocetona es alquilada utilizando, por ejemplo, el reactivo de Grignard u otro agente alquilante, para generar el alcohol tercinrio que, después, se convierte en un grupo saliente. El experto en el arte apreciará que pueden utilizarse muchos grupos salientes posibles. Entre los ejemplos específicos, cabe incluir – aunque no son todos - triflato, mesilato, sulfonato de paratolueno, nosilato y brosilato. A continuación, el grupo saliente es desplazado por medio de una azida, como por ejemplo DPPA (azida difenil fosforil) o NaN_3.Pueden utilizarse azidas sustituidas en lugar de una azida no sustituida. Alternativamente, pueden generarse los compuestos deseados a partir del alcohol directamente, sin tener que convertir primero el alcohol para incorporarlo al grupo saliente. Dichas transformaciones pueden lograrse de inmediato a través de condiciones SN_1 convencionales de acuerdo con procedimientos disponibles en la literatura.

Después, la azida resultante se reduce para generar la amina deseada. Se conocen muchos agentes reductores que tendrán efecto en la transformación deseada. Entre los ejemplos, cabe mencionar: H_2 y Pd, H_2 y Pt, $NaBH_4$ y $NaCNBH_3$. Pueden utilizarse agentes reductores más fuertes tales como $LiAlH_4$ y DIBAL; sin embargo, también puede reducirse la sulfona. En este último caso, la sulfona podrá reoxidarse mediante el uso de métodos conocidos en el arte, tales como MCPBA.

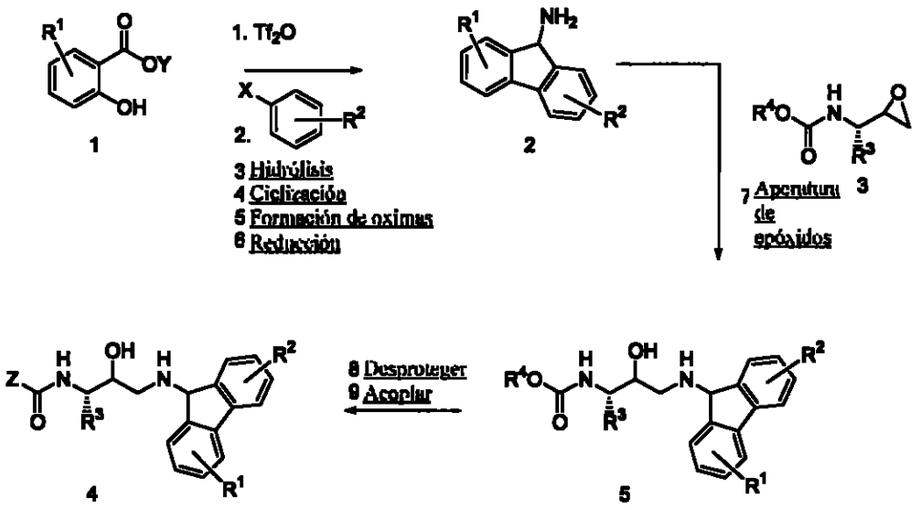
Esquema IV



Según se indica en el esquema IV, pueden generarse espirociclos por alquilación de un compuesto en presencia de una base fuerte. A modo de ejemplos de bases fuertes, cabe mencionar: LDA, KHMDS y litio de butilo terciario. El experto en el arte apreciará que muchas otras bases son lo suficientemente fuertes como para desprotonar el material inicial y realizar la transformación deseada.

El agente alquilante dicta el tamaño del espirociclo que se forma. El dibromoetano, el diyodoetano o el bromoyodoetano generarán un compuesto de espirociclopropilo, donde n es 1. Sin embargo, las cadenas de alquilos más largas generan compuestos de espirocicloalquilos más grandes. Por ejemplo, un 1,5-dihalopentano genera un compuesto de espirociclohexilo, donde n es 4. Si bien se ilustran los compuestos dihalo, el experto en el arte apreciará que pueden utilizarse otros grupos salientes tales como, por ejemplo, mesilato, tosilato, triflato, brosilato y nosilato. Los grupos salientes pueden, aunque no tienen que, ser idénticos.

Esquema V: Preparación de Derivados del Fluoreno



344

El Esquema V ilustra la preparación de derivados del fluoreno mediante el uso de ésteres salicílicos opcionalmente sustituidos como materiales iniciales. Los ésteres salicílicos sustituidos y no disponibles en el comercio pueden obtenerse mediante una variedad de métodos conocidos para los expertos en el arte de la síntesis orgánica. Entre los métodos cabe mencionar –aunque no son los únicos – halogenaciones [Rozen y Lerman (J. Org. Chem. (Diario de Quím. Org.) 1993, 239 – 240)], acoplantes Suzuki [Miyaura y Suzuki (Chem. (Química) Rev. 1995, 2457 – 2483)], acoplantes Sonagashiri [Sonagashira (Metal-Catalyzed Cross-Coupling Reactions (Reacciones de Acoplantes Cruzados Catalizados con Metales), 1998, Wiley-VCH publishers)], acoplantes Negishi [Zhu, *y otros*. (J. Org. Chem.(Diario de Quím. Org.) 1991, 1445 – 1453)], acoplantes cruzados Stille [Littke y otros. (Angew. Chem. Int. Ed. 1999, 2411 – 2413)], acoplantes Heck [Whitcombe y otros. (Tetrahedron 2001, 7449 – 7476)], aminaciones [Wolfe y otros. (J. Org. Chem.(Diario de Quím. Org.) 2000, 1144 – 1157)], oxigenaciones [Fu y Littke (Angew. Chem. Int. Ed. 2002, 4177 – 4211)] y carbonilaciones [Cai y otros. (J Chem Soc, Perkin Trans 1 1997, 2273 – 2274)]. El experto en el arte reconocerá que los ortohalobenzoatos opcionalmente sustituidos también pueden emplearse como materiales iniciales.

Los fenoles de la fórmula general (1) se convierten rápidamente en triflatos que emplean una fuente de triflato y una base en un solvente inerte. Entre las fuentes de triflato se incluyen, aunque no son todas, el anhídrido trifluorometanesulfónico, el cloruro trifluorometanosulfonilo y N-feniltrifluorometanosulfonimida. Algunas de las bases son: trialquilaminas (preferiblemente diisopropiletilamina o trietilamina), aminas aromáticas (preferiblemente piridina, 4-dimetilaminopiridina o 2,6-lutidina) o hidruros de metal alcalino (preferiblemente hidruro sódico). Entre los solventes inertes se incluyen, aunque no son todos, acetonitrilo, éteres de dialquilo (preferiblemente, éter diéter), éteres cíclicos (preferiblemente tetrahidrofuran o 1,4-dioxano), N, N-dialquilacetamidas (preferiblemente dimetilacetamida), N, N-dialquilformamidas (preferiblemente dimetilformamida), diaquilsulfoxidas (preferiblemente dimetilsulfoxida), hidrocarburos aromáticos (preferiblemente benceno o tolueno) o haloalcanos (preferiblemente diclorometano). Las temperaturas de reacción preferidas oscilan entre 0°C y la temperatura ambiente. El progreso de esta conversión es monitoreado por métodos estándar cromatográficos y espectroscópicos conocidos por el experto en el arte de la síntesis orgánica.

Los triflatos pueden tratarse con un ácido de boro arílico o éster de ácido de boro arílico, donde X es equivalente a $B(OH)_2$ o $B(OR^a)(OR^b)$ (donde R^a y R^b son un alquilo menor, es decir, C_1-C_6, o en conjunto R^a y R^b son un alquileno menor, es decir, C_2-C_{12}) en presencia de un catalizador de metal con o sin una base en un solvente inerte para dar biarilos. Entre los catalizadores de metal se incluyen, aunque no están todos, sales o complejos de fosfamina de Cu, Pd or Ni (por ej.:

345

$Cu(OAc)_2$, $Pd(PPh_3)_4$, $NiCl_2(PPh_3)_2$). Entre las bases se incluyen, aunque no están todas, carbonatos de metal de tierra alcalina, bicarbonatos de metal de tierra alcalina, hidróxidos de metal de tierra alcalina, , hidruros de metal alcalino (preferiblemente hidruro sódico), alcóxidos de metal alcalino (preferiblemente etóxido de sodio o metóxido de sodio), trialquilaminas (preferiblemente diisopropiletilamina o trietilamina) o aminas aromáticas (preferiblemente piridina). Entre los solventes inertes se incluyen, aunque no se enumeran todos, acetonitrilo, éteres de dialquilo (preferiblemente éter diéter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), N,N-dialquilacetamidas (preferiblemente dimetilacetamida), N,N-dialquilforamidas (preferiblemente dimetilformamida), dialquilsulfoxidas (preferiblemente dimetilsulfoxida), hidrocarburos aromáticos (preferiblemente benceno o tolueno), haloalcanos (preferiblemente diclorometano), alcoholes de alquilo (preferiblemente alcohol metílico o alcohol etílico) o agua. Las temperaturas de reacción preferidas oscilan entre la temperatura ambiente y el punto de ebullición del solvente empleado. Los ácidos de boro o ésteres de boro no disponibles en el comercio pueden obtenerse del correspondiente haluro arílico sustituído opcionalmente, según lo descrito por Gao y otros (Tetrahedron (Tetrahedrón), 1994, *50*, 979 –988). El progreso de la reacción acoplante es monitoreado por métodos cromatográficos y espectroscópicos estándar conocidos por el experto en el arte de la síntesis orgánica.

Alternativamente, los triflatos pueden tratarse con reactivos de organozinc, según lo enseñado por Zhu y otros (J. Org. Chem. (Diario de Quím. Org.) 1991, 1445 – 1453).

El experto en el arte de la síntesis orgánica apreciará que la naturaleza de los socios de acoplamiento descritos anteriormente podrían revertirse y la reacción de acoplamiento realizarse sustancialmente de la misma manera que se describió anteriormente.

El éster de biarilo es hidrolizado para formar un ácido carboxílico. La reacción por hidrólisis puede ser ejecutada bajo una variedad de condiciones familiares para el experto en el arte de la síntesis orgánica. La reacción por hidrólisis se realiza en presencia de una base, como por ejemplo – aunque no son todas- hidróxido de litio e hidróxido de sodio. Entre los solventes típicos se incluyen, aunque no están todos, tetrahidrofurano, éter de dietilo, diclorometano, alcoholes de alquilo (incluidos alcohol metílico y alcohol etílico) y agua. Las reacciones pueden realizarse con éxito a temperaturas que oscilan entre la temperatura ambiente y el punto de ebullición del solvente empleado. El progreso de la reacción por hidrólisis es monitoreado por métodos cromatográficos y espectrográficos estándar conocidos por el experto en el arte de la síntesis orgánica.

El ácido carboxílico puede estar sujeto a una reacción por ciclización, bajo una amplia variedad de condiciones conocidas por el experto en el arte de la síntesis orgánica, para formar el triciclo deseado. La reacción por ciclización se lleva a cabo en presencia de un reactivo acídico. Tanto los ácidos de Bronsted que incluyen, aunque no se limitan a, ácido sulfúrico, ácido hidroclorhídrico, ácido metanosulfónico y ácido polifosfórico, como los ácidos de Lewis que incluyen, aunque no se limitan a, tricloruro de alumnio, tetracloruro de titanio y tetracloruro de estaño resultan de utilidad para efectuar esta transformación. La reacción puede ser llevada a cabo en forma prolija o con el agregado de un co-solvente. Entre los solventes típicos se incluyen, aunque no se limitan a, acetonitrilo, éteres de dialquilo (preferiblemente éter de diéter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), N,N-dialquilacetamidas (preferiblemente dimetilacetamida), N,N-dialquilforamidas (preferiblemente dimetilformamida), dialquilsulfoxidas (preferiblemente dimetilsulfoxida), hidrocarburos aromáticos (preferiblemente benceno o tolueno), haloalcanos (preferiblemente diclorometano) o alcoholes de alquilo (preferiblemente alcohol metílico o alcohol etílico). Las reacciones pueden ser ejecutadas con éxito a temperaturas que oscilan entre la temperatura ambiente y el punto de ebullición del solvente empleado. El progreso de la reacción por hidrólisis es monitoreado por métodos cromatográficos y espectroscópicos estándar conocidos para el experto en el arte de la síntesis orgánica.

Alternativamente, el ácido carboxílico puede ser ciclizado a través del ácido activado correspondiente, según lo enseña Alder y otros (Justus Liebigs Ann. Chem. 1950; 230 238) Stiles y Libbey (J. Org. Chem. (Diario de Quím. Org.) 1957, 1243 – 1245 y Ladd y otros (J. Med. Chem. (Diario de Quím. Méd.) 1986 1904 – 1912).

La cetona puede convertirse en la oxima correspondiente. La reacción por condensación se lleva a cabo en presencia de una hidroxilamina (de la fórmula general $RONH_2$; donde R = H, C_1-C_4) con o sin una base en un solvente inerte. Las bases incluyen, aunque no se limitan a, carbonatos de metal de tierra alcalina, bicarbonatos de metal de tierra alcalina, hidróxidos de metal de tierra alcalina, hidruros de metal alcalino (preferiblemente hidruro sódico), alcóxidos de metal alcalino (preferiblemente etóxido de sodio o metóxido de sodio), trialquilaminas (preferiblemente diisopropiletilamina o trietilamina) o aminas aromáticas (preferiblemente piridina). Los solventes inertes incluyen, aunque no se limitan a acetonitrilo, éteres de dialquilo (preferiblemente éter diéter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), N,N-dialquilacetamidas (preferiblemente dimetilacetamida), N,N-dialquilforamidas (preferiblemente dimetilformamida), dialquilsulfoxidas (preferiblemente dimetilsulfoxida), hidrocarburos aromáticos (preferiblemente benceno o tolueno), haloalcanos (preferiblemente diclorometano), alcoholes de alquilo (preferiblemente alcohol metílio o alcohol etílico) o agua. Las temperaturas de reacción preferidas

347

oscilan entre la temperatura ambiente y el punto de ebullición del solvente empleado. El progreso de la reacción por condensación es monitoreado por métodos cromatográficos y espectroscópicos estándar conocidos para el experto en el arte de la síntesis orgánica.

La reducción de la oxima correspondiente hasta la amina deseada procede en presencia de un agente reductor en un solvente inerte. Los agentes reductores adecuados incluyen, aunque no se limitan a, metales de transición con o sin agentes donantes con hidrógeno e hidruro. Los metales de transición que pueden o no ser usados catalíticamente con o sin la adición de hidrógeno incluyen, aunque no se limitan a, Pd, Pt y Zn. Los agentes donantes con hidruros incluyen, aunque no se limitan, a, BH_3, $NaBH_4$, $LiBH_4$, $NaCNBH_3$ y $LiAlH_4$. Los solventes inertes pueden incluir, aunque no se limitan a, acetonitrilo, éteres de dialquilo (preferiblemente éter diéter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), N,N-dialquilacetamidas (preferiblemente dimetilacetamida), N,N-dialquilforamidas (preferiblemente dimetilformamida), dialquilosulfoxidas (preferiblemente dimetilsulfoxido), hidrocarburos aromáticos (preferiblemente benceno o tolueno), haloalcanos (preferiblemente diclorometano), alcoholes de alquilo (preferiblemente alcohol metílico o alcohol etílico) o agua. Las temperaturas de reacción preferidas oscilan entre 0°C y el punto de ebulición del solvente empleado. El progreso de la reacción por condensación es monitoreado por métodos cromatográficos y espectroscópicos estándar conocidos por el experto en el arte de la síntesis orgánica.

El experto en el arte apreciará, alternativamente al procedimiento indirecto descrito anteriormente, que la cetona puede convertirse directamente en la amina correspondiente directamente a través de una aminación reductiva, según enseña Dei y otros (Biorg. Med. Chem. 2001, 2673-2682).

Las aminas resultantes de la fórmula general (2) pueden tratarse con un epóxido protegido de la fórmula general (3) que incluye, aunque no se limita a, epóxidos protegidos con butoxicarbonilos, con o sin catálisis en un solvente inerte. Entre los catalizadores se incluyen, aunque no se limitan a, sales o complejos de Yb, Sn, Ti, B y Cu. Los solventes inertes incluyen, aunque no se limitan a, acetonitrilo, acetonitrilo, éteres de dialquilo (preferiblemente diéter éter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), N,N-dialquilacetamidas (preferiblemente dimetilacetamida), N,N-dialquilforamidas (preferiblemente dimetilformamida), dialquil-sulfóxidos (preferiblemente sulfóxido de dimetilo), hidrocarburos aromáticos (preferiblemente benceno o tolueno), haloalcanos (preferiblemente diclorometano), alquil alcoholes (preferiblemente alcohol isopropílico o tert-butil alcohol). Las temperaturas de reacción preferidas oscilan entre la temperatura ambiente y el punto de ebullición del solvente empleado.

348

El progreso de la reacción acoplante es monitoreado por métodos cromatográficos y espectroscópicos estándar conocidos para el experto en el arte de la síntesis orgánica.

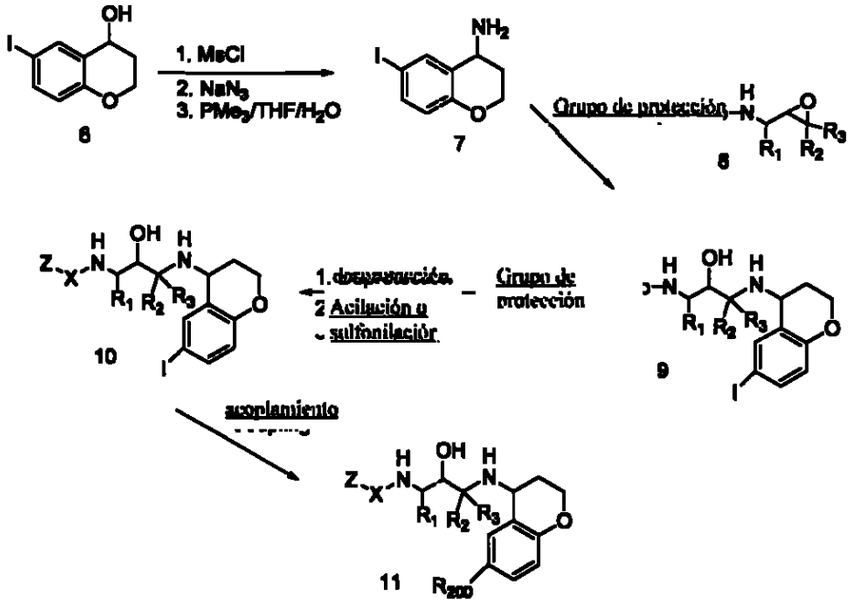
Los productos acoplados resultantes de la fórmula general (4) pueden ser desprotegidos a fin de producir la amina por tratamiento con aditivos acídicos en solventes inertes. Los aditivos acídicos incluyen, aunque no se limitan a, TFA, HCl, HBr, AcOH y ácido tricloroacético. Los solventes inertes pueden incluir, aunque no se limitan a, acetonitrilo, éteres de dialquilo (preferiblemente diéter éter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), haloalcanos (preferiblemente diclorometano), alquil alcoholes (preferiblemente alcohol isopropílico o tert-butil-alcohol). Las temperaturas de reacción preferidas oscilan entre 0°C y la temperatura ambiente. El progreso de la reacción de desprotección es monitoreado por métodos cromatográficos y espectroscópicos estándar conocidos por el experto en el arte de la síntesis orgánica.

La amina resultante puede ser tratada con un ácido a fin de otorgar el producto final de la fórmula general (5). La transformación puede efectuarse utilizando un ácido (o fuente equivalente) y un reactivo acoplante o sin una base y en un solvente inerte. Los agentes acoplantes incluyen, aunque no se limitan a, DCC, EDC, HBTU, HATU, CDI y PyBOP. Las bases incluyen, aunque no se limitan a, carbonatos de metal de tierra alcalina, bicarbonatos de metal de tierra alcalina, hidróxidos de metal de tierra alcalina, alcóxidos de metal alcalino (preferiblemente etóxido de sodio o metóxido de sodio), trialquilaminas (preferiblemente diisopropiletilamina o trietilamina) o aminas aromáticas (preferiblemente piridina). Los solventes inertes pueden incluir, aunque no se limitan a, acetonitrilo, dialquil éteres (preferiblemente diéter éter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), N,N-dialquilacetamidas (preferiblemente dimetilacetamida), N,N-dialquilforamidas (preferiblemente dimetilformamida), dialquilsulfóxidos (preferiblemente dimetilsulfóxido), hidrocarburos aromáticos (preferiblemente benceno o tolueno), haloalcanos (preferiblemente diclorometano), alquil alcoholes (preferiblemente alcohol metílico o alcohol etílico) o agua. Las temperaturas de reacción preferidas oscilan entre 0 °C y la temperatura ambiente. El progreso de la reacción por condensación es monitoreado por métodos cromatográficos y espectrométricos estándar conocidos para el experto en el arte de la síntesis orgánica.

Alternativamente, la amina resultante puede tratarse con un agente acilante activado para otorgar el producto final de la fórmula general (5). La transformación puede ser efectuada utilizando un agente acilante activo y con o sin una base y en un solvente inerte. Los agentes acilantes activos incluyen, aunque no se limitan a, halogenuros de acilo, imidazolcs de acilo, anhídridos de acilo (simétricos y asimétricos) y oximas de acilo. Las bases incluyen, aunque no se limitan a,

carbonatos de metal de tierra alcalina, bicarbonatos de metal de tierra alcalina, hidróxidos de metal de tierra alcalina, hidruros de metal alcalino (preferiblemente hidruro sódico), alóxidos de metal alcalino (preferiblemente etóxido de sodio o metóxido de sodio), trialquilaminas (preferiblemente diisopropiletilamina o trietilamina) o aminas aromáticas (preferiblemente piridina). Los solventes inertes pueden incluir, aunque no se limitan a, acetonitrilo, dialquil éteres (preferiblemente diéter éter), éteres cíclicos (preferiblemente tetrahidrofurano o 1,4-dioxano), N,N-dialquilacetamidas (preferiblemente dimetilacetamida), N,N-dialquil foramidas (preferiblemente dimetilformamida), dialquilsulfóxidos (preferiblemente dimetilsulfóxido), hidrocarburos aromáticos (preferiblemente benceno o tolueno), haloalcanos (preferiblemente diclorometano), alquil alcoholes (preferiblemente alcohol metílico o alcohol etílico) o agua. Las temperaturas de reacción preferidas oscilan entre 0 °C y la temperatura ambiente. El progreso de la reacción por condensación es monitoreado por métodos cromatográficos y espectroscópicos estándar conocidos para el experto en el arte de la síntesis orgánica.

Esquema VI



Esquema VI

Según se describió más arriba y se detalla a continuación, un aspecto del invento dispone los compuestos de la fórmula (11), según se indica más arriba. Dichos compuestos pueden ser fabricados por métodos conocidos por los expertos en el arte de los compuestos iniciales, también

350

conocidos por los expertos en el arte, quienes también están familiarizados con la química de procesos. En el Esquema VI antes indicado se expone un proceso adecuado para la preparación de compuestos de fórmula (11).

El Esquema VI ilustra la preparación de los compuestos deseados utilizando 6-yodo-croman-4-ol (6), de fácil obtención, como material inicial (ver *Synthesis* (Síntesis), 1997, 23-25). El experto en el arte reconocerá que existen varios métodos para la conversión de la funcionalidad del alcohol hasta los compuestos amino deseados de la fórmula (7). En el Esquema VI el alcohol (6) se activa primero con cloruro de sulfonil metano y el mesilato resultante, desplazado con la azida sódica NaN_3. El experto en el arte está bien familiarizado con los métodos alternativos para la conversión de un alcohol en una azida. La azida resultante es posteriormente reducida utilizando la trimetilfosfina en una mezcla de THF y agua. El experto en el arte reconocerá que existen varios métodos para la reducción de una azida a la amina correspondiente. Para ejemplos, ver Larock, R.C. en *Comprehensive Organic Transformations* (Transformaciones Orgánicas Completas), Wiley-VCH Publishers, 1999. Esta reducción de la azida produce una mezcla de enantiómeros de la amina (7). Esta mezcla enantiomérica puede estar separada por medios conocidos para los expertos en el arte, como por ejemplo, recristalización a baja temperatura de una sal quiral o HPLC con preparado quiral, más preferiblemente por HPLC, empleando columnas quirales disponibles en el comercio.

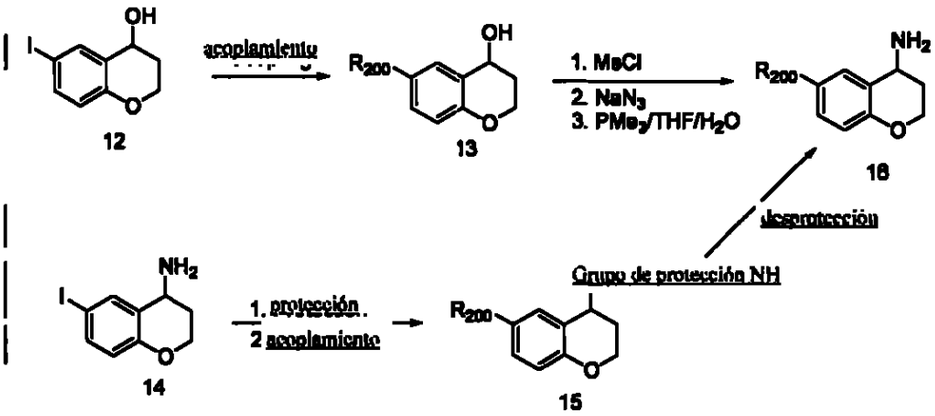
La amina resultante (7) se utiliza para abrir el epóxido (8) a fin de proporcionar el (6-yodo-3,4-dihidro-2H-cromen-4-il)amino propil carbamato protegido (9). Entre las condiciones de reacción adecuadas para la apertura del epóxido (8), se incluyen: ejecutar la reacción en una amplia gama de solventes comunes e inertes. Se prefieren solventes alcoholes C_1-C_6, mayormente alcohol isopropílico. Las reacciones pueden ejecutarse a temperaturas que oscilen entre 20 y 25 °C hasta la temperatura de reflujo del alcohol empleado. El rango de temperaturas preferido para llevar a cabo la reacción se encuentra entre 50°C y la temperatura de reflujo del alcohol empleado. El yodo-cromen protegido (9) es desprotegido hasta la amina correspodiente por medios conocidos por los expertos en el arte de eliminar los grupos de protección de aminas. Los medios adecuados para la eliminación del grupo de protección de aminas dependen de la naturaleza del grupo de protección. Los expertos en el arte, al estar familiarizados con la naturaleza de un grupo de protección específico, saben qué reactivo se recomienda para esta eliminación. Por ejemplo, se prefiere eliminar el grupo de protección preferido, BOC, disolviendo el yodo-croman protegido en una mezcla de ácido trifluoroacético/ diclorometano (1/1). Una vez finalizado el proceso, se eliminan los solventes bajo presión reducida para dar la amina correspondiente (como la sal correspondiente, es decir, sal de ácido trifluoroacético), que se usa sin mayor purificación. Sin

embargo, si se desea, la amina puede purificarse más por medios bien conocidos por los expertos en el arte, como por ejemplo, la recristalización. Asimismo, si se desea la forma sin sal, también puede obtenerse por medios con los que los expertos en el arte se encuentran familiarizados, tales como preparar la amina de base libre por medio del tratamiento de la sal con condiciones básicas leves. En T. W. Green y P. G. M. Wuts, *Protecting Groups in Organic Chemistry* (Protección de Grupos en Química Orgánica), 3ra. Edición, John 'Wiley and Sons, 1999, hallará otras condiciones de desprotección de BOC para otros grupos de protección.

Después, la amina se hace reaccionar con un agente de formación de amida debidamente sustituido Z-(CO)-Y para producir amidas acopladas (10) por medios de acilación de nitrógeno conocidos por los expertos en el arte. Las condiciones de acilación de nitrógeno para la reacción de la amina con un agente de formación de amidas Z-(CO)-Y son conocidas por los expertos en el arte y se encuentran en la publicación de R.C. Larock *Comprehensive Organic Transformations* (Transformaciones Orgánicas Completas), VCH Publishers, 1989, p. 981, 979 y 972. Y abarca –OH (ácido carboxílico) o halogenuro (halogenuro de acilo), preferiblemente cloro, imidazol (acilimidazol) o un grupo adecuado para producir un anhídrido mezclado.

El yodo-cromen acilado (10) se acopla con un organometálico debidamente funcionalizado $R_{200}M$ para producir compuestos de fórmula (11) empleando las condiciones conocidas por los expertos en el arte. Un experto en el arte reconocerá que existen varios métodos para el acoplamiento de diversos grupos alquilos y arilos a un yoduro aromático. Para ejemplos, ver L. S. Hegedus *Transition Metals in the Synthesis of Complex Organic Molecules* (Metales de Transición en la Síntesis de Moléculas Orgánicas Complejas), University Science, 1999.

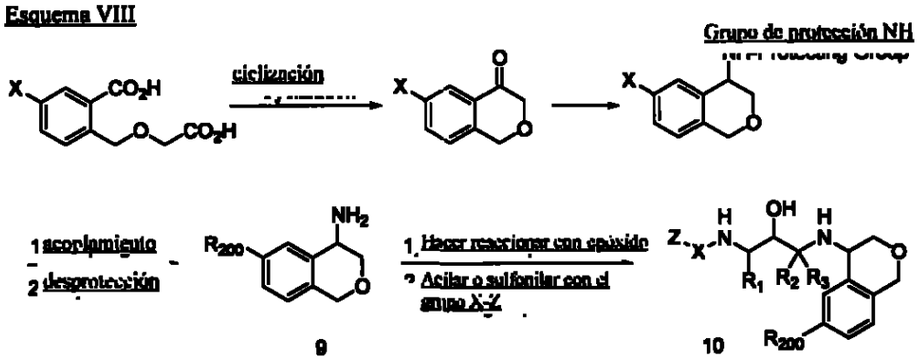
Esquema VII



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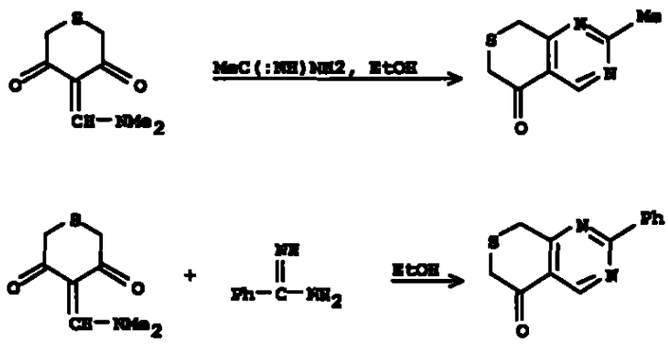
El Esquema VII especifica rutas alternativas a los 4-aminocromanos, que resultan de utilidad para la preparación de compuestos de fórmula (11). Las aminas de fórmula (16) pueden prepararse por acoplamiento del organometálico debidamente funcionalizado con 6-yodo-croman-4-ol (12) o con el yodo-amino croman debidamente protegido de la fórmula (14). La elaboración adicional de los productos acoplados mediante métodos conocidos por el experto en el arte finalmente produce las aminas de fórmula deseadas (16). De aquí en adelante, la química sigue las generalizaciones descritas en el Esquema VIII para la conversión de los compuestos 9 a 10.

Esquema VIII

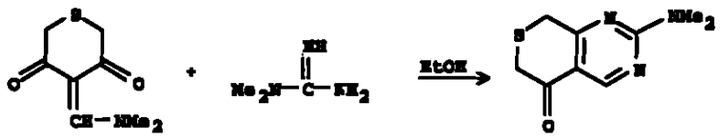


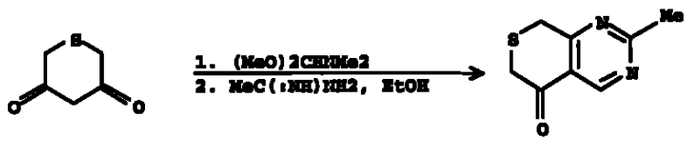
El Esquema VIII ilustra otra preparación general de aminas de fórmula (9) que, una vez observadas las generalizaciones detalladas en los Esquemas VI y VII, resultarán en compuestos de fórmula (10). A partir de aquí la química es, esencialmente, la misma descrita para los Esquemas VI y VII.

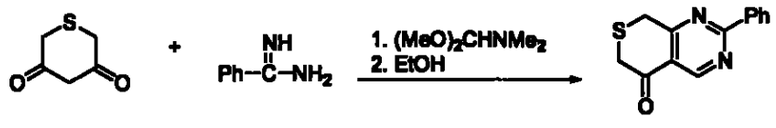
Esquema IX

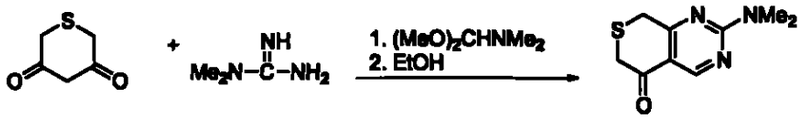


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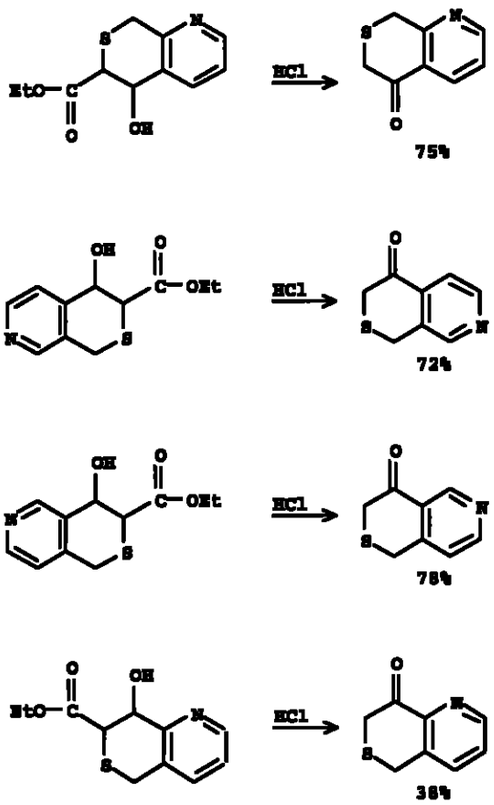




El Esquema IX ilustra la síntesis de diversas 5-H-tiopiranopirimidinonas a partir de una variedad de materiales iniciales. Las condiciones adecuadas de reacción se describen en, por ejemplo, J. Heterocycl. Chem. (Diario de Quím. Heterocíclica), 21(5), 1437-40; 1984.
Un individuo con conocimientos comunes apreciará que el tratamiento del sulfuro con un agente oxidante, como por ejemplo ácido paraclorobenzoico (MCPBA) u oxono, genera el sulfóxido o la sulfona. La oxidación del sulfuro puede realizarse secuencialmente, es decir, generando y aislando al sulfóxido y, después, oxidándolo hasta la sulfona, o bien ésta puede generarse directamente a partir del sulfuro. En la aplicación se describen otras manipulaciones de la cetona. También se entiende que el anillo de pirimidilo puede sustituirse además por medios conocidos en el arte. Por ejemplo, el anillo de piridilo puede ser alquilado, halogenado, acilado y/o nitrado. Ver *Organic Transformations* (Transformaciones Orgánicas), de Richard C. LaRock. Se incorpora al presente toda la bibliografía por referencia en su totalidad para cualquier propósito.

354

Esquema X

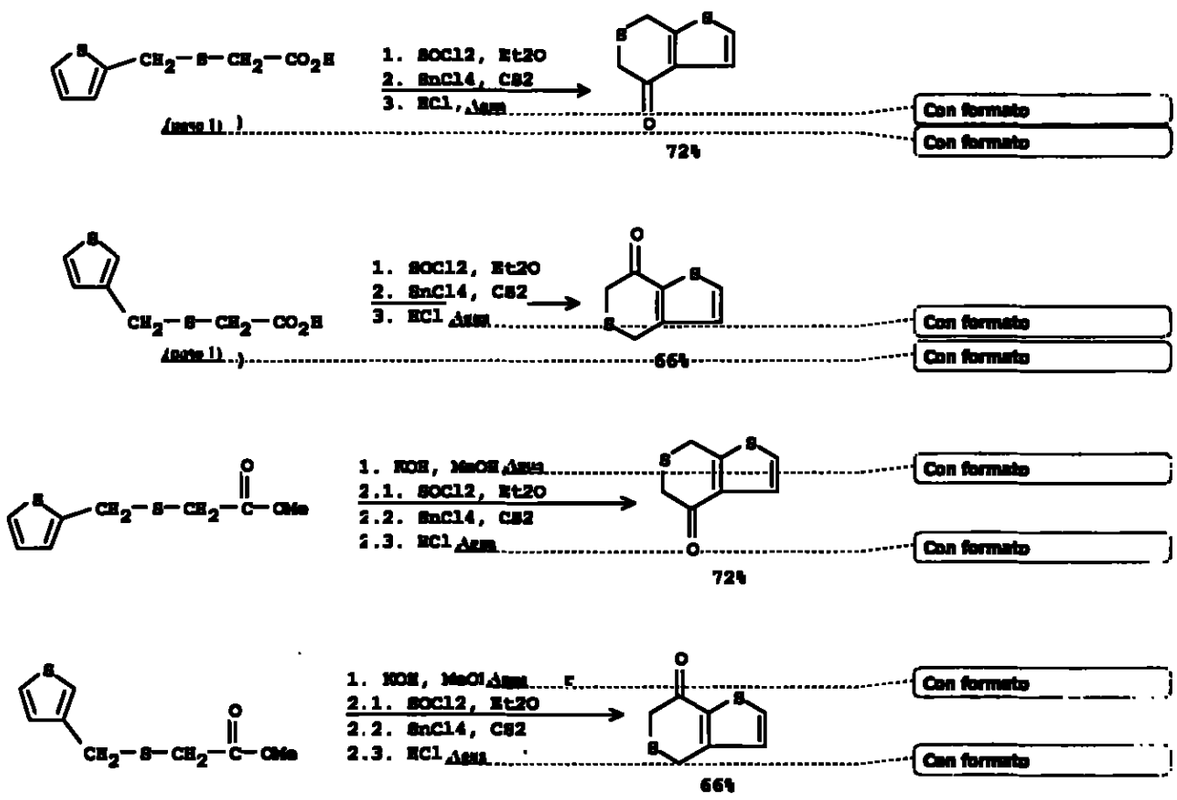


El Esquema X ilustra la síntesis de diversas 1H-tiopiranopiridinonas. Las condiciones de reacción adecuadas se describen, por ejemplo, en J. Chem. Soc., Perkin Trans. 1, (7), 1501-5; 1984.

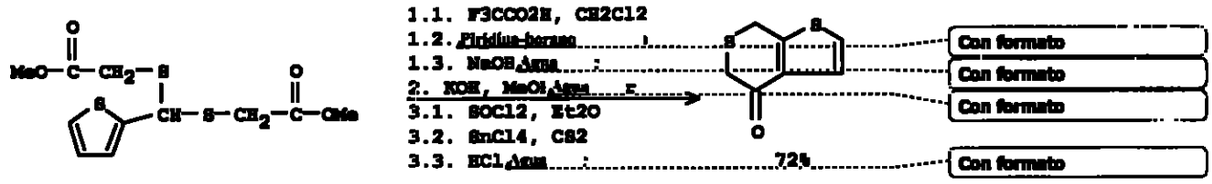
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Un individuo con conocimientos comunes apreciará que el tratamiento del sulfuro con un agente oxidante, como por ejemplo ácido paraclorobenzoico (MCPBA) u oxono, genera el sulfóxido o la sulfona. La oxidación del sulfuro puede realizarse secuencialmente, es decir, generando y aislando al sulfóxido y, después, oxidándolo hasta la sulfona, o bien ésta puede generarse directamente a partir del sulfuro. En la aplicación se describen otras manipulaciones de la cetona. También se entiende que el anillo de piridilo puede sustituirse además por medios conocidos en el arte. Por ejemplo, a modo ilustrativo, el anillo de piridilo puede ser alquilado, halogenado, acilado y/o nitrado. Ver *Organic Transformations* (Transformaciones Orgánicas), de Richard C. LaRock.

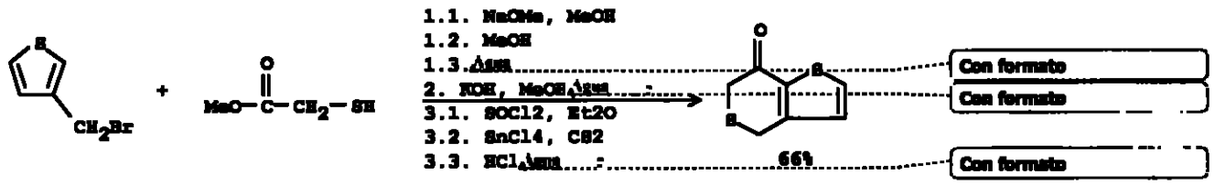
Esquema XI



356









Nota: 1) Inicialmente agitada con calentamiento; después, fotoquímica.

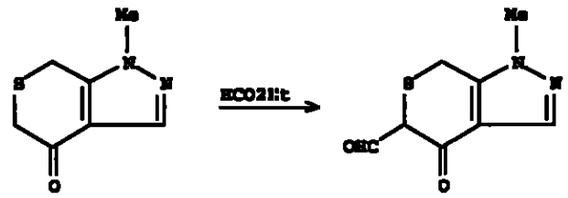
El Esquema XI ilustra la síntesis de diversas tienotiopiranonas a partir de una variedad de materiales iniciales. Las condiciones adecuadas de reacción se describen, por ejemplo, en el *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* (Diario de la Sociedad de Química, Transacciones Perkin 1: Química Orgánica y Bio-Orgánica), (18), 2639-2644; 1999.

Un individuo con conocimientos comunes apreciará que el tratamiento del sulfuro con un agente oxidante, como por ejemplo ácido paraclorobenzoico (MCPBA) u oxono, genera el sulfóxido o la sulfona. La oxidación del sulfuro puede realizarse secuencialmente, es decir, generando y aislando al sulfóxido y, después, oxidándolo hasta la sulfona, o bien ésta puede generarse directamente a partir del sulfuro. En la aplicación se describen otras manipulaciones de la cetona.

357

También se entiende que el anillo de tieno puede sustituirse además por medios conocidos en el arte. Por ejemplo, a modo ilustrativo, el anillo de tieno puede ser alquilado, halogenado, acilado y/o nitrado. Ver, por ejemplo, *Organic Transformations* (Transformaciones Orgánicas), de Richard C. LaRock.

Esquema XII



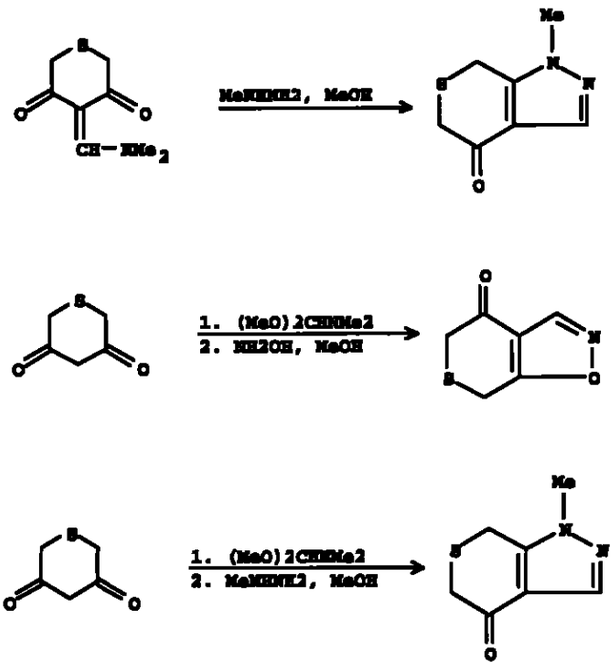
El Esquema XII ilustra un método para introducir funcionalidad en el anillo con contenido de sulfuro. Las condiciones de reacción adecuadas se describen, por ejemplo, en la Patente de EE.UU. Nº 4734431.

Un individuo con conocimientos comunes apreciará que el tratamiento del sulfuro con un agente oxidante, como por ejemplo ácido paracloroberzoico (MCPBA) u oxono, genera el sulfóxido o la sulfona. La oxidación del sulfuro puede realizarse secuencialmente, es decir, generando y aislando al sulfóxido y, después, oxidándolo hasta la sulfona, o bien ésta puede generarse directamente a partir del sulfuro. En la aplicación se describen otras manipulaciones de la cetona. También se entiende que el anillo de pirazola puede sustituirse además por medios conocidos en el arte. Por ejemplo, a modo ilustrativo, el anillo de pirazola puede ser alquilado, halogenado y/o acilado. Ver *Organic Transformations* (Transformaciones Orgánicas), de Richard C. LaRock.

Esquema XIII



358

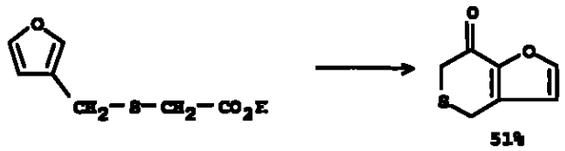


El Esquema XIII ilustra la preparación de los sistemas de anillos bicíclicos con contenido de isoxazola y pirazola. Las condiciones adecuadas de reacción se describen, por ejemplo, en J. Heterocycl. Chem. (Diario de Química Heterocíclica), 21(5), 1437-40; 1984. El experto en el arte reconocerá que pueden emplearse diversos reactivos para introducir funcionalidad en los sistemas de anillos antes mencionados. Por ejemplo, las hidrazinas sustituidas están disponibles en el comercio y pueden utilizarse para preparar pirazolas sustituidas. Asimismo, las reacciones estándar tales como alquilaciones y halogenaciones son conocidas en el arte.

Un individuo con conocimientos comunes apreciará que el tratamiento del sulfuro con un agente oxidante, como por ejemplo ácido paraclorobenzoico (MCPBA) u oxono, genera el sulfóxido o la sulfona. La oxidación del sulfuro puede realizarse secuencialmente, es decir, generando y aislando al sulfóxido y, después, oxidándolo hasta la sulfona, o bien ésta puede generarse directamente a partir del sulfuro. En la aplicación se describen otras manipulaciones de la cetona. También se entiende que el anillo de pirazola o isoxazola puede sustituirse además por medios conocidos en el arte. Por ejemplo, a modo ilustrativo, los anillos de pirazola e isoxazola pueden

ser alquilados, halogenados y/o acilados. Ver, por ejemplo, *Organic Transformations* (Transformaciones Orgánicas), de Richard C. LaRock.

Esquema XIV



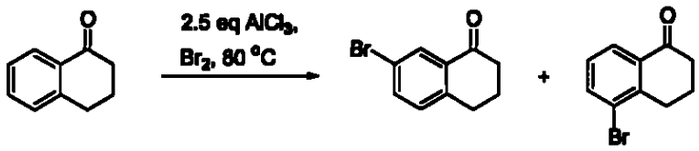
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El Esquema XIV ilustra la formación de un sistema de anillos bicíclicos con contenido de furano. Las condiciones adecuadas de reacción se describen, por ejemplo, en J. Heterocycl. Chem. (Diario de Química Heterocíclica) 13(2), 365-7; 1976.

Un individuo con conocimientos comunes apreciará que el tratamiento del sulfuro con un agente oxidante, como por ejemplo ácido paraclorobenzoico (MCPBA) u oxono, genera el sulfóxido o la sulfona. La oxidación del sulfuro puede realizarse secuencialmente, es decir, generando y aislando al sulfóxido y, después, oxidándolo hasta la sulfona, o bien ésta puede generarse directamente a partir del sulfuro. En la aplicación se describen otras manipulaciones de la cetona. También se entiende que el anillo de furilo puede sustituirse además por medios conocidos en el arte. Por ejemplo, a modo ilustrativo, el anillo de furilo puede ser alquilado, halogenado y/o acilado. Ver *Organic Transformations* (Transformaciones Orgánicas), de Richard C. LaRock.

Procedimientos Experimentales

Ejemplo 1: Preparación de 7-Bromo-1-tetralona



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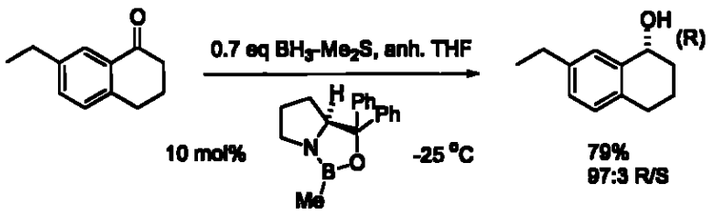
Ver, en general: Cornelius, L. A.M.; Combs, D. W. *Synthetic Communications* (Comunicaciones Sintéticas) 1994, *24*, 2777-2788. Más específicamente, un frasco de tres cuellos de 500 mL, con embudo, condensador de reflujo y termómetro, se cargó con cloruro de aluminio (33,34 g, 250

360

mmol) y calentó a una temperatura aproximada de 75-80 °C. Se agregó 1-Tetralona (14,6 g, 13,3 mL, 100 mmol), gota a gota, durante 10 min. La lechada color marrón resultante se agitó durante 3 minutos antes de agregar gota a gota bromo (19,21 g, 6,15 ml, 120 mmol) durante 15 min. La mezcla se agitó durante 5 min. y, después, se vertió en una mezcla de hielo (300 g) y 12N HCl (40 mL). La mezcla se agitó hasta que se disolvió el cloruro de aluminio y, después, se diluyó con agua (200 mL). La mezcla se extrajo con éter dietilo (3 X 300 mL) y la sustancia orgánica combinada se lavó con agua (2 X 300 mL), secó (sulfato sódico), filtró y evaporó *en vacío* para producir una mezcla marrón oscura de 5- y 7-bromo-1-tetralona. Los isómeros se separaron mediante cromatografía tipo flash con sílica gel (Equipo Flash 75 de Biotage, solvente de elución 20/1 hexanos:MTBE) para producir 5-bromo-1-tetralona (11,59 g, 51%) y 7-bromo-1-tetralona (9,45 g, 42%).

Los compuestos de tetralina-1-ol pueden prepararse según se indica en el Ejemplo 2 que se ofrece más abajo. Más específicamente, se preparó (R)-7-etil tetralina-1-ol en tres pasos, a partir de 7-etil-1-tetralona. El primer paso implicó una reducción asimétrica de la cetona con borano y el auxiliar quiral con oxazaborolidina de Corey. Esta reducción produjo una mezcla de enantiómeros (presumiblemente) R/S con una relación 97:3. Una conversión de S_N2 similar a la de Mitsunobu para la azida y la reducción de $LiAlH_4$ a la amina produjo el material S/R a una relación 98:2.

Ejemplo 2: Preparación de (R)-7-etil tetralina 1-ol



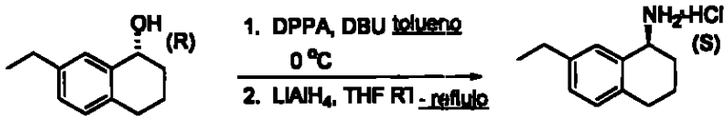
Ver, en general: T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner-Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* (Diario de Química Orgánica) 1991, *56*, 763-769. Más especialmente, se colocó 7-etil-1-tetralona (2,29 g, 13,1 mmol) en un frasco redondo de 100 mL y disolvió en tetrahidrofurano (THF) anhidro (40 mL). Se agregaron cribas moleculares 4Å activadas y la mezcla se envejeció durante 2 horas antes de transferirla por medio de una sonda a un frasco redondo de 250 ml con tres cuellos y con embudo de goteo, termómetro y entrada de nitrógeno. La solución se enfrió –25 °C y se agregó 1M (S)-tetrahidro-1-metilo-3,3-difenil-1H,3H-pirolo[1,2-c][1,3,2]oxazoborola en tolueno (1,3 mL, 1,3 mmol). La fuente de la oxaborola fue Aldrich, cat. no. 45.770-1, "(S)-2-metilo-CBS-

361

oxazaborolidina". El uso del auxiliar S producirá alcoholes R. De cuerdo con las referencias de forjado, el uso del catalizador de oxazaborolidina al 5 mol% debería proporcionar resultados comparables.

El embudo de goteo fue cargado con una solución de sulfuro de metilo-borano (0,70 g, 0,87 mL, 9,3 mmol) en THF anhidro (15 mL, secado sobre cribas 4A). La solución de borano se agregó gota a gota durante 20 minutos manteniendo la temperatura de reacción a menos de –20 °C. La mezcla se agitó durante 1 hora a una temperatura comprendida entre –15 y –20 °C, después de lo cual el análisis de cromatografía en capa fina (TLC) indicó el consumo de la cetona. La reacción fue apagada mediante el cuidadoso agregado de metanol (15 mL) a –20 °C y se dejó entibiar a temperatura ambiente y agitar durante 16 horas. Los compuestos volátiles se eliminaron en vacío y el residuo fue purificado por cromatografía con sílica gel (Equipo Flash 65 de Biotage, solvente de elución 6/1 hexanos:acetato de etilo) para producir (R)-7-etil tetralina-1-ol (1,82 g, 79%). La HPLC quiral analítica indicó una mezcla de 96,6/3,4 de enantiómeros (columna Chirocel OD-H, elución isocrática 2:98 IPA/hexano, 0,9 mL/min, RT 15,2 min (enantiómetro menor), 17,5 min (enantiómetro mayor).

Ejemplo 3: Preparación de (S)-7-Etil-1,2,3,4-tetrahidro-1-hidrocloruro de naftilamina



51%
98:2 S/R

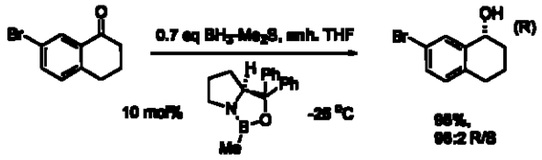
Ver, en general: Rover, S.; Adam, G.; Cesura, A. M.; Galley, G.; Jenck, F.; Monsma Jr., F. J.; Wichmann, J.; Dautzenberg, F. M. *J. Med. Chem (Diario de Química Médica).* **2000**, *43*, 1329-1338. Los autores del trabajo reportan una producción levemente disminuida debido a la formación parcial de un dihidronaftaleno por eliminación de la mitad del hidroxilo.

Más específicamente, una solución de (R)-7-etiltetralina-1-ol (1,77 g, 10,1 mmol) en tolueno (25 mL), se enfrió en un baño de hielo y trató con difenilfosforilazida (DPPA, 3,3 g, 2,7 mL, 12 mmol). Se agregó una solución de 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU, 1,8 g, 1,8 mL, 12 mmol) en tolueno (8 mL) durante 20 minutos y se agitó la mezcla a 0 °C durante 2 horas y a temperatura ambiente durante 16 horas. La mezcla se filtró a través de una almohadilla de sílica gel (con elución de hexanos/acetato de etilo, a una relación de 6:1) para remover los precipitados y los compuestos volátiles se eliminaron en vacío para producir un residuo aceitoso de la azida S cruda. Este material se utilizó directamente en el siguiente paso sin mayor caracterización.

362

La azida fue disuelta en THF (20 mL) seco y se agregó gota a gota a temperatura ambiente a una lechada de hidruro de litio aluminio (0,459 g, 12 mmol) en THF seco (20 mL). La mezcla se agitó a temperatura ambiente durante 1 hora y, después, se calentó para reflujo durante 1 hora. La reacción se enfrió a temperatura ambiente y apagó por el agregado sucesivo de agua (0,45 mL), 15% NaOH (acuoso) (0,45 mL) y agua (1,4 mL). La mezcla resultante se agitó durante 1 hora, para después filtrarse a través de una almohadilla de celite (éter de dietilo elucionado). Los compuestos volátiles fueron eliminados en vacío y el residuo absorbido en el acetato de etilo (40 mL) y tratado con 4N HCl en dioxano (3 mL). El precipitado resultante se filtró (acetato de etilo lavado), juntó y secó al vacío para dar (S)-7-etil-1,2,3,4-tetrahidro-1-hidrocloruro de naftilamina como sólido blanco (1,09 g, 51%). El HPLC quiral analítico indicó una mezcla de enantiómeros a una relación de 96:4 (Daicel Crownpak (-) columna, elución isocrática 10% metanol en agua (0,1% TFA), 0,8 mL/min, RT 56,2 min (enantiómero menor), 78,2 min. (enantiómetro mayor). El Esquema VIII que se indica más abajo describe la formación de un tetralinol, preparado en tres pasos a partir de 7-bromo-1-tetralona. El primer paso implica una reducción asimétrica de la cetona con burano y el auxiliar quiral de oxazaborolidina de Corey. Esta reducción produjo una mezcla de enantiómetros (presumiblemente) R/S a una relación de 98:2. Una conversión de S_N2 similar a la de Mitsunobu hacia la azida y la reducción de $LiAlH_4$ a la amina produjo el material S/R a una relación de 96:4.

Ejemplo 4: Preparación de (R)-7-Bromotetralina-1-ol

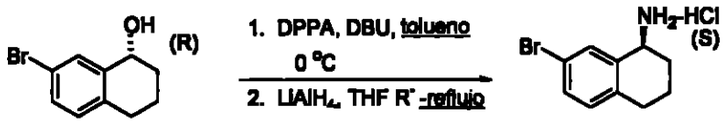


Ver, en general: Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner-Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* (Diario de Quím. Org.) 1991, *56*, 763-769. Más específicamente, se colocó 7-bromo-1-tetralona (8,28 g, 36,8 mmol) en un frasco redondo de 250 mL y se disolvió en THF anhidro (100 mL). Se agregaron cribas moleculares 4A activadas y se envejeció la mezcla durante 5 horas antes de transferirla por sonda a un frasco redondo de 500 ml, de tres cuellos, con embudo de goteo, termómetro y entrada de nitrógeno. La solución se enfrió a –25 °C y se agregó 1M (S)-tetrahidro-1-metilo-3,3-difenil-1H,3H-pirolo[1,2-c][1,3,2]oxazaborola en tolueno (3,7 mL, 3,7 mmol). La fuente de la oxazoborola fue Aldrich, cat. No. 45,770-1, "(S)-2-metilo-CBS-oxazaborolidina". El

363

uso del auxiliar S producirá alcoholes R. De acuerdo con las referencias de forjado, el uso del catalizador de oxazaborolidina de 5 mol% debería proporcionar resultados comparables.
El embudo de goteo fue cargado con una solución de sulfuro de metilo-borano (1,96 g, 2,44 mL, 25,8 mmol) en THF anhidro (45 mL, secado sobre cribas 4A). La solución de borano se agregó gota a gota durante 20 minutos manteniendo la temperatura de reacción a menos de –20 °C. La mezcla se agitó durante 1 hora a una temperatura comprendida entre –15 y –20 °C, después de lo cual el análisis de cromatografía en capa fina (TLC) indicó el consumo de la cetona. La reacción fue apagada mediante el cuidadoso agregado de metanol (50 mL) a –20 °C y se dejó entibiar a temperatura ambiente y agitar durante 16 horas. Los compuestos volátiles se eliminaron en vacío y el residuo fue purificado por cromatografía con sílica gel (Equipo Flash 65 de Biotage, solvente de elución 6/1 hexanos:acetato de etilo) para producir (R)-7-bromotetralina-1-ol (8,18 g, 98%, notas 4 y 5). El HPLC quiral analítico indicó una mezcla de 98;2 de enantiómeros (columna Chirocel OD-H, elución isocrática 2:98 IPA/hexano, 0,9 mL/min, RT 18,4 min (enantiómetro menor), 19,5 min (enantiómetro mayor). La resonancia magnética nuclear de protones fue consistente con lo reportado anteriormente para el racemato: Saito, M.; Kayama, Y.; Watanabe, T.; Fukushima, H.; Hara, T. *J. Med. Chem.* (Diario de Química Médica) 1980, *23*, 1364-1372.

Ejemplo 5: Preparación de (S)-7-Bromo-1,2,3,4-tetrahidro-1-hidrocloruro de naftilamina



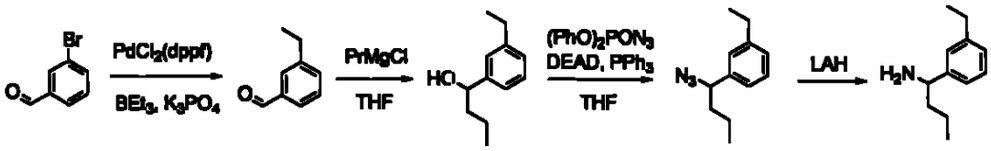
66%
98:4 S/R

Ver, en general: Rover, S.; Adam, G.; Cesura, A. M.; Galley, G.; Jenck, F.; Monsma Jr., F. J.; Wichmann, J.; Dautzenberg, F. M. *J. Med. Chem.* (Diario de Química Médica) 2000, *43*, 1329-1338. Los autores de este informe de referencia reportan una producción levemente disminuida debido a la formación parcial de un dihidronaftaleno por eliminación de la mitad del hidroxilo. Más específicamente, una solución de (R)-7-etiltetralina-1-ol (8,13 g, 35,.8 mmol) en tolueno (75 mL), se enfrió en un baño de hielo y trató con difenilfosforilazida DPPA, 11,8 g, 9,6 mL, 43 mmol). Se agregó una solución de 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU, 6,5 g, 6,4 mL, 43 mmol) en tolueno (20 mL) durante 35 minutos y se agitó la mezcla a 0 °C durante 2 horas y a temperatura ambiente durante 16 horas. La mezcla se filtró a través de una almohadilla de sílica gel (elución con hexanos/acetato de etilo, a una relación de 6:1) para remover los precipitados y

364

los compuestos volátiles se eliminaron en vacío para producir un residuo aceitoso de la azida S cruda. Este material se utilizó directamente en el siguiente paso sin mayor caracterización.
La azida se disolvió en THF (60 mL) seco y se agregó gota a gota a temperatura ambiente a una lechada de hidruro de litio aluminio (1,63g, 43 mmol) en THF seco (50 mL). La mezcla se agitó a temperatura ambiente durante 1 hora y, después, se calentó para reflujo durante 1 hora. La reacción se enfrió a temperatura ambiente y apagó por el agregado sucesivo de agua (1,63 mL), 15% de NaOH (ac.) (1,63 mL) y agua (4,9 mL). La mezcla resultante se agitó durante 1 hora, para después filtrarse a través de una almohadilla de celite (éter de dietilo elucionado). Los compuestos volátiles fueron eliminados en vacío y el residuo, absorbido en el acetato de etilo (120 mL) y tratado con 4N HCl en dioxano (10 mL). El precipitado resultante se filtró (acetato de etilo lavado), juntó y secó al vacío para dar (S)-7-bromo-1,2,3,4-tetrahidro-1-hidrocloruro de naftilamina como sólido blanco (6,23 g, 66,3%). El HPLC quiral analítico indicó una mezcla de enantiómeros a una relación de 96:4 (Daicel Crownpak (-) columna, elución isocrática 10% de metanol en agua (0,1% TFA), 0,8 mL/min, temperatura ambiente 39,4 min. (enantiómero menor), 57,6 min. (enantiómetro mayor).

Ejemplo 6: Preparación de las Aminas Sustituidas Precursoras



Las aminas precursoras pueden prepararse según se muestra, en general, en el Ejemplo 6, más arriba. Más específicamente, estas aminas se preparan esencialmente de acuerdo con los procedimientos descritos a continuación.

Ejemplo 7: Preparación de 3-Etilbenzaldehído a partir de 3-bromobenzaldehído

Se disolvió 3-Bromobenzaldehído (Aldrich, 1,17 mL, 10,0 mmol) en THF (20 mL) a temperatura ambiente. A ello se agregó el complejo $PdCl_2(dppf)$-CH_2Cl_2 (Aldrich, 82 mg, 0,10 mmol), 2 M de fosfato de potasio (ac., 10 mL, 20 mmol) y trietilborano (Aldrich, solución en hexanos de 1,0 M, 10 mL, 10 mmol). Esto se calentó para reflujo durante 4 horas, después de lo cual se dejó enfriar la mezcla a temperatura ambiente. La mezcla de reacción fue repartida entre EtOAc y agua. La

365

capa orgánica fue separada, secada ($MgSO_4$) y concentreada bajo presión reducida. El residuo fue purificado por cromatografía tipo flash (20% EtOAc/elución de hexanos) para producir un aceite transparente e incoloro que se utilizó sin mayor purificación; espec. masa (CI) 135.1.

Ejemplo 8: Preparación de 3-Etil-□-alcohol de propilbenzilo a partir de 3-etilbenzaldehído

A una solución de 3-etilbenzaldehído (641 mg, 4,78 mmol) en THF (15 mL) enfriada a 0 °C se agregó una solución de cloruro de propilmagnesio (Aldrich, 2,.0 M en dietil éter, 7,0 mL, 14,0 mmol), gota a gota y con agitación. Una vez finalizada la adición, se dejó calentar la mezcla de reacción a temperatura ambiente durante 2 horas. Después, la reacción se apagó con agua (1mL); a continuación, se concentró bajo presión reducida. El residuo fue purificado por cromatografía tipo flash (R_f = 0,71 en 30% EtOAc/hexanos) para producir un aceite incoloro como producto (804 mg, 94%): espec. masa (CI) 161,1 (M-OH).

Ejemplo 9: Preparación de 3-Etil-□-azida de propilbenzilo a partir de 3-etil-□-alcohol de propilbenzilo.

Se disolvió 3-Etil-□-alcohol de propilbenzilo (803 mg, 4,51 mmol) en THF (10 mL) y se dejó enfriar a 0 °C. Se agregó trifenilfosfina (Aldrich, 1,416 g, 5,40 mmol), azodicarboxilato de dietilo (Aldrich, 0,85 mL, 5,40 mmol) y difenil fosforil azida (1,16 mL, 5,38 mmol) en sucesión por medio de una jeringa. Esta solución se agitó a 0 °C durante 1 ¼ horas; después, a temperatura ambiente durante 2 horas; al cabo de lo cual la mezcla de reacción se concentró bajo presión reducida. El residuo fue purificado por cromatografía tipo flash (EtOAc/elución de hexanos) para dar un aceite transparente e incoloro como producto: ^{1}H NMR (300 MHz) □ 7,35-7,25 (m, 1H), 7,20-7,05 (m, 2H), 4,39 (t, J = 7,2 Hz, 1H), 2,67 (q, J = 7,6 Hz, 2H), 1,95-1,60 (m, 2H), 1,52-1,25 (m, 2H), 1,25 (t, J = 7,6 Hz, 3H), 0,93 (t, J = 7,3 Hz, 3H).

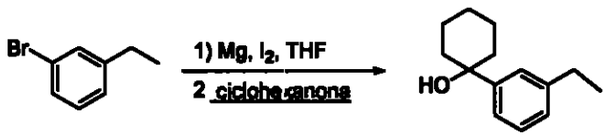
Ejemplo 10: Preparación de 3-Etil-□-propilbenzil amina a partir de 3-etil-□-propilbenzil azida

Se agregó 3-Etil-□-propilbenzil azida (724 mg, 3,57 mmol) en THF seco (10 mL) a una suspensión de hidruro de aluminio-litio (280 mg, 7,38 mmol) en THF (10 mL) a 0 °C. Esto se agitó a 0 °C durante 30 min.; después, a temperatura ambiente durante 1 hora; al cabo de lo cual la reacción se apagó con agua (0,2 mL), 15% de NaOH ac. (0,2 mL) y agua (0,6 mL) en sucesión. Esto se agitó a temperatura ambiente durante 1 hora. Después, la mezcla de reacción fue filtrada a

366

través de tierra diatomácea (elución con CH_2Cl_2) y el filtrado, concentrado bajo presión reducida. Este material se utilizó en reacciones subsiguientes sin mayor purificación: ^{1}H NMR (300 MHz) □ 7,35-7,20 (m, 1H), 7,20-7,04 (m, 2H), 3,87 (t, J = 6,9 Hz, 1H), 2,65 (q, J = 7,6 Hz, 2H), 1,72-1,57 (m, 2H), 1,50-1,20 (m, 2H), 1,24 (t, J = 7,6 Hz, 3H), 0,91 (t, J = 7,3 Hz, 3H); espec. masa (Cl) 161,1 (M-NH_2).

Ejemplo 11: Preparación de 1-(3-Etil-fenil)-ciclohexanol a partir de 1-bromo-3-etilbenceno



Los turnings de magnesio (1,35g, 55,53mmol) fueron activados por agitación enérgica durante toda la noche bajo entrada de N_2 (g). Se agregaron unos pocos cristales de yodo al frasco que, después, fue secado a las llamas bajo vacío. Se agregó THF anhidro (3 mL) al frasco de reacción, seguido de 1-bromo-3-etilbenceno (Avocado, 2.0mL, 14,59 mmol). La reacción se inició después de calentar brevemente con una pistola de calor. A esto se agregó el resto de 1-bromo-3-etilbenceno (1,7mL, 12,43mmol) en una solución de THF (15mL). La mezcla de reacción fue a reflujo durante 2 horas. Se agregó un ciclohexano (2,2mL, 21,22mmol) en solución de THF (8mL) una vez enfriado el frasco a 0°C. Después de 3,5 horas, la mezcla de reacción fue apagada con H_2O sobre un baño de hielo y separada entre Et_2O y H_2O. La capa orgánica fue removida y acidificada con 1N HCl. La capa orgánica fue separada, secada (Na_2SO_4) y concentrada bajo presión reducida. El residuo fue purificado por cromatografía tipo flash (100% $CHCl_3$) para dar el alcohol deseado (4,152g, 96%): espec. masa (Cl) 187,1 (M-16).

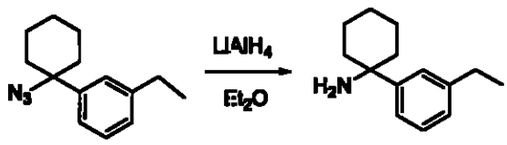
Ejemplo 12: Preparación de 1-(1-Azida-ciclohexil)-3-etil-benceno a partir de 1-(3-Etil-fenil)-ciclohexanol

1-(3-Etil-fenil)-ciclohexanol (4,02g, 19,68mmol) en cloroformo anhidro (45mL) fue enfriado a 0°C bajo entrada de N_2 (g). Se agregó azida sódica (3,97g, 61,07mmol), seguido de la adición gota a gota de ácido trifluoroacético (7,8mL, 101,25mmol). La mezcla de reacción fue a reflujo durante 2 horas y se dejó agitar a temperatura ambiente durante toda la noche. Después, se repartió entre H_2O y Et_2O. La capa acuosa se removió y se lavó la mezcla con H_2O, seguido de

367

1,0N NH_4OH. La capa orgánica se separó, secó (Na_2SO_4) y concentró bajo presión reducida. El producto crudo fue utilizado sin mayor purificación (3,30g, 73%): espec. masa (Cl) 187,1 (M-42).

Ejemplo 13: Preparación de 1-(3-Etil-fenil)-ciclohexilamina a partir de 1-(1-azida-ciclohexil)-3-etil-benceno



Esquema E13

Una solución de 1-(1-azida-ciclohexil)-3-etil-benceno (1,94g, 8,39mmol) en Et_2O (8mL) se agregó gota a gota a una suspensión de hidruro de aluminio-litio (0,31g, 8,17mmol) en THF (30mL). Esto se agitó a temperatura ambiente bajo entrada de N_2 (g) durante 3 horas; después de lo cual, la reacción fue apagada con 1,0N NaOH. A continuación, la mezcla de reacción fue repartida entre EtO_2 y 1N HCl. La capa acuosa fue recolectada y basificada con 2N NH_4OH y extraída con $CHCl_3$. La capa orgánica fue separada, secada (Na_2SO_4), filtrada y concentrada bajo presión reducida. El producto crudo fue utilizado sin mayor purificación: espec. masa (Cl) 187,1 (M-16).

Ejemplo 14: Preparación de N-{(1S,2R)-1-(3,5-difluorobenzil)-3-[(2-etil-7-fluoro-9H-fluoreno-9-il)amino]-2-hidroxipropil}acetamida.

Paso 1: A 3,0 g (16,6 mmol) de metilo 5-etilo-2-hidroxibenzoato en 100 mL de CH_2Cl_2 a 0 °C se agregaron 5,8 mL (41,5 mmol, 2,5 eq.) de Et_3N. A esta solución agitada se agregaron gota a gota 3,6 mL (21,6 mmol, 1,3 eq.) de Tf_2O. Después de la adición completa se agregaron 0,2 g (cat.) de 4-dimetilamino piridina y la mezcla de reacción se dejó calentar a temperatura ambiente. Después de agitar durante 4 horas a esta temperatura, se consideró que la reacción se había completado y se apagó por el agregado de una solución acuosa saturada de $NaHCO_3$ (100 mL). Las capas resultantes se separaron y la capa acuosa se extrajo dos veces con CH_2Cl_2 (100 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, filtraron y concentraron bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna para producir el metilo 5-etil-2-{[(trifluorometilo)sulfonil]oxi}benzoato deseado. ^1H NMR (400 MHz, $CDCl_3$): δ = 7,94 (d, J = 2,3 Hz, 1 H), 7,47 (dd, J = 2,3, 8,4 Hz, 1 H), 7,24 (d, J = 8,4 Hz, 1 H), 4,00 (s, 3 H), 2,76 (q, J = 7,6 Hz, 2 H), 1,28 (t, J = 7,6 Hz, 3 H).

368

Paso 2: A 1,5 g (4,8 mmol) del producto del Paso 1 en 12,5 mL de tolueno a temperatura ambiente se agregaron 0,28 g (0,24 mmol, 0,05 eq.) de $Pd(PPh_3)_4$. Después de agitar durante 5 min., se agregaron 1,1 g (5,7 mmol, 1,2 eq.) de 4-ácido fluorofenilborónico en 5,5 mL de EtOH, seguido de 11,5 mL de 2 M de Na_2CO_3 acuoso. Después de calentar a una temperatura de 90 °C durante 12 horas, se consideró que la reacción se había completado, se dejó enfriar y diluyó con Et_2O (100 mL) y agua (50 mL). Las capas resultantes fueron separadas y la capa acuosa, extraída dos veces con Et_2O (100 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, filtraron y concentraron bajo presión reducida. El residuo resultante fue purificado por cromatografía de columna para producir el metilo 4-etil-4'-fluoro-1,1'-bifenil-2-carboxilato deseado. $C_{16}H_{15}O_2F+H^+$ requiere 258 hallados 258.

Paso 3: A 1,1 g (4,3 mmol) del producto del Paso 2 en 50 mL de 2:2:1 THF:agua:MeOH se agregó 0,9 g (21 mmol) de LiOH. La mezcla se calentó a 55 °C durante 5 horas, en ese punto se consideró que la reacción se había completado. Una vez enfriada, los compuestos volátiles se removieron bajo presión reducida y el residuo se repartió entre un 10% de HCl (50 mL) acuoso y EtOAc (200 mL). Las capas resultantes se separaron y la capa acuosa se extrajo dos veces con EtOAc (100 mL). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, filtraron y concentraron. El residuo resultante, 4-etil-4'-fluoro-1,1'-bifenil-2-ácido carboxílico, fue lo suficientemente puro como para usarlo directamente en el siguiente paso. $C_{15}H_{13}F_1O_2 + H^+$ requiere 244, hallados 244.

Paso 4: A 0,25 g (1 mmol) del producto del Paso 3 se agregó 1 mL de H_2SO_4 y la mezcla resultante se calentó a 110 °C durante 20 min.; después de lo cual se consideró que la reacción se había completado. Después de enfriada, la mezcla fue vertida en agua con hielo (100 mL) y extrajo dos veces con Et_2O (200 mL). Los extractos orgánicos combinados se lavaron dos veces con una solución acuosa saturada de $NaHCO_3$ (100 mL), secaron sobre $MgSO_4$ y concentraron bajo presión reducida. El residuo resultante, 2-etil-7-fluoro-9H-fluoreno-9-uno fue lo suficientemente puro como para usarlo directamente en el siguiente paso. $C_{15}H_{11}F_1O_1 + H^+$ requiere 226, hallados 226.

Paso 5: A 0,8 g (3,6 mmol) del producto del Paso 4 se agregaron 10 mL de EtOH y 3,2 mL de piridina. A esta solución agitada se agregó 1,0 g (14,6 mmol, 4 eq.) de $NH_2OH{\cdot}HCl$ y la mezcla se calentó a 65 °C durante 6 horas; después de lo cual se consideró que la reacción se había completado. Una vez enfriada, se eliminaron los compuestos volátiles bajo presión reducida y el residuo se repartió entre un 10 % de HCl acuoso (50 mL) y EtOAc (250 mL). Las capas resultantes se separaron y las capas orgánicas se lavaron dos veces más con 10% de HCl (50 mL) acuoso. La capa orgánica se secó sobre $MgSO_4$, filtró y concentró bajo presión reducida. El

residuo resultante, (9Z)-2-etil-7-fluoro-9H-fluoreno-9-uno oxima fue lo suficientemente puro como para usarse directamente en el siguiente paso. $C_{15}H_{12}F_1O_1N_1 + H^+$ requiere 242, hallados 242.

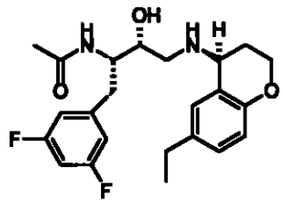
Paso 6: A 0,8 g (3,3 mmol) del producto del Paso 5 se agregaron 3 mL de AcOH, 0,1 mL de agua y 0,7 g (9,9 mmol, 3 eq.) de Zn. La mezcla resultante fue agitada enérgicamente durante 20 min.; al cabo de lo cual se consideró que la reacción se había completado. Después de la filtración para remover los sólidos, se eliminaron los compuestos volátiles bajo presión reducida. El residuo resultante fue repartido entre EtOAc (200 mL) y 10% de KOH (100 mL) acuoso. Las capas resultantes fueron separadas y la capa orgánica, lavada una vez más con 10 % de KOH (50 mL) acuoso. La capa orgánica fue secada sobre Na_2SO_4, filtrada y concentrada bajo presión reducida. El residuo resultante 2-etil-7-fluoro-9H-fluoreno-9-amina fue lo suficientemente puro como para usarse directamente en el siguiente paso. $C_{15}H_{14}F_1N_1 + H^+$ requiere 227, hallados 211 ($-NH_3$)

Paso 7: A 0,45 g (2,0 mmol) del producto del Paso 6 se agregaron 6 mL de alcohol isopropílico y 0,55 g (1,8 mmol, 0,9 eq.) del Ejemplo 134. La mezcla fue calentada a 65 °C durante 12 horas; después de lo cual, se consideró que la reacción se había completado. Después de enfriada, se eliminaron los compuestos volátiles bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna para producir el tert-butil (1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-7-fluoro-9H-fluoreno-9-il)amino]-2-hidroxipropilcarbamato deseado. $C_{30}H_{33}F_3N_2O_3 + H^+$ requiere 527, hallados 527.

Pasos 8 y 9: A 0,1 g (0.19 mmol) del producto del Paso 7 se agregaron 3 mL de CH_2Cl_2 y 0,5 mL (exceso) de TFA. La mezcla resultante fue agitada durante 1 hora a temperatura ambiente; después de lo cual, se consideró que la reacción se había completado. La mezcla de reacción fue diluida con tolueno (2 mL) y se removieron los compuestos volátiles bajo presión reducida. Después del secado bajo alto vacío durante 1 hora, el residuo fue disuelto en 5 mL de CH_2Cl_2 y 0,061 mL (0,4 mmol, 2,2 eq.) de Et_3N, seguido del agregado de 0,02 g (0,2 mmol, 1,05 eq.) de imidazol de acetilo. Después de agitar durante 12 horas a temperatura ambiente, se consideró que la reacción se había completado y se vertió en una solución acuosa saturada de $NaHCO_3$ (10 mL). Las capas resultantes se separaron y la capa acuosa se extrajo con EtOAc (50 mL). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, filtraron y concentraron bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna para producir la N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-7-fluoro-9H-fluoreno-9-il)amino]-2-hidroxipropil}acetamida deseada. $C_{27}H_{27}F_3N_2O_2 + H^+$ requiere 469, hallados 469.

370

Ejemplo 15: Preparación de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida

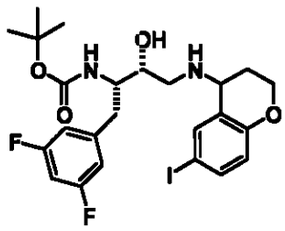


Paso 1 Preparación de 6-Yodo-croman-4-ilamina

A una solución de CH_2Cl_2 (80 ml) de 6-yodo-4-cromanol (10,0 g, 36 mmol) y diisopropiletilamina (19 ml, 108 mmol), a 0°C, se agregó MsCl (4,2 ml, 54 mmol). Después de agitar durante 1,5 hora, se eliminó el solvente en vacío y el residuo resultante se disolvió en 150 ml de DMF, seguido de la adición de Na N_3 (3,5 g, 54 mmol). La reacción fue calentada a 70°C durante 6,5 horas; después, enfriada a temperatura ambiente; a continuación se agregaron 900 ml de 1 N HCl y la extracción con Et_2O (4 x 200 ml). Las capas de Et_2O combinadas fueron secadas sobre $MgSO_4$ y concentradas en vacío para producir 9,5 g de la azida como aceite amarillo. MS (ESI+) para $C_9H_8IN_3O$ *m/z* 300,97 $(M+H)^+$. La azida cruda (5,0 g, 16,6 mmol) fue disuelta en THF (50 ml) y tratada con PPh_3 (5,2 g, 20,0 mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos, seguido del agregado de 4 ml de H_2O. A continuación, la mezcla se calentó a 60°C durante toda la noche. Después de enfriada, la mezcla fue concentrada en vacío y el residuo resultante, tratado con 1 N HCl. La capa acuosa fue lavada con CH_2Cl_2; después, ajustada a un pH = 12 con pastillas de NaOH. La capa acuosa básica fue extraída con CH_2Cl_2 y las capas orgánicas combinadas, secadas sobre Na_2SO_4 y tratadas con carbono activado. La mezcla fue filtrada por Celite® y concentrada en vacío para producir 6-yodo-croman-4-ilamina a 3,6 g (79%) como aceite transparente que se solidifica al estancarse. MS (ESI+) para $C_9H_{10}INO$ *m/z* 275,98 $(M+H)^+$.

Paso 2 Preparación de tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-yodo-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato

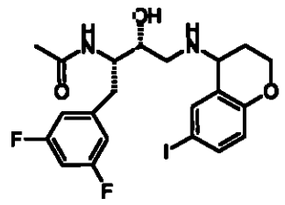
371



Una solución de alcohol isopropílico (25 ml) del Ejemplo 134 (2,2 g, 7,2 mmol) y 6-yodo-croman-4-ilamina (3,0 g, 10,9 mmol) fue agitada a 75°C durante 0 horas.

El alcohol isopropílico fue removido en vacío y el residuo resultante, disuelto en EtOAc (200 ml). La capa orgánica fue lavada con 1 N HCl (4 x 50 ml), seguido de $NaHCO_3$ (2 x 50 ml) y salmuera (1 x 50 ml). La capa orgánica fue secada sobre Na_2SO_4 y concentrada en vacío para producir 3,5 g (85%) del compuesto del título como una mezcla de diastereomeros como un sólido blancuzco. MS (ESI+) para $C_{24}H_{29}F_2IN_2O_4$ *m/z* 574,8 $(M+H)^+$.

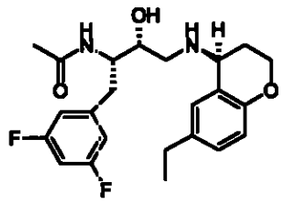
Paso 3 Preparación de N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-yodo-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida



Tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-yodo-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato (3,0 g, 5,2 mmol) fue disuelto en 30 mL de 25% de TFA/CH_2Cl_2 y agitado a temperatura ambiente durante 30 min. La mezcla fue diluida con CH_2Cl_2 50 mL y lavada con $NaHCO_3$ (2 x 30 mL). La capa orgánica fue lavada con salmuera (1 x 50 mL) y secada sobre Na_2SO_4. El solvente fue removido en vacío y el residuo resultante, disuelto en 52 mL de CH_2Cl_2. La mezcla fue enfriada a 0°C, seguido del agregado de Et_3N (1,0 mL, 11,9 mmol) e imidazol de acetilo (0,68 g, 6,2 mmol). La mezcla se calentó espontáneamente durante la noche. El CH_2Cl_2 fue removido en vacío y el residuo, disuelto en EtOAc (100 mL) y lavado con 1N HCl (2 x 30 mL), $NaHCO_3$ (1 x 30 mL), salmuera, secado sobre Na_2SO_4 y concentrado en vacío para producir 2,5 g (92%) del compuesto del título como un sólido de color amarillo claro. MS (ESI+) para el $C_{21}H_{23}F_2IN_2O_3$ *m/z* 517,0 $(M+H)^+$.

372

Paso 4 Preparación N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida



N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-yodo-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida(1,0 g, 1,9 mmol) y $Pd(dppf)Cl_2$ (0,078 g, 0,1 mmol) fue disuelta en 20 mL de THF desgasificado. A la mezcla se agregaron 10 mL de 2,0 M de K_3PO_4, seguido del agregado de Et_3B (3,8 mL, 3,8 mmol, 1,0 M en THF) con una jeringa. La mezcla de reacción fue calentada a 65°C bajo una atmósfera de nitrógeno. 2,5 horas después, se determinó que la reacción se había completado y se la diluyó con EtOAc (100 mL) y lavó con salmuera (3 x 30 mL). La capa orgánica se secó sobre Na_2SO_4 y concentró en vacío para producir un sólido de color marrón (café). Los diastereomeros del compuesto del título fueron separados por HPLC con preparado quiral (Chiralpak AD, 20% IPA/80%heptano, 0,1% DEA). MS (ESI+) para el $C_{23}H_{26}F_2N_2O_3$ *m/z* 419 $(M+H)^+$.

Los siguientes compuestos se preparan esencialmente de acuerdo con los procedimientos descritos en los esquemas y preparaciones especificadas anteriormente:

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-isopropil-3,4-dihidro-2H-cromen-4-il)amino]propul}acetamida; MS (ESI+) para el $C_{24}H_{30}F_2N_2O_3$ *m/z* 432,9 $(M+H)^+$;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida; MS (ESI+) para el $C_{25}H_{32}F_2N_2O_3$ *m/z* 447,4 $(M+H)^+$;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida; MS (ESI+) para el $C_{26}H_{34}F_2N_2O_3$ *m/z* 461,3 $(M+H)^+$;

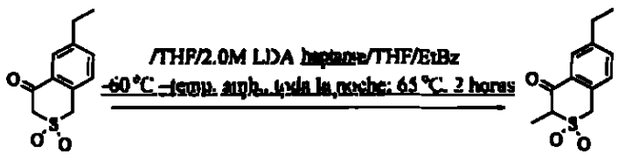
N-[(1S,2R)-3-{[(4S)-6-ciano-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida; MS (ESI+) para $C_{22}H_{23}F_2N_3O_3$ *m/z* 416,4 $(M+H)^+$;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1H-pirol-3-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida; MS (ESI+) para $C_{25}H_{27}F_2N_3O_3$ *m/z* 456,2 $(M+H)^+$; y

N-[(1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamina)-2-hidroxipropil]acetamida; MS (ESI+) para $C_{21}H_{24}F_2N_2O_3$ *m/z* 391,3 $(M+H)^+$.

393

Ejemplo 16: Preparación de Intermedios Cromanos Representativos



A 0,9 g (4 mmole) de cetona sulfona en 40 ml de THF se agregan 2,5 ml (5 mmole, 1,25 eq.) de 2 M de diisopropilamina de litio (LDA) en heptano/THF/ etilbenceno a –60 °C. La mezcla se agita durante aproximadamente 15 minutos; después, se agregan 1,24 ml (20 mmole, 5 eq.) de yoduro de metilo. La mezcla de reacción se agita durante 1 hora a –60 °C,; después de lo cual se elimina el baño en frío. Después de agitarla durante toda la noche, la mezcla de reacción se reparte entre EtOAc y agua, se lava con 0,5N HCl, solución acuosa de bicarbonato de sodio y salmuera, se seca sobre sulfato sódico anhidro, se filtra y concentra. El concentrado fue purificado por cromatografía en columna para suministrar 0,68 g del producto deseado como aceite, que se solidificó al asentarse. TLC (30%EtOAc/Hexano, Rf=0.39). Espec. masa m/e = 239,1.

Los siguientes compuestos se prepararon esencialmente de acuerdo con los procedimientos descritos anteriormente:

N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-propionamida;(MS 481,1)

N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-2-(1H-imidazol-4-il)-acetamida; (MS 533,1)

N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-2-metilo-2-metilamino-propionamida; (MS 524,1)

{[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propilcarbamoyl]-metilo}-metilo-ácido carbámico tert-butil éster; (MS 596,1)

N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-2-fenilacetamida; (MS 543,1)

N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-3-hidroxi-butiramida; (MS 511,1)

N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-3-hidroxi-propionamida; (MS 497,1)

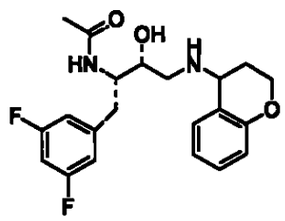
N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-3-hidroxi-2,2-dimetilo-propionamida; (MS 525,1)

N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-3-metilo-butiramida; (MS 509,1)

374

2-Amino-N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-acetamida; (MS 482,1) y
N-[1-(3,5-Difluorobencil)-3-(6-etil-2,2-dioxo-2l6-isotiocroman-4-ilamina)-2-hidroxi-propil]-2-metilaminoacetamida (MS 496,1).

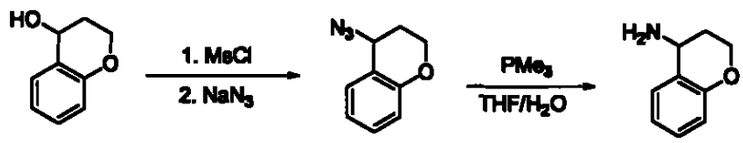
Ejemplo 17: N-[(1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamina)-2-hidroxipropil]acetamida.



Paso *Uno*: Croman-4-ol.

A una solución de MeOH (250 ml) de 4-cromanona (16,6 g, 11 mmol), a 0°C, se agregó $NaBH_4$ (5,5 g, 145 mmol) en porciones de 1 g durante un período de 30 minutos. Después de completada la adición, la mezcla se agitó durante 1 hora con calentamiento espontáneo. La reacción se apagó con un agregado lento de NH_4Cl (100 ml) acuoso. El
MeOH se removió en vacío y el residuo se extrajo con Et_2O (2 x 100 ml). Las capas orgánicas se secaron sobre $MgSO_4$ y trataron con carbono activado. Después del filtrado, se eliminó el Et_2O en vacío para producir 15,8 g de croman-4-ol en la forma de un aceite tansparente. HRMS (ESI+) calculado para $C_9H_{10}O_2$ *m/z* 150,0681 $(M+H)^+$. Hallados 150,0679.

Paso Dos: 3,4-dihidro-2H-cromen-4-ilamina.

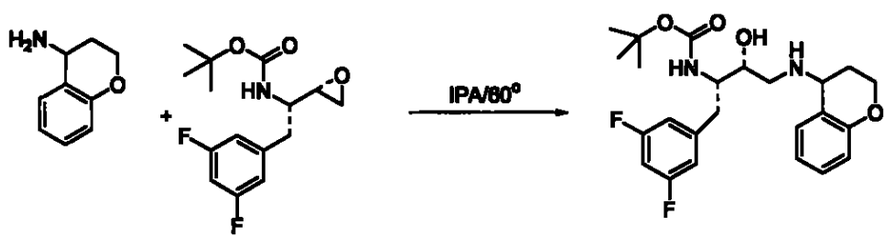


A una solución de CH_2Cl_2 (80 ml) de croman-4-ol (3,1 g, 20,6 mmol) y DIEA (8 ml, 42 mmol), a 0°C, se agregaron MsCl (2,1 ml, 27 mmol) con jeringa. Una vez completada la adición, se removió el baño frío y continuó la agitación a temperatura ambiente. Después de 15 horas, se

375

removió el CH_2Cl_2 en vacío y el residuo fue disuelto en 80 ml de DMF, seguido del agregado de NaN_3 (1,8 g, 27 mmol). La mezcla fue calentada a 75°C (baño de aceite) durante 5 horas; a continuación, enfriada a temperatura ambiente. La mezcla fue diluida con Et_2O (400 ml) y lavada con 1 N HCl (2 x 100 ml); $NaHCO_3$ (2 x 100 ml) y salmuera (100 ml). La capa orgánica fue secada sobre Na_2SO_4 y concentrada en vacío para producir la azida bajo la forma de un aceite amarillo. ^1H NMR (400 MHz, $CDCl_3$) δ 7,27-7,21 (m, 2 H), 6,97-6,87 (m, 2 H), 4,61 (appt, J = 3,84 Hz, 1 H), 4,31-4,19 (m, 2 H), 2,18 (m, 1 H), 2,03 (m, 1 H). MS (ESI-) para $C_9H_{10}N_3O$ *m/z* 173,0 $(M-H)^-$. La azida cruda fue disuelta en 60 ml de THF, seguido del agregado de PPh_3 (6,5 g, 25 mmol) y la mezcla agitada a temperatura ambiente durante 30 minutos. La mezcla fue tratada con 8 ml de H_2O y calentada a 60°C (baño de aceite) durante toda la noche. La mezcla fue concentrada en vacío y el residuo resultante, tratado con 1 N HCl. La mezcla acuosa fue extraída con CH_2Cl_2; después, se ajustó el pH en 12 con NaOH y se volvió a extraer con CH_2Cl_2. Las capas del segundo CH_2Cl_2 fueron combinadas; se secaron sobre Na_2SO_4 y volvieron a concentrarse en vacío para producir 3,4-dihidro-2H-cromen-4-ilamina bajo la forma de un aceite de color levemente amarillo. HRMS (ESI+) calculado para $C_9H_{11}NO$ *m/z* 150,0919 $(M+H)^+$. Hallados 150,0920.

Paso Tres: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamina)-2-hidroxipropilcarbamato.



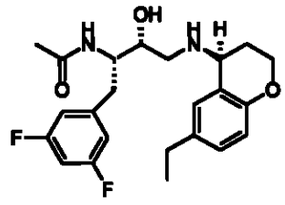
Una solución de alcohol isopropílico (15 ml) del Ejemplo 134 (0,54 g, 1,8 mmol) y 3,4-dihidro-2H-cromen-4-ilamina (0,40 g, 2,6 mmol) fue calentada a 60°C (baño de aceite) con agitación durante toda la noche. El alcohol isopropílico fue eliminado en vacío y el residuo, disuelto en EtOAc y lavado con 1 N HCl. La capa orgánica fue secada sobre $MgSO_4$ y concentrada en vacío para producir 0,75 g of *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamina)-2-hidroxipropilcarbamato como mezcla de epímeros. HRMS (ESI+) calculado para $C_{24}H_{30}N_2O_4F_2$ *m/z* 449,2252 $(M+H)^+$. Hallados 449,2258.

376

Paso Cuatro: N-[(1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamina)-2-hidroxipropil]acetamida.

Tert-butil (1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamina)-2-hidroxipropilcarbamato como mezcla de epímeros (0,49 g, 1,1 mmol) fue tratado con 10 ml de 20% de TFA/CH_2Cl_2 a la temperatura ambiente durante 1 hora. La mezcla fue diluida con 50 ml de CH_2Cl_2 y lavada con 0,5 M de NaOH (2 x 20 ml). La capa orgánica fue secada sobre Na_2SO_4, filtrada y concentrada en vacío para producir la amina bajo la forma de un aceite de color amarillo. El residuo fue disuelto en 10 ml de CH_2Cl_2 y tratado con Et_3N (0,4 ml, 2,5 mmol) e imidazol de acetilo a 0°C. La reacción fue calentada espontáneamente y agitada durante toda la nocha a temperatura ambiente. El solvente fue removido en vacío y el residuo, disuelto en EtOAc y lavado con 1N HCl (2 x 15 ml); $NaHCO_3$ (2 x 15 ml); salmuera (1 x 15 ml); secado sobre Na_2SO_4 y concentrado en vacío para dar N-[(1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamina)-2-hidroxipropil]acetamida bajo la forma de un cristal transparente. La HPCL en fase inversa del preparado produjo dos fracciones:
^{1}H NMR (400 MHz, $CDCl_3$) δ 7,29 (m, 1 H), 7,20 (m, 1 H), 6,92 (m, 1 H), 6,85 (dd, *J* = 6,85, 0,93 Hz, 1 H), 6,79-6,67 (m, 3 H), 5,69 (d, *J* = 8,91 Hz, 1 H), 4,35-4,23 (m, 2 H), 4,15 (m, 1 H), 3,87 (m, 1 H), 3,58 (m, 1 H), 3,03 (m, 1 H), 2,91-2,75 (m, 3 H), 2,15-2,08 (m, 1 H), 2,04-1,99 (m, 1H), 1,94 (s, 3 H). MS (ESI+) para $C_{21}H_{24}F_2N_2O_3$ *m/z* 391,3 $(M+H)^+$.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7,31 (m, 1 H), 7,21 (m, 1 H), 6,93 (m, 1 H), 6.86 (dd, *J* = 8.29, 1.04 Hz, 1 H), 6.79-6.67 (m, 3 H), 5.69 (d, *J* = 8.91 Hz, 1 H), 4.36-4,24 (m, 2 H), 4,17 (m, 1 H), 3,87 (appt, *J* = 4,04 Hz, 1 H), 3,54 (m, 1 H), 3,03 (dd, *J* = 14,31, 4,56 Hz, 1 H), 2,95 (m, 1 H), 2,88-2,79 (m, 2 H), 2,16-2,00 (m, 2 H), 1,92 (s, 3 H). MS (ESI+) para $C_{21}H_{24}F_2N_2O_3$ *m/z* 391,3 $(M+H)^+$.

Ejemplo 18: N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida:



377

Paso Uno: 6-yodocroman-4-ol

A una solución de croman-4-ol (19,6g, 131 mmol) en CH_2Cl_2 (500 mL), a temperatura ambiente se agregó HgO (29,7g, 137 mmol) e I_2 (34,8g, 137 mmol) bajo N_2. Después de agitar la mezcla durante 48 horas, fue filtrada a través de un tapón de sílica gel y el tapón fue lavado con EtOAc/Hexanos al 30%. El filtrado fue lavado con $Na_2S_2O_3$ al 15% y la capa orgánica fue secada sobre Na_2CO_3, filtrada y concentrada en vacío para producir 6-yodocroman-4-ol como un sólido blancuzco (32,44g, 90% de producto crudo). La recristalización fue realizada disolviendo el producto en diclorometano caliente (250 mL) y agregando lentamente éter de petróleo (250 mL). Producción general, 25,9g, 72% del producto. Anál. calculado para $C_9H_9IO_2$; C, 39.16, H, 3,29; hallados C, 39,26, H, 3,27.

Paso Dos: 6-Yodo-croman-4-ilamina.

A una solución de CH_2Cl_2 (150 ml) de 6-Yodo-4-cromanol (10,0 g, 36 mmol) y diisopropiletilamina (19 ml, 108 mmol), a 0°C, se agregó MsCl (4,2 ml, 54 mmol). Después de agitar durante 1,5 horas, el solvente fue removido en vacío y el residuo resultante, disuelto en 150 ml de DMF, seguido del agregado de Na N_3 (3,5 g, 54 mmol). La reacción fue calentada a 70°C durante 6,5 horas; después, enfriada a la temperatura ambiente, seguido por el agregado de 900 ml de 1 N HCl y extracción con Et_2O (4 x 200 ml). Las capas de Et_2O combinadas fueron secadas sobre $MgSO_4$ y concentradas en vacío para producir 9,5 g de la azida bajo la forma de un aceite de color amarillo. HRMS (ESI+) calculado para $C_9H_8IN_3O$ *m/z* 300,9714 $(M+H)^+$. Hallados 300,9709. La azida cruda (5,0 g, 16,6 mmol) fue disuelta en THF (50 ml) y tratada con PPh_3 (5,2 g, 20,0 mmol). La mezcla fue agitada a temperatura ambiente durante 30 min., seguido del agregado de 4 ml de H_2O. La mezcla fue después calentada a 60°C durante toda la noche. Una vez enfriada, la mezcla fue concentrada en vacío y el residuo resultante, tratado con 1 N HCl. La capa acuosa fue lavada con CH_2Cl_2 y posteriormente ajustada para un pH = 12 con pastillas de NaOH. La capa acuosa básica fue extraída con CH_2Cl_2 y las capas orgánicas combinadas, secadas sobre Na_2SO_4 y tratadas con carbono activado. La mezcla fue filtrada a través de Celite® y concentrada en vacío para producir 6-Yodo-croman-4-ilamina 3.6 g (79%) bajo la forma de un aceite transparente que se solidifica al asentarse. HRMS (ESI+) calculado para $C_9H_{10}INO$ *m/z* 275,9887 $(M+H)^+$. Hallados 275,9893.

Paso Tres: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-Yodo-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato

378

Una solución de alcohol isopropílico (25 ml) del Ejemplo 134 (2,2 g, 7,2 mmol) y 6-Yodo-croman-4-ilamina (3,0 g, 10,9 mmol) fue agitada a 75°C durante 9 horas. El alcohol isopropílico (AIP) fue removido en vacío y el residuo resultante, disuelto en EtOAc (200 ml). La capa orgánica fue lavada con 1 N HCl (4 x 50 ml), seguido de $NaHCO_3$ (2 x 50 ml) y salmuera (1 x 50 ml). La capa orgánica fue secada sobre Na_2SO_4 y concentrada en vacío para producir 3,5 g (85%) de *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-Yodo-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato como una mezcla de diastereomeros. MS (ESI+) para $C_{24}H_{29}F_2IN_2O_4$ *m/z* 574,8 $(M+H)^+$. Este material fue tomado hasta el siguiente paso sin mayor purificación.

Paso Cuatro: N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-Yodo-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida

El compuesto del título se obtiene a partir del propilcarbamato, esencialmente de acuerdo con el método descrito en el presente, como un sólido de color amarillo claro. MS (ESI+) para $C_{21}H_{23}F_2IN_2O_3$ *m/z* 517,0 $(M+H)^+$. El HPLC con preparado quiral (20% AIP/Heptano, 0,1% DEA) produce los dos diastereomeros.
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-Yodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,73 (d, J = 9,12 Hz, 1 H), 7,62 (d, J = 2,07 Hz, 1 H), 7,40 (dd, J = 8,50, 2,28 Hz, 1 H), 7,01 (m, 1 H), 6,89 (m, 2 H), 6,58 (d, J = 8,50 Hz, 1 H), 4,97 (d, J = 6,01 Hz, 1 H), 4,23 (m, 1 H), 4,14 (m, 1 H), 3,93 (m, 1 H), 3,68 (m, 1 H), 3,47 (m, 1 H), 3,01 (dd, J = 13,89, 3,32 Hz, 1 H), 2,61 (m, 2 H), 1,90 (m, 2 H), 1,71 (s, 3 H).
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4R)-6-Yodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida ^{1}H NMR (400 MHz, DMSO-d_6) δ 7,75 (d, J = 9,33 Hz, 1 H), 7,64 (d, J = 2,07 Hz, 1 H), 7,41 (dd, J = 8,60, 2,18 Hz, 1 H), 7,02 (m, 1 H), 6,92 (m, 2 H), 6,59 (d, J = 8,50 Hz, 1 H), 4,96 (d, J = 5,80 Hz, 1 H), 4,22 (m, 1 H), 4,15 (m, 1 H), 3,95 (m, 1 H), 3,68 (m, 1 H), 3,45 (m, 1 H), 2,98 (dd, J = 13,99, 2,80 Hz, 1 H), 2,73 (m, 1 H), 2,63-2,57 (m, 1 H), 1,87 (m, 2 H), 1,70 (s, 3 H).

Paso Cinque: N-((1S,2R)-1-(3,5-difluorobencil)-3-{[6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida

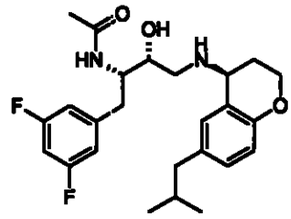
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-Yodo-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida (1,0 g, 1,9 mmol) y $Pd(dppf)Cl_2$ (0,078 g, 0,1 mmol) fue disuelta en 20 mL de THF desgasificada. A la mezcla se agregaron 10 mL de 2,0 M de K_3PO_4 seguido del

379 380

agregado de Et_3B (3,8 mL, 3,8 mmol, 1,0 M en THF) con una jeringa. La mezcla de reacción fue calentada a 65°C bajo una atmósfera de nitrógeno. Después de 2,5 horas, se determinó que la reacción se había completado y diluyó con EtOAc (100 mL) y lavó con salmuera (3 x 30 mL). La capa orgánica fue secada sobre Na_2SO_4 y concentrada en vacío para producir un sólido de color marrón. Los diastereomeros de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida fueron separados por HPLC con preparado quiral (Chiralpak AD, 20% AIP/80%heptano, 0,1% DEA). MS (ESI+) para $C_{23}H_{28}F_2N_2O_3$ *m/z* 419 $(M+H)^+$.

A una solución de MTBE (20 ml), CH_2Cl_2 (5 ml), MeOH (0,5 ml) de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida (0,2 g, 0,5 mmol) se agregó 1N HCl en Et_2O (0,38 ml) y la mezcla se agitó a temperatura ambiente. El sólido blanco final de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)hidrocloruro de acetamida fue aislado removiendo el solvente y tritación con Et_2O. HRMS (ESI+) calculado para $C_{23}H_{28}F_2N_2O_3$ *m/z* 419,2146 $(M+H)^+$. Hallados 419,2166.

Ejemplo 19: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



Paso Uno: (4R)-6-Yodocroman-4-ol

A una solución de croman-4-ol (19,6g, 131 mmol, 1,00 eq.) en diclorometano (500 mL) se agregó HgO (29,7g, 0,137 mol, 1,05 eq.) e I_2 (34,8g, 0,137 mol, 1,05 eq) bajo N_2, con agitación durante 48 horas. La mezcla de reacción cambió de color púrpura oscuro a incolora el fin de semana. Se filtró a través de un tapón de sílica gel y se lavó el tapón con EtOAc/Hexanos al 30%. El filtrado fue lavado con 15% $Na_2S_2O_3$ y la capa orgánica se secó con Na_2CO_3 durante 30 min. La mezcla fue filtrada y el filtrado, concentrado en vacío, produciendo el 6-Yodocroman-4-ol como un sólido blancuzco (32,44 g, 90% de producto crudo). La recristalización se llevó a cabo por disolución del producto en diclorometano caliente (250 mL) y agregando lentamente éter de

386

petróleo (250 mL). Producto general, 25,9 g, 72% de producto. En esta etapa se realizó la separación del HPLC quiral. HRMS (EI) calculado para $C_9H_9IO_2$ 275,9649, hallados 275,9646. (4S)-6-Yodocroman-4-ol $[\square]^{20}_D$ = +13 (20 mg, MeOH) (4R)-6-Yodocroman-4-ol $[\square]^{20}_D$ = -13 (20 mg, MeOH).

Paso Dos: (4S)-6-Yodocroman-4-amina

A una solución de (4R)-6-Yodocroman-4-ol (6,85 g, 24,81 mmol) y tolueno (100 mL) bajo nitrógeno a 0°C se agregó difenilfosforilazida (6,42 mL, 29,76 mmol). A esta mezcla se agregó una solución enfriada de DBU (4,45 mL, 29,76 mmol) como una solución de tolueno (25 mL) con una jeringa. La mezcla de reacción se dejó calentar a temperatura ambiente durante toda la noche. La solución de azida fue filtrada a través de sílica gel usando hexanos:EtOAc como eluyente a una relación de 6:1. El filtrado fue concentrado en vacío; después, disuelto en THF anhidro (100 mL), al cual se agregó 1,0 M Me_3P en THF (29,76 mL, 29,76 mmol). Al cabo de una hora, se agregó H_2O desionizada (5 mL) y la mezcla de reacción se agitó durante toda la noche bajo nitrógeno. Concentrada en vacío, disuelta en EtOAc, lavada con 10% $NaHCO_3$, salmuera; después, las capas orgánicas fueron secadas sobre Na_2SO_4, filtradas y concentradas en vacío para dar (4S)-6-Yodocroman-4-amina como un sólido de color blanco. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,70 (s, 2 H), 1,86 (m, 1 H), 2,13 (m, 1 H), 4,03 (t, J = 5 Hz, 1 H), 4,23 (m, 2 H), 6,60 (d, J = 9 Hz, 1 H), 7,42 (d, J = 9 Hz, 1 H), 7,64 (s, 1 H). MS (ESI+) para $C_9H_{10}INO$ *m/z* 258,8 $(M+H)^+$.

Paso Tres: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-Yodo-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato.

A una solución de [2-(3,5-Difluoro-fenil)-1-oxiranil-etil]-ácido carbámico tert-butil éster (8,34 g, 30,32 mmol) en alcohol isopropílico (75 mL) se agregó (4S)-6-Yodocroman-4-amina (4,54 g, 15,16 mmol) bajo nitrógeno con agitación durante toda la noche a 60 °C. La mezcla de reacción fue concentrada en vacío; después, redisuelta en acetato de etilo y lavada con 1N HCl. Las capas orgánicas se combinaron; después, se lavaron con 10% de $NaHCO_3$, seguido de un lavado en salmuera. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, filtradas y concentraron en vacío para producir el producto crudo como un sólido incoloro (9,31 g, 95% de crudo recuperado). El producto crudo fue purificado por cromatografía en columna usando MeOH/DCM al 3% como eluyente. *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-Yodo-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato era un sólido incoloro (6,89 g,

381

79%). HRMS (ESI); calculado para $C_{24}H_{29}N_2O_4IF_2$+H1 575,1220, hallados 575,1194; Rotación Específica (25 C D) = 30 (c = 1.04) MeOH.

Paso Cuatro: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-Yodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

El compuesto del título está preparado empleando los procedimientos descritos en el presente, y aislado como un sólido amarillo. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,93 (s, 3 H), 1,97 (m, 1 H), 2,08 (m, 1 H), 2,80 (m, 3 H), 3,09 (dd, *J* = 4, 14 Hz, 1 H), 3,55 (m, 1 H), 3,84 (m, 1 H), 4,13 (m, 1 H), 4,24 (m, 1 H), 4,31 (m, 1 H), 5,61 (m, 1 H), 6,62 (d, *J* = 9 Hz, 1 H), 6,70 (m, 1 H), 6,77 (d, *J* = 6 Hz, 2 H), 7,44 (dd, *J* = 2, 9 Hz, 1 H), 7,62 (s, 1 H).

Paso Cinco: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

A una solución de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-Yodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida (0,300 g, 0,58 mmol) y THF anhidro (2,3 mL) se agregó $Pd(dppf)Cl_2$ (0,024 g, 0,03 mmol) bajo nitrógeno con agitación. A esta solución se agregó bromuro de isobutilo de zinc (9,2 mL de una solución de 0,5 M de, 4,6 mmol) y la mezcla de reacción fue agitada durante toda la noche. Apagada con metanol; después se agregó resina Dowex 50WX2-400 (utilizada como exceso, 4,6 meq/g). Filtrada a través de una resina frita y lavada con metanol. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida fue liberada de la resina usando 7N NH_3/MeOH. El filtrado fue concentrado en vacío y, después, purificado por HPLC preparado para producir un sólido incoloro totalmente caracterizado como la sal HCl.
A una solución de MeOH (10 ml) de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida (2,0 g, 4,5 mmol), a 0°C, se agregaron 3 equiv. de HCl como una solución en MeOH. Resultó en 1,97 g de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromen-4-il]amino}propil)hidrocloruro de acetamida como un polvo blando después de la titración con CH_2Cl_2. HRMS (ESI+) calculado para $C_{25}H_{32}F_2N_2O_3$ *m/z* 447,2459 $(M+H)^+$. Hallados 447,2440. Anál calculado para $C_{25}H_{32}F_2N_2O_3$•HCl; C, 62,17; H, 6,89; N, 5.80; hallados C, 62,68; H, 7,05; N, 5,75.

382

Ejemplos 20-50: Procedimiento General para el Acoplamiento de Negishi a 6 Cromanos Sustituidos de fórmula (6):

A una solución de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-Yodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida (0,300 g, 0,58 mmol) y THF anhidro (2,3 mL) se agregó $Pd(dppf)Cl_2$ (0,024 g, 0,03 mmol) bajo nitrógeno con agitación. A esta solución se agregó el reactivo de bromuro de zinc (9,2 mL de una solución de 0,5M de THF, 4,6 mmol) y la mezcla de reacción se agitó durante toda la noche. Apagada con metanol, después se le agregó resina Dowex 50WX2-400 (usada como exceso, 4,6 meq/g). Filtrada a través de una resina frita y lavada con metanol para remover impurezas. El producto fue liberado de resina mediante 7N NH_3/MeOH. El filtrado fue concentrado en vacío y, después, purificado por HPLC con preparado. El producto final fue un sólido incoloro.

Ejemplo 20	N-[(1S,2R)-3-{[(4S)-6-(2-cianofenil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{28}H_{27}F_2N_3O_3$ *m/z* 492,2205 $(M+H)^+$.
Ejemplo 21	N-[(1S,2R)-3-{[(4S)-6-(4-cianofenil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{28}H_{27}F_2N_3O_3$ *m/z* 492,3219 $(M+H)^+$.
Ejemplo 22	N-[(1S,2R)-3-{[(4S)-6-sec-butil-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{25}H_{32}F_2N_2O_3$ *m/z* 447,316 $(M+H)^+$.
Ejemplo 23	N-[(1S,2R)-3-{[(4S)-6-ciclopentyl-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{26}H_{32}F_2N_2O_3$ *m/z* 459,3178 $(M+H)^+$.
Ejemplo 24	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-(1,1-dimetilpropil)-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida	MS (ESI+) para $C_{26}H_{34}F_2N_2O_3$ *m/z* 461,2516 $(M+H)^+$.
Ejemplo 25	N-[(1S,2R)-3-{[(4S)-6-ciclohexyl-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{27}H_{34}F_2N_2O_3$ *m/z* 473,3156 $(M+H)^+$.
Ejemplo 26	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(3-metilbutil)-3,4-dihidro-2H-cromen-4-	MS (ESI+) para $C_{26}H_{34}F_2N_2O_3$ *m/z*

383

	il]amino}propil)acetamida	461,3249 $(M+H)^+$.
Ejemplo 27	N-[(1S,2R)-3-{[(4S)-6-(2-cianobencil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{29}H_{29}F_2N_3O_3$ *m/z* 506,2569 $(M+H)^+$.
Ejemplo 28	N-[(1S,2R)-3-{[(4S)-6-(4-cianobencil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{29}H_{29}F_2N_3O_3$ *m/z* 506,2145 $(M+H)^+$.
Ejemplo 29	N-[(1S,2R)-3-({(4S)-6-[(1S,4R)-biciclo[2.2.1]hept-2-il]-3,4-dihidro-2H-cromen-4-il}amino)-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{28}H_{34}F_2N_2O_3$ *m/z* 485,3293 $(M+H)^+$.
Ejemplo 30	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1-metilbutil)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{26}H_{34}F_2N_2O_3$ *m/z* 461,3311 $(M+H)^+$.
Ejemplo 31	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1-metilpentyl)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{27}H_{36}F_2N_2O_3$ *m/z* 475,3686 $(M+H)^+$.
Ejemplo 32	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-(1-etilpropil)-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida	MS (ESI+) para $C_{26}H_{34}F_2N_2O_3$ *m/z* 461,3334 $(M+H)^+$.
Ejemplo 33	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-(1-etilbutil)-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida	MS (ESI+) para $C_{27}H_{36}F_2N_2O_3$ *m/z* 475,3723 $(M+H)^+$.
Ejemplo 34	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1-propilbutil)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{28}H_{38}F_2N_2O_3$ *m/z* 489,2886 $(M+H)^+$.
Ejemplo 35	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-(2-etilbutil)-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida	MS (ESI+) para $C_{27}H_{36}F_2N_2O_3$ *m/z* 475,334 $(M+H)^+$.
Ejemplo 36	N-[(1S,2R)-3-{[(4S)-6-(ciclohexilmetil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{28}H_{36}F_2N_2O_3$ *m/z* 487,4099 $(M+H)^+$.
Ejemplo 37	N-[(1S,2R)-3-{[(4S)-6-(5-ciano-5-metilhexil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-	MS (ESI+) para $C_{29}H_{37}F_2N_3O_3$ *m/z*

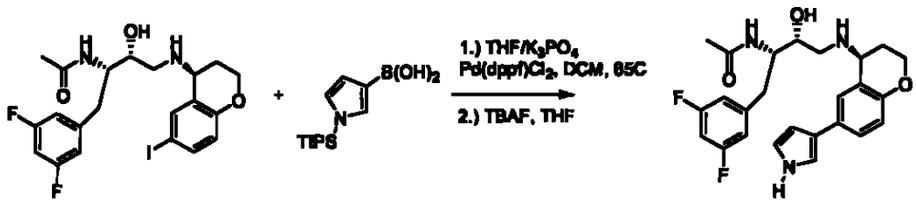
384

	2-hidroxipropil]acetamida	514,1028 $(M+H)^+$.
Ejemplo 38	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(4-metoxifenil)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{28}H_{30}F_2N_2O_4$ *m/z* 497,2083 $(M+H)^+$.
Ejemplo 39	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(6-metilpiridina-2-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{27}H_{29}F_2N_3O_3$ *m/z* 482,3209 $(M+H)^+$.
Ejemplo 40	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(5-metilpiridina-2-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{27}H_{29}F_2N_3O_3$ *m/z* 482,2673 $(M+H)^+$.
Ejemplo 41	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(4-metilpiridina-2-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{27}H_{29}F_2N_3O_3$ *m/z* 482,3107 $(M+H)^+$.
Ejemplo 42	N-[(1S,2R)-3-{[(4S)-6-(4-cianobutil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{26}H_{31}F_2N_3O_3$ *m/z* 472,2164 $(M+H)^+$.
Ejemplo 43	N-[(1S,2R)-3-{[(4S)-6-(6-cianohexil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{28}H_{35}F_2N_3O_3$ *m/z* 500,2705 $(M+H)^+$.
Ejemplo 44	N-[(1S,2R)-3-{[(4S)-6-(3-cianofenil)-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{28}H_{27}F_2N_3O_3$ *m/z* 492,1755 $(M+H)^+$.
Ejemplo 45	(2S)-3-((4S)-4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3,4-dihidro-2H-cromen-6-il)-2-metilpropanoato	MS (ESI+) para $C_{26}H_{33}F_2N_2O_5$ *m/z* 491,3261 $(M+H)^+$.
Ejemplo 46	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-(4-fluorofenil)-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida	MS (ESI+) para $C_{27}H_{27}F_3N_2O_3$ *m/z* 485,3275 $(M+H)^+$.
Ejemplo 47	metilol (2R)-3-((4S)-4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3,4-dihidro-2H-cromen-6-il)-2-metilpropanoate	MS (ESI+) para $C_{26}H_{33}F_2N_2O_5$ *m/z* 491,2724 $(M+H)^+$.
Ejemplo 48	N-[(1S,2R)-1-(3,5-difluorobencil)-3-({(4S)-6-[2-(1,3-dioxolano-2-il)etil]-3,4-dihidro-2H-cromen-4-il}amino)-	MS (ESI+) para $C_{26}H_{32}F_2N_2O_5$ *m/z*

385

	2-hidroxipropil]acetamida	491,2323 $(M+H)^+$.
Ejemplo 49	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(6-metoxipiridina-2-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida	MS (ESI+) para $C_{27}H_{29}F_2N_3O_4$ *m/z* 498,3047 $(M+H)^+$.
Ejemplo 50	N-[(1S,2R)-3-{[(4S)-6-ciano-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	MS (ESI+) para $C_{22}H_{23}F_2N_3O_3$ *m/z* 416,4 $(M+H)^+$.

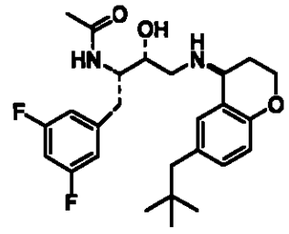
Ejemplo 51: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1H-pirrol-3-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



A una solución de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida (0.300 g, 0.58 mmol) y THF anhidro (5 mL), se agregó $Pd(dppf)Cl_2$ (0.030 g, 0.03 mmol) y K_3PO_4 (2.9 mL, 5.80 mmol). A esta mezcla se agregó ácido borónico (0.310 g, 1.16 mmol) (*J. Org. Chem* **1992**, *57*, 1653) y la mezcla de reacción se calentó a 65° C de un día para otro bajo nitrógeno con agitación. La reacción se extinguió con agua desionizada y luego se extrajo con acetato etílico. Las capas orgánicas se lavaron con solución salina, luego se secaron con $MgSO_4$, se filtraron y se concentraron *in vacuo*. El compuesto protegido por TIPS (0.100 g, 0.16 mmol) se disolvió en THF (3 mL) y luego se agregó 0.1M de la solución de TBAF en THF (0.32 mL, 0.32 mmol). La mezcla de reacción se agitó por 2 horas y luego se concentró *in vacuo*. Se disolvió en acetato etílico, se filtró a través de un tapón de gel de sílice y luego se concentró *in vacuo* para producir N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1H-pirrol-3-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida como un aceite ámber (130 mg). Purificado por medio de HPLC preparativa de fase inversa. HRMS (ESI); calculado para C25H27N3O3F2 + H1 456.2099, se obtuvo 456.2092.

Ejemplo 52: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

386



Paso Uno: 6-neopentilcroman-4-ol.

A una solución de 6-iodocroman-4-ol (1.0 g, 3.6 mmol) en 18 ml de THF, a 0°C, se agregó el $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.15 g, 0.18 mmol), seguido de bromuro de neopentilmagnesio (10.8 ml, 10.8 mmol, 1.0 M en Et_2O). El baño frío se mantuvo por 10 min., luego se quitó y la agitación continuó de un día para otro. La mezcla se extinguió con NH_4Cl (30 ml) y se extrajo con EtOAc (3 x 50 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron *in vacuo* para producir un aceite marrón. El aceite crudo fue absorbido en gel de sílice, seguido de cromatografía rápida (Biotage 40S) de 10% de EtOAc/heptanos para producir 0.36 g (46%) de 6-neopentilcroman-4-ol como un sólido blanco. $R_f = 0.11$. HRMS (ESI+) calculado para $C_{14}H_{20}O_2$ *m/z* 220.1463 $(M+H)^+$; se obtuvo 220.1460.

Paso Dos: 6-neopentil-3,4-dihidro-2H-cromen-4-ilamina.

A una solución de tolueno (30 ml) de 6-neopentilcroman-4-ol (1.6 g, 7.3 mmol), a 0°C, se agregó DPPA (1.9 ml, 8.7 mmol) con jeringa. La mezcla fue entonces tratada con una solución de 5 ml de tolueno de DBU (1.3 ml, 8.7 mmol). La mezcla se agitó a 0°C por 1 hora y luego 36 horas a t.a. La mezcla se filtró a través de un tapón de gel de sílice y luego el tapón se lavó con 15% de EtOAc/hexanos y el filtrado se concentró *in vacuo* para producir la azida como un aceite transparente. ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, $J = 8.40, 2.18$ Hz, 1 H), 6.89 (d, $J = 2.07$ Hz, 1 H), 6.71 (d, $J = 8.29$ Hz, 1 H), 4.50 (appt, $J = 3.73$ Hz, 1 H), 4.15 (m, 2 H), 2.36 (s, 2 H), 2.08 (m, 1 H), 1.93 (m, 1 H), 0.83 (s, 9 H). La azida cruda se disolvió en THF (20 ml) y se trató con PMe_3 (1.0 M en THF) y se agitó a t.a. por 30 min. La mezcla fue entonces tratada con H_2O (5 ml) y calentada a 50°C (baño de aceite) por 6 horas. La reacción se concentró *in vacuo* y el residuo se diluyó con H_2O (50 ml) y se extrajo con CH_2Cl_2 (3 x 50 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir 6-neopentil-3,4-dihidro-2H-cromen-4-ilamina como un aceite de color ligero (1.6 g). La amina se llevó al siguiente paso sin ninguna purificación. HRMS (ESI+) calculado para $C_{14}H_{21}NO$ *m/z* 219.1623 $(M+H)^+$. Se obtuvo 219.1628.

387

Paso Tres: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato.

A una solución de IPA (35 ml) de 6-neopentil-3,4-dihidro-2H-cromen-4-ilamina (2.0 g, 9.0 mmol), a t.a., se agregó el Ejemplo 134 (1.8 g, 6.0 mmol) como un sólido. La mezcla se calentó a 55°C (baño de aceite) por 28 horas y luego se enfrió a la temperatura ambiente. Se eliminó el solvente *in vacuo* y el residuo se diluyó con EtOAc (100 ml) y se lavó con 1N de HCl (4 x 50 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir un sólido blanquecino. La cromatografía rápida (3% de MeOH/CHC_3, 1 ml de NH_4OH por litro) produce 2.3 g (74%) de *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato como una mezcla de epímeros. HRMS (ESI+) calculado para $C_{29}H_{40}N_2O_4F_2$ *m/z* 519.3034 $(M+H)^+$. Se obtuvo 519.3040.

Paso Cuatro: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

El *tert*-Butyl (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (1.94 g, 3.7 mmol) se disolvió en CH_2Cl_2 y se enfrió a 0°C. La mezcla fue tratada con 35 ml de 4:1 CH_2Cl_2/TFA a 4:1 y el baño frío se quitó después de completarse la adición. Después de 2 horas a temperatura ambiente, la mezcla se diluyó con 100 ml de H_2O y se ajustó el pH a 10 con NaOH acuoso. La mezcla se extrajo con CH_2Cl_2 y las capas orgánicas se secaron sobre Na_2SO_4 y se concentraron *in vacuo* para producir amina cruda como un aceite amarillo. La amina cruda se disolvió en 30 ml de CH_2Cl_2 y se enfrió a 0°C, seguido de la adición de Et_3N (1.3 ml, 9.0 mmol). Esta mezcla fue tratada con una solución de 5 ml de CH_2Cl_2 de imidiazol de acetilo (0.44 g, 4.0 mmol) por gotas con jeringa durante un período de 30 min. Después de completarse la adición, se quitó el baño frío y se continuó agitando de un día para otro a temperatura ambiente. El solvente se eliminó *in vacuo*. El residuo resultante se disolvió en 50 ml de EtOAc y se lavó con 1 N de HCl (2 x 15 ml); $NaHCO_3$ (2 x 15 ml); solución salina (1 x 15 ml); se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir 1.6 g de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida como una mezcla de epímeros. La columna preparativa quiral de HPLC (10% de IPA/heptanos, 0.1% de DEA) AD produce dos compuestos finales:

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 1.87 Hz, 1 H), 6.96 (dd, J = 8.29, 2.07 Hz, 1 H), 6.79-6.67 (m, 4 H), 5.69 (d, J = 8.50 Hz, 1 H), 4.32-4.15 (m, 3 H), 3.85

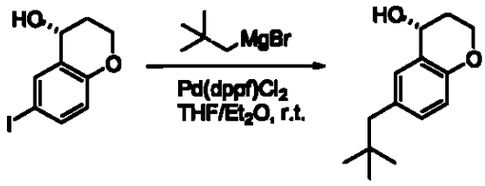
388

(bs, 1 H), 3.60 (bs, 1 H), 3.02 (m, 1 H), 2.88 (m, 2 H), 2.76 (dd, J = 12.13, 6.74 Hz, 1 H), 2.46 (s, 2 H), 2.15-2.08 (m, 1 H), 2.04-1.98 (m, 1 H), 1.94 (s, 3 H), 0.91 (s, 9 H). HRMS (ESI+) calculado para $C_{26}H_{34}F_2N_2O_3$ *m/z* 461.2615 $(M+H)^+$. Se obtuvo 461.2621.

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4R)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 2.07 Hz, 1 H), 6.96 (dd, J = 8.29, 1.87 Hz, 1 H), 6.77-6.67 (m, 4 H), 5.69 (d, J = 8.91 Hz, 1 H), 4.31-4.16 (m, 3 H), 3.86 (bs, 1 H), 3.57 (bs, 1 H), 3.00 (m, 2 H), 2.82 (m, 2 H), 2.44 (s, 2 H), 2.18-2.00 (m, 3 H), 1.90 (s, 3 H), 0.91 (s, 9 H). HRMS (ESI+) calculado para $C_{26}H_{34}F_2N_2O_3$ *m/z* 461.2615 $(M+H)^+$. Se obtuvo 461.2630. Anal. calculado para $C_{26}H_{34}F_2N_2O_3$; C, 67.81; H, 7.44; N, 6.08. Se obtuvo C, 67.65; H, 7.51; N, 6.05.

Síntesis Quiral

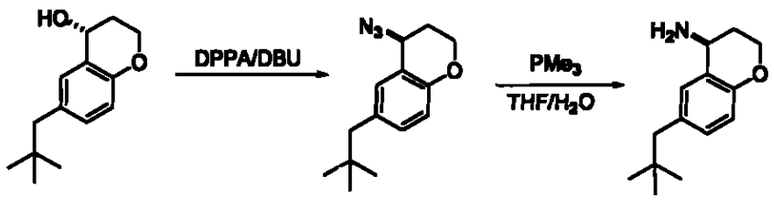
Paso Uno: (4R)-6-neopentilcroman-4-ol.



A una solución de (4R)-6-iodocroman-4-ol (10 g, 36.2 mmol) y $Pd(dppf)Cl_2$ (1.5 g, 1.81 mmol) en THF (100 ml), a 0 °C, se agregó bromuro de neopentil magnesio por gotas con jeringa durante un período de 30 min. Se quitó el baño frío y se continuó agitando a t.a. por 24 horas. La reacción se extinguió con NH_4Cl y se extrajo con EtOAc. Las capas orgánicas se secaron sobre $MgSO_4$ y se concentraron *in vacuo* para producir un aceite marrón. Los residuos se disolvieron en CH_2Cl_2 y se absorbieron en gel de sílice, seguido de cromatografía rápida (15% de EtOAc/heptanos, Biotage 40M) para producir 5.0 g (63%) de (4R)-6-neopentilcroman-4-ol como un sólido blanco. Anal. calculado para $C_{14}H_{20}O_2$; C, 76.33; H, 9.15. Se obtuvo C, 76.31; H, 9.06. $[\alpha]_D$ = 22.3, c = 1.14 (CH_2Cl_2).

Paso Dos: (4S)-6-neopentil-3,4-dihidro-2H-cromen-4-ilamina.

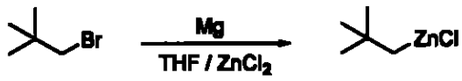
390
389



A una solución de tolueno (90 ml) de (4R)-6-neopentilcroman-4-ol (4.9 g, 22 mmol), a 0 °C, se agregó azida dipehenilfosforil (DPPA) (5.65 ml, 26 mmol) con jeringa. La mezcla fue tratada luego con una solución de tolueno (15 ml) de DBU (3.92 ml, 26 mmol) por gotas durante un período de 30 min. Se quitó el baño frío después de 1 hora y se continuó agitando de un día para otro a t.a. La mezcla fue filtrada a través de gel de sílice y el tapón se enjuagó con 15% de EtOAc/Hexanos. El filtrado fue concentrado *in vacuo* para producir la azida cruda como un aceite amarillo. La azida se disolvió en THF (50 ml) seguido de la adición de PMe_3 (22 ml, 1.0 M en THF). Después de 30 min. a t.a., se agregaron 15 ml de agua y la mezcla se calentó a 50°C de un día para otro. El solvente fue eliminado *in vacuo* y el residuo fue tratado con 1 N de HCl. El sólido blanco resultante fue recogido por medio de filtración y fue lavado con Et_2O y secado para producir la sal de HCL. HRMS (ESI+) calculado para $C_{14}H_{21}N_1O_1$ 220.1701; se obtuvo *m/z* 220.1698 $(M+H)^+$. Anal. calculado para $C_{11}H_{21}NO{\cdot}HCl$: C, 65.74; H, 8.67; N, 5.48. Se obtuvo: C, 65.62; H, 8.53; N, 5.42. $[\alpha]^{23}_D$ = 15.6, c = 1.17 en CH_3OH. La sal fue suspendida en H_2O y se ajustó al pH = 12 con NaOH. La mezcla fue extraída con CH_2Cl_2 y la capa orgánica fue secada sobre Na_2SO_4, y fue concentrada *in vacuo* para producir 4.7 g (95%) de (4S)-6-neopentil-3,4-dihidro-2H-cromen-4-ilamina.

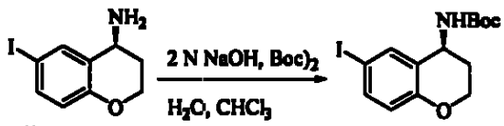
Alternativamente

Preparación del reactivo neopentil zinc:



Referencia: *Tetrahedron Lett.* 1983, *24*, 3823-3824.

terc-butil (4S)-6-iodo-3,4-dihidro-2H-cromen-4-ilcarbamato.

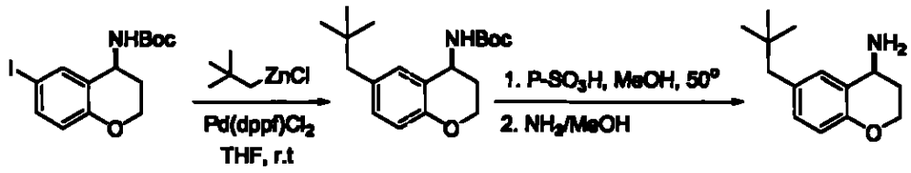


(S) sal mandélica

390

A una suspensión de sal amino (S)-mandélica (4.55 g, 10.6 mmol) en agua (50 mL), se agregó hidróxido de sodio (21 mL, 2 N, 42 mmol) seguido de di-*tert*-butil dicarbonato (2.58 g, 11.7 mmole) y cloroformo (50 mL). La mezcla de reacción fue agitada a temperatura ambiente por 2 horas y luego diluida con cloruro de metileno (100 mL) y agua (50 mL). La capa orgánica fue separada y lavada con cloruro de sodio saturado, secada (sulfato de sodio), filtrada y concentrada bajo presión. El residuo fue triturado con hexanos/éter etílico a 1:1. El sólido blanco resultante fue recogido por filtración y lavado con hexanos para proporcionar *tert*-butil (4S)-6-iodo-3,4-dihidro-2H-cromen-4-ilcarbamato (3.30 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.55 (d, J = 1.8 Hz, 1H), 7.42 (dd, J = 8.6,2.2 Hz, 1H), 6.58 (d, J = 8.6 Hz, 1H), 4.78 (m, 2H), 4.28–4.20 (m, 1H), 4.18–4.10 (m, 1H), 2.19–2.10 (m, 1H), 2.06–1.96 (m, 1H), 1.49 (s, 9H).

Combinando el reactivo de neopentil zinc con *tert*-butil (4S)-6-iodo-3,4-dihidro-2H-cromen-4-ilcarbamato.

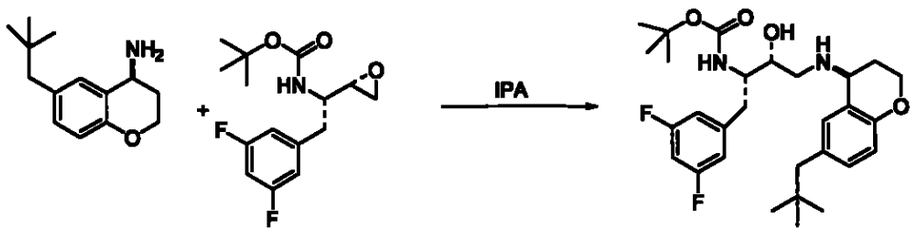


A una suspensión del reactivo de neopentil zinc de 0.3 M en THF (60 ml, 15 mmol), se agregó el *tert*-butil (4S)-6-iodo-3,4-dihidro-2H-cirom:en-4-ilcarbamato (1.8 g, 5.0 mmol) y $Pd(dppf)Cl_2$ (0.2 g, 0.25 mmol) como sólidos en una porción. La mezcla fue agitada a t.a. bajo nitrógeno por 48 horas (el progreso fue vigilado por medio de LC/MS y HPLC). La mezcla se extinguió con NH_4Cl acuoso (20 ml) y fue extraída con EtOAc (3 x 50 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo*. El residuo crudo se disolvió en MeOH (25 ml) y se trató con resina de intercambio de iones 50WX2-400 de DOWEX®. La mezcla se calentó a 50°C por seis horas y luego la resina fue recogida mediante filtración. La resina fue lavada sucesivamente con MeOH y CH_2Cl_2 y estos lavados fueron desechados. La resina fue entonces tratada con 7 N NH_3/MeOH para levigar la amina libre de la resina. Las levigaciones fueron concentradas *in vacuo* para producir un aceite marrón claro (0.63 g, 57%) de (4S)-6-neopentil-3,4-dihidro-2H-cromen-4-ilamina. Este material era consistente con las preparaciones previas y se utilizó como se obtuvo para la apertura subsiguiente del epóxido di-fluoroPhe. S)-6-neopentil-3,4-dihidro-2H-cromen-4-ilamina fue previamente caracterizado como la sal mono•HCl. ^{1}H NMR (300 MHz, DMSO-d_6) δ); 7.25 (s, 1H), 7.02 (m, 1H,), 6.76 (m, 1H), 4.47 (bs, 1H), 4.21 (m, 2H), 2.38 (s, 2H), 2.24 (m, 1H), 2.10 (m, 1H), 0.87 (s, 9H). HRMS (ESI+) calculado para $C_{14}H_{21}N_1O_1$

391

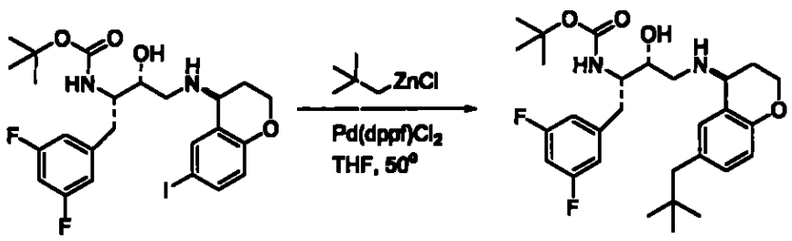
220.1701; se obtuvo *m/z* 220.1698 $(M+H)^+$. Anal. calculado para $C_{14}H_{21}NO \cdot HCl$: C, 65.74; H, 8.67; N, 5.48. Se obtuvo: C, 65.62; H, 8.53; N, 5.42. $[\alpha]^{23}_D = 15.6$, c = 1.17 en CH_3OH.

Paso Tres: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amina}propilcarbamato.



A una solución de IPA (70 ml) de (4S)-6-neopentil-3,4-dihidro-2H-cromen-4-ilamina (4.7 g, 21.5 mmol), se agregó el Ejemplo 134 (4.6 g, 15.4 mmol) como un sólido. La mezcla se calentó a 70°C (temperatura del baño de aceite) por 18 horas. El IPA se eliminó *in vacuo* y el residuo se disolvió en 300 ml de EtOAc. La capa orgánica se lavó con 1 N de HCl (4 x 100 ml) y luego $NaHCO_3$ (2 x 100 ml), solución salina, y luego se secó sobre Na_2SO_4. La capa orgánica fue concentrada *in vacuo* y el residuo fue absorbido en gel de sílice, seguido de cromatografía rápida (3% de MeOH/$CHCl_3$, 1 ml de NH_4OH por litro) para producir 6.2 g (78%) de *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato como una espuma blanca. $R_f = 0.25$. HRMS (ESI+) calculado para $C_{29}H_{40}N_2O_4F_2$ *m/z* 519.3034 $(M+H)^+$. Se obtuvo 519.3057.

Alternativamente: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato.



A cloruro de neopentil zinc (preparado como se describió previamente) (51 ml, 11 mmol, 0.2 M en THF) bajo una atmósfera de nitrógeno a t.a., se agregó *tert*-butil (1S,2R)-1-(3,5-

392

difluorobencil)-2-hidroxi-3-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (1.3 g, 2.2 mmol) y $Pd(dppf)Cl_2$ (0.09 g, 0.1 mmol) como sólidos. La mezcla de reacción se agitó a t.a. por 12 horas y luego se calentó a 50°C por 8 horas. La reacción se enfrió a t.a. y luego se extinguió con 20 ml de NH_4Cl acuoso y fue extraída con EtOAc (3x100 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron *in vacuo* para producir un aceite marrón. El residuo se disolvió en CH_2Cl_2 y fue absorbido en 6g de gel de sílice. La cromatografía rápida (3-5% de MeOH/$CHCl_3$ con 20 gotas de NH_4OH/L, Biotage 40M) produce *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato idéntico al material preparado por medio de los métodos previamente descritos.

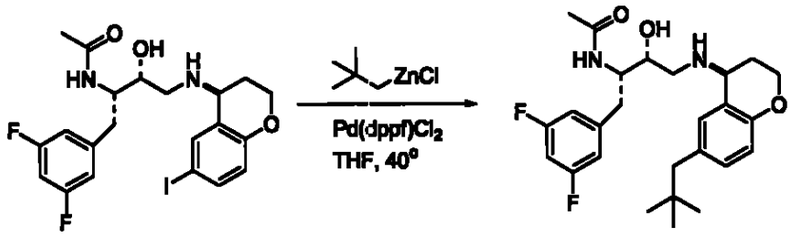
Paso Cuatro: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

Se disolvió *tert*-Butyl (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (5.7g, 11.0 mmol) en CH_2Cl_2 y se enfrió a 0°C. La mezcla fue tratada con 40 ml de CH_2Cl_2/TFA a 1:1 y se quitó el baño frío después de completarse la adición. Después de 1 hora a temperatura ambiente, la mezcla fue diluida con 100 ml de H_2O y se ajustó el pH a 10 con NaOH acuosa. La mezcla se extrajo con CH_2Cl_2 y las capas orgánicas se secaron sobre Na_2SO_4 y se concentraron *in vacuo* para producir amina cruda como un aceite amarillo. ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 2.07 Hz, 1 H), 6.95 (dd, J = 8.29, 2.28 Hz, 1 H), 6.78-6.68 (m, 4 H), 4.26 (m, 2 H), 3.82 (appt, J = 4.15 Hz, 1 H), 3.57 (ddd, J = 8.60, 5.29, 3.52 Hz, 1 H), 3.13 (ddd, J = 9.89, 5.55, 3.73 Hz, 1 H), 3.07 (dd, J = 11.82, 3.52 Hz, 1 H), 2.96 (dd, J = 13.58, 3.42 Hz, 1 H), 2.83 (dd, J = 11.71, 8.60 Hz, 1 H), 2.53 (dd, J = 13.58, 9.85 Hz, 1 H), 2.44 (s, 2 H), 2.14-1.99 (m, 2 H), 0.91 (s, 9 H). La amina cruda fue disuelta en 40 ml de CH_2Cl_2 y fue enfriada a 0°C, seguido de la adición de Et_3N (3.1 ml, 22 mmol). Esta mezcla fue tratada con una solución de 10 ml de CH_2Cl_2 de imidazol de acetilo (1.3 g, 12 mmol) por gotas con jeringa durante un período de 30 min. Después de la adición completa, se quitó el baño frío y se continuó agitando de un día para otro a la temperatura ambiente. Se eliminó el solvente *in vacuo* y el residuo se disolvió en 50 ml de MeOH y se trató con 0.5 g de K_2CO_3 y se agitó por 20 min. para hidrolizar cualquier producto derivado de OAc. La mezcla fue filtrada y concentrada. El residuo resultante fue disuelto en 200 ml de EtOAc y fue lavado con 1 N de HCl (2 x 50 ml); $NaHCO_3$ (2 x 50 ml); solución salina (1 x 50 ml); fue secado sobre Na_2SO_4 y concentrado *in vacuo*. La cromatografía rápida (3.5% MeOH/CHC_3 con 1 ml de NH_4OH por litro), Biotage 40L produjo 4.6 g de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-

393

2H-cromen-4-il]amino}propil)acetamida como un polvo blanco. Este material era espectroscópicamente idéntico a la N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida preparada por métodos previos.

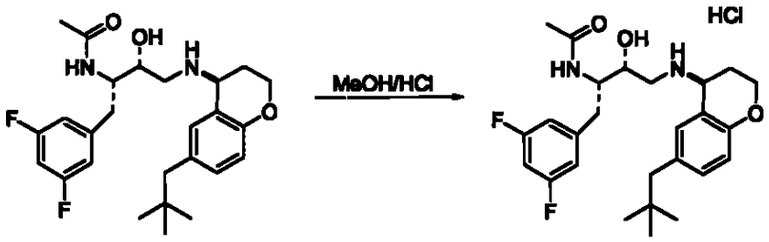
Alternativamente N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



Al cloruro de neopentil zinc (preparado como se describió previamente) (60 ml, 18 mmol, 0.3 M en THF) bajo una atmósfera de nitrógeno a t.a., se agregó N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida (1.5 g, 2.9 mmol) y $Pd(dppf)Cl_2$ como sólidos. La mezcla producida por la reacción se agitó a t.a. por 48 horas y luego se extinguió con 20 ml de NH_4Cl acuoso y se extrajo con EtOAc (3x100 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron *in vacuo* para producir un aceite marrón. El residuo fue disuelto en CH_2Cl_2 y fue absorbido en 6g de gel de sílice. La cromatografía rápida (3-5% de MeOH/$CHCl_3$ con 20 gotas de NH_4OH/L, Biotage 40M) produce dos fracciones. La primera fracción produjo 650 mg del producto deseado que era 93% puro mediante HPLC analítico. La segunda fracción (430 mg) fue una mezcla a 60:40 del producto deseado y el compuesto deshalogenado. La primera fracción fue sometida nuevamente a una HPLC preparativa de fase inversa (1% de TFA en agua/0.6% de TFA en CH_3CN) para producir 500 mg (38%) de un polvo blanco después de la neutralización. Este material era espectroscópicamente idéntico a la N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida preparada por métodos previos.

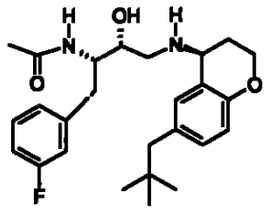
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida hidroclorato.

394

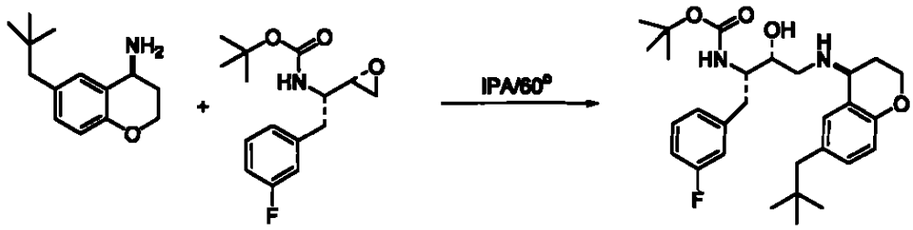


La base libre (0.5 g, 1.08 mmol) fue disuelta en MeOH (10 ml) y fue tratada con HCl/Et_2O (2.5 ml, 1.0 M). La solución se agitó a t.a. por 10 min. y luego el solvente fue eliminado *in vacuo* para producir un vidrio transparente. El vidrio fue triturado con Et_2O para producir 536 mg de un sólido blanco que fue secado *in vacuo* a 40°C por 48 horas. Anal. calculado para $C_{25}H_{34}F_2N_2O_3 \cdot HCl \cdot 0.5\ H_2O$, C, 61.71; H, 7.17; N, 5.54. Se obtuvo C, 61.69; H, 7.31; N, 5.64. HRMS (ESI+) calculado para $C_{25}H_{34}N_2O_3F_2$ *m/z* 461.2615 $(M+H)^+$. Se obtuvo 461.2627.

Ejemplo 53: N-((1S,2R)-1-(3-fluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



Paso Uno: tert-butil (1S,2R)-1-(3-fluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato.



Una mezcla de IPA (15 ml) de (4S)-6-neopentil-3,4-dihidro-2H-cromen-4-ilamina (0.63 g, 2.8 mmol) y *tert*-butil (1S)-2-(3-fluorofenil)-1-[(2S)-oxiran-2-yl]etilcarbamato (0.65 g, 2.2 mmol) se agitó a 50°C (baño de aceite) por 6 horas y luego 48 horas a t.a. El solvente se eliminó *in vacuo* y el residuo se disolvió en CH_2Cl_2 y fue absorbido en gel de sílice. La cromatografía rápida (3%

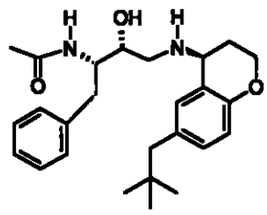
395

de MeOH/$CHCl_3$) produce 200 mg de amina recuperada y 390 mg (35%) de *tert*-butil (1S,2R)-1-(3-fluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato. HRMS (ESI+) calculado para $C_{29}H_{41}N_2O_4F$ *m/z* 501.3128 $(M+H)^+$. Se obtuvo 501.3150.

Paso Dos: N-((1S,2R)-1-(3-fluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

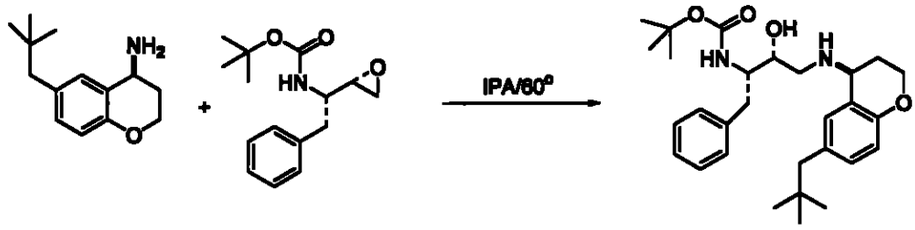
Una solución de tert-butil (1S,2R)-1-(3-fluorobenzil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (0.39 g, 0.8 mmol) en 20% de TFA/CH_2Cl_2 (30 ml) se agitó a t.a. por 1 hora. El solvente se eliminó *in vacuo* y el residuo fue disuelto en CH_2Cl_2 (50 ml) y lavado con $NaHCO_3$ acuoso. La capa orgánica fue lavada con solución salina y secada sobre Na_2SO_4 y luego concentrada *in vacuo*. La amina fue disuelta en DCM (20mL) con Et_3N (.23 ml, 1.7 mmol). Esta solución fue enfriada a 0°C y agitada a medida que se agregaba 1-acetilimidizol (0.098 g, 0.89 mmol)) como una solución en DCM (1mL). La reacción se agitó a 0°C por 1 hora, luego se quitó el baño frío y se permitió que la reacción se agitara de un día para otro a temperatura ambiente. La mezcla de reacción fue diluida con EtOAc (20mL) y lavada con 1M de HCl (2x 10mL) y luego con solución salina (20mL). La capa orgániza se secó y se concentró, y luego se volvió a disolver en MeOH (2mL) y se purificó por medio de HPLC preparativa de fase inversa, lo cual produjo 50 mg. HRMS (ESI+) calculado para $C_{26}H_{35}N_2O_3F$ *m/z* 443.2710 $(M+H)^+$. Se obtuvo 443.2710.

Ejemplo 54: N-((1S,2R)-1-bencil-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



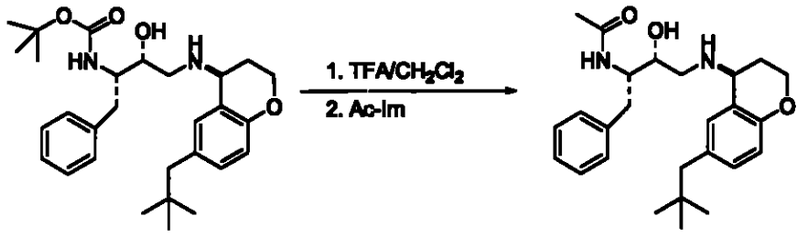
Paso Uno: *tert*-butil (1S,2R)-1-bencil-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato.

396



Una mezcla de IPA (5 ml) de (4S)-6-neopentil-3,4-dihidro-2H-cromen-4-ilamina (0.20 g, 0.9 mmol) y tert-butil (1S)-1-[(2S)-oxiran-2-yl]-2-feniletilcarbamato (0.2 g, 0.8 mmol) se agitó a 60°C (baño de aceite) por 8 horas y luego 48 horas a t.a. El solvente se eliminó *in vacuo* y el residuo se purificó por medio de HPLC preparativa (1% de TFA en agua/0.6% de TFA en CH_3CN) para producir 200 mg (52%) de tert-butil (1S,2R)-1-bencil-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato. HRMS (ESI+) calculado para $C_{29}H_{42}N_2O_4$ *m/z* 483.3222 $(M+H)^+$. Se obtuvo 483.3219.

Paso Dos: N-((1S,2R)-1-bencil-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

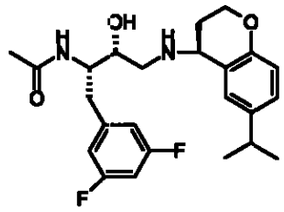


Una solución de tert-butil (1S,2R)-1-bencil-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (0.19 g, 0.4 mmol) en 20% de TFA/CH_2Cl_2 (25 ml) se agitó a t.a. por 1 hora. El solvente se eliminó *in vacuo* y el residuo se disolvió en CH_2Cl_2 (75 ml) y se lavó con $NaHCO_3$ acuoso. La capa orgánica se lavó con solución salina y se secó sobre Na_2SO_4 y luego se concentró *in vacuo*. La amina fue disuelta en DCM (5 mL) con Et_3N (0.12 ml, 0.86 mmol). Esta solución se enfrió a 0°C y se agitó a medida que se agregaba 1-acetilimidizol (0.050 g, 0.45 mmol)) como una solución en DCM (1mL). La reacción se agitó a 0°C por 1 hora, luego se quitó el baño frío y se permitió que la reacción se agitara de un día para otro a la temperatura ambiente. La mezcla de reacción se diluyó con EtOAc (20mL) y se lavó con 1M de HCl (2x 10mL) y luego con solución salina (20mL). La capa orgánica se secó y se concentró, y luego se volvió a disolver en MeOH (5 mL) y se purificó por medio de HPLC preparativa de fase inversa,

397

lo cual produjo un polvo blanco. HRMS (ESI+) calculado para $C_{26}H_{36}N_2O_3$ *m/z* 425.2804 $(M+H)^+$. Se obtuvo 425.2801.

Ejemplo 55: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



Paso Uno: 6-isopropil-2,3-dihidro-4H-cromen-4-ona.

Una solución de CH_2Cl_2 (350 ml) de 1-isopropil-4-metoxi benceno (25 g, 166 mmol) y 3-cloro-propionil cloruro (21 ml, 216 mmol), a t.a., fue tratada con $AlCl_3$ (33 g, 249 mmol) en porciones de 1-2 g durante un período de 1 hora. Se mantuvo la agitación a t.a. por 24 horas, en cuyo momento la mezcla fue vertida sobre hielo triturado, seguido de la adición de 30 ml de HCl conc. La mezcla fue diluida con 300 ml de CH_2Cl_2 y lavada cuidadosamente (evitando la emulsión) con 2 N de NaOH. La capa orgánica se secó sobre $MgSO_4$ y se concentró *in vacuo* un aceite amarillo pálido. La cromatografía rápida (10% de EtOAc/Heptanos) produce 6-isopropil-2,3-dihidro-4H-cromen-4-ona (7.5 g, 24%). $R_f = 0.3$. HRMS (ESI+) calculado para $C_{12}H_{14}O_2$ *m/z* 191.1072 $(M+H)^+$. Se obtuvo 191.1071.

Paso Dos: 6-isopropilcroman-4-ol.

A una solución de MeOH (100 ml) de 6-isopropil-2,3-dihidro-4H-cromen-4-ona (7.5 g, 39.4 mmol), a 0°C, se agregó $NaBH_4$ (1.9 g, 51 mmol) en porciones. Se permitió que la mezcla se calentara espontáneamente por 45 min., seguido de la adición de NH_4Cl acuoso (25 ml). Se eliminó el MeOH bajo presión reducida y el residuo fue extraído con Et_2O (2 x 75 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron *in vacuo* para producir 7.6 g (cant.) de un sólido blanco. HRMS (ESI+) calculado para $C_{12}H_{16}O_2$ *m/z* 192.1150 $(M+H)^+$. Se obtuvo 192.1152.

Paso Tres: 6-isopropil-3,4-dihidro-2H-cromen-4-ilamina.

398

A una solución de 6-isopropil-croman-4-ol (7.79g, 40.52 mmol), diisopropiletilamina (21.18 mL, 121.56 mmol) y CH_2Cl_2 (200 mL), se agregó MsCl (4.71 mL, 60.78 mmol) bajo nitrógeno con agitación. Después de 2 horas, la reacción se completó por medio de HPLC. La mezcla se concentró *in vacuo*, luego se volvió a disolver de nuevo en anh. DMF (200 mL) seguido de la adición de NaN_3 (3.95 g, 60.78 mmol). La reacción se agitó de un día para otro a 70 °C. Se extinguió con 1N de HCl, se extrajo con éter dietílico, luego se lavó la capa orgánica con 10% de $NaHCO_3$, se secó con $MgSO_4$, se filtró y se concentró *in vacuo* para producir 4-azido-6-isopropil-croman crudo como un aceite amarillo (7.53 g, 86% de producto crudo. HRMS calculado para $C_{12}H_{15}N_3O$ + H1 217.1215, se encontró 217.1218. A una solución de 4-azido-6-isopropil-croman (7.53 g, 34.66 mmol) en THF (100 mL), se agregó una solución de 1.0M de Me_3P en THF (42.00 mL, 41.59 mmol). La mezcla producida por la reacción se agitó por 30 min. y luego se agregó agua desionizada (15 mL) a la mezcla de reacción, agitándose durante 48 horas. La mezcla de reacción se extinguió con 1N de HCl, se lavó con CH_2Cl_2, luego se le agregaron pelotillas de NaOH a la capa acuosa hasta que el pH=12. Se extrajo la capa acuosa básica con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró *in vacuo*, produciendo 6-isopropil-croman-4-ilamina cruda como un aceite amarillo (3.5 g, 53% de producto crudo). HRMS calculado para $C_{12}H_{17}NO$ + H1 192.1388, se obtuvo 192.1384. La amina racémica cruda fue purificada y resuelta utilizando HPLV preparativa quiral (5% de EtOH/heptanos, 0.1% DEA) usando una columna Chiralpak AD. Se obtuvo 1.5 g de (+)-(*4R*)- 6-isopropil-croman-4-ilamina, tiempo de retención 15.5 min. $[\alpha]_D$ = 4.2 (c = 2.0 en MeOH) y 1.5 g de (-)-(*4S*)- 6-isopropil-croman-4-ilamina, tiempo de retención 18.3 min. $[\alpha]_D$ = -3.9 (c = 2.0 en MeOH). ^{1}H NMR como sal de HCl (300 MHz, CD_3OD) δ 1.25 (d, *J* = 6 Hz, 6 H), 2.15 (m, 1 H), 2.38 (m, 1 H), 2.89 (m, 1 H), 4.27 (m, 2 H), 4.55 (t, *J* = 6 Hz, 1 H), 6.83 (d, *J* = 9 Hz, 1 H), 7.19 (dd, *J* = 3, 9 Hz, 1 H), 7.25 (d, *J* = 3 Hz, 1 H).

Paso Cuatro: *tert*-Butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato.

Ejemplo 134 – Se combinaron (1 equiv) y (-)-(*4S*)- 6-isopropil-croman-4-ilamina (1.25 equiv) en i-PrOH y se calentaron a 65°C por 18 horas. Luego la mezcla de reacción se concentró y se dividió entre 1M de HCl y EtOAc. La capa acuosa se quitó y se lavaron los orgánicos (3x 100mL 1M de HCl), luego $NaHCO_3$, y se secaron sobre $MgSO_4$ y se concentraron. ^{1}H NMR (crudo-DMSO-d_6) δ 7.75 (d, *J* = 9 Hz, 1 H), 7.14 (br s, 1 H), 7.02 (m, 2 H), 6.9 (m, 1 H), 6.68 (d, *J* = 9 Hz, 1 H), 5.3 (br s, 2 H), 4.22 (m, 1 H), 4.12 (m, 1 H), 3.9 (m, 1 H), 3.68 (m, 1 H), 3.50 (m, 1 H),

399
402

3.02 (dd, J = 11, 3 Hz, 1 H), 2.78 (sept, J = 7 Hz, 1 H), 2.67 (s, 1 H), 2.57 (dd, J = 4, 10 Hz, 1 H), 1.59 (s, 9 H), 1.14 (d, J = 7 Hz, 6 H). LRMS (*m/z*) M+H: 490.3.

Paso Cinco: (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(4S)-6-isopropil-3,4-dihidro-2H-cromen-4-il]amino}butan-2-ol.

Se disolvió *tert*-Butyl (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato crudo (1 eq.) en 10:1 de DCM:TFA (a 0.1M) por 3 horas à temperatura ambiente. La mezcla de reacción se concentró y el residuo se dividió entre EtOAc y 1M de NaOH. Se quitó la capa acuosa y se lavaron los orgánicos con solución salina (50mL) y luego se secaron sobre $MgSO_4$ y se concentraron en forma de sólido/espuma vidriosa. ^{1}H NMR (crudo-$CDCl_3$) δ 7.75 (d, J = 9 Hz, 1 H), 7.14 (br s, 1 H), 7.02 (m, 2 H), 6.9 (m, 1 H), 6.68 (d, J = 9 Hz, 1 H), 4.4 (br s, 2 H), 4.12 (m, 1 H), 3.9 (m, 1 H), 3.68 (m, 1 H), 3.50 (m, 1 H), 3.32 (m, 1 H), 3.02 (dd, J = 11, 3 Hz, 1 H), 2.78 (sept, J = 7 Hz, 1 H), 2.67 (s, 1 H), 2.57 (dd, J = 4, 10 Hz, 1 H), 1.11 (d, J = 7 Hz, 6 H). LRMS (*m/z*) M+H:390.2

Paso Seis: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



Se disolvió (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(4S)-6-isopropil-3,4-dihidro-2H-cromen-4-il]amino}butan-2-ol crudo en CH_2Cl_2 y se trató con imidizol acetílico (1.25 equiv) y luego Et3N (2 equiv). La mezcla de reacción se agitó por 2 horas para asegurar la reacción completa, luego se extinguió con metanol y se concentró. La mezcla de reacción se dividió entre 1M de HCl y EtOAc, se sacaron los orgánicos, se secaron y se concentraron para producir un aceite que fue purificado por medio de HPLC preparativa para producir N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida. HRMS (ESI+) calculado para $C_{24}H_{30}F_2N_2O_3$ *m/z* 433.2303 $(M+H)^+$. Se obtuvo 433.2307.
El mismo procedimiento utilizando (+)-(*4R*)- 6-isopropil-croman-4-ilamina resultó en el epímero N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4R)-6-isopropil-3,4-dihidro-2H-cromen-4-

400

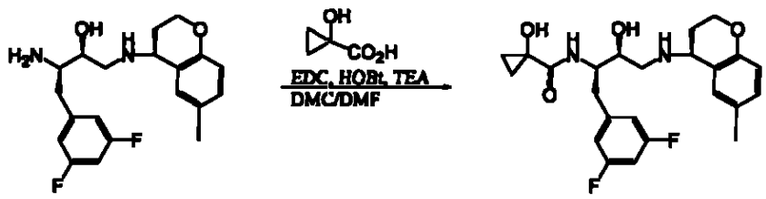
l]amino}propil)acetamida. ^{1}H NMR (DMSO-d_6) δ 7.76 (d, J = 9 Hz, 1 H), 7.01 (m, 2 H), 7.14 (d, J = 2 Hz, 1 H), 6.99 (dd, J = 8.5, 2 Hz, 1 H), 6.91 (m, 1 H), 6.65 (d, J = 8.5 Hz, 1 H), 4.96 (d, J = 6 Hz, 1 H), 4.2 (dt, J = 10, 3.4 Hz, 1 H), 4.1 (m, 1 H), 3.99 (m, 1 H), 3.64 (br s, 1 H), 3.47 (m, 1 H), 3.0 (dd, J = 14, 3 Hz, 1 H), 2.78 (sept, J = 8 Hz, 1 H), 2.75 (m, 1 H), 2.6 (m, 2 H), 1.86 (m, 3 H), 1.7 (s, 3 H), 1.16 (d, J = 7 Hz, 6 H). HRMS (ESI+) calculado para $C_{24}H_{30}F_2N_2O_3$ *m/z* 433.2303 $(M+H)^+$. Se obtuvo 433.2301.

Ejemplo 56: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}propil)-2-hidroxi-2-metilpropanamida.



(2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}butan-2-ol (1 equiv) se combinó con ácido 2-metilacético, (1.25 equiv), EDC (1.5 equiv) y HOBt (1.5 equiv) en DMF/DCM (1:1, 10mL). La mezcla de reacción fue tratada con Et_3N y agitada a la temperatura ambiente por 6 horas. La HPLC determinó que la amina se había consumido para este tiempo, y la reacción fue vertida en EtOAc y lavada con 1M de HCl, luego los orgánicos fueron secados sobre $MgSO_4$ y concentrados para producir un aceite que fue purificado por medio de HPLC preparativa de fase inversa. HRMS (ESI+) calculado para $C_{23}H_{27}F_2IN_2O_4$ *m/z* 561.1063 $(M+H)^+$. Se obtuvo 561.1047.

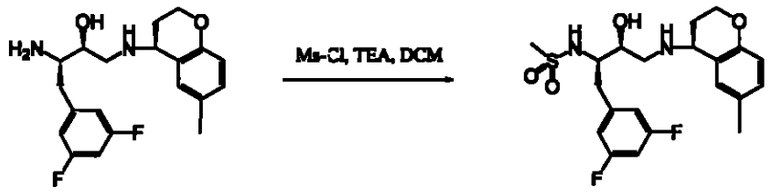
Ejemplo 57: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}propil)-1-hidroxiciclopropanecarboxamida.



Se prepara utilizando la metodología básica que se describe en el Ejemplo 56. HRMS (ESI+) calculado para $C_{23}H_{25}F_2IN_2O_4$ *m/z* 559.0907 $(M+H)^+$. Se obtuvo 559.0903.

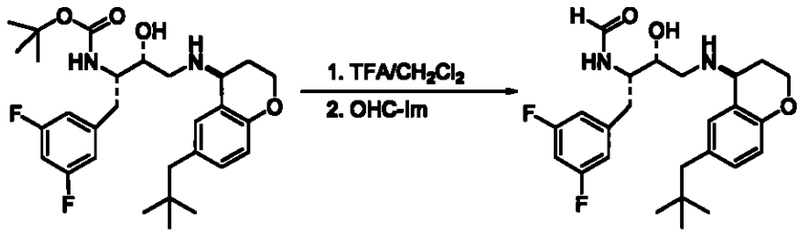
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Ejemplo 58: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}propil)metanesulfonamida.



(2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(4S)-6-iodo-3,4-dihidro-2H-cromen-4-il]amino}butan-2-ol (1 equiv) se disolvió en DCM con TEA (2 equiv), luego se enfrió a 0°C y se trató con MsCl (1.25 equiv) mientras se agitaba. La mezcla de reacción fue sacada del baño frío, se llevó a la temperatura ambiente y luego se extinguió con MeOH y se concentró. El residuo fue disuelto en EtOAc y lavado con 1M de HCl (2x10mL). Los orgánicos se secaron y concentraron y fueron cromatografiados sobre gel de sílice. ^{1}H NMR (CD_3OD) δ 7.74 (d, J = 2.0 Hz, 1 H), 7.53 (dd, J = 2.0, 8.7 Hz, 1 H), 6.88 (m, 2 H), 6.77 (m, 1 H), 6.67 (d, J = 8.7 Hz, 1 H), 4.23-4.39 (m, 2 H), 4.25 (br m, 1 H), 4.12 (m, 1 H), 3.87 (td, J = 3.1, 7.8 Hz, 1 H), 3.29 (dd, J = 3.5, 13.9 Hz, 1 H), 3.11 (s, 3H), 3.05 (dd, J = 3.2, 12.7 Hz, 1 H), 2.98 (dd, J = 7.9, 12.6 Hz, 1 H), 2.74 (dd, J = 11.0, 13.9 Hz, 1 H), 2.14 (br m, 2 H). MS (ESI+) calculado para $C_{20}H_{23}F_2IN_2O_4S$ *m/z* 553.38 $(M+H)^+$. Se obtuvo 553.4.

Ejemplo 59: (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propilformamida.

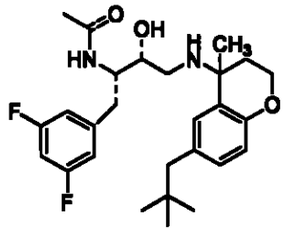


La amina protegida por BOC (1 equiv) fue disuelta en DCM:TFA de 10:1 (a 0.1M) por 3 horas a la temperatura ambiente. La mezcla de reacción fue concentrada y el residuo fue dividido entre EtOAc y 1M de NaOH. La capa acuosa se sacó y los orgánicos se lavaron con solución salina (50mL) y luego se secaron sobre $MgSO_4$ y se concentraron produciendo un sólido/espuma vidriosa. LRMS (*m/z*) M+H:418.5. Esto se disolvió en CH_2Cl_2 (a 0.1M), se enfrió a 0°C y se trató con imidizol de formilo (1.25 equiv). La reacción se quitó del baño frío, luego se agitó por 2 horas a la temperatura ambiente. Cuando se hizo con HPLC, la mezcla se concentró y se disolvió

402

en MeOH (1.5mL) y se purificó por medio de HPLC preparativa de fase inversa (columna de 2 pulg) para producir una película que se raspó para producir un polvo blanco. ^{1}H NMR (DMSO-d_6) δ 8.46 (br s, 1H), 7.75 (d, J = 9 Hz, 1 H), 7.14 (br s, 1 H), 7.02 (m, 2 H), 6.91 (m, 1 H), 6.69 (d, J = 9 Hz, 1 H), 5.0 (br s, 2 H), 4.21 (m, 1 H), 4.09 (m, 1 H), 3.94 (m, 1 H), 3.72 (m, 1 H), 3.43 (m, 1 H), 3.08 (dd, J = 11, 3 Hz, 1 H), 2.77 (s, 2 H), 2.57 (dd, J = 4, 10 Hz, 1 H), 1.69 (s, 3 H), 1.04 (s, 9 H). MS (ESI+) for $C_{25}H_{32}F_2N_2O_3$ *m/z* 446.54 $(M+H)^+$. Se obtuvo 446.3.

Ejemplo 60: N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(4-metil-6-neopentil-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida.



Paso Uno: 6-iodo-2,3-dihidro-4H-cromen-4-ona

A una suspensión de CH_2Cl_2 (300 ml) de 6-iodo-4-cromanol (15 g, 54.3 mmol) y 30 g de gel de sílice, a t.a., se agregó PCC (15.2 g, 70.6 mmol) como un sólido. La mezcla se agitó a t.a. por 3 horas, en cuyo momento el TLC (20% de EtOAc/hexanos) indicó la reacción completa. La mezcla de reacción se filtró a través de un tapón de gel de sílice y el filtrado se concentró *in vacuo* para producir 14.9 g (95%) de 6-iodo-2,3-dihidro-4H-cromen-4-ona como un sólido blanco consistente con el informe en la literatura (*Synthesis* 1997, 23-25). HRMS (ESI+) calculado para $C_9H_7IO_2$ *m/z* 273.9492; se obtuvo 273.9500.

Paso Dos: 6-iodo-4-metilcroman-4-ol

Se secó $CeCl_3$ (4.9 g, 19.8 mmol) *in vacuo* a 140°C por 3 horas y luego se formó en una suspensión acuosa con THF seco (100 ml) por 1 hora. La suspensión blanca se enfrió a -78°C seguido de la adición de MeLi•LiBr (14.2 ml, 21.4 mmol) durante 15 minutos. La mezcla se agitó durante 30 min., seguido de la adición de una solución de THF (20 ml) de 6-iodo-2,3-dihidro-4H-cromen-4-ona por gotas con jeringa. Después de 30 min., TLC (15% de EtOAc/hexanos) indicó la reacción completa. La mezcla fue tratada con NH_4Cl (aq.) 30 ml y

403

diluida con 150 ml de agua. La mezcla fue extraída con EtOAc y la capa orgánica fue secada sobre Na_2SO_4. El Na2SO4 fue sacado por filtración y el filtrado se concentró *in vacuo* para producir 6-iodo-4-metilcroman-4-ol como un sólido blanquecino de 4.7 g (95%). HRMS (ESI+) calculado para $C_{10}H_{11}IO_2$ *m/z* 289.9806 $(M+H)^+$. Se obtuvo 289.9803.

Paso Tres: 6-iodo-4-metilcroman-4-amina

A una mezcla de 6-iodo-4-metilcroman-4-ol (1.0 g, 3.4 mmol) y NaN_3 (0.7 g, 10.3 mmol) en $CHCl_3$ (15 ml), a 0°C, se agregó TFA (1.3 ml, 17.2 mmol) como una solución en 10 ml de $CHCl_3$ por gotas a través de un embudo de adición. La adición se llevó a cabo durante 2 horas y la agitación continuó durante 2 horas adicionales a 0°C. La mezcla fue calentada a la t.a. y agitada de un día para otro. La mezcla fue diluida con 30 ml de agua y extraída con CH_2Cl_2. La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir 4-azido-6-iodo-4-metilcromano como un aceite amarillo. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.07 Hz, 1 H), 7.50 (dd, J = 8.71, 2.07 Hz, 1 H), 6.66 (d, J = 8.71 Hz, 1 H), 4.27 (m, 2 H), 2.06 (m, 2 H), 1.68 (s, 3 H). MS (ESI+) para $C_{10}H_{10}IN_3O$ *m/z* 273.0 $(M+H)^+$ pérdida de azida. La azida cruda fue disuelta en THF (15 ml) seguido de la adición de trimetilfosfina (4 ml, 1.0 M en THF) a t.a. Después de 15 min., se agregaron 3 ml de agua y se continuó agitando a t.a. por 2 horas hasta completarse como lo indicó LC/MS. El solvente se eliminó *in vacuo* y el residuo se diluyó con agua (75 ml) y se extrajo con CH_2Cl_2 (3 x 50 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir 6-iodo-4-metilcroman-4-amina (0.900 g, 91%) como un aceite amarillo. Este material se usó en el próximo paso sin purificación. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 2.07 Hz, 1 H), 7.40 (dd, J = 8.60, 2.18 Hz, 1 H), 6.59 (d, J = 8.50 Hz, 1 H), 4.25 (m, 2 H), 2.01 (m, 2 H), 1.53 (s, 3 H). MS (ESI+) para $C_{10}H_{12}INO$ *m/z* 273.2 $(M+H)^+$ pérdida de NH_3.

Paso Cuatro: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-iodo-4-metil-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato.

Una mezcla de 6-iodo-4-metilcroman-4-amina (0.9 g, 3.1 mmol) y el Ejemplo 134 (0.6 g, 2.1 mmol) en 10 ml de alcohol isopropílico se agitó bajo una atmósfera de nitrógeno a 60°C (temp. del baño de aceite) por 24 horas, en cuyo momento LC/MS indicó el consumo completo del epóxido. Después de enfriarse a t.a., se eliminó el solvente *in vacuo* para producir un aceite ámbar. El material crudo se disolvió en CH_2Cl_2 y se absorbió en 7.8 g de gel de sílice. La

404

cromatografía rápida de 50% de EtOAc/Heptanos (columna Biotage de 40 M) produjo tres fracciones. La tercera fracción final era amina recuperada. Se obtuvo 0.500 g de cada uno de los siguientes diastereómeros, producto general de epóxido 83%.

Diastereómero A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (bs, 1 H), 7.42 (dd, *J* = 8.50, 2.07 Hz, 1 H), 6.71 (m, 3 H), 6.59 (d, *J* = 8.50 Hz, 1 H), 4.52 (d, *J* = 9.12 Hz, 1 H), 4.35 (m, 1 H), 4.21 (m, 1 H), 3.82 (m, 1 H), 3.42 (m, 1 H), 3.06 (m, 1 H), 2.81 (dd, *J* = 14.3, 8.7 Hz, 1 H), 2.62 (m, 2 H), 2.26 (m, 1 H), 1.84 (m, 1 H), 1.40 (m, 2 H), 1.35 (m, 12 H). HRMS (ESI+) para $C_{25}H_{31}N_2O_4F_2I$ +1H calculado para 589.1376 *m/z*, se obtuvo 589.1397 $(M+H)^+$.

Diastereómero B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.07 Hz, 1 H), 7.44 (d, *J* = 8.50 Hz, 1 H), 6.71 (m, 3 H), 6.67 (d, *J* = 8.71 Hz, 1 H), 4.54 (bs, 1 H), 4.34 (m, 1 H), 4.16 (m, 1 H), 3.77 (m, 1 H), 3.48 (m, 1 H), 3.10 (m, 1 H), 2.75 (m, 1 H), 2.75 (m, 1 H), 2.62 (m, 2 H), 2.24 (m, 1 H), 1.93 (m, 1 H), 1.60 (m, 2 H), 1.42 (s, 9 H), 1.39 (s, 3 H). HRMS (ESI+) para $C_{25}H_{31}N_2O_4F_2I$ + 1H calculado para *m/z* 589.1376; se obtuvo 589.1375 $(M+H)^+$.

Paso Cinco: N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-iodo-4-metil-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida.

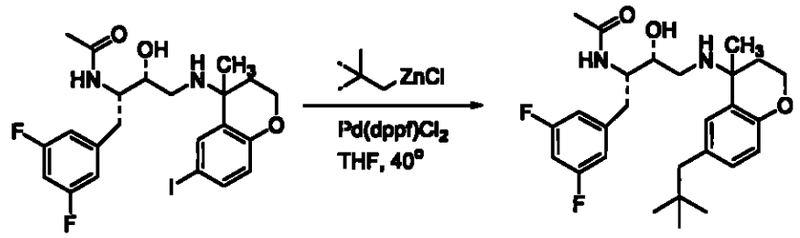
A una solución de CH_2Cl_2 (5 ml) de tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-iodo-4-metil-3,4-dihidro-2H-cromen-4-il)amino]propilcarbamato (Diastereómero B) (0.47 g, 0.79 mmol), a t.a., se agregó 25 ml de 20% de TFA/CH_2Cl_2. La mezcla se agitó a t.a. por 30 min. El solvente se eliminó *in vacuo* y el residuo se disolvió en CH_2Cl_2 (75 ml) y se lavó con $NaHCO_3$ acuoso y solución salina. La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir una espuma blanca. El residuo se disolvió en CH_2Cl_2 (5 ml) y se enfrió a 0°C, seguido de la adición de Et_3N (0.24 ml, 1.7 mmol) e imidazol acetílico (0.10 g, 0.90 mmol). La mezcla entonces se calentó a t.a. y se agitó de un día para otro. La mezcla de reacción se diluyó con CH_2Cl_2 (25 ml) y se lavó con agua y solución salina. La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir una espuma blanca (0.35 g, 84%) después de la cromatografía rápida de 5% de MeOH/$CHCl_3$ (Biotage 40 S). R_f = 0.29. HRMS (ESI+) calculado para $C_{22}H_{23}N_2O_3IF_2$ + 1H calculado *m/z* 531.0958; se obtuvo 531.0958 $(M+H)^+$.

Con el mismo procedimiento, el diastereómero A produce 0.28 g (70%) del epímero ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 2.28 Hz, 1 H), 7.36 (dd, *J* = 8.71, 2.28 Hz, 1 H), 6.79 (m, 3 H), 6.57 (d, *J* = 8.50 Hz, 1 H), 4.31 (m, 1 H), 4.17 (m, 1 H), 4.08 (m, 1 H), 3.51 (m, 1 H), 3.11 (dd, *J* = 14.1, 3.73 Hz, 1 H), 2.62 (dd, *J* = 14.1, 10.4 Hz, 1 H), 2.52 (m, 1 H), 2.45 (dd, *J* = 11.9,

405

3.63 Hz, 1 H), 2.25 (m, 1 H), 1.79 (s, 3 H), 1.74 (m, 1 H), 1.47 (s, 3 H). Anal. calculado para $C_{27}H_{35}F_2IN_2O_3$; C, 49.82; H, 4.75; N, 5.28. Se obtuvo C, 49.87; H, 4.94; N, 5.05.

Paso Seis: N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(4-metil-6-neopentil-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida.



A una ampolla tapada de 20 ml de suero que contenía N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-iodo-4-metil-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida (0.20 g, 0.37 mmol) y $Pd(dppf)Cl_2$ (0.015 g, .018 mmol) bajo nitrógeno, se agregó 3.7 ml de 0.5 M de cloruro de neopentil zinc (1.85 mmol) preparado como se describió previamente. La mezcla se agitó en un agitador orbital por 12 horas, en cuyo momento LC/MS indicó sólo trazas del compuesto deseado. Se agregaron 5 eq. adicionales del reactivo de zonc y otros 5 mol% de catalizador y se calentó la mezcla de reacción a 40 °C. Después de 6 horas, LC/MS indicó el consumo completo de SM. La mezcla de reacción se extinguió con NH_4Cl y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* para producir un sólido marrón claro (150 mg) después de la cromatografía rápida (4% de MeOH/$CHCl_3$ Biotage 40S). Este material se sometió a una columna preparativa de fase inversa final (1% de TFA en H_2O/0.6% de TFA en CH_3CN) para producir 50 mg de un sólido amarillo claro. Este material fue disuelto en 4 ml de CH_2Cl_2 y fue tratado con 0.5 g de gel de sílice funcionalizada de 3-mercaptopropilo y se agitó a t.a. por 30 min. La mezcla fue filtrada a través de Celite® para quitar la resina y el filtrado fue concentrado *in vacuo* para producir un polvo blanco (44 mg, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.08 (d, J = 2.07 Hz, 1 H), 6.87 (dd, J = 8.29, 2.07 Hz, 1 H), 6.78 (m, 3 H), 6066 (d, J = 8.29 Hz, 1 H), 4.27 (m, 1 H), 4.12 (m, 1 H), 4.04 (m, 1 H), 3.54 (m, 1 H), 3.06 (dd, J = 13.99, 3.63 Hz, 1 H), 2.56 (m, 2 H), 2.45 (bs, 2 H), 2.37 (dd, J = 11.82, 7.67 Hz, 1 H), 2.25 (m, 1 H), 1.81 (s, 3 H), 1.78 (m, 1 H); 1.49 (s, 3 H), 0.91 (s, 9 H). MS (ESI+) para $C_{27}H_{36}N_2O_3F_2$ *m/z* 475.2772 $(M+H)^+$; se obtuvo, 475.2774.

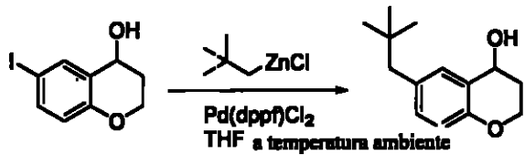
El mismo procedimiento produce 0.049 g (28%) del epímero ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (d, J = 2.07 Hz, 1 H), 6.87 (dd, J = 8.29, 2.07 Hz, 1 H), 6.77 (m, 3 H), 6.66 (d, J = 8.29 Hz, 1 H), 4.27 (m, 1 H), 4.11 (m, 2 H), 3.53 (m, 1 H), 3.06 (dd, J = 14.10, 3.52 Hz, 1 H), 2.53 (m, 3 H),

46C

2.43 (s, 2 H), 2.27 (m, 1 H), 1.78 (m, 4 H), 1.49 (s, 3 H), 0.90 (s, 9 H). MS (ESI+) calculado para $C_{27}H_{36}N_2O_3F_2$ *m/z* 475.2772 $(M+H)^+$; se obtuvo 475.2788.

Alternativamente:

6-neopentilcroman-4-ol.

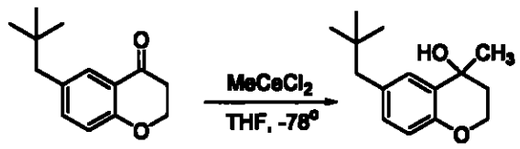


En un frasco de fondo redondo secado por llama que contenía 6-iodo-croman-4-ol (3.0 g, 10.8 mmol) y $Pd(dppf)Cl_2$ (0.44 g, 0.54 mmol), se agregó 6 ml de THF anhidro y la mezcla se enfrió a 0°C. La mezcla fue tratada con cloruro de neopentil zinc (preparado como se describió previamente) (50 ml, 30 mmol, 0.6 M en THF) y se agitó bajo nitrógeno a t.a. por 19 horas, seguido de 5 horas a 50°C (baño de aceite). La reacción se enfrió a la t.a. y se extinguió con NH_4Cl y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4 y se concentró *in vacuo* a 1.9 g (79%) de un sólido blanco después de la cromatografía rápida (10% de EtOAc/heptanos, Biotage 40M) R_f = 0.11. HRMS (ESI+) calculado para $C_{14}H_{20}O_2$ *m/z* 220.1463 $(M+H)^+$; se obtuvo 220.1460.

6-neopentil-2,3-dihidro-4H-cromen-4-ona.

A una suspensión de CH_2Cl_2 (45 ml) de 6-neopentilcroman-4-ol (1.9 g, 8.6 mmol) y gel de sílice (5g), a t.a., se agregó el PCC (2.7 g, 12.9 mmol) como un sólido. Después de 45 min., TLC indicó la reacción completa. La mezcla se filtró a través de un tapón de gel de sílice y el tapón se lavó con 20% de EtOAc/hexanos. El filtrado se concentró *in vacuo* para producir 1.9 g (100%) de un aceite transparente. Este material se llevó adelante sin más purificación.. HRMS (ESI+) calculado para $C_{14}H_{18}O_2$ *m/z* 219.1385 $(M+H)^+$; se obtuvo 219.1393.

4-metil-6-neopentilcroman-4-ol.

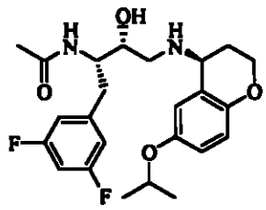


$CeCl_3$ (2.4 g, 9.9 mmol) fue secado al vacío a 140°C por 2 horas y luego convertido en una suspensión acuosa en 55 ml de THF anhidro por 3 horas. La suspensión de $CeCl_3$ se enfrió a -78°C (baño de hielo seco/IPA) seguido de la adición de MeLi•LiBr (7.1 ml, 10.7 mmol, 1.5 M en

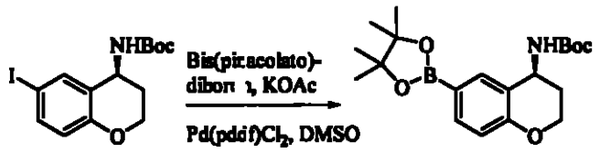
407

Et_2O) por gotas con jeringa. La mezcla se agitó a -78°C por 1 hora seguido de la adición de 6-neopentil-2,3-dihidro-4H-cromen-4-ona (1.8 g, 8.2 mmol) como una solución de THF (10 ml). Se permitió que la mezcla se calentara espontáneamente por 30 min., en cuyo momento TLC indicó la reacción completa. La reacción se extinguió con 25 ml de NH_4Cl acuoso y se diluyó con agua (100 ml). La mezcla se extrajo con EtOAc (3x75 ml) y las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron *in vacuo* para producir 1.9 g de un aceite transparente. Este material se utilizó sin más purificación. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 2.07 Hz, 1 H), 6.95 (dd, J = 8.29, 2.26 Hz, 1 H), 6.73 (d, J = 8.29 Hz, 1 H), 4.25 (m, 2 H), 2.44 (s, 2 H), 2.09 (m, 2 H), 1.64 (s, 3 H), 0.91 (s, 9 H). MS (ESI+) calculado para $C_{15}H_{22}O_2$ *m/z* 234.2 $(M+H)^+$; se obtuvo pérdida de agua de 217.3.

Ejemplo 61: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



Paso Uno: *tert*-butil (4S)-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-yl)-3,4-dihidro-2H-cromen-4-ilcarbamato.



A una mezcla de *tert*-butil (4S)-6-iodo-3,4-dihidro-2H-cromen-4-ilcarbamato (3.30 g, 8.8 mmol) y bis(pinacolato)diboro (2.51 g, 9.7 mmol) en sulfóxido de metilo (30 mL), se agregó acetato de potasio (2.60 g, 26.4 mmol) seguido del complejo [1,1'-bis(difenilfosfino)ferrocene]dicloropaladio(II) con diclorometano (1:1) (410 mg, 0.5 mmol). La mezcla de reacción fue calentada bajo argón a 80 °C por 2 horas y luego enfriada a la temperatura ambiente. La mezcla de reacción fue diluida con éter etílico (100 mL), lavada con agua y cloruro de sodio saturado, secada (sulfato de sodio), filtrada, y concentrada bajo presión reducida. La purificación por medio de columna de cromatografía rápida (gel de sílice, 10-20% de acetato etílico/hexanos) proporcionó el producto deseado (3.25 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) □

408

7.72 (s, 1H), 7.62 (dd, J = 8.2, 1.5 Hz, 1H), 5.80 (d, J = 8.2 Hz, 1H), 4.79 (m, 2H), 4.31–4.24 (m, 1H), 4.21–4.15 (m, 1H), 2.14–2.11 (m, 2H), 1.48 (s, 9H), 1.34 (s, 6 H), 1.33 (s, 6 H).

Paso Dos: *tert*-butil (4S)-6-hidroxi-3,4-dihidro-2H-cromen-4-ilcarbamato

A una solución de *tert*-butil (4S)-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3,4-dihidro-2H-cromen-4-ilcarbamato (1.09 g, 2.90 mmol) en tetrahidrofurano (10 mL), se agregó hidróxido de sodio (6 mL, 1 N, 6 mmol) seguido de peróxido de hidrógeno (10 mL, 30%). La mezcla de reacción se agitó a temperatura ambiente por 2 horas y luego se extinguió con sulfito de hidrógeno sódico (5 g en 10 mL de agua). La mezcla se ajustó a pH 4 con 2 N de hidróxido de sodio y luego se extrajo con acetato etílico (3 x 50 mL). Los extractos combinados se lavaron con cloruro de sodio saturado, se secaron (sulfato de sodio), se filtraron, y se concentraron bajo presión reducida. La cromatografía rápida (gel de sílice, 10–25% de acetato etílico/hexanos) proporcionó *tert*-butil (4S)-6-hidroxi-3,4-dihidro-2H-cromen-4-ilcarbamato (650 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.89 (s, 1H), 6.75 (d, J = 2.7 Hz, 1H), 6.72–6.63 (m, 1H), 5.03 (d, J = 7.5 Hz, 1 H), 4.77–4.75 (m, 1H), 4.16–4.08 (m, 2H), 2.30 (s, 1H), 2.16–2.13 (m, 1H), 2.05–1.99 (m, 1H), 1.47 (s, 9H).

Paso Tres: *tert*-butil (4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-ilcarbamato

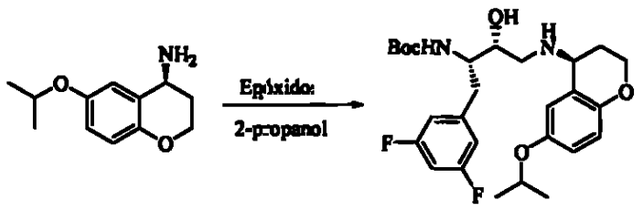
A una solución de *tert*-butil (4S)-6-hidroxi-3,4-dihidro-2H-cromen-4-ilcarbamato (325 mg, 1.22 mmol) en acetona (10 mL), se agregó carbonato de cesio (800 mg, 2.45 mmol) seguido de 2-bromopropano (360 mg, 2.93 mmol). La mezcla de reacción se agitó a 60 °C por 24 horas. El solvente se eliminó bajo presión reducida. El residuo se diluyó con acetato etílico (100 mL) y agua (50 mL). La capa orgánica se separó y se lavó con cloruro de sodio saturado, se secó (sulfato de sodio), se filtró, y se concentró bajo presión reducida para proporcionar *tert*-butil (4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-ilcarbamato (340 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 6.80 (d, J = 2.1 Hz, 1H), 6.77–6.62 (m, 2H), 4.81 (m, 2 H), 4.45–4.35 (m, 1H), 4.23–4.16 (m, 1H), 4.14–4.06 (m, 1H), 2.22–2.14 (m, 1H), 2.05–1.95 (m, 1H), 1.48 (s, 9H), 1.29 (d, J = 6.2 Hz, 6H). Este material se utilizó en el próximo paso sin más purificación.

Paso Cinco: (4S)-6-isopropoxicroman-4-amina.

409 440

A una solución de *tert*-butil (4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-ilcarbamato (340 mg, 1.11 mmol) en metanol (2 mL), se agregó ácido clorhídrico (2 mL, 4 N in 1,4-dioxano, 8 mmol). La mezcla de reacción se agitó a la temperatura ambiente por 2 horas. El solvente se eliminó bajo presión reducida. El residuo se diluyó con cloruro de metileno (50 mL) y agua (50 mL). La capa orgánica se separó y la capa acuosa se extrajo con cloruro de metileno (2 x 50 mL). Los extractos combinados se lavaron con cloruro de sodio saturado, se secaron (sulfato de sodio), se filtraron, y se concentraron bajo presión reducida para proporcionar (4S)-6-isopropoxicroman-4-amina (240 mg, 99% de producto crudo): ^{1}H NMR (300 MHz, $CDCl_3$) □ 6.96 (d, J = 2.7 Hz, 1H), 6.90–6.86 (m, 1H), 6.80 (d, J = 9.0 Hz, 1H), 4.55–4.46 (m, 2H), 4.24–4.17 (m, 2H), 2.40–2.31 (m, 1H), 2.18–2.08 (m, 1H), 1.28 (d, J = 6.0 Hz, 6H). Este material se utilizó en el próximo paso sin más purificación.

Paso Seis: *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato.



Una mezcla de (4S)-6-isopropoxicroman-4-amina (240 mg, 1.1 mmol) y el Ejemplo 134 (330 mg, 1.1 mmol) en 2-propanol (5 mL) se agitó a 60 °C por 16 horas y luego a 80 °C por 5 horas. El solvente se eliminó bajo presión reducida. La cromatografía rápida (gel de sílice, 20–50% de acetato etílico/hexanos) recuperó 95 mg de amina y proporcionó *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (330 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 6.84 (s, 1H), 6.79–6.73 (m, 4H), 6.70–6.63 (m, 1H), 4.52 (d, J = 9.4 Hz, 1H), 4.45–4.37 (m, 1H), 4.25–4.13 (m, 2H), 3.77–3.69 (m, 2H), 3.45–3.39 (m, 1H), 3.09–3.03 (m, 1H), 2.83–2.75 (m, 3H), 2.05–2.01 (m, 1H), 1.95–1.87 (m, 1H), 1.37 (s, 9H), 1.30 (d, J = 6.1 Hz, 6H).

Paso Siete: (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}butan-2-ol hidroclorato.

A una solución de *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (330 mg, 0.65 mmol) en 1,4-dioxano (2 mL), se

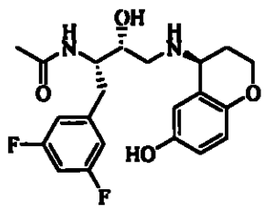
410

agregó ácido clorhídrico (2 mL, 4 N en 1,4-dioxano, 8 mmol). La mezcla de reacción se agitó a la temperatura ambiente por 4 horas. El solvente se eliminó bajo presión reducida. El residuo se trituró con éter etílico. El sólido blanco resultante se recogió por filtración y se lavó con éter etílico para proporcionar (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-yl]amino}butan-2-ol hidroclorato (302 mg, 97%): ESI MS *m/z* 407 $[C_{22}H_{28}F_2N_2O_3 + H]^+$. Este material se utilizó en el próximo paso sin más purificación.

Paso Ocho: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.

A una solución de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}butan-2-ol hidroclorato (302 mg, 0.63 mmol) en cloruro de metileno (5 mL), se agregó trietilamina (322 mg, 3.15 mmol) seguido de 1-acetilimidazol (71 mg, 0.63 mmol). La mezcla de reacción se agitó a la temperatura ambiente de un día para otro. La mezcla se lavó sucesivamente con 1N de ácido clorhídrico, agua, bicarbonato de sodio saturado y cloruro de sodio saturado, y se secó (sulfato de sodio), se filtró, y se concentró bajo presión reducida. La purificación por medio de columna de cromatografía rápida (gel de sílice, 0–5% de metanol/cloruro de metileno proporcionó N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropoxi-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida (190 mg, 67%) como un sólido blanco: ESI MS *m/z* 449 $[C_{24}H_{30}F_2N_2O_4 + H]^+$; HPLC (Método A) 98.7% (AUC), t_R = 8.69 min. Anal. calculado para $C_{24}H_{30}F_2N_2O_4$: C, 64.27; H, 6.74; N, 6.24. Se obtuvo: C, 64.11; H, 6.65; N, 6.17.

Ejemplo 62: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-hidroxi-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida.



Paso Uno: *tert*-butyl n0-hjy(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-hidroxi-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato.

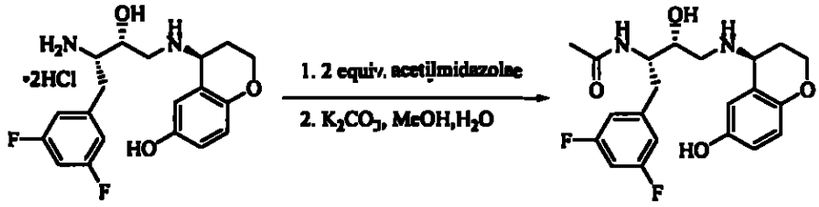
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Una mezcla de (4S)-4-aminocroman-6-ol (165 mg, 1.0 mmol) y el Ejemplo 134 (300 mg, 1.0 mmol) en 2-propanol (5 mL) se agitó a 60 °C por 16 horas. El solvente se eliminó bajo presión reducida. La cromatografía rápida (gel de sílice, 0–5% de metanol/cloruro de metileno) recuperó 54 mg del material de inicio y proporcionó el producto deseado (200 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.26–6.63 (m, 6H), 4.55 (d, J = 9.0 Hz, 1H), 4.21–4.14 (m, 2H), 3.73–3.71 (m, 2H), 3.47–3.44 (m, 1H), 3.10–3.02 (m, 1H), 2.84–2.75 (m, 3H), 2.10–2.02 (m, 1H), 1.94–1.90 (m, 1H), 1.37 (s, 9H).

Paso Dos: (4S)-4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hidroxibutil]amino}croman-6-ol clorhidrato.

A una solución de *tert*-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-hidroxi-3,4-dihidro-2H-cromen-4-il]amino}propilcarbamato (200 mg, 0.43 mmol) en 1,4-dioxano (2 mL), se agregó ácido clorhídrico (2 mL, 4 N en 1,4-dioxano, 8 mmol). La mezcla de reacción se agitó a temperatura ambiente por 16 horas. El solvente se eliminó bajo presión reducida para proporcionar (4S)-4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hidroxibutil]amino}croman-6-ol hidroclorato (200 mg, 99% de producto crudo): ESI MS *m/z* 365 [$C_{19}H_{22}F_2N_2O_3$ + H]$^+$. Este material se utilizó en el próximo paso sin más purificación.

Paso Tres: N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-hidroxi-3,4-dihidro-2H-cromo-4-il]amino}propil)acetamida.

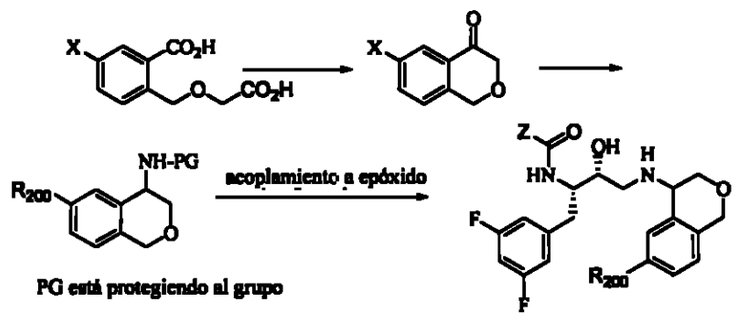


A una solución de (4S)-4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hidroxibutil]amino}croman-6-ol hidrocloruro (200 mg, 0.43 mmol) en cloruro de metileno (5 mL) se le agregó trietilamina (217 mg, 2.15 mmol) seguida por 1-acetilmidazola (95 mg, 0.86 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. Se retiró el solvente bajo presión reducida.. El residuo fue disuelto en metanol (6 mL) y agua (3 mL) y tratado con carbonato de potasio (300 mg, 2.17 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Se retiró el solvente bajo presión reducida.. El residuo fue acidificado con 1N de ácido hidroclórico y extraído con acetato etílico (3 x 50 mL). Los extractos combinados fueron lavados con cloruro

412

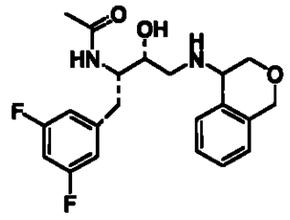
de sodio saturado y luego secados (sulfato sódico), filtrados y concentrados bajo presión reducida.. La purificación por cromatografía flash en columna (gel de sílice, 0–5% cloruro de metanol/metileno) proporcionó el producto deseado (85 mg, 49%) como una espuma blanca. ESI MS *m/z* 407 $[C_{21}H_{24}F_2N_2O_4 + H]^+$; HPLC (Método B) 98.0% (AUC), t_R = 7.01 min. Análisis calculado para $C_{21}H_{24}F_2N_2O_4 \cdot 0.25H_2O$: C, 61.38; H, 6.01; N, 6.82. Encontrado: C, 61.60; H, 5.68; N, 6.59.

Esquema para la preparación de compuestos isocromáticos -4-il



PG está protegiendo al grupo

Ejemplo 63: N-[(1S,2R)-1-(3,5-difluorobenzilo)-3-(3,4-dihidro-1H-isocromo-4-ilamino)-2-hidroxipropil]acetamida.



Paso Uno: 2-[(carboximetoxi)metil]ácido benzoico.

Una mezcla de (2-ciano-benziloxi)- éster etílico del ácido acético (*J. Org. Chem.* 1985, *50*, 2128) (30 g, 136 mmol) y KOH (38 g, 680 mmol) en 1:1 EtOH/H_2O (270 ml) fue calentada a 90°C (baño de aceite) durante 15 h. Luego de enfriar a temperatura ambiente, la mezcla fue tratada con conc. HCl hasta el pH = 1 y extraída con CH_2Cl_2. Las capas orgánicas combinadas se secaron concentradas *in vacuo* para que exhumaran un aceite anaranjado. El aceite fue disuelto en Na_2CO_3 acuosa, tratado con carbonato activado, filtrado y ajustado su pH a 1 con conc. HCl. El sólido resultante fue recogido por filtración y secado hasta exhumar 8.2 g de 2-[(carbometoxi)metil]ácido benzoico como un sólido color cobre. ^{1}H NMR (400 MHz, DMSO-d_6)

413

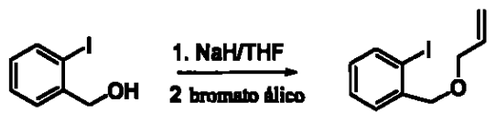
δ 12.9 (bs, 1 H), 7.87 (dd, J = 7.77, 1.14 Hz, 1 H), 7.66 (m, 1 H), 7.59 (m, 1 H), 7.39 (m, 1 H), 4.90 (s, 2 H), 4.15 (m, 2 H).

Paso 2: 1H-isocromo-4(3H)-uno.

Se calentó a reflujo una mezcla del producto del paso uno (8.2 g, 39.0 mmol), KOAc (16.5 g, 167.8 mmol) y Ac_2O (117 ml) durante 2 horas. La mezcla se enfrió a temperatura ambiente y luego se volcó sobre hielo. La mezcla fue extraída con Et_2O (3 x 100 ml) y las capas orgánicas combinadas fueron secadas con $MgSO_4$ y concentradas *in vacuo*. El residuo resultante fue disuelto en 40 ml de EtOH seguido por el agregado de 15 ml de 2 N NaOH. Se continuó revolviendo la mezcla a temperatura ambiente durante dos horas, luego se retiró el EtOH *in vacuo*. La capa acuosa resultante fue extraída con Et_2O (3 x 75 ml) y las capas orgánicas combinadas, secadas con $MgSO_4$, concentradas *in vacuo* para exhumar 2.7 g de 1H-isocromo-4(3H)-uno como un aceite amarillento luego de la cromatografía (10% EtOAc/Hexanos) R_f = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.88 Hz, 1 H), 7.59 (m, 1 H), 7.43 (appt, J = 7.36 Hz, 1 H), 7.24 (d, J = 7.67 Hz, 1 H), 4.91 (s, 2 H), 4.39 (s, 2 H). Análisis calculado para $C_9H_8O_2$; C, 72.96; H, 5.44; encontrado C, 72.50; H, 5.29. MS (ESI+) para $C_9H_8O_2$ *m/z* 148.8 $(M+H)^+$.

Alternativamente, 1H-isocromo-4(3H)-uno se prepara como sigue:

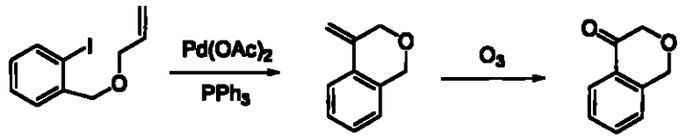
Paso Uno A: 1-[(aliloxi)metil]-2-iodobenceno.



A una solución THF (200 ml) de 2-iodo-benzilo alcohol (25 g, 107 mmol), a temperatura ambiente, se le agregó NaH (5.12 g, 128 mmol) en pequeñas porciones. Luego de un agregado completo de NaH el bromato álico (11.1 ml , 128 mmol) fue añadido vía jeringa. La mezcla se agitó durante toda la noche a temperatura ambiente. La mezcla blanca heterogénea resultante fue enfriada con H_2O (100 ml) y diluida con 300 ml de Et_2O seguida por un baño con H_2O (2 x 100 ml) y salmuera (1 x 100 ml). La capa orgánica fue secada en $MgSO_4$ y concentrada *in vacuo* para exhumar 31 g de 1-[(aliloxi)metil]-2-iodobenceno como un aceite amarillento. HRMS (ESI+) calculado para $C_{10}H_{11}IO$ *m/z* 273.9857 $(M+H)^+$. Encontrado 273.9855.

414

Paso Dos B: 1H-isocromo-4(3H)-uno.



1-[(aliloxi)metil]-2-iodobenceno (23 g, 83.9 mmol) fue disuelto en 100 ml de CH_3CN y 58 ml de Et_3N. La solución fue desgasificada al vacío (3 ciclos) seguida por el agregado de $Pd(OAc)_2$ (0.9 g, 4.2 mmol) y PPh_3 (2.2 g, 8.4 mmol). La mezcla se calentó a 80°C hasta que el HPLC indicó reacción completa. La mezcla fue enfriada a temperatura ambiente y diluida con Et_2O (200 ml). La mezcla fue lavada con 1N HCl (2x 50 ml); $NaHCO_3$ (2 x 50 ml); salmuera (1 x 50 ml); secada con Na_2SO_4 y concentrada *in vacuo* para exhumar 4-metileno-3,4-dihidro-1H-isocromo (*Heterocycles* 1994, *39*, 497) como un aceite. HRMS (ESI+) calculado para $C_{10}H_{10}O$ *m/z* 146.0732 $(M+H)^+$. Encontrado 146.0728. El aceite crudo fue disuelto en 1:1 CH_3OH/CH_2Cl_2 (500 ml) y se agregaron 5 ml de piridina. La mezcla fue congelada a -78°C y se inyectó ozono a través de la mezcla durante 1 hora, tiempo en que el TLC indicó reacción completa. La mezcla fue purgada con N_2 at -78°C y tratada con Me_2S, luego se la calentó a temperatura ambiente, revolviéndola durante 3 horas. Posteriormente la reacción fue diluida con CH_2Cl_2 y lavada con H_2O y salmuera. La capa orgánica fue secada con Na_2SO_4 y concentrada *in vacuo* para exhumar 5.1 g de 1H-isocromo-4(3H)-uno como un aceite amarillento luego de la cromatografía (10% EtOAc/Hexanos) $R_f = 0.25$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 7.88$ Hz, 1 H), 7.59 (m, 1 H), 7.43 (appt, $J = 7.36$ Hz, 1 H), 7.24 (d, $J = 7.67$ Hz, 1 H), 4.91 (s, 2 H), 4.39 (s, 2 H. Análisis calculado para $C_9H_8O_2$; C, 72.96; H, 5.44; encontrado C, 72.50; H, 5.29. MS (ESI+) para $C_9H_8O_2$ *m/z* 148.8 $(M+H)^+$.

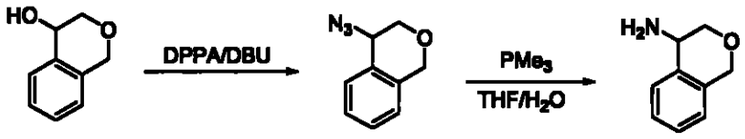
Paso Tres: 3,4-dihidro-1H-isocromo-4-ol.

1H-isocromo-4(3H)-uno (5.1 g, 34.4 mmol) fue disuelto en 100 ml de MeOH y enfriado a 0°C, seguido por el agregado de $NaBH_4$ (1.4 g, 38 mmol) en pequeñas porciones. La mezcla de reacción se revolvió durante 2 horas y se calentó espontáneamente. Una vez completada la reacción, se agregaron 25 ml de NH_4Cl acuoso y se retiró el MeOH *in vacuo*. La mezcla acuosa resultante fue extraída con CH_2Cl_2 (2 x 50 ml), secada con $MgSO_4$, y concentrada *in vacuo* para exhumar 4.8 g de 3,4-dihidro-1H-isocromo-4-ol como un sólido blanco. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 1 H), 7.31 (m, 2 H), 7.04 (m, 1 H), 4.84 (d, $J = 15$ Hz, 1 H), 4.72 (d, $J = 15$ Hz, 1 H), 4.58 (appt, $J = 2.38$ Hz, 1 H), 4.14 (dd, $J = 12.02, 2.70$ Hz, 1 H), 3.91 (dd, $J = 12.02, 2.70$

415

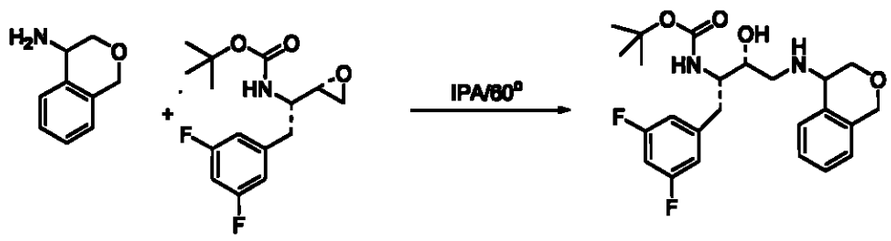
Hz, 1 H), 2.24 (bs, 1 H). Análisis calculado para $C_9H_{10}O_2$; C, 71.98; H, 6.71; encontrado C, 71.80; H, 6.94.

Paso Cuatro: 3,4-dihidro-1H-isocromo-4-amino.



3,4-dihidro-1H-isocromo-4-ol (6.1 g, 40.6 mmol) en 100 ml de tolueno, a 0°C, fue tratado con DPPA (10.5 ml, 49 mmol) via jeringa. La solución fue luego tratada con DBU (7.3 ml, 49 mmol) en 20 ml de tolueno agregado en porciones durante 1h. El baño frío fue quitado luego de 2 horas y se continuo revolviendo durante toda la noche a temperatura ambiente. La mezcla fue filtrada a través de un tapón de gel de sílice, luego el tupón lavado con 25 % EtOAc/hexanos y el filtrado concentrado *in vacuo* para exhumar el ácido como un aceite amarillo. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.09 (m, 4 H), 4.90 (d, J = 15.26 Hz, 1 H), 4.75 (d, J = 15.26 Hz, 1 H), 4.23 (m, 2 H), 3.98 (dd, J = 12.43, 3.39 Hz, 1 H). El ácido crudo fue disuelto en 75 ml de THF seguido por la adición de PPh_3 (13.1 g, 50 mmol) a temperatura ambiente. Luego de 30 minutos, se agregaron. 6 ml de H_2O y se continuó revolviendo a temperatura ambiente durante 3 horas, luego 3 horas a 60°C. La mezcla fue entonces enfriada a temperatura ambiente y revuelta durante toda la noche. La mezcla fue concentrada *in vacuo* y el residuo resultante disuelto en 1H HCl (300 ml). La capa acuosa fue lavada con CH_2Cl_2 (3 x 75 ml) y las capas orgánicas combinadas extraídas con 1N HCl. Las capas acuosas combinadas se ajustaron a pH = 12 con pastillas de NaOH y fueron extraídas con CH_2Cl_2 (3 x 100 ml). Las capas orgánicas combinadas fueron secadas con Na_2SO_4 y concentradas *in vacuo* para exhumar 5g of 3,4-dihidro-1H-isocromo-4-amino. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 1 H), 7.30-7.22 (m, 2 H), 7.01 (m, 1 H), 4.85 (d, J = 15 Hz, 1 H), 4.75 (d, J = 15 Hz, 1 H), 4.00-3.86 (m, 3 H), 1.80 (bs, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.6, 128.6, 127.5, 127.4, 124.5, 72.75, 68.61, 48.23.MS (ESI+) for $C_9H_{11}NO$ *m/z* 133.2 $(M+H)^+$ (pérdida de NH_2).

Paso Cinco: *tert*-butilo(1S,2R)-1-(3,5-difluorobenzilo)-3-(3,4-dihidro-1H-isocromo-4-ilamino)-2-hidroxipropilcarbamato



Una solución IPA (125 ml) de 3,4-dihidro-1H-isocromo-4-amino (5.0 g, 33.5 mmol) y Ejemplo 134 (7.1 g, 23.9 mmol) fue mezclada a 60°C durante la noche. La IPA fue quitada *in vacuo* para exhumar aceite amarillo. El residuo fue disuelto en EtOAc (300 ml) y lavado con 1N HCl (6 x 100 ml); $NaHCO_3$ (2 x 50 ml), luego salmuera (1 x 50 ml). La capa orgánica fue secada con Na_2SO_4 para rendir 9.4 g de *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-3-(3,4-dihidro-1H-isocromo-4-ilamino)-2-hidroxipropilcarbamato como un sólido blanco. Este material fue usado en el paso siguiente sin otra purificación como mezcla de epímeros. HRMS (ESI+) calculado para C24 $H_{30}F_2N_2O_4$ *m/z* 449.2252 $(M+H)^+$. Encontrado 449.2244.

Paso Seis: N-[(1S,2R)-1-(3,5-difluorobenzilo)-3-(3,4-dihidro-1H-isocromo-4-ilamino)-2-hidroxipropilo]acetamida.

tert-butilo (1S,2R)-1-(3,5-difluorobenzilo)-3-(3,4-dihidro-1H-isocromo-4-ilamino)-2-hidroxipropilcarbamato(2.0 g, 4.5 mmol) fue tratado con 20% TFA/CH_2Cl_2 (35 ml), a 0°C, y calentado a temperatura ambiente. Luego de 1.5 h la mezcla fue neutralizada con 0.5 N NaOH y extraída con CH_2Cl_2 (2 x 50 ml). Las capas orgánicas combinadas fueron secadas con Na_2SO_4 y carbono activado. Luego de la filtración, el solvente fue quitado *in vacuo* para que exhumara el amino como una espuma blanca. El amino crudo y el ET_3N se disolvieron en 30 ml de CH_2Cl_2 y fueron enfriados a 0°C seguido por un lento agregado de una solución de 5 ml CH_2Cl_2 de acetil-imidazola (0.5 g, 4.9 mmol). Se dejó que la mezcla se calentara espontáneamente y se la revolvió durante 36 h. El solvente fue quitado *in vacuo* y el residuo disuelto en EtOAc (50 ml); lavado con 1N HCl (2 x 20 ml); $NaHCO_3$ (2 x 20 ml); salmuera (1 x 20 ml; secado con Na_2SO_4 con carbono activado, filtrado y concentrado *in vacuo* para exhumar 1.2 g de N-[(1S,2R)-1-(3,5-difluorobenzilo)-3-(3,4-dihidro-1H-isocromo-4-ilamino)-2-hidroxipropilo]acetamida como una espuma blanca. La fase reversa en pequeña escala del HPLC de la mezcla de epímeros lleva a una separación parcial.

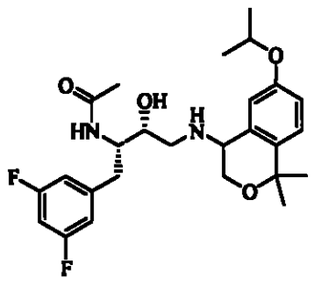
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 1 H), 7.28 (m, 2 H), 7.04 (m, 1 H), 6.77 (m, 2 H), 6.68 (m, 1 H), 5.90 (d, *J* = 8.50 Hz, 1 H), 4.83 (d, *J* = 15.13 Hz, 1 H), 4.73 (d, *J* = 15.13 Hz, 1 H), 4.18 (m, 2 H), 3.85 (dd, *J* = 11.82, 2.90 Hz, 1 H), 3.70 (m, 1 H), 3.62 (m, 1 H), 3.00-2.84 (m, 3 H),

417

2.71 (dd, J = 12.34, 7.15 Hz, 1 H), 1.93 (s, 3 H). MS (ESI+) for $C_{21}H_{24}F_2N_2O_3$ *m/z* 391.5 $(M+H)^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 1 H), 7.29 (m, 2 H), 7.05 (m, 1 H), 6.77 (m, 2 H), 6.68 (m, 1 H), 5.88 (d, J = 8.91 Hz, 1 H), 4.87 (d, J = 15.13 Hz, 1 H), 4.74 (d, J = 15.13 Hz, 1 H), 4.26-4.16 (m, 2 H), 3.84 (m, 2 H), 3.75 (bs, 1 H), 3.57 (m, 2 H), 3.04-2.85 (m, 3 H), 2.76 (dd, J = 12.34, 6.53 Hz, 1 H), 1.90 (s, 3 H). MS (ESI÷) for $C_{21}H_{24}F_2N_2O_3$ *m/z* 391.5 $(M+H)^+$.

Ejemplo 64: N-{(1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-il)amino]propilo}acetamida.



Paso Uno: 6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo.

Se agitó una solución de 1,1-dimetilo-3,4-dihidro-1H-isocromo-6-ol (2.0 g, 11.2 mmol), carbonato de cesio (9.14 g, 28.05 mmol) y 2-bromopropano (2.07 g, 16.8 mmol) en acetona (20 mL) a 57 °C, bajo nitrógeno, durante 20 h. La mezcla de reacción fue enfriada a temperatura ambiente, diluida con acetato etílico (150 mL) y lavada con agua (70 mL), cloruro de sodio saturado (70 mL), secada (sulfato de sodio) y concentrada bajo presión reducida para rendir 6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo (2.31 g, 94%) como un aceite amarillo pálido: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.00 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.6 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 4.54–4.46 (m, 1H), 3.92 (t, J = 5.5 Hz, 2H), 2.77 (t, J = 5.5 Hz, 2H), 1.49 (s, 6H), 1.32 (d, J = 6.0 Hz, 6H).

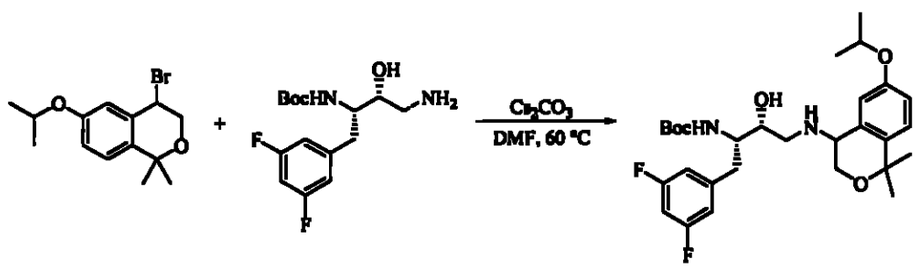
Paso Dos: 4-bromo-6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo

Se desgasificó una solución de 6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo (0.22 g, 1.0 mmol), *N*-bromosuccinimida (0.19 g, 1.05 mmol), y AIBN (catalítico) en tetracloruro de carbono (3 mL) con nitrógeno durante 10 min, y luego se revolvió a 65 °C durante 2.5 h. La mezcla de reacción fue enfriada en un baño de agua helada, diluida con cloruro de metileno (150 mL) y lavada con agua (2 × 50 mL), cloruro de sodio saturado (50 mL), secada (sulfato de sodio), y concentrada bajo presión reducida. El producto crudo fue purificado mediante cromatografía

418

flash (sílice, 10:1 hexanos/acetato etílico) para propiciar 4-bromo-6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo (1.02 g, 53%) como un aceite amarillo pálido: ^{1}H NMR (300 MHz, $CDCl_3$) □ 6.98 (d, J = 8.5 Hz, 1H), 6.86 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.5, 2.6 Hz, 1H), 5.18 (m, 1H), 4.54–4.48 (m, 1H), 4.19 (dd, J = 12.8, 3.0 Hz, 1H), 4.11 (dd, J = 12.8, 3.0 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H).

Paso Tres: *tert*-butilo (1S,2R)-1-(3,5-diflucrobenzilo)-2-hidroxi-3-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-il)amino]propilcarbamato.



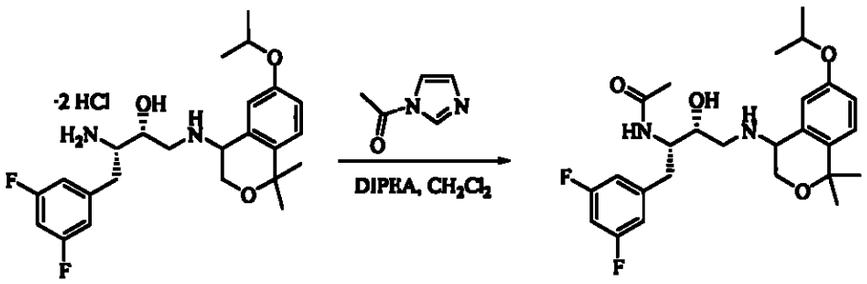
Se revolvió una solución de 4-bromo-6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo (0.61 g, 2.04 mmol), carbonato de cesio (1.33 g, 4.08 mmol), y *tert*-butilo (1S,2R)-3-amino-1-(3,5-difluorobenzilo)-2-hidroxipropilcarbamato (0.64 g, 2.04 mmol) en *N,N*-dimetilformamida (10 mL) a 60 °C, bajo nitrógeno, durante 24 h. La mezcla de reacción fue diluida con acetato etílico (100 mL) y lavada con 5% cloruro de litio (3 × 40 mL), agua (2 × 30 mL), cloruro de sodio saturado (30 mL), secada (sulfato de sodio), y concentrada bajo presión reducida El producto crudo fue purificado mediante cromatografía flash (sílice, 95:5 cloruro de metileno/metanol) para propiciar *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-il)amino]propilcarbamato (0.51 g, 47%) como una espuma amarillo pálido: ESI MS *m/z* 535 $[C_{29}H_{40}F_2N_2O_5 + H]^+$.

Paso Cuatro: (2R,3S)-3-amino-4-(3,5-difluorofenilo)-1-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-yl)amino]butano-2-ol hidrocloruro.

Se mezcló una solución de *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-il)amino]propilcarbamato (0.50 g, 0.94 mmol) y ácido hidroclórico (solución de 3.3 mL, 4M en 1,4 dioxano, 13.2 mmol) en 1,4-dioxano (4 mL) a temperatura ambiente durante 9 horas. La mezcla de reacción fue diluida con éter dietílico (40 mL) y concentrada bajo presión reducida. El aceite crudo resultante fue disuelto en metanol (40 mL) y luego en cloruro metílico (4 × 40 mL), concentrando bajo presión reducida cada vez para

propiciar (2R,3S)-3-amino-4-(3,5-difluorofenilo)-1-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo 4-il)amino]butano-2-ol hidroclorato (0.47 g, 100%) como un sólido amarillo: ESI MS *m/z* 435 $[C_{24}H_{32}F_2N_2O_3 + H]^+$.

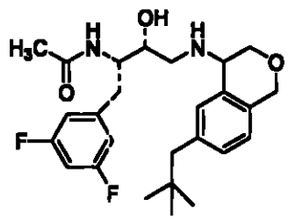
Paso Cinco: N-{(1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-il)amino]propil}acetamida.



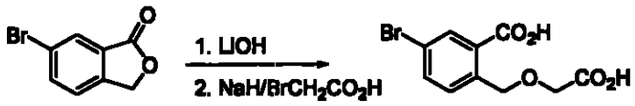
A una solución de (2R,3S)-3-amino-4-(3,5-difluorofenilo)-1-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-il)amino]butano-2-ol hidrocloruro (0.15 g, 0.30 mmol) en cloruro de metileno (3 mL) se le agregó *N,N*-diisopropiletilamina (0.19 g, 1.47 mmol) seguido por acetilimidazola (0.03 g, 0.30 mmol). La mezcla de reacción se agitó a temperatura ambiente, bajo nitrógeno, durante 18 h. La mezcla de reacción fue diluida con cloruro de metileno (20 mL), lavada con agua (2 × 10 mL), cloruro de sodio saturado (20 mL), secada (sulfato de sodio), y concentrada bajo presión reducida. El producto crudo fue purificado mediante cromatografía flash (sílice, 95:5 cloruro de metileno/metano) para propiciar N-{(1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-isopropoxi-1,1-dimetilo-3,4-dihidro-1H-isocromo-4-il)amino]propilo}acetamida (0.05 g, 36%) como una espuma blanca: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.01 (d, *J* = 8.4 Hz, 1H), 6.82–6.74 (m, 4H), 6.69–6.63 (m, 1H), 5.81–5.78 (m, 1H), 4.56–4.52 (m, 1H), 4.21–4.17 (m, 1H), 3.94 (d, *J* = 2.1 Hz, 2H), 3.50–3.48 (m, 2H), 3.00–2.85 (m, 3H), 2.71–2.64 (m, 1H), 1.88 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 6H); ESI MS *m/z* 477 $[C_{26}H_{34}F_2N_2O_4 + H]^+$; HPLC (Método A) >99% mezcla de diasterómeros (AUC), t_R = 6.12 y 6.77 min.

Ejemplo 65: N-{(1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-neopentilo-3,4-dihidro-1H-isocromo-4-yl)amino]propilo}acetamida

420

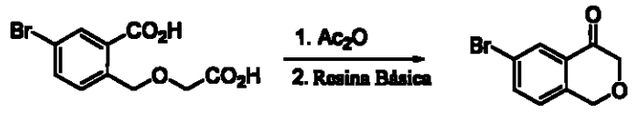


Paso Uno: 5-Bromo-2-carboximetoximetil-ácido benzoico



El monohidrato hidróxido de litio (11.80 g, 281.6 mmol) fue agregado a temperatura ambiente durante varios minutos a una solución de 5-bromoftalida (20.0 g, 93.88 mmol) en una solución 2:1:1 de tetrahidrofuran/metanol/agua (570 mL) y la mezcla de reacción realizada a temperatura ambiente durante la noche. La mezcla de reacción fue concentrada bajo presión reducida y azeotropicalmente secada con benceno para dar 5-bromo-2- hidroximetil-ácido benzoico como un sólido blanco. El material fue usado sin otra purificación: ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) □ 7.89 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 1.9 Hz, 1H), 7.50 (dd, J = 8.3, 1.9 Hz, 1H), 3.99 (s, 2H); ESI MS (modo negativo) *m/z* 229 [$C_8H_7BrO_3$ - H]$^-$. Iruro de sodio (15.0 g, 375 mmol, 60% de dispersión en aceite mineral) fue agregado en pequeñas porciones durante el curso de 0.5 h a temperatura ambiente a una solución de 5-Bromo-2- ácido hidroximetil-benzoico en tetrahidrofuran (235 mL) con contenido de ácido bromoacético (14.35 g, 103.2 mmol) y ioduro de sodio (1.41 g, 9.4 mmol). La mezcla de rencción fue calentada a reflujo durante la noche. La mezcla de reacción fue enfriada a temperatura ambiente y volcada en agua, y luego extraída con éter dietílico. La fase acuosa fue acidificada con 10% de ácido hidroclórico a un pH 3–4 y extraída varias veces con acetato etílico. Las fases combinadas de acetato etílico fueron lavadas con agua y cloruro de sodio saturado, secadas (sulfato de sodio), filtradas, y concentradas para dar -Bromo-2-ácido carboximetoxymetil -benzoico como un sólido blanco. El material fue usado sin otra purificación: ^{1}H NMR (300 MHz, CD_3OD) □ 7.93–7.86 (m, 2H), 7.55–7.50 (m, 1H), 4.98 (s, 2H), 4.23 (s, 2H); ESI MS (modo negativo) *m/z* 287 [$C_{10}H_9BrO_5$ - H]$^-$.

Paso Dos: 6-Bromo-isocromo-4-uno



421

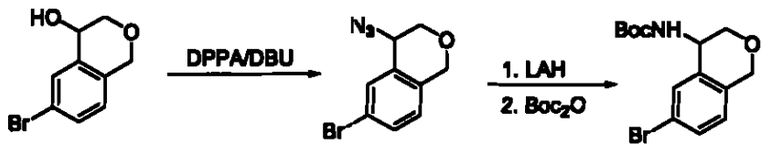
Una solución de Bromo-2-ácido carboximetoximetil-benzoico en anhídrido acético (350 mL) con contenido de acetato potásico (170 g) fue calentada a reflujo durante 2 h. La mezcla de reacción fue enfriada a temperatura ambiente y concentrada bajo presión reducida y el residuo dividido entre el acetato etílico y el agua. Las fases fueron separadas y la fase acuosa extraída con acetato etílico. La fase combinada de acetato etílico fue entonces lavada con cloruro de sodio saturado, secada (sulfato de sodio), filtrada, y concentrada para rendir un semi-sólido rojo. La purificación por cromatografía flash en sílice (85:15 hexanos/acetato etílico) dio el acetato enólico (7.59 g, 29% durante tres pasos) como una jalea dorada: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.37 (dd, J = 8.2, 1.9 Hz, 1H), 7.19 (d, J = 1.9 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.04 (s, 2H), 2.29 (s, 3H). Una resina de intercambio anion Dowex no-activada 500A OH (1 g) agregada en una porción a una solución del acetato enólico acetato (5.95 g, 22.11 mmol) en metanol (50 mL) y la mezcla de reacción revuelta a temperatura ambiente durante la noche. La mezcla de reacción fue filtrada por gravedad y la resina lavada con metanol fresco. El filtrado combinado fue entonces concentrado bajo presión reducida para dar 6-Bromo-isocromo-4-uno (4.32 g, 86%) como un aceite amarillo, el cual solidificó: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.90 (d, J = 8.3 Hz, 1H), 7.56 (dd, J = 8.3, 1.7 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 4.86 (s, 2H), 4.36 (s, 2H).

Paso Tres: 6-Bromo-isocromo-4-ol

Se añadió por goteo una solución de borohidrato de sodio (300 mg, 7.93 mmol) disuelta en una cantidad mínima de agua congelada a 0 °C a una solución de 6-Bromo-isocromo-4-uno (1.49 g, 6.56 mmol) en etanol absoluto (27.0 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción fue dividida entre el acetato etílico y una solución saturada de bicarbonato de sodio. Las fases fueron separadas y la fase orgánica lavada con agua y cloruro de sodio saturado, secada (sulfato de sodio), filtrada, y concentrada bajo presión reducida para rendir 6-Bromo-isocromo-4-ol (1.44 g, 95%) como un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.40 (dd, J = 8.3, 1.8 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 1.8 Hz, 1H), 4.63 (ABq, J = 15.3 Hz, 2H), 4.49 (d, J = 8.6 Hz, 1H), 4.07 (dd, J = 12.0, 2.8 Hz, 1H), 3.83 (dd, J = 12.0, 2.8 Hz, 1H), 2.60 (d, J = 9.2 Hz, 1H).

Paso Cuatro: (6-Bromo-isocromo-4-il)-éster tert-butílico ácido carbámico

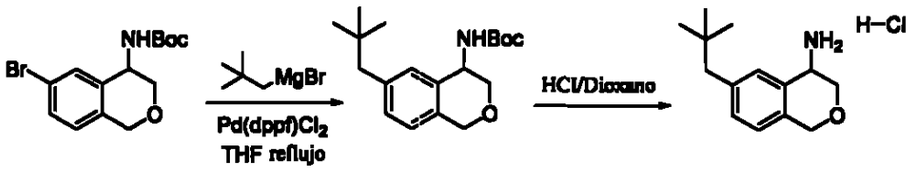
422



Azida difenilfosfórico (2.11 mL, 9.8 mmol) fue agregado a 0 °C a una solución de 6-Bromo-isocromo-4-ol (1.87 g, 8.16 mmol) en tolueno (17 mL). A esto se añadió por goteo durante 0.5 h una mezcla de 1,8-diazabiciclo[5.4.0]undec-7-ene (1.46 ml, 9.8 mmol) en tolueno (5.0 ml). La mezcla de reacción fue entonces realizada a temperatura ambiente durante la noche. La mezcla de reacción se pasó a través de un tapón de sílice y el tapón propició 6:1 hexanos/acetato etílico. Los filtrados combinados fueron concentrados bajo presión reducida para proporcionar el azida como un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) □7.46–7.33 (m, 3H), 4.76 (ABq, J = 15.5 Hz, 2H), 4.22–4.16 (m, 3H), 3.93 (dd, J = 11.7, 2.6 Hz, 1H). Se agregó por goteo una solución de hidrato de aluminio y litio (391 mg, 9.79 mmol) en una cantidad mínima de tetrahidrofuran (2.0 mL) a 0 °C a una solución del azida en tetrahidrofuran (30 mL) y la mezcla de reacción fue calentada a reflujo durante 1 h. La mezcla de reacción fue enfriada a temperatura ambiente y luego con agua (0.5 mL), 15% hidróxido de sodio (1.2 ml), agua (0.5 mL) y la mezcla de reacción se realizó a temperatura ambiente durante 1 h. La mezcla resultante se pasó a través de un tapón de sílice y el tapón se enjuagó con éter. Los filtrados combinados fueron concentrados bajo presión reducida para propiciar un aceite que se disolvió en una cantidad mínima de acetato etílico, al cual se agregó cloruro de hidrógeno (3.0 ml, 4 N in 1,4-dioxano, 12 mmol) y la mezcla de reacción se realizó a temperatura ambiente durante la noche. La mezcla de reacción fue filtrada al vacío para propiciar la deseada sal amina (1.54 g, 72 % durante dos pasos) como un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$)□ 7.54–7.44 (m, 2H), 7.37 (s, 1H), 4.80 (ABq, J = 15.5 Hz, 2H), 4.42 (d, J = 12.8 Hz, 1H), 4.34 (s, 1H), 3.87 (dd, J = 12.8, 2.2 Hz, 1H), 3.66 (s, 3 H); ESI MS *m/z* 228 $[C_9H_{10}BrNO+H]^+$. Se agregó dicarbonato di-*tert*-butílico (1.40 g, 6.40 mmol) en porciones a una solución de amina (1.54 g, 5.82 mmol) en acetonitril (25 mL) que contenía *N,N*-diisopropiletilamina (4.0 mL, 23.28 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción fue concentrada bajo presión reducida y dividida entre el acetato etílico y el agua. La fase orgánica fue secada (sulfato de sodio), filtrada, y concentrada bajo presión reducida para propiciar una jalea amarilla. La purificación por cromatografía flash en sílice (80:20 hexanos/acetato etílico) rindió el producto deseado (1.05 g, 55%) como un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.41–7.23 (m, 2H), 7.15 (s, 1H), 5.10–5.07 (m, 1H), 4.69 (ABq, J = 15.5 Hz, 2H), 4.04–4.00 (m, 1H), 3.89–3.81 (m, 1H), 1.45 (s, 9 H).

423

Paso Cinco: 6-(2,2-Dimetilo-propil)-isocromo-4-hidrocloruro de ilamina.



Bromuro de *Neo*-pentilmagnesio (10 mL, 9.1 mmol, 1.0 M en éter) fue agregado por goteo a una solución de cloruro de zinc (18.2 mL, 0.5 M en tetrahidrofuran 9.1 mmol) durante 0.5 h y la mezcla de reacción se realizó a temperatura ambiente durante una media hora adicional. [1,1'-Bis(difenilfosfino] ferroceno (II) complejo dicloropaladio con diclorometano(1:1) (250 mg, 0.30 mmol) fue agregado a la mezcla de reacción seguido por (6-Bromo-isocromo-4-il)- éster tert-butílico ácido carbámico (1.00 g, 3.04 mmol) y la mezcla de reacción se calentó a reflujo durante 1 h. La mezcla de reacción fue enfriada y luego concentrada bajo presión reducida. El residuo fue vuelto a disolver en acetato etílico y lavado con agua, cloruro de sodio, secado (sulfato de sodio), filtrado, y concentrado bajo presión reducida. La purificación por cromatografía flash con sílice (83:17 hexanos/acetato etílico) rindió el amino protegido deseado (303 mg, 31%) como un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.30–7.23 (m, 1H), 7.00 (d, J = 6.3 Hz, 1H), 6.74 (s, 1H), 5.09–5.06 (m, 1H), 4.79–4.65 (m, 3H), 4.13–3.85 (m, 2H), 2.45 (s, 2H), 1.46 (s, 9 H), 0.89 (s, 9H); ESI MS *m/z* 320 $[C_{19}H_{29}NO_3 + H]^+$. Se mezcló una solución de amino protegido (303 mg, 0.95 mmol) en cloruro de hidrógeno (20 mL, 4 N en 1,4-dioxano, 80 mmol) a temperatura ambiente durante la noche. La mezcla de reacción fue concentrada bajo presión reducida para dar 6-(2,2-Dimetilo-propil)-isocromo-4-hidroclorato ilamínico (210 mg, cuantitativo) como un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.28 (d, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6, 1.2 Hz, 1H), 6.73 (d, J = 1.2 Hz, 1H), 4.75 (ABq, J = 15.0 Hz, 2H), 3.96–3.80 (m, 3H), 2.44 (s, 2H), 1.73 (m, 2H), 0.89 (s, 9H); ESI MS *m/z* 220 $[C_{14}H_{21}NO + H]^+$.

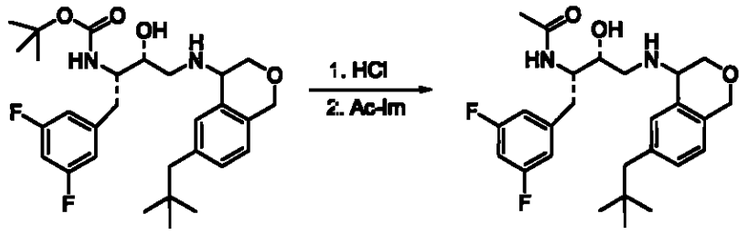
Paso Seis: *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-1H-isocromo-4-il)amino]propilcarbamato.

Se calentó una solución de 6-(2,2-Dimetilo-propil)-isocromo-4-ilamina (210 mg, 0.95 mmol) y Ejemplo 134 (309 mg, 1.03 mmol) en 2-propanol (9.5 mL) a reflujo durante 2 h. La mezcla de reacción fue concentrada bajo presión reducida. El residuo fue vuelto a disolver en cloruro de

424

metileno y lavado con 0.5 N cloruro de hidrógeno, agua, cloruro de sodio, secado (sulfato de sodio), filtrado, y concentrado bajo presión reducida. La purificación por cromatografía flash en sílice (94:6 cloroformo/metanol) rindió el deseado *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-1H-isocromo-4-il)amino]propilcarbamato (260 mg, 52%) como una espuma blanca: ESI MS *m/z* 519 $[C_{29}H_{40}F_2N_2O_4 + H]^+$.

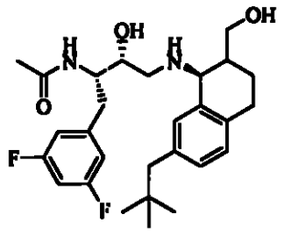
Paso Siete: N-{(1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-1H-isocromo-4-il)amino]propil}acetamida.



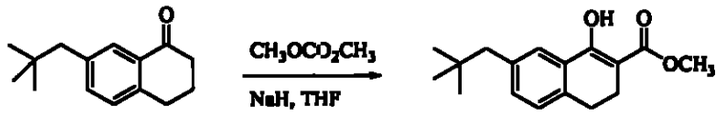
Se mezcló una solución de *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-1H-isocromo-4-il)amino]propilcarbamato (260 mg, 0.50 mmol) en cloruro de hidrógeno (10 mL, 4 N in 1,4-dioxano, 40 mmol) a temperatura ambiente durante la noche. La mezcla de reacción fue concentrada bajo presión reducida para rendir el hidrocloruro de amino (250 mg, cuantitativo) como un sólido blanco: ESI MS *m/z* 419 $[C_{24}H_{32}F_2N_2O_2 + H]^+$. 1-Acetilimidazole (50 mg, 0.46 mmol) fue agregado a temperatura ambiente a una solución de sal (250 mg, 0.50 mmol) en cloruro de metileno (3.5 mL) que contenía trietilamina (600 □L, 4.0 mmol) y se mezcló la reacción durante 1.0 h. La mezcla de reacción fue luego diluida con cloruro de metileno y lavada con agua, cloruro de sodio saturado, secada (sulfato de sodio), filtrada, y concentrada bajo presión reducida para dar un sólido blanco. La purificación por cromatografía flash en sílice (94:6 cloroformo/metanol) propició N-{(1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-1H-isocromo-4-il)amino]propil}acetamida (52 mg, 22%) como un sólido blanco (mezcla de epímeros): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.24–7.16 (m, 2H), 7.01–6.98 (m, 1H), 6.76–6.66 (m, 4H), 5.83 (ABq, *J* = 15.0 Hz, 2H), 4.10–4.05 (m, 2H), 3.83–3.79 (m, 1H), 3.55–3.51 (m, 2H), 2.93–2.72 (m, 3H), 2.69–2.65 (m, 1H), 2.45 (s, 2H), 1.89 (m, 4H), 0.89 (s, 9H); ESI MS *m/z* 461 $[C_{26}H_{34}F_2N_2O_3 + H]^+$; HPLC (1-99, 220) 68.1% Epímero Mayor (AUC), t_R = 10.89 min y 31.8% Epímero Menor (AUC), t_R = 11.19 min.

425

Ejemplo 66: N-((1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[(1S)-2-(hidroximetil)-7-neopentil-1,2,3,4-tetrahidronaftaleno-1-il]amino}propilo)acetamida.



Paso Uno: 7-(2,2-Dimetilo-propilo)-1-hidroxi-3,4-dihidro-naftaleno-2-éster metílico ácido carboxílico



A una solución de tetralona (2.16 g, 10 mmol) en tetrahidrofuran (50 mL) se le agregó hidrato de sodio (60%, 1.49 g, 37.1 mmol) seguido por carbonato dimetílico (2.73g, 30 mmol). La mezcla de reacción fue calentada a reflujo durante 3 h y luego se dejó que enfriara a temperatura ambiente y con ácido acético (3.6 mL). Se quitó el solvente bajo presión reducida y el residuo fue diluido con éter etílico (100 mL) y agua (50 mL). La capa orgánica fue separada y la capa acuosa fue extraída con éter etílico (2 × 50 mL). Los extractos combinados fueron lavados con cloruro de sodio saturado, secados (sulfato de sodio), filtrados, y concentrados bajo presión reducida. Una cromatografía flash (gel de sílice, 10–20% acetato etílico/hexanos) proporcionó el producto deseado (2.50 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 12.48 (s, 1H), 7.60 (s, 1H), 7.17–7.08 (m, 2H), 3.85 (s, 3H), 2.84–2.79 (m, 2H), 2.62–2.57 (m, 2H), 2.54 (s, 2H), 0.94 (s, 9H).

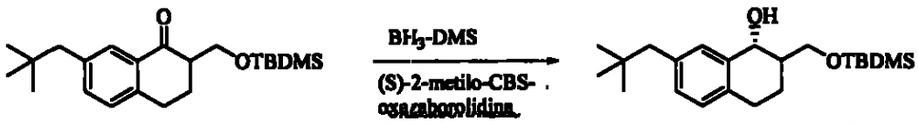
Paso Dos: 2-(tert-Butilo-dimetilo-silaniloximetil)-7-(2,2-dimetilo-propilo)-3,4-dihidro-2H-naftaleno-1-uno.

A una solución enfriada a hielo de 7-(2,2-Dimetilo-propilo)-1-hidroxi-3,4-dihidro-naftaleno-2-éster metílico ácido carboxílico (2.49 g, 9.07 mmol) en tetrahidrofuran (20 mL) se le agregó hidrato de aluminio de litio (1 M en tetrahidrofuran, 9 mL, 9 mmol). La mezcla de reacción se agitó a 0 °C durante 2 h y luego enfriada con cloruro de amonio saturado y acetato etílico. La emulsión resultante fue filtrada a través de tierra diatomácea. La capa orgánica fue separada y la capa acuosa fue extraída con acetato etílico. Los extractos combinados fueron lavados con cloruro de sodio saturado, secados (sulfato de sodio), filtrados, y concentrados bajo presión

426

reducida. Una cromatografía flash (gel de sílice, 10–20% acetato etílico/hexanos) proporcionó tetralona hidroximetílica (1.55 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.78 (d, J = 1.4 Hz, 1H), 7.27 (dd, J = 7.8, 1.4 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 4.00–3.90 (m, 1H), 3.85–3.75 (m, 1H), 3.20–3.10 (m, 1H), 3.08–2.90 (m, 2H), 2.75–2.60 (m, 1H), 2.52 (s, 2H), 2.15–2.05 (m, 1H), 2.00–1.85 (m, 1H), 0.90 (s, 9H). A una solución de tetralona hidroximetílica (1.50 g, 6.09 mmol) en *N,N*-formamida dimetílica (6 mL) se le agregó *imidazola* (500 mg, 7.25 mmol) seguida por cloruro tert-butílico-dimetilsílico (1.03 g, 6.64 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y luego diluida con 1:1 hexanos/acetato etílico (100 mL). La mezcla fue lavada sucesivamente con 1N ácido hidroclórico, agua, bicarbonato de sodio saturado y cloruro de sodio saturado, y secada (sulfato de sodio), filtrada, y concentrada bajo presión reducida para rendir 2-(tert-Butilo-dimetilo-silaniloxymetil)-7-(2,2-dimetilo-propilo)-3,4-dihidro-2H-naftaleno-1-uno (2.20g, 99% rendición cruda): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.76 (d, J = 1.8 Hz, 1H), 7.23 (dd, J = 7.8, 1.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 4.16–4.08 (m, 2H), 3.90–3.84 (m, 1H), 3.01–2.95 (m, 2H), 2.68–2.60 (m, 1H), 2.51 (s, 2H), 2.42–2.33 (m, 1H), 2.03–1.95 (m, 1H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). Este material fue usado en el paso siguiente sin otra purificación.

Paso Tres: 2-(tert-Butilo-dimetilo- silaniloximetilo)-7-(2,2-dimetilo-propilo)-1,2,3,4-tetrahidro-naftaleno-1-ol.



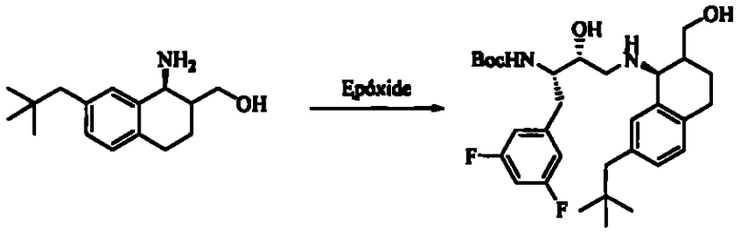
A una solución enfriada a –30 °C de 2-(tert-Butilo-dimetilo-silaniloximetilo)-7-(2,2-dimetilo-propilo)-3,4-dihidro-2H-naftalina-1-uno (2.20 g, 6.09 mmol) en tetrahidrofuran (20 mL) se le agregó (S)-2-metill-Cbs-oxazaborolidina (1 M in tolueno, 0.61 mL, 0.61 mmol) y una solución de complejo de sulfuro metílico-borano (2 M en tetrahidrofuran, 2.15 mL, 4.3 mmol) en tetrahidrofuran (5 mL). La mezcla de reacción fue calentada a –20 a –5 °C durante 5 h. La mezcla de reacción fue enfriada con metanol (8.3 mL) a –5 °C y luego se la dejó calendar a temperatura ambiente, revolviéndola durante la noche. El solvente fue quitado bajo presión reducida. La cromatografía flash (gel de sílice, 0–5% acetato etílico/hexanos) recuperó 790 mg de ketona y proporcionó chiral 2-(tert-Butilo-dimetilo-silanyloxymetil)-7-(2,2-dimetilo-propilo)-1,2,3,4-tetrahidro-naftaleno-1-ol (980 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.14 (s, 1H), 7.03–6.96 (m, 2H), 4.84 (d, J = 2.5 Hz, 1H), 3.92–3.82 (m, 2H), 3.04 (d, J = 3.7 Hz, 1H), 2.92–

427

2.67 (m, 2H), 2.46 (s, 2H), 2.04–1.86 (m, 2H), 1.75–1.63 (m, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

Paso Cuatro: [1-Amino-7-(2,2-dimetilo-propilo)-1,2,3,4-tetrahidro-naftaleno-2-il]-metanol. A una mezcla enfriada a hielo de 2-(tert-Butilo-dimetilo-silaniloximetil)-7-(2,2-dimetilo-propilo)-1,2,3,4-tetrahidro-naftaleno-1-ol (980 mg, 2.7 mmol) y difenilfosforilizado (908 mg, 3.2 mmol) en tolueno (10 mL) se le agregó a goteo una solución de 1,8-diazobiciclo[5.4.0]-undec-7-ene (504 mg, 3.2 mmol) en tolueno (2 mL). La mezcla de reacción se agitó a 0 °C durante 2 h y luego a temperatura ambiente durante la noche. La mezcla fue filtrada a través de un corto trayecto de gel de sílice (eluido con 6:1 hexanos/acetato etílico) para quitar los precipitados. El filtrado fue concentrado. La cromatografía flash (gel de sílice 0–5% acetato etílico/hexanos) recuperó 210 mg de alcohol y proporcionó el azida (600 mg, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.15 (s, 1H), 7.03–6.97 (m, 2H), 4.42 (d, J = 2.5 Hz, 1H), 3.75 (dd, J = 10.1, 5.1 Hz, 1H), 3.67 (dd, J = 10.1, 4.8 Hz, 1H), 2.81–2.67 (m, 2H), 2.48 (s, 2H), 2.07–1.98 (m, 2H), 1.80–1.67 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). A una solución de azida (600 mg, 1.55 mmol) en tetrahidrofuran (4 mL) se le agregó a goteo una solución de hidrato de aluminio de litio (1 M in trahidrofuran, 2 mL, 2 mmol). La mezcla de reacción fue calentada a reflujo durante 1 h. Otros 0.5 mL de hidrato de aluminio de litio fueron agregados y la mezcla de reacción calentada a reflujo durante 1 h. La mezcla fue enfriada a temperatura ambiente y luego por sucesivas adiciones de agua (0.1 mL), 15% hidróxido de sodio (0.1 mL) y agua (0.3 mL). La mezcla resultante fue revuelta durante 1 h y luego filtrada a través de tierra diatomáceas (eluida con éter etílico). El filtrado fue concentrado bajo presión reducida para proporcionar [1-Amino-7-(2,2-dimetilo-propilo)-1,2,3,4-tetrahidro-naftaleno-2-il]-metanol (400 mg, 99% rendimiento crudo): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.06 (s, 1H), 7.01–6.92 (m, 2H), 3.83–3.70 (m, 3H), 2.92–2.72 (m, 3H), 2.47 (s, 2H), 1.85–1.69 (m, 2H), 1.48–1.33 (m, 1H), 0.90 (s, 9H).

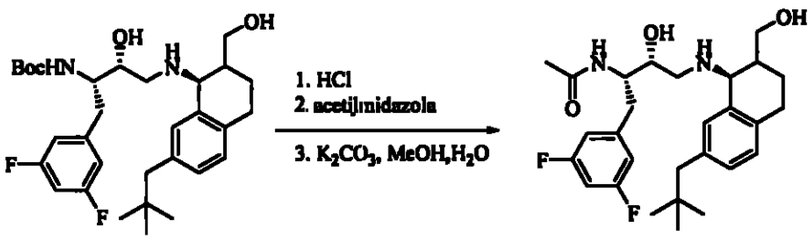
Paso Cinco: *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[(1S)-2-(hidroximetilo)-7-neopentilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}propilcarbamato.



428

Una mezcla de [1-Amino-7-(2,2-dimetilpropilo)-1,2,3,4-tetrahidro-naftaleno-2-il]-metanol (200 mg, 0.77 mmol) y Ejemplo 134 (240 mg, 0.8 mmol) en 2-propano (5 mL) se agitó a 60 °C durante 24 h. Se quitó el solvente bajo presión reducida. La cromatografía flash (gel de sílice 1–10% metanol/cloruro de metileno) proporcionó *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[(1S)-2-(hydroximetilo)-7-neopentilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}propilcarbamato(225 mg, 54%): ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.01–6.91 (m, 3H), 6.76–6.60 (m, 5H), 4.62 (d, J = 8.9 Hz, 1H), 4.34–4.30 (m, 1H), 4.07–3.89 (m, 2H), 3.83–3.61 (m, 4H), 3.53–3.47 (m, 2H), 2.95–2.86 (m, 2H), 2.80–2.63 (m, 3H), 2.59–2.57 (m, 2H), 2.45 (s, 2H), 2.15–2.05 (m, 1H), 1.81–1.77 (m, 1H), 1.36 (s, 9H), 0.89 (s, 9H).

Paso Seis: N-((1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[(1S)-2-(hidroximetilo)-7-neopentilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}propilo)acetamida



A una solución de *tert*-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[(1S)-2-(hidroximetilo)-7-neopentilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}propilcarbamato (225 mg, 0.41 mmol) en 1,4-dioxano (1 mL) se agregó ácido clorhídrico (1 mL, 4 N in 1,4-dioxano, 4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h. Se quitó el solvente bajo presión reducida para proporcionar la sal de hidrocloruro de amino (194 mg, 91% rendimiento crudo): ESI MS *m/z* 447 [$C_{26}H_{36}F_2N_2O_2$ + H]$^+$. A una solución de sal de hidrocloruro de amino (194 mg, 0.37 mmol) en clorato de metileno (5 mL) se agregó trietilamina (191 mg, 1.87 mmol) seguida por 1-acetilimidazola (42 mg, 0.37 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 15 h. Se quitó el solvente bajo presión reducida. El residuo fue disuelto en metanol (6 mL) y agua (3 mL) y tratado con carbonato de potasio (300 mg, 2.17 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se quitó el solvente bajo presión reducida. El residuo fue acidificado con 1N ácido hidroclórico y extraído con acetato etílico (3 x 50 mL). Los extractos combinados fueron lavados con cloruro de sodio saturado, y secados (sulfato de sodio) filtrados, y concentrados bajo presión reducida. La purificación por

cromatografía flash (gel de sílice, 0–5% metanol/cloruro de metileno proporcionó N-((1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[(1S)-2-(hydroximetilo)-7-neopentilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}propilo)acetamida (80 mg, 44%) como una espuma blanca: IR (ATR) 3265, 3072, 2948, 2864, 1626, 1595, 1550, 1459, 1364, 1315, 1115, 1071, 984, 842 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) □ 7.15 (s, 1H), 7.07–7.00 (m, 2H), 6.83–6.72 (m, 3H), 4.18 (d, J = 5.9 Hz, 1H), 4.06–3.99 (m, 1H), 3.74–3.64 (m, 2H), 3.57 (t, J = 8.4 Hz, 1H), 3.34 (s, 2H), 3.13–3.07 (m, 1H), 2.94–2.59 (m, 5H), 2.49 (s, 2H), 2.30–2.20 (m, 1H), 2.04–1.98 (m, 1H), 1.81 (s, 3H), 1.64–1.57 (m, 1H), 0.91 (s, 9H); ESI MS *m/z* 489 $[C_{28}H_{38}F_2N_2O_3 + H]^+$; HPLC (Method C) 98.2% (AUC), t_R = 9.41 min. Anal. Calcd for $C_{21}H_{24}F_2N_2O_4 \cdot H_2O$: C, 66.38; H, 7.96; N, 5.53. Encontrado: C, 66.18; H, 7.80; N, 5.45.

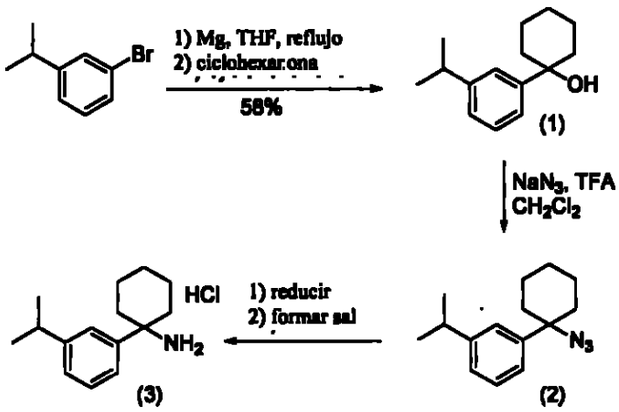
Ejemplo 67: 5-[((1S,2R)-1-(3,5-difluorobenzilo)-3-{[(1S)-7-etilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}-2-hidroxipropilo)amino]-5- ácido oxopentanoico. A una solución de 3-amino-4-(3,5-difluorofenil)-1-(7-etilo1,2,3,4-tetrahidro-naftaleno1-ilamino)-butano-2-ol (0.240g, 0.64 mmol), trietilamina (0.268 mL, 1.92 mmol), y cloroformo (3 mL) se le agregó anhídrido glutárico (0.073 g, 0.64 mmol) y la reación fue mezclada durante la noche a 60°C. La reacción fue lavada con 1N HCl, 10% $NaHCO_3$, salmuera, secada con $MgSO_4$, filtrada, concentrada *in vacuo* para rendir 5-[((1S,2R)-1-(3,5-difluorobenzilo)-3-{[(1S)-7-etilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}-2-hidroxipropilo)amino]-5-ácido oxopentanoico (100 mg). Purificado vía prep-HPLC. ^1H NMR (400 MHz, CD_3OD) δ 1.26 (t, J = 8 Hz, 3 H), 1.73 (m, 2 H), 1.89 (m, 1 H), 2.01 (m, 1 H), 2.17 (m, 6 H), 2.68 (d, J = 8 Hz, 2 H), 2.93 (d, J = 6 Hz, 1 H), 3.02 (m, 1 H), 3.30 (m, 2 H), 3.88 (m, 1 H), 4.09 (m, 1 H), 4.57 (m, 1 H), 6.79 (m, 1 H), 6.88 (m, 3 H), 6.93 (d, J = 6 Hz, 1 H), 7.20 (m, 2 H), 7.31 (s, 1 H); OAMS: ES+ 488.9 ES- 486.9

Ejemplo 68: 4-[((1S,2R)-1-(3,5-difluorobenzilo)-3-{[(1S)-7-etilo-1,2,3,4-tetrahidronaftaleno-1-il]amino}-2-hidroxipropilo)amino]-4-ácido oxobutanoico. A una solución de 3-amino-4-(3,5-difluorofenil)-1-(7-etilo1,2,3,4-tetrahidro-naftaleno-1-ilamino)-butano-2-ol (0.240g, 0.64 mmol), trietilamina (0.268 mL, 1.92 mmol), y cloroformo (3 mL) se le agregó anhídrido succínico (0.064 g, 0.64 mmol) y la reacción fue mezclada durante la noche a 60°C. La reacción fue lavada con 1N HCl, secada en $MgSO_4$, filtrada, concentrada *in vacuo* para dar el producto deseado (100 mg). Purificada via prep-HPLC. ^1H NMR (400 MHz, CD_3OD) δ 1.27 (t, J = 8 Hz, 3 H), 1.88 (m, 1 H), 2.04 (m, 1 H), 2.25 (m, 3 H), 2.48 (m, 2 H), 2.70 (m, 4 H), 2.81 (m, 1 H), 2.93 (m, 1 H), 3.12 (dd, J = 8, 13 Hz, 1 H), 3.32 (m, 2 H), 3.87 (m, 1 H), 4.04 (m, 1 H), 4.51

430

(s, 1 H), 6.80 (m, 1 H), 6.86 (d, J = 6 Hz, 2 H), 7.18 (dd, J = 8, 19 Hz, 2 H), 7.32 (s, 1 H); OAMS: ES+ 474.9, ES- 472.9.

Ejemplo 69: Preparación de 1-(3-isopropilofenil) hidrocloruro de ciclohexanamina



Paso 1. Preparación de 1-(3-isopropilofenil)ciclohexanol 1

A 1.2 g (50 mmol) de *turnings* de magnesio en 15 mL de THF seco, se le agrega un pequeño cristal de *iodo* seguido por 40 □L de dibrometano. Esta mezcla se coloca en un baño de agua a 50 °C y se agregan por goteo 3-isopropilobromobenceno (5.0 g, 25 mmol) en 15 mL de tetrahidrofuran seco (THF) durante 20 min, mientras la temperatura del baño se eleva a 70 °C. La mezcla se revuelve y se mantiene en reflujo durante 40 minutos adicionales. La solución se enfría en un baño de agua helada y se agrega por goteo ciclohexanona (2.0 mL, 19 mmol) en 10 mL de THF seco durante 15 min. Se retira el baño de hielo y la mezcla se deja calentar a temperatura ambiente durante 1 hora. La solución se decanta en NH_4Cl acuosa saturada y se combina con un baño de éter del magnesio residual. La fase orgánica se lava dos veces más con NH_4Cl acuosa secada sobre Na_2SO_4 anhídrica, filtrada y concentrada. La cromatografía en gel de sílice, eluida con un 10% de acetato etílico en heptano, propicia 2.7 g (12 mmol, 60%) de 1-(3-isopropilfenil)ciclohexanol 1 como aceite: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 1 H), 7.3 (m, 2 H), 7.12 (m, 1 H), 2.92 (m, 1 H), 1.84-1.54 (m, 10 H), 1.26 (d, J = 7 Hz, 6 H).

Paso 2. Preparación de 1-(3-isopropilfenil)ciclohexilazida (2).

431

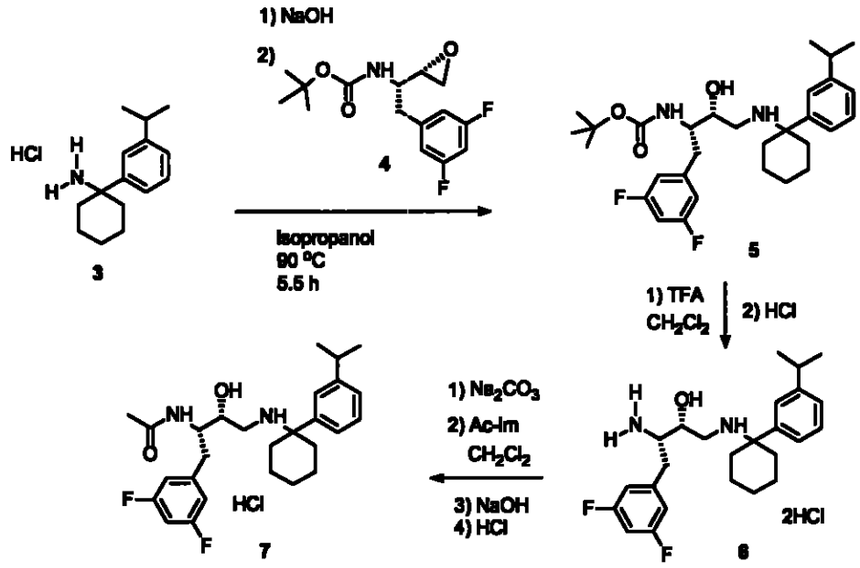
A 3.20 g (14.7 mmol) de1-(3-isopropilfenil)ciclohexanol 1 en 60 mL of CH_2Cl_2 bajo nitrógeno se agregan 2.10g (32.3 mmol) de *azida* de sodio. La suspensión mezclada se enfría a -5°C y se agrega por goteo durante 1 hora una solución de ácido trifluoracético (9.0 mL, 120 mmol) en 35 mL de diclorometano. La suspensión resultante se mezcla a 0 °C durante una hora más. A la mezcla fría, vigorosamente revuelta, se le agregan por goteo 10 mL de agua, seguida por una adición, también por goteo, de una mezcla de 10 mL de agua y 10 mL de hidróxido de amonio concentrado. Después de 30 min la mezcla se vierte en un recipiente separatorio que contiene 350 mL de una mezcla 1:1 de heptano y acetato etílico, y 100 mL de agua. La fase orgánica se lava con una porción adicional de agua, seguida sucesivamente por 1 N KH_2PO_4, agua, y salmuera. Luego se seca sobre Na_2SO_4 anhídrica, se filtra y se concentra para propiciar 3.6 g (14.7 mmol, 100%) de 2 como un aceite amarillo pálido: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 2 H), 7.25 (m, 1 H), 7.16 (m, 1 H), 2.92 (m, 1 H), 2.01 (m, 2 H), 1.83 (m, 2 H), 1.73-1.64 (m, 5 H), 1.3 (m, 1 H), 1.26 (d, J = 7 Hz, 6 H).

Paso 3. Preparación de 1-(3-isopropilfenil)hidrocloruro de ciclohexanamina 3.
A 1-(3-isopropilfenil)*ciclohexilazida* 2 (2.7 g, 11 mmol) en 200 mL de etanol se le agregan 20 mL de ácido acético glacial y 0.54 g de 10% paladio en carbono. La mezcla se evacua y coloca bajo 16 psi de hidrógeno, sacudiéndola durante 2.5 h. La mezcla de reacción se filtra, el catalítico se lava con etano y los solventes se quitan *in vacuo*. El ácido acético residual se quita al capturar el residuo con tolueno. La sal de acetato se disuelve en acetato etílico y se agrega 1 N NaOH. La fase orgánica se lava con otra 1 N NaOH y luego con agua, se seca con Na_2SO_4, se filtra y se concentra. El residuo se disuelve en éter y se agrega HCl etéreo (HCl concentrado en éter que ha sido almacenado en $MgSO_4$) para propiciar un sólido blanco. Este se filtra, se lava con éter, se recoge como una solución in diclorometano y se concentra para propiciar 2.1 g (8.3 mmol, 75%) de hidrocloruro 3 como un sólido blanco: ^{1}H NMR ($CDCl_3$) δ 8.42 (br s, 3 H), 7.43 (m, 2 H), 7.25 (m, 1 H), 7.15 (m, 1 H), 2.92 (hept, J = 7 Hz, 1 H), 2.26 (m, 2 H), 2.00 (m, 2 H), 1.69 (m, 2 H), 1.45-1.3 (m, 4 H), 1.24 (d, J = 7 Hz, 6 H); IR (reflejo difuso) 2944, 2864, 2766, 2707, 2490, 2447, 2411, 2368, 2052, 1599, 1522, 1455, 1357, 796, 704 cm -1. MS (EI)m/z(intensidad *rel*) 217 (M+,26), 200 (13), 175 (18), 174 (99), 157 (15), 146 (23), 132 (56), 131 (11), 130 (16), 129 (18). HRMS (ESI) calculado para $C_{15}H_{23}N+H_1$ 218.1909, encontrado 218.1910. Análisis calculado para $C_{15}H_{23}N.HCl$: C, 70.98; H, 9.53; N, 5.52; Cl, 13.97. Encontrado: C, 70.98; H, 9.38; N, 5.49.

EJEMPLO 70: Preparación de N-((1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexyl]amino}propilo) hidrocloruro de acetamida 7

432

Scheme 2



Paso 1. Preparación de tert-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[1-(3-isopropilofenil)ciclohexyl]amino}propilcarbamato(5).

1-(3-isopropilfenil) hidrocloruro de ciclohexanamina 3 (2.1 g, 8.3 mmol) se sacuden con 1 N NaOH acuosa y acetato etílico. Las capas se separan y la fase orgánica se lava secuencialmente con NaOH acuosa y luego con 1N $NaHCO_3$. La capa orgánica se seca con Na_2SO_4, se filtra, y se concentra para propiciar un rendimiento cuantitativo (1.8 g) del amino libre como aceite. El ejemplo 134 (4, 1.5 g, 5.0 mmol) se combina con el amino libre en 35 mL de alcohol isopropilo, y la mezcla se calienta a reflujo durante 5.5 h, bajo nitrógeno. La mezcla se enfría y concentra *in vacuo*. El residuo resultante se disuelve en 250 mL de éter etílico, que se lava cuatro veces con porciones de 30 mL de 10% HCl acuosa para quitar gran parte del amino excedente. 3. La fase del éter se lava entonces dos veces con 1N $NaHCO_3$, una vez con salmuera, se seca con Na_2SO_4, se filtra, y se concentra. El concentrado se cromatografica con gel de sílice, diluyendo con 4% to 6% metanol (que contiene 2% NH_4OH) en CH_2Cl_2 para propiciar 1.98g (3.8 mmol, 77%) de 5 como un aceite viscoso: ^1H NMR ($CDCl_3$) δ 7.28-7.21 (m, 3 H), 7.09 (m, 1 H), 6.69 (m, 2 H), 6.62 (m, 1 H), 4.68 (d, J = 10 Hz, 1 H), 3.74 (m, 1 H), 3.47 (m, 1 H), 2.93-2.86 (m, 2 H), 2.67

433

(dd, J = 8, 14 Hz, 1 H), 2.32 (m, 2 H), 1.88 (m, 4 H), 1.63-1.52 (m, 5 H), 1.36 (s +m, 10 H), 1.24 (d, J = 7 Hz, 6 H); MS (CI) m/z 517.4 (MH+).

Paso 2. Preparación de (2R,3S)-3-amino-4-(3,5-difluorfenil)-1-{[1-(3-isopropilfenil)ciclohexyl] amino}butano-2-ol dihidrocloruro 6

A 1.98 g (3.8 mmol) de tert-butilo (1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil] amino}propilcarbamato 5 en 15 mL de CH_2Cl_2 se le agregan 6.5 mL de ácido trifluoroacético. La mezcla se revuelve bajo una atmósfera de nitrógeno durante 1 h y luego se concentra. El residuo resultante se mezcla en acetato etílico y se lava dos veces con Na_2CO_3 al 10% y una vez con 1 N $NaHCO_3$. La capa orgánica se seca con Na_2SO_4 anhidrico, se filtra y se concentra para propiciar 1.6 g (cuantitativo) de un aceite amarillo pálido (base libre de 6), que generalmente se traslada al paso siguiente sin caracterización. El aceite amarillo se puede disolver en éter y tratar con HCl etéreo para precipitar (dihidrocloruro 6 como un sólido blanco luego de trituración con éter: ^{1}H NMR ($CDCl_3$ +CD_3OD drop) δ 7.55 (s, 1 H), 7.45-7.15 (m, 3 H), 6.85 (m, 2 H), 6.75 (m, 1 H), 4.4 (d, J = 9.5 Hz, 1 H), 3.82 (m, 1 H), 2.97 (m, 2 H), 2.81 (dd, J = 8, 14 Hz, 1 H), 2.65 (m, 2 H), 2.5 (oscurecido por el agua) 2.26 (m, 1 H), 2.13 (m, 2 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.45-1.25 (m, 3 H), 1.28 (d, J = 7 Hz, 6 H); MS (CI) m/z 417.3 (MH+).

Paso 3. Preparación de N-((1S,2R)-1-(3,5-difluorobenzilo)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexyl]amino}propilo)hidrocloruro de acetamida 7

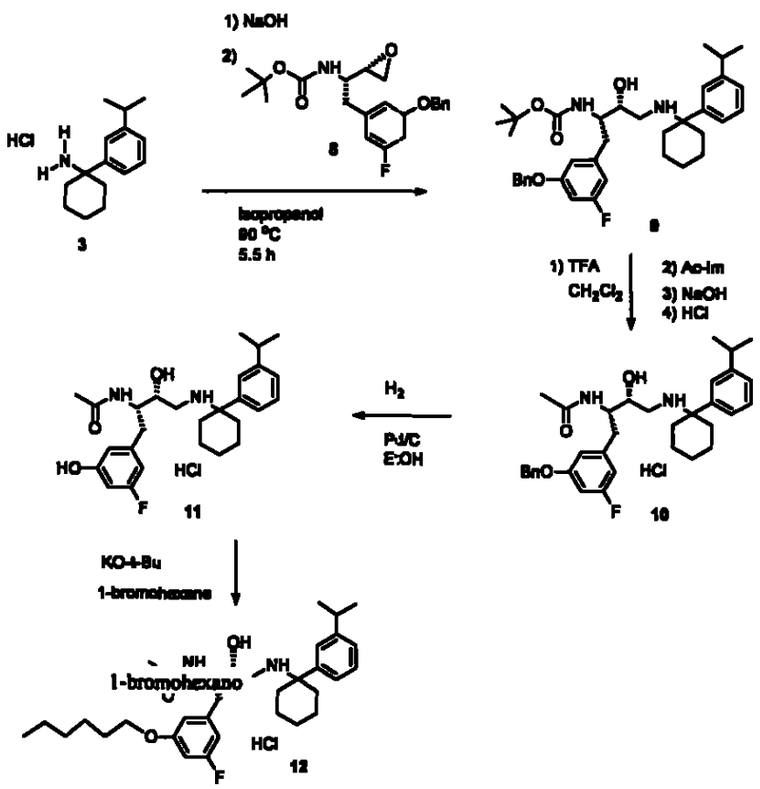
La base libre de (2R,3S)-3-amino-4-(3,5-difluorofenil) -1-{[1-(3-isopropilfenil) ciclohexyl]amino}butano-2-ol dihidrocloruro 6 (1.6 g, 3.8 mmol) se disuelve en 20 mL of CH_2Cl_2 bajo nitrógeno, y 0.87 g (7.9 mmol) de imidazola acetílica se agrega revolviendo. Luego de 15 min., se agregan 30 mL de metanol, seguidos por 15 mL de 1 N NaOH para saponificar el éster que se forma junto con la amida. Se quita el CH_2Cl_2 *in vacuo*, y la mezcla se neutraliza con 1N KH_2PO_4. El producto se extrae en acetato etílico y la fase orgánica se lava con agua, con 1 N $NaHCO_3$, y con salmuera. La solución se seca con Na_2SO_4, se filtra y se concentra en un aceite, que es cromatografiado con gel de sílica, diluyendo con metanol al 5%-7% (que contiene 1% de NH_4OH) en CH_2Cl_2. Las fracciones que contienen producto se filtran, concentradas, disueltas en un pequeño volumen de etano, y se acidifican con 0.6 N HCl en éter seco. La concentración a partir de esta mezcla solvente propicia un material símil gel. Este puede disolverse en etano y en acetato etílico, y concentrado a 1.65 g (3.3 mmol, 87%) de un sólido blanco. Este sólido se tritura con acetato etílico para quitar un licor madre color amarillo pálido, dejando el hidrocloruro 7 como un sólido blanco: ^{1}H NMR ($CDCl_3$ + gota de CD_3OD) δ 7.44 (s, 1 H), 7.37 (m, 2 H), 7.29

434

(m, 1 H), 6.70 (m, 2 H), 6.62 (m, 1 H), 3.94 (m, 1 H), 3.87 (m, 1 H), 3.0-2.94 (m, 2 H), 2.64 (m, 4 H), 2.36 (m, 1 H), 2.09 (m, 2 H), 1.84 (s, 3 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.5-1.3 (m, 3 H), 1.27 (d, J = 7 Hz, 6 H); IR (reflejo difuso) 3343, 3254, 2958, 2937, 2866, 2497, 2442, 2377, 1660, 1628, 1598, 1553, 1460, 1116, cm $^{-1}$. MS (EI) m/z (intensidad relativa) 458 (M+, 7), 415 (20), 230 (35), 202 (18), 201 (99), 200 (26), 159 (35), 157 (32), 133 (41), 129 (28), 117 (17). HRMS (ESI) calculado para $C_{27}H_{36}N_2O_2F_2$+H, 459.2823, encontrado 459.2837. Análisis calculado para $C_{27}H_{36}F_2N_2O_2$.HCl: C, 65.51; H, 7.53; N, 5.66; Cl, 7.16; F, 7.68. Encontrado: C, 65.19; H, 7.70; N, 5.67. Encontrado; Cl, 7.08.

Ejemplo 71: Preparación de N-((1S,2R)-1-(3-(hexiloxy)-5-fluorobenzil)-2-hidroxi-3-{[1-(3-isopropilfenil)cyclohexyl]amino}propil)hidrocloruro de acetamida 12

Esquema 3



435

Paso 1. Preparación de tert-butilo (1S,2R)-1-(3-(benziloxi)-5-fluorobenzil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexyl]amino}propilcarbamato (9).

Siguiendo en esencia el procedimiento descrito en el Paso 1 de EJEMPLO 70, la base libre de 1-(3-isopropilfenil) hidrocloruro de ciclohexanamina 3 (3.9 mmol) reacciona con tert-butilo (1S)-2-[3-(benziloxy)-5-fluorofenil]-1-[(2S)-oxiran-2-il]etilcarbamato (8, 0.80 g, 2 mmol) en 20 mL de alcohol de isopropilo a reflujo durante la noche. Luego del trabajo de lavado y secado, y la cromatografía en gel de sílice, diluyendo con metanol al 4% (que contiene 2% NH_4OH) en CH_2Cl_2, 9 se obtiene una jalea incolora (0.92 g, 1.5 mmol, 74%): MS (CI) m/z 605.5 (MH+).

Paso 2 Preparación de N-((1S,2R)-1-(3-(benziloxi)-5-fluorobenzil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexyl]amino}propil)hidrocloruro de acetamida (10).

Siguiendo en esencia los procedimientos de los pasos 2 y 3 de EJEMPLO 70, el compuesto 9 (0.92 g, 1.5 mmol) se desprotege con ácido trifluoroacético y se reacciona con un exceso de imidazola acetílica. Luego se somete a una hidrólisis alcalina para propiciar, luego del lavado y secado y la cromatografía en gel de sílice, diluyendo con metanol al 7%-10 % (que contiene 1% NH_4OH) en CH_2Cl_2, y conversión a sal HCl, 0.75g (1.3 mmol, 85%) de hidrocloruro 10 como un blanco sólido ^{1}H NMR ($CDCl_3$+gota de CD_3OD) δ 7.46-7.25 (m, 9 H), 6.26 (s, 1 H), 6.53-6.47 (m, 2 H), 5.00 (s, 2 H), 4.01 (m, 1 H), 3.88 (m, 1 H), 2,98-2,89 (m, 2 H), 2.68-2.62 (m, 4 H), 2.3 (m, 1H, oscurecido por agua), 2.14 (m, 2 H), 1.88 (s, 3 H), 1.78 (m, 2 H), 1.58 (m, 1 H), 1.5-1.3 (m, 3 H), 1.26 (d, J = 7 Hz, 6 H); MS (CI) m/z 547.5 (MH+).

Paso 3. Preparación de N-((1S,2R)-1-(3-hidroxi-5-fluorobenzil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)hidrocloruro de acetamida 11.

A una solución de compuesto 10 (0.70 g, 1.2 mmol) in 70 mL de etanol en una botella Parr se le agregan 0.33 g de paladio en carbono al 10%. La mezcla se coloca bajo 20 psi de hidrógeno y se sacude durante 21 h. La mezcla se filtra y el catalítico se lava con etanol. La concentración *in vacuo* propicia un aceite incoloro, que se trata con HCl etéreo para dar un rendimiento cuantitativo de hidrocloruro 11 como un sólido blanco: ^{1}H NMR ($CDCl_3$ +CD_3OD drop) δ 7.44 (s, 1 H), 7.37 (m, 2 H), 7.28 (m, 1 H), 6.59 (s, 1 H), 6.40 (m, 1 H), 6.31 (m, 1 H), 4.0 (m, 1 H), 3.79 (m, 1 H), 2.95 (m, 2 H), 2.63 (m, 4 H), 2.44 (m, 1 H), 2.05 (m, 2 H), 1.90 (s, 3 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.5-1.3 (m, 3 H), 1.26 (d, J = 7 Hz, 6 H);
MS (CI) m/z 457.4 (MH+).

436

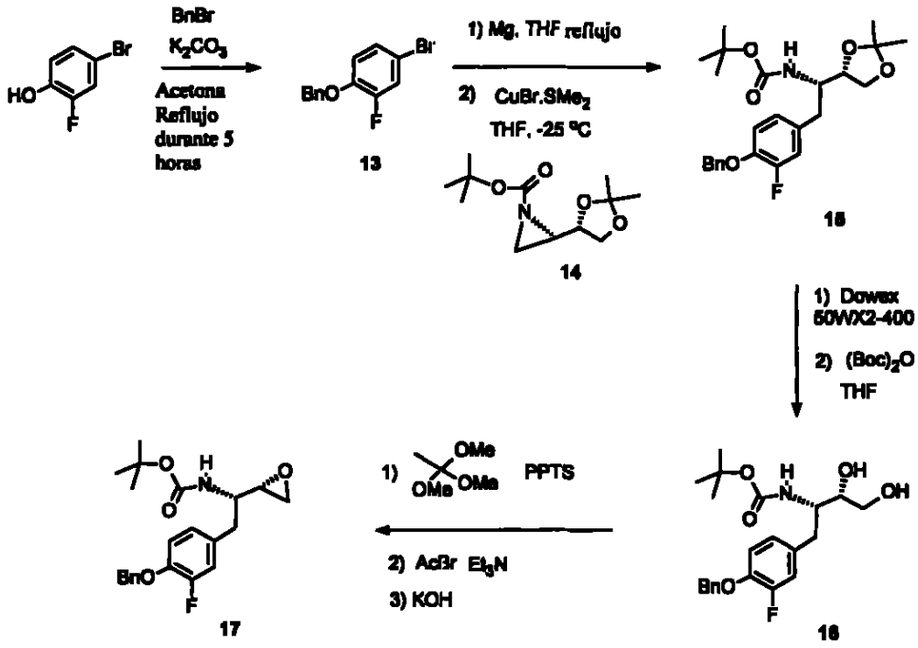
Paso 4. Preparación de N-((1S,2R)-1-(3-(hexiloxi)-5-fluorobenzil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil) hidrocloruro de acetamida 12

A 0.40 mmol de N-((1S,2R)-1-(3-hidroxi-5-fluorobenzil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil] amino}propil) hidrocloruro de acetamida 11 en 3 mL de acetona se agregan 0.29 mL (2.1 mmol) de 1-bromohexano. La mezcla se calienta a reflujo, y se agrega 0.6 mL de una solución 1 M de potasio t-butóxido en THF (0.6 mmol). Luego de 1.2 h la mezcla se enfría y se agrega 1 N KH_2PO_4 acuosa y acetato etílico. La fase orgánica se lava dos veces con 1 N $NaHCO_3$ y una con salmuera, se seca con Na_2SO_4, y se concentra. Se la somete a una cromatografía con gel de sílice, diluyendo con metanol al 7% (que contiene 1% de NH_4OH) en CH_2Cl_2, lo que propicia un aceite incoloro. El tratamiento con HCl etéreo produce 147 mg (0.25 mmol, 64%) de hidrocloruro 12 como un sólido blanco: ^1H NMR ($CDCl_3$ + gota de CD_3OD) δ 7.45 (s, 1 H), 7.37 (m, 2 H), 7.27 (m, 1 H), 6.50 (s, 1 H), 6.43 (m, 2 H), 3.98 (m, 1 H), 3.88 (m + t, J = 6.5 Hz, 3 H), 2.93 (m, 2 H), 2.63 (m, 4 H), 2.38 (m, 1 H), 2.09 (m, 2 H), 1.89 (s, 3 H), 1.75 (m, 4 H), 1.59 (m, 1 H), 1.43-1.32 (m, 10 H), 1.27 (d, J = 7 Hz, 6 H), 0.90 (t, J = 7 Hz, 3 H); MS (Cl) m/z 541.5 (MH+).

Ejemplo 72: Preparación de tert-butil (1S)-2-[4-(benciloxi-3 fluorofenil]-1-[(2S)-oxiran-2-il]etilcarbamato 17

437

Esquema 4



Step 1. Preparación de 1-Benziloxi-2-fluoro-4-bromobenceno 13.

A una suspensión agitada de K_2CO_3 pulverizado (49 g, 350 mmol) en 250 mL de acetona se agregan 6,5 mL (11,3 g, 59 mmol) de 2-fluoro-4-bromofenol y 7 mL (10 g, 59 mmol) de bromuro de bencilo. La mezcla va a reflujo bajo nitrógeno durante 5 hora. Se enfría y filtra, lavándose el K_2CO_3 residual con acetona. La remoción del solvente deja 17 g de un sólido blancuzco. Esto se tritura dos veces con hexanos, se disuelve nuevamente en 250 mL de CH_2Cl_2 y se lava sucesivamente con Na_2CO_3 al 10%, agua y salmuera. La fase orgánica se seca sobre Na_2SO_4 y trata con carbón vegetal descolorante. La filtración y evaporación produce 1-benciloxi-2-fluoro-4-bromobenceno 13 (13,7g, 49 mmol, 83%) como un aceite incoloro que se cristaliza hasta formar un sólido de color blanco: ^{1}H NMR ($CDCl_3$) δ 7,43-7,33 (m, 5 H), 7,24 (dd, J = 2,3, 10 Hz, 1 H), 7,14 (dt, J = 2, 8,7 Hz, 1 H), 6,86 (t, J = 8,7 Hz, 1 H), 5,12 (s, 2 H).

438

Paso 2. Preparación de tert-butil (1S)-2-(4-(benciloxi-3-fluorofenil)-1-[(4S)-2,2-dimetilo-1,3-dioxolano-4-il]etilcarbamato (15).

Una solución de 1-benciloxi-2-fluoro-4-bromobenceno 13 (7,0 g, 25 mmol) en 20 mL de THF seco se agrega, gota a gota, durante 20 min. a 1,22 g (50 mmol) de turninga de magnesio en 10 mL de THF a reflujo bajo nitrógeno y la mezcla se somete a reflujo durante otros 25 min. Para formar el reactivo de Grignard. La solución de Grignard se enfría y agrega por sonda a una suspensión de un complejo de CuBr-dimetilsulfido (0,52 g, 2,5 mmol) en 15 mL de THF seco a –25 °C. La suspensión de color marrón se agita a –25 °C durante 20 min.; después se agrega una solución de tert-butil (2R)-2-[(4S)-2,2-dimetilo-1,3-dioxolan-4-il]aziridina-1-carboxilato 14 (3,4 g, 14 mmol) en 15 mL de THF, gota a gota, durante 5 minutos. La mezcla se deja calentar gradualmente a la temperatura ambiente durante 3 horas. Se agrega NH_4Cl acuoso saturado y éter de etilo y la fase orgánica se lava con dos porciones más de NH_4Cl saturado y una con salmuera. La solución se seca sobre Na_2SO_4 y trata con carbono descolorante. La filtración y concentración produce un sólido de color amarillo que se tritura dos veces con éter/heptano para proporcionar 5,4 g (12 mmol, 86%) de 15 como un sólido color crema: MS (CI) m/z 468,3 (MNa+), 446,3 (MH+).

Paso 3. Preparación de tert-butil (1S,2S)-1-[4-(benciloxi-3-fluorobencil]-2,3-dihidroxipropilcarbamato 16

A una solución de crudo (sólido y licor madre combinados) tert-butil (1S)-2-(4-(benciloxi-3-fluorofenil)-1-[(4S)-2,2-dimetilo-1,3-dioxolan-4-il]etilcarbamato 15 (máximo, 14 mmol) en 90 mL de metanol se agregan 12 g de Dowex 50WX2-400, que se han lavado extensivamente con agua, metanol y CH_2Cl_2 y secado al aire. La mezcla se calienta a 50 °C y agita durante 2 horas. Se filtra, lava primero con metanol y una mezcla de metanol y CH_2Cl_2 a una relación de 1:1. Después, el receptor cambia y se realiza la elución del producto a partir de la resina con metanol: CH_2Cl_2 con contenido de 10% de NH_4OH. El filtrado se concentra para producir 2,7 g de un sólido de color blanco. Este sólido se disuelve en 60 mL de THF seco bajo nitrógeno, enfriado a 0 °C, y se agregan 2,0 g (9,2 mmol) de di-tert-butildicarbonato. Se remueve el baño de hielo y la mezcla se agita a la temperatura ambiente durante 18 horas. Se concentra y cromatografía sobre sílica gel, con elución a una relación de 49:49:2 a 58:38:4 de acetato de etilo:heptano:metanol, para proporcionar 3,0 g (7,4 mmol, 53%, dos pasos) de 16 como un sólido de color blanco: ^1H NMR ($CDCl_3$) δ 7,45-7,30 (m, 5 H), 7,01-6,88 (m, 3 H), 5,12 (s, 2 H), 4,52 (d, J = 9 Hz, 1 H),

439 440

3,78 (m, 1 H), 3,62 (m, 2 H), 3,32 (m, 2 H), 3,02 (dd, J = 4, 14 Hz, 1 H), 2,82 (m, 2 H), 1,39 (s, 9 H); MS (CI) m/z 428,2 (MNa+), 406,3 (MH+).

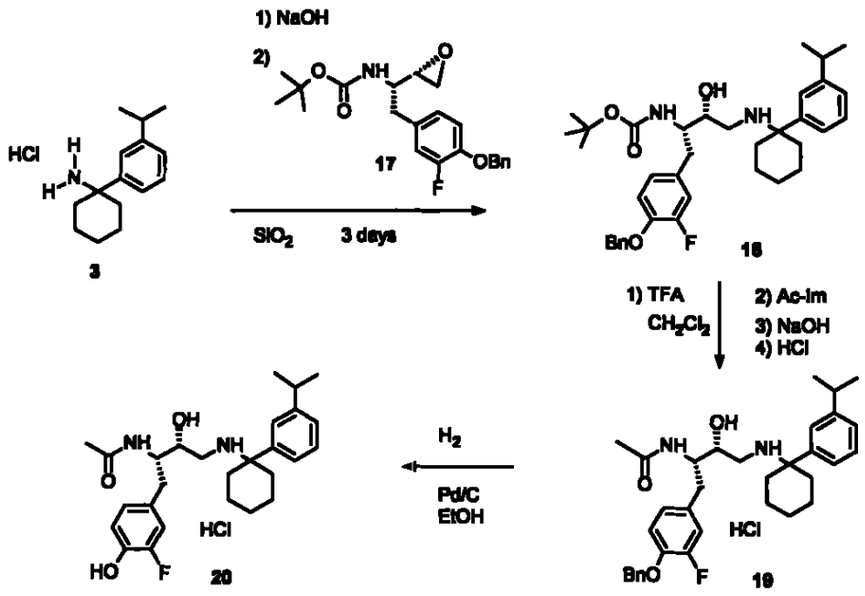
Paso 4. Preparación de tert-butil (1S)-2-[4-(benciloxi-3 fluorofenil]-1-[(2S)-oxiran-2-il]etilcarbamato (17)

Se agrega ortoacetato de trimetilo (0,94 mL, 7,4 mmol) a una suspensión de tert-butil (1S,2S)-1-[4-(benciloxi-3-fluorobencil]-2,3-dihidroxipropilcarbamato 16 (2,9 g, 7,2 mmol) en 30 mL de CH_2Cl_2 agitados bajo nitrógeno. Se agrega Piridino *p*-toluenosulfonato (18 mg, 0,07 mmol) y la solución de color amarillo pálido resultante se agita durante 30 minutos, para después concentrarla en un sólido de color blanco. Este sólido se disuelve en 30 mL de CH_2Cl_2, se agrega trietilamina (0,10 mL, 0,72 mmol) y la mezcla, bajo nitrógeno, se enfría en un baño de hielo. El bromuro de acetilo recién destilado (0,55 mL, 7,4 mmol) se agrega, gota a gota, durante 3 a 4 min. con agitación. Después de una hora, se remueve el baño de hielo y se agregan 1 N $NaHCO_3$ acuoso y CH_2Cl_2. La fase acuosa se extrae con más CH_2Cl_2 y las fases orgánicas combinadas se secan sobre $MgSO_4$ y concentran hasta formar un sólido de color blanco. Este sólido queda suspendido en 25 mL de metanol y 6 mL de THF y se enfría en un baño de hielo bajo nitrógeno. El KOH pulverizado (0,60 g, 11 mmol) en 6 mL de metanol se agrega todo de una vez. Después de 15 min., se remueve el baño de hielo y se deja que la mezcla llegue a la temperatura ambiente durante 70 minutos. La mezcla se concentra y absorbe en el acetato de etilo y 1N KH_2PO_4 acuoso. La fase orgánica se lava con N $NaHCO_3$ y, después, con salmuera, se seca sobre Na_2SO_4 y se concentra. La cromatografía sobre sílica gel, con elución con acetato de etilo al 20% y CH_2Cl_2 del 5% al 10% en heptano proporciona 2,0 g (5,2 mmol, 72%) de 17 bajo la forma de un sólido de color blanco: ^{1}H NMR ($CDCl_3$) δ 7,45-7,30 (m, 5 H), 6,99-6,86 (m, 3 H), 5,12 (s, 2 H), 4,43 (br, 1 H), 3,63 (br, 1 H), 2,90 (m, 2 H), 2,79 (m, 2 H), 2,74 (m, 1 H), 1,39 (s, 9 H); MS (CI) m/z 410,3 (MNa+), 388,3 (MH+).

EJEMPLO 73: Preparación de N-((1S,2R)-1-(3-fluoro-4-hidroxibencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil] amino}propil)hidrocloruro de acetamida 20

440

Esquema 5



Paso 1. Preparación de tert-butil (1S,2R)-1-(3-fluoro-4-(beniloxi)bencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propilcarbamato (18).

La base libre se obtiene de (270 mg, 1,24 mmol) de 1-(3-isopropilfenil) hidrocloruro de ciclohexanamina 3 se obtiene como un aceite incoloro por neutralización de la sal con 1N NaOH, extracción en acetato de etilo, secándose sobre Na_2SO_4 y concentración. Ésta se disuelve en 10 mL de CH_2Cl_2 y a ella se agrega tert-butil (1S)-2-[4-(benciloxi-3 fluorofenil]-1-[(2S)-oxiran-2-il]etilcarbamato 17 (280 mg, 0,73 mmol) y 1,25 g de sílica gel. El solvente se remueve en vacío y los reactantes sobre la sílica pueden asentarse a la temperatura ambiente durante tres días. Se realiza la elución de la mezcla del producto a partir de la sílica con metanol al 10% en CH_2Cl_2, concentrado y cromatografiado sobre sílica gel, con elución con metanol al 4% (con contenido de NH_4OH al 2%) en CH_2Cl_2 para proporcionar 18 (238 mg, 0,39 mmol, 54%) bajo la forma de un aceite incoloro: ^1H NMR ($CDCl_3$) δ 7,43-7,26 (m, 8 H), 7,12 (m, 1 H), 6,94-6,84 (m, 3 H), 5,09 (s, 2 H), 4,64 (d, J = 9 Hz, 1 H), 3,80 (br, 1 H), 3,31 (br, 1 H), 2,92-2,83 (m, 2 H), 2,7 (m, 1 H), 2,37 (m, 2 H), 2,0-1,95 (m, 4 H), 1,67-1,50 (m, 5 H), 1,35 (s+m, 10 H), 1,25 (d, J = 7 Hz, 6 H).

491

Paso 2. Preparación de N-((1S,2R)-1-(3-fluoro-4-(benciloxibencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)hidrocloruro de acetamida (19).

Siguiendo, en esencia, los procedimientos indicados en los Pasos 2 y 3 del EJEMPLO 70, el compuesto 18, (0,238 g, 0,39 mmol) según lo preparado en el paso 1, más arriba, es desprotegido con ácido trifluoroacético y se hace reaccionar con un exceso de imidazol de acetilo. A esto sigue la hidrólisis alcalina para proporcionar, después del workup y cromatografía sobre sílica gel, con elución con metanol al 7%-10 % (con contenido de NH_4OH al 1%) en CH_2Cl_2 y la conversión a la sal HCl, 0,19g (0,32 mmol, 75%) hidrocloruro 19 como un sólido de color blanco: MS (CI) m/z 547,5 (MH+).

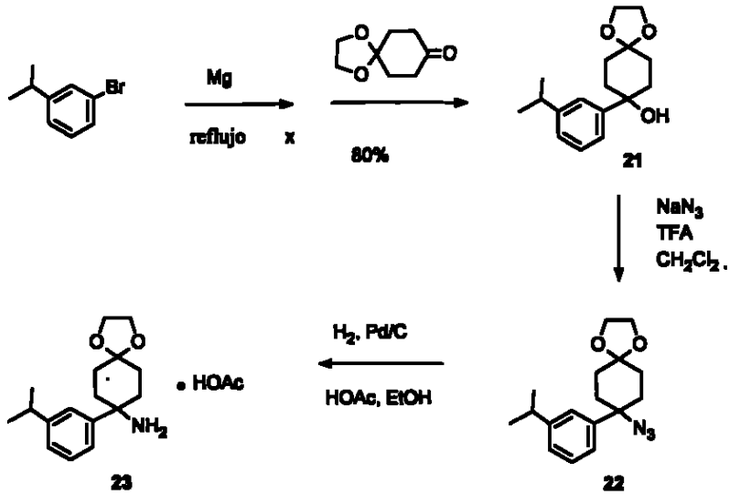
Paso 3. Preparación de N-((1S,2R)-1-(3-fluoro-4-hidroxibencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)hidrocloruro de acetamida 20

Siguiendo, en esencia, el procedimiento del EJEMPLO 71, Paso 3, el producto del paso 2, el compuesto 19, (0,19 g, 0,32 mmol) es desprotegido bajo una presión de 20 psi de H_2 en presencia de 54 mg de paladio al 10% sobre carbono en 3, 5 horas para proporcionar, después de la filtración, concentración y tratamiento con HCl etéreo, 20 (0,16 g, 0,32 mmol, cuant.) como un sólido de color blanco crema: ^{1}H NMR (gota de $CDCl_3$ + CD_3OD) δ 7,43-7,27 (m, 4 H), 6,86-6,77 (m, 3 H), 3,95 (br, 1 H), 3,8 (br, 1 H), 2,93 (m, 2 H), 2,6 (m, 4 H), 2,4 (m, 1 H), 2,06 (m, 2 H), 1,85 (s, 3 H), 1,8 (m, 2 H), 1,59 (m, 1 H), 1,5-1,3 (m, 3 H), 1,27 (d, J = 7 Hz, 6 H); IR (reflectancia difusa) 3251, 3113, 3087, 3061, 3053, 3028, 2956, 2941, 2865, 2810, 1645, 1596, 1520, 1446, 1294 cm -1. MS (CI) m/z (intensidad relativa) 457 (MH+,99), 459 (5), 458 (25), 457 (99), 439 (3), 257 (7), 218 (5), 202 (3), 201 (9), 96 (4), 77 (3). HRMS (ESI) calculado para $C_{27}H_{37}N_2O_3F$+H_1 457,2866, hallados 457.2855. Anál. calculado para $C_{27}H_{37}FN_2O_3$.HCl.1,5 H_2O: C, 62,35; H, 7,95; N, 5,39; Hallados: C, 62,63; H, 7,76; N, 5,47.

EJEMPLO 74: Preparación de 8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-acetato de amina 23.

442

Esquema 6



Paso 1. Preparación de 8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-alcohol (21)

Siguiendo, en esencia, el procedimiento descrito en el EJEMPLO 72, Paso 2, el reactivo de Grignard formado a partir de 3-bromoisopropilbenceno (25 mmol) se hace reaccionar con 1,4-ciclohexanediona, cetal monoetileno (3,9 g, 25 mmol) para proporcionar, después de la cromatografía sobre sílica gel, con elución con acetato de etilo del 20% al 30% en heptano, alcohol 21 (5,6 g, 20 mmol, 80%) como un aceite incoloro que se cristaliza para formar un sólido de color blanco al enfriarse: ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 7,33 (m, 1 H), 7,28 (t, J = 7,5 Hz, 1 H), 7,13 (d, J = 7,5 Hz, 1 H), 4,0 (m, 4 H), 2,91 (hept, J = 7 Hz, 1 H), 2,15 (m, 4 H), 1,82 (br d, J = 11,5 Hz, 2 H), 1,70 (br d, J = 11,5 Hz, 2 H), 1,25 (d, J = 7 Hz, 6 H); MS (CI) m/z 259,2 (M-OH).

Paso 2. Preparación de 8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-azida (22).

Siguiendo, en esencia, el procedimiento descrito en el EJEMPLO 69, Paso 2, 8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-alcohol 21 (5,5 g, 20 mmol) se hace reaccionar con azida sódica (2,9 g, 45 mmol) y ácido trifluoroacético (TFA, 13 mL, 170 mmol) en 120 mL de CH_2Cl_2 a 0 °C, para permitir la agitación de la reacción durante 2 horas después del agregado, gota a gota, de ácido trifluoroacético. La reacción se apaga por el agregado, gota a gota, de 18 mL de NH_4OH concentrado.

La mezcla se absorbe en agua, acetato de etilo y heptano y la fase orgánica se lava tres veces más con agua y una vez con salmuera. La solución se seca (Na_2SO_4), filtra, concentra y cromatografía sobre sílica gel, con elución con acetona al 3% en heptano. La concentración de las fracciones que contienen producto proporciona 2,2 g (7,3 mmol, 36%) de 22 bajo la forma de un aceite incoloro: ^{1}H NMR ($CDCl_3$) δ 7,33-7,26 (m, 3 H), 7,17 (m, 1 H), 3,98 (m, 4 H), 2,92 (hept, J = 7 Hz, 1 H), 2,2-2,12 (m, 2 H), 2,07-1,95 (m, 4 H), 1,72 (m, 2 H), 1,26 (d, J = 7 Hz, 6 H).

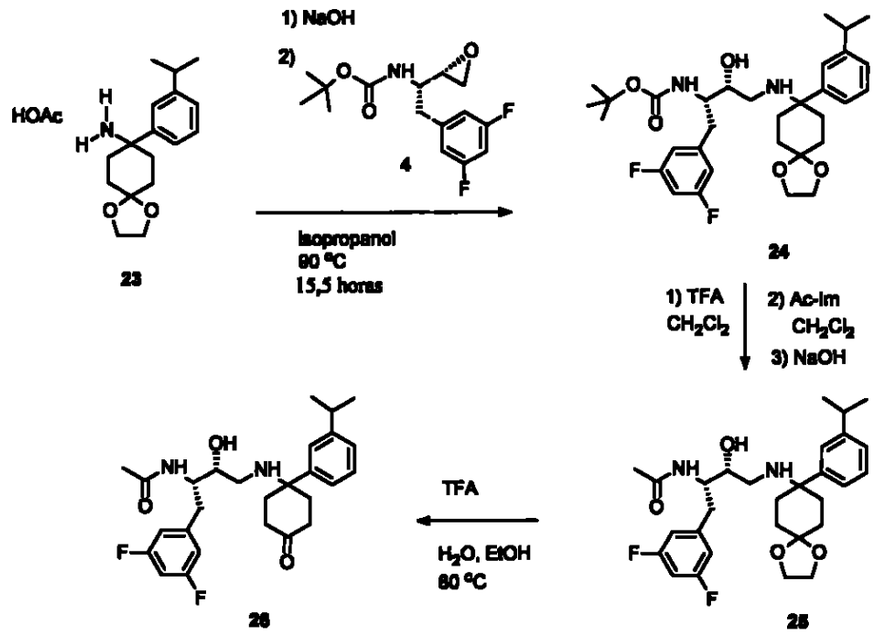
Paso 3. Preparación de 8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-acetato de amina 23.

Siguiendo, en esencia, el procedimiento descrito en el EJEMPLO 69, Paso 3, 2,2 g (7,3 mmol) de 8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-azida 22 en 200 mL de etanol se reduce bajo una presión de 16 psi de hidrógeno en presencia de 0,7 g de paladio al 10% sobre carbono durante 4,5 horas. La filtración y el retiro de solventes con azeotropo de tolueno proporciona un sólido de color blanco que se tritura con pentano para producir 2,14 g (6,4 mmol, 87%) de 23 bajo la forma de un sólido de color blanco: ^{1}H NMR ($CDCl_3$) δ 7,37-7,33 (m, 2 H), 7,30-7,26 (m, 1 H), 7,13 (d, J = 7,5 Hz, 1 H), 5,91 (br, 3 H), 3,96 (m, 4 H), 2,90 (hept., J = 7 Hz, 1 H), 2,32 (m, 2 H), 2,03 (s, 3 H), 2,0-1,85 (m, 4 H), 1,63 (m, 2 H), 1,25 (d, J = 7 Hz, 6 H); MS (CI) m/z 259,2 ($M-NH_2$).

EJEMPLO 75: Preparación de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexano-4-uno]amino}propil) acetamida 26

444

Esquema 7



Paso 1. Preparación de tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-amino}propilcarbamato (24)

Siguiendo, en esencia, el procedimiento del EJEMPLO 70, 8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-acetato de amina 23 (3,2 mmol) se neutraliza y hace reaccionar con el Ejemplo 134 (4, 0,6 g, 2,0 mmol) en isopropanol de reflujo (15 mL) durante 15,5 horas. La mezcla de reacción es concentrada y cromatografiada sobre sílica gel, con elución con metanol al 4% (con contenido de 2% de NH_4OH) en CH_2Cl_2 para separar el producto crudo del exceso de 8-(3-isopropilfenil) -1,4-dioxa-espiro[4.5]decano-8-amina. El producto crudo es, después, cromatografiado nuevamente sobre sílica gel, con elución con acetona del 10% al 20% en CH_2Cl_2 para proporcionar 0,600 g (1,04 mmol, 52%) de 24 bajo la forma de un aceite incoloro: ^{1}H NMR ($CDCl_3$) δ 7,27-7,20 (m, 3 H), 7,09 (d, J = 7 Hz, 1 H), 6,69 (m, 2 H), 6,63 (m, 1 H), 4,64 (d, J = 9 Hz, 1 H), 3,95 (m, 4 H), 3,72 (m, 1 H), 3,28 (m, 1 H), 2,88 (m, 2 H), 2,69 (dd, J = 8,5, 14 Hz, 1 H), 2,32 (m, 2 H), 2,15 (m, 2 H), 1,99-1,86 (m, 4 H), 1,63 (m, 2 H), 1,35 (s, 9 H), 1,24 (d, J = 7 Hz, 6 H); MS (Cl) m/z 575,4 (MH+)

445

Paso 2. Preparación de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-amino}propil)acetamida (25)

Siguiendo, en esencia, los procedimientos descritos en el EJEMPLO 70, Pasos 2 y 3, el tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-amino}propilcarbamato 24 (0,600 g, 1,04 mmol) es desprotegido, acetilado y saponificado para proporcionar, después de la cromatografía sobre sílica gel, con elución con acetona al 32,5% y metanol al 2,5% en CH_2Cl_2, acetamida 25 (335 mg, 0,65 mmol, 62%) como un sólido blando por concentración del éter de etilo: ^{1}H NMR ($CDCl_3$) δ 7,31-7,26 (m, 3 H), 7,15 (m, 1 H), 6,69-6,61 (m, 3 H), 5,9 (br, 1 H), 4,13 (m, 1 H), 3,95 (m, 4 H), 3,48 (m, 1 H), 2,92-2,83 (m, 2 H), 2,73 (dd, *J* = 8,5, 14 Hz, 1 H), 2,45-2,25 (m, 4 H), 2,10 (m, 2 H), 1,88 (s+m, 5 H), 1,62 (m, 2 H), 1,25 (d, *J* = 7 Hz, 6 H); MS (CI) m/z 517,4 (MH+)

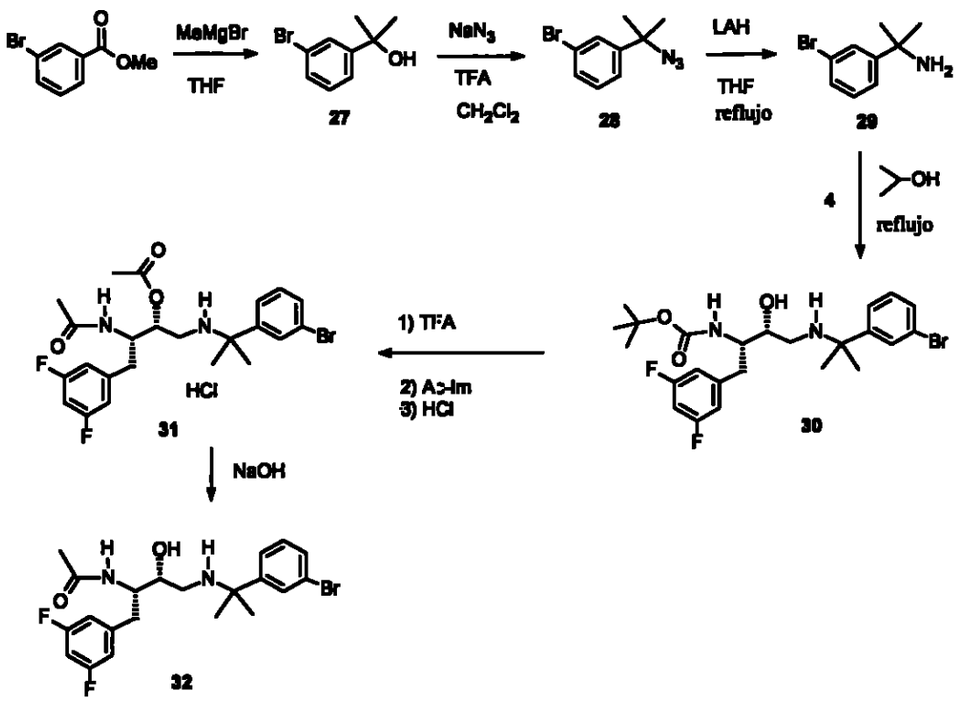
Paso 3. Preparación de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexano-4-one]amino}propil)acetamida 26

A N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{8-(3-isopropilfenil)-1,4-dioxa-espiro[4.5]decano-8-amino}propil) acetamida 25 (255 mg, 0,49 mmol) en 5 mL de etanol y 5 mL de agua se agregan 6 mL de ácido trifluoroacético y la mezcla va a reflujo durante 2 horas bajo nitrógeno. Se concentra y absorbe en Na_2CO_3 acuoso al 10% y acetato de etilo. La fase orgánica se lava dos veces más con Na_2CO_3 al 10% y, después, con salmuera. Se seca sobre Na_2SO_4 y concentra hasta formar un aceite incoloro. La evaporación en vacío del éter de etilo proporciona 26 (140 mg, 0,30 mmol, 60 %) bajo la forma de un sólido de color blanco: ^{1}H NMR ($CDCl_3$) δ 7,35-7,18 (m, 4 H), 6,71-6,64 (m, 3 H), 5,65 (br, 1 H), 4,12 (m, 1 H), 3,43 (m, 1 H), 2,95-2,90 (m, 2 H), 2,75 (dd, *J* = 8,5, 14 Hz, 1 H), 2,64 (m, 2 H), 2,4-2,25 (m, 8 H), 1,87 (s, 3 H), 1,25 (d, *J* = 7 Hz, 6 H); MS (CI) m/z 473,4 (MH+). El espectro LC-MS en el solvente de metal muestra una pequeña señal en 505,4 ($MH+CH_3OH$) debido a la formación hemicetal. Reflectancia difusa (IR) 3311, 2958, 1710, 1646, 1628, 1595, 1550, 1544, 1460, 1372, 1315, 1116, 983, 846, 707 cm -1. MS (EI)m/z(intensidad relativa) 472 (M+, 6), 472 (6), 417 (5), 416 (33), 415 (99), 398 (8), 397 (30), 327 (11), 244 (9), 215 (13), 214 (6). HRMS (ESI) calculado para $C_{27}H_{34}N_2O_3F_2+H_1$ 473,2615, hallados 473,2627. Anál. calculado para $C_{27}H_{34}F_2N_2O_3$+ 0,5 H_2O: C, 67,34; H, 7,33; N, 5,82; Halladod (av): C, 67,89; H, 7,32; N, 5,86.

446

EJEMPLO 76: Preparación de N-[(1S,2R)-3-{[1-(3-bromofenil)-1-metiletil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida 32

Esquema 8



Paso 1. Preparación de 2-(3-bromofenil)-2-propanol 27

A 75 mmol de bromuro de metilmagnesio en 25 mL de éter agitándose a 6 °C se agrega, gota a gota durante 10 minutos, una solución de metil-3-bromobenzoato (4,3 g, 20 mmol) en 25 mL de THF seco. Después, la mezcla se deja calentar a la temperatura ambiente y agitar durante 3,5 horas; a continuación, se enfría a 0°C y apaga por el agregado, gota a gota, de HCl al 10% acuoso. La mezcla acidificada se extrae dos veces con acetato de etilo y las fases orgánicas combinadas se lavan con 1 N $NaHCO_3$ y con salmuera. La solución se seca sobre Na_2SO_4, concentrada y cromatografiada sobre sílica gel, con elución con acetato de etilo al 15% en heptano para proporcionar 4,00 g (18,6 mmol, 93%) de 2-(3-bromofenil)-2-propanol 27 bajo la

447

forma de un aceite de color amarillo pálido: ^{1}H NMR ($CDCl_3$) δ 7,65 (t, J = 2 Hz, 1 H), 7,39 (m, 2 H), 7,20 (t, J = 8 Hz, 1 H), 1,78 (br s, 1 H), 1,57 (s, 6 H).

Paso. Preparación de 2-(3-bromofenil)-2-propilazida (28).

A una solución de 2-(3-bromofenil)-2-propanol 27 (4,00 g, 18,6 mmol) en 260 mL de CH_2Cl_2 bajo nitrógeno, se agregan 2,64 g (40 mmol) de azida sódica. La suspensión se enfría a 0°C y una solución de 12,2 mL (160 mmol) de ácido trifluoroacético (TFA) en 50 mL de CH_2Cl_2 se agrega, gota a gota, durante 75 min. La mezcla se agita a temperatura ambiente durante 4 horas; después, se enfría a 0°C y apaga por el agregado, gota a gota, de 25 mL de agua, seguido de la adición, gota a gota, de una solución de 8 mL de NH_4OH concentrado en 25 mL de agua. La fase acuosa básica se separa y lava con más CH_2Cl_2 y las fases orgánicas combinadas se lavan dos veces con agua y secan sobre Na_2SO_4. La concentración y cromatografía sobre sílica gel, con elución con heptano, proporciona 3,4 g (14 mmol, 76%) de 28 bajo la forma de un aceite incoloro:^{1}H NMR ($CDCl_3$) δ 7,.58 (t, J = 2 Hz, 1 H), 7,74-7,36 (m, 2 H), 7,24 (t, J = 8 Hz, 1 H), 1,62 (s, 6 H).

Paso 3. Preparación de 2-(3-bromofenil)-2-propilamina 29.

Se agrega, gota a gota, una solución de 2-(3-bromofenil)-2-propilazida 28 (3,4 g, 14 mmol) en 30 mL de THF seco durante 10 minutos a una lechada agitada de hidruro de aluminio-litio (0,80 g, 21 mmol) en 25 mL de THF bajo nitrógeno. A continuación, la mezcla se lleva a reflujo durante 50 min. La mezcla se enfría y apaga por el agregado secuencial de 0,8 mL de agua, 0,8 mL de NaOH al 15% y, después, 2,5 mL de agua. Después de dejar que la suspensión se agite durante 30 min. los sólidos se filtran para extraerlos y lavan con éter. El filtrado combinado se concentra y cromatografía sobre sílica gel, con elución con metanol al 6% (con contenido de NH_4OH al 1%) en CH_2Cl_2 para proporcionar 29 (7 mmol, 50%) bajo la forma de un aceite de color ámbar pálido: ^{1}H NMR ($CDCl_3$) δ 7,67 (t, J = 2 Hz, 1 H), 7,43 (m, 1 H), 7,35 (m, 1 H), 7,20 (t, J = 8 Hz, 1 H), 1,68 (br s, 2 H), 1,48 (s, 6 H).

Paso 4. Preparación de 2-(3-bromofenil)-2-hidrocloruro de propilamina

A 2-(3-bromofenil)-2-propilamina 29 en éter, se agrega HCl etéreo. La remoción del solvente proporciona un sólido de color tostado, que se disuelve en un pequeño volumen de etanol y diluye con acetato de etilo. Los cristales tostados que se forman se filtran para proporcionar 2-(3-

948

bromofenil)-2-hidrocloruro de propilamina :^{1}H NMR (gota de $CDCl_3$+ CD_3OD) δ 7,65 (n m, 1 H), 7,51 (app t, 2 H), 7,32 (m, 1 H), 1,77 (s, 6 H); MS (CI) m/z 214,0 (MH+)

Paso 5. Preparación de tert-butil (1S,2R)-3-{[1-(3-bromofenil)-1-metiletil] amino}-1-(3,5-difluorobencil)-2-hidroxipropilcarbamato 30

En 10 mL de isopropanol bajo nitrógeno, se combinan 2-(3-bromofenil)-2-propilamina 29 (0,47 g, 2,2 mmol) y el Ejemplo 134 (4, 0,31 g, 1,0 mmol) y la mezcla va a reflujo durante 44 horas. Se enfría, diluye con acetato de etilo y extrae tres veces con HCl al 10% para remover la mayoría del exceso de amina. La fase orgánica se lava con N $NaHCO_3$ y con salmuera, se seca sobre Na_2SO_4, filtra y concentra. La cromatografía sobre sílica gel, con elución con de 4% a 6% de metanol (con contenido de 1% de NH_4OH) en CH_2Cl_2 proporciona 365 mg (0,71 mmol, 69%) de 30 bajo la forma de un aceite incoloro: ^{1}H NMR ($CDCl_3$) δ 7,52 (m, 1 H), 7,35 (m, 2 H), 7,19 (t, J = 8 Hz, 1 H), 6,73 (m, 2 H), 6,64 (m, 1 H), 4,54 (d, J = 9 Hz, 1 H), 3,73 (m, 1 H), 3,29 (m, 1 H), 2,99 (dd, J = 4, 14 Hz, 1 H), 2,73 (dd, J = 8,5, 14 Hz, 1 H), 2,46-2,35 (m, 2 H), 1,45 (s, 6 H), 1,37 (s, 9 H); MS (CI) m/z 514,2 (MH+).

Paso 6. Preparación de (1R,2S)-2-(acetilamina)-1-({[1-(3-bromofenil)-1-metiletil]amina}metil)-3-(3,5-difluorofenil) hidrocloruro de acetato de propilo 31

A 365 mg (0,71 mmol) de tert-butil (1S,2R)-3-{[1-(3-bromofenil)-1-metiletil] amino}-1-(3,5-difluorobencil)-2-hidroxipropilcarbamato 30 en 2 mL de CH_2Cl_2 se agrega 1 mL de ácido trifluoroacético y la mezcla se agita durante 30 minutos. Se concentra en vacío, diluida con acetato de etilo y lava con 10% de Na_2CO_3 y, después, con salmuera. La solución se seca sobre Na_2SO_4, filtra y concentra hasta formar un aceite incoloro, que se disuelve en 3 mL de CH_2Cl_2 y se agregan 172 mg (1,56 mmol) de imidazol de acetilo. Después de 2,5 horas, la mezcla se concentra y absorbe en el acetato de etilo y 1 N KH_2PO_4. La fase orgánica se lava con 1N KH_2PO_4, con salmuera, se seca sobre Na_2SO_4, concentra y cromatografía sobre sílica gel. La elución con 4% de metanol (con 1% de NH_4OH) en CH_2Cl_2 proporciona un sólido pegajoso, que se disuelve en éter y trata con HCl etéreo. La concentración proporciona 260 mg (0,49 mmol, 68%) de 31 bajo la forma de un sólido de color blanco: ^{1}H NMR (gota de $CDCl_3$ + CD_3OD) δ 7,79 (n m, 1 H), 7,59 (m, 2 H), 7,36 (t, J = 8 Hz, 1 H), 6,69-6,62 (m, 3 H), 5,15 (m, 1 H), 4,17 (m, 1 H), 3,07 (d, J = 12,5 Hz, 1 H), 2,87-2,75 (m, 2 H), 2,61 (dd, J = 7, 13,5 Hz, 1 H), 2,21 (s, 3 H), 1,95 (s, 3 H), 1,92 (s, 3 H), 1,84 (s, 3 H); reflectancia difusa (DR) 2985, 2958, 2940, 2755, 2738,

1449 450

2730, 1749, 1645, 1628, 1596, 1569, 1463, 1372, 1227, 1118 cm -1. MS (CI)m/z(intensidad relativa) 497 (MH+, 86), 500 (15), 499 (99), 497 (86), 419 (28), 283 (18), 231 (22), 136 (17), 77 (46), 60 (13), 58 (18). HRMS (ESI) calculado para $C_{23}H_{27}N_2O_3F_2Br+H_1$ 497,1252, hallados 497,1248. Anál. calculado para $C_{23}H_{27}BrF_2N_2O_3$ + HCl + 0,5H_2O: C, 50,89; H, 5,38; N, 5,16; Hallados: C, 50,95; H, 5,37; N, 5,05.

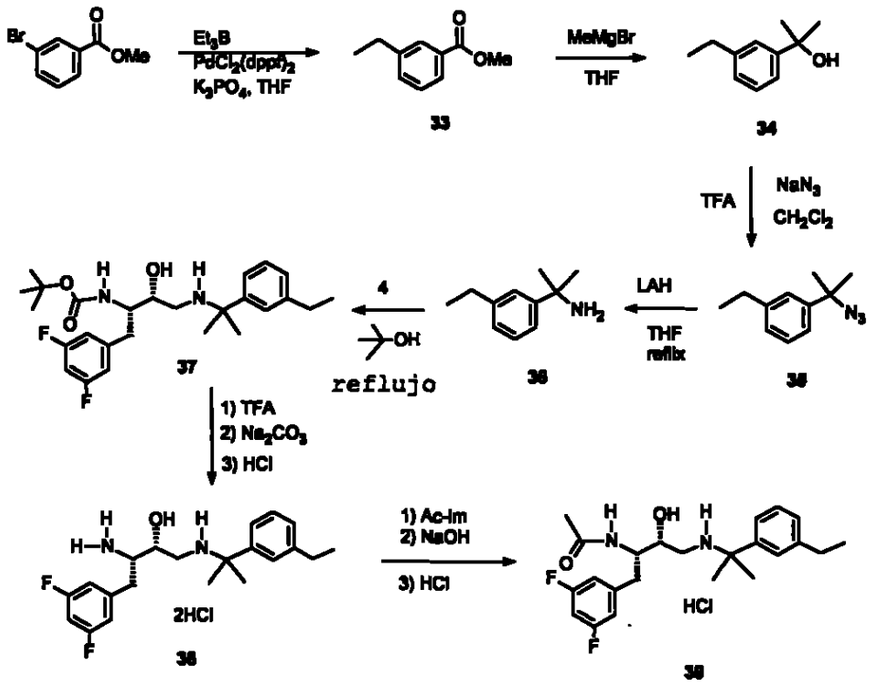
Paso 7. Preparación de N-[(1S,2R)-3-{[1-(3-bromofenil)-1-metiletil]amina}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida 32

A una solución de 107 mg (0,21 mmol) de (1R,2S)-2-(acetilamina) -1-({[1-(3-bromofenil)-1-metiletil]amina}metil)-3-(3,5-difluorofenil)hidrocloruro de propilacetato 31 en 10 mL de metanol, se agrega 1 mL de 1N NaOH. La mezcla se agita durante 45 min. a temperatura ambiente; después se apaga con 1N KH_2PO_4 y diluye con acetato de etilo. La fase orgánica se lava con salmuera, seca sobre Na_2SO_4, filtra y concentra hasta formar un sólido cristalino, que se disuelve en metanol y trata con HCl etéreo para proporcionar 70 mg (0,14 mmol, 68%) de 32 bajo la forma de un sólido de color blanco: ^{1}H NMR (gota de $CDCl_3$+ CD_3OD) δ 7,69 (s, 1 H), 7,56 (m, 2 H), 7,35 (t, J = 8 Hz, 1 H), 6,71 (m, 2 H), 6,63 (m, 1 H), 3,98 (m, 2 H), 2,98 (m, 1 H), 2,8 (m, 1 H), 2,68 (m, 1 H), 2,39 (m, 1 H), 1,92 (s, 3 H), 1,83 (s, 6 H); IR (reflectancia difusa) 3311, 3283, 3257, 3249, 3058, 3007, 2757, 1655, 1646, 1628, 1596, 1551, 1459, 1116, 697 cm -1. MS (CI)m/z(intensidad relativa) 457 (15), 455 (MH+,97), 458 (17), 457 (99), 456 (15), 455 (97), 377 (5), 259 (9), 216 (6), 214 (6), 96 (27), 69 (5). HRMS (ESI) calculado para $C_{21}H_{25}N_2O_2F_2Br+H_1$ 455,1146, hallado 455,1145. Anál. calculado para $C_{21}H_{25}BrF_2N_2O_2$.HCl+ H_2O: C, 49,47; H, 5,54; N, 5,49; Hallados: C, 49,45; H, 5,50; N, 5,54.

EJEMPLO 77: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil]amino}-2-hidroxipropil)acetamida 39

450

ESQUEMA 9



Paso 1. Preparación de metil-3-etilbenzoato 33

En un matraz que contiene metil-3-bromobenzoato (8,6 g, 40 mmol), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio II: complejo de CH_2Cl_2 ((dppf)PdCl:DCM(1:1), 0,32 g, 0,39 mmol),y 40 mL de 2 N K_3PO_4 bajo nitrógeno, se introduce, por medio de una jeringa, 40 mL de 1M trietilboro en THF. La mezcla de color rojo intenso se agita vigorosamente y se deja refluir durante 2 horas. Después de 2 horas más a temperatura ambiente, la mezcla, ahora marrón, se templa con agua y se diluye con acetato de etilo. La fase orgánica se lava sucesivamente con una solución acuosa de 10% HCl, 1 N Na_2CO_3, y salmuera, se seca sobre Na_2SO_4, y se concentra. Usando cromatografía sobre gel de sílice y elución con 2% a 3% de acetato de etilo en hexanos, se obtuvo 6,1 g (37 mmol, 93%) de metil-3-etilbenzoato 33 en forma de un aceite incoloro: ^{1}H NMR ($CDCl_3$) δ 7,89-7,84 (m, 2 H), 7,40-7,33 (m, 2 H), 3,91 (s, 3 H), 2,70 (q, J = 7,6 Hz, 2 H), 1,26 (t, J = 7,6 Hz, 3 H).

451

Paso 2. Preparación de 2-(3-etilfenil)-2-propanol **34**

Siguiendo esencialmente el procedimiento del Ejemplo 76, Paso 1, se convierte metil-3-etilbenzoato **33** (6,0 g, 37 mmol) en 2-(3-etilfenil)-2-propanol **34** (6 g, cuantitativo) el que se obtiene en forma de un aceite amarillo pálido, suficientemente puro sin usar cromatografía: ^{1}H NMR ($CDCl_3$) δ 7,34 (m, 1 H), 7,28 (m, 2 H), 7,09 (m, 1 H), 2,66 (q, *J* = 7,6 Hz, 2 H), 1,75 (s, 1 H, 1,59 (s, 6 H), 1,25 (t, *J* = 7,6 Hz, 3 H).

Paso 3. Preparación de 2-(3-etilfenil)-2-propilazida **35**

Siguiendo esencialmente el procedimiento del Ejemplo 69, Paso 2, pero sólo agitando a temperatura ambiente durante 1 hora, se convierte 2-(3-etilfenil)-2-propanol **34** (6,0 g, 37 mmol) en 2-(3-etilfenil)-2-propilazida **35** (6,6 g, 35 mmol, 94%) la que se obtiene en forma de un aceite amarillo pálido, suficientemente puro sin el uso de cromatografía: ^{1}H NMR ($CDCl_3$) δ 7,25 (m,3 H), 7,12 (m,1 H), 2,67 (q, *J* = 7,6 Hz, 2 H), 1,64 (s, 6 H),1,25 (t, *J* = 7,6 Hz, 3 H).

Paso 4. Preparación de 2-(3-etilfenil)-2-propilamina **36**

Siguiendo esencialmente el procedimiento descrito en el Ejemplo 76, Paso 3, **35** (6,6 g, 35 mmol) se convierte en **36** (3,2 g, 20 mmol.56%) que se obtiene en forma de un aceite amarillo pálido después de la cromatografía: ^{1}H NMR ($CDCl_3$) δ 7,35-7,24 (m.3 H).7,07 (d,J = 7,4 Hz.1 H).2,66 (q,J = 7,6 Hz.2 H).1,55 (s, 2 H), 1,49 (s, 6 H), 1,25 (t, *J* = 7,6 Hz, 3 H).

Paso 5. Preparación de hidrocloruro de 2-(3-etilfenil)-2- propilamina

A 2-(3-etilfenil)-2-propilamina **36** en éter se añade HCl etéreo. La eliminación de la lejía matriz proporciona hidrocloruro de 2-(3-etilfenil)-2-propilamina en forma de un sólido blanco: 1H NMR (CDCl3) δ 8,93 (s, 3 H), 7,44 (s, 1 H), 7,36 (m, 1 H), 7,26 (t,J = 7,6 Hz, 1 H), 7,13 (d,J = 7,6 Hz, 1 H), 2,63 (q,J = 7,6 Hz, 2 H), 1,81 (s, 6 H), 1,22 (t,J = 7,6 Hz, 3 H); MS (CI) m/z 147,0 ($MH - NH_2$).

Paso 6. Preparación de (1S,2R)-3-{[1-(3-etilfenil)-1-metiletil] amino}-1-(3,5-difluorobencil)-2-hidroxipropilcarbamato de terc-butilo **37**

452

Se sigue esencialmente el procedimiento descrito en el Ejemplo 76, Paso 5, excepto que se utiliza t-butanol en lugar de isopropanol, y se hace reaccionar 2-(3-etilfenil)-2-propilamina 36 (3,0 g, 18,4 mmol) con el compuesto del Ejemplo 134 (4, 3,0 g, 10 mmol) para obtener, después de la cromatografía, 37 (3,8 g, 8,2 mmol, 82%) en forma de un aceite incoloro: ^{1}H NMR ($CDCl_3$) δ 7,27 (m, 3 H), 7,09 (m, 1 H), 6,74 (m, 2 H), 6,65 (m, 1 H), 4,69 (d, *J* = 9,4 Hz, 1 H), 3,76 (m, 1 H), 3,32 (m, 1 H), 2,97 (dd, *J* = 4,14 Hz, 1 H), 2,72 (m, 1 H), 2,67 (q, *J* = 7,6 Hz, 2 H), 2,45 (m, 2 H), 1,49 (s, 6 H), 1,40 (s, 9 H), 1,26 (t, *J* = 7,6 Hz, 3 H).

Paso 7. Preparación de hidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[1-(3-etilfenil)-1-metiletil]amino}butan-2-ol **38**

Siguiendo esencialmente el procedimiento descrito en el Ejemplo 76, Paso 6, se desprotege el compuesto 37 (3,5 g, 7,6 mmol) con TFA para proporcionar una producción cuantitativa de un aceite ligeramente amarillo: ^{1}H NMR ($CDCl_3$) δ 7,25 (m, 3 H),7,08 (m, 1 H), 6,72-6,6 (m, 3 H), 3,39 (m, 1 H), 3,02 (m, 1 H), 2,82 (dd, = 3,8, 13,6 Hz, 1 H), 2,67 (q, *J* = 7,6 Hz, 2 H), 2,59 (dd, *J* = 3,6, 11,8 Hz, 1 H), 2,45-2,37 (m, 2 H), 1,48 (s, 6 H), 1,24 (t, J = 7,6 Hz, 3 H). Un tratamiento con HCl etéreo proporciona hidrocloruro 38 (86%) en forma de un sólido blanco: MS (Cl) m/z 363,3 (MH+).

Paso 8. Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil]amino}-2-hidroxipropil)acetamida **39**

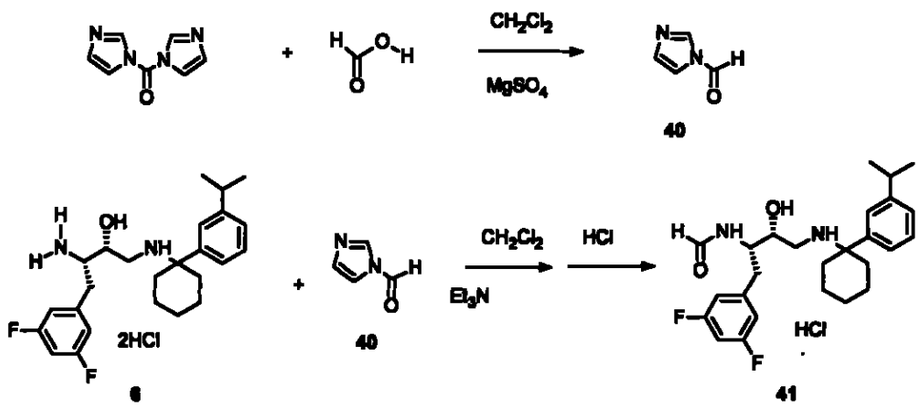
Siguiendo esencialmente el procedimiento descrito para el Ejemplo 76, Paso 6, el compuesto 38 (1,1 mmol) se convierte en N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil]amino}-2-hidroxipropil)acetamida, que, tras cromatografía sobre gel de sílice, utilizando una elución con 8% a 10% metanol (que contiene 1% NH_4OH) en CH_2Cl_2, se obtiene en forma de un aceite incoloro: ^{1}H NMR ($CDCl_3$) δ 7,28-7,20 (m, 3 H), 7,07 (d,J = 7 Hz, 1 H), 6,69-6,61 (m, 3 H), 6,28 (d,J = 9 Hz, 1 H), 4,11 (m, 1 H), 3,40 (m, 1 H), 2,83 (dd,J = 5,2, 14,3 Hz, 1 H), 2,73 (dd,J = 8,4, 14,2 Hz, 1 H), 2,65 (q,J = 7,6 Hz, 2 H), 2,44 (dd,J = 4, 12 Hz, 1 H), 2,34 (dd,J = 5,3, 12 Hz, 1 H), 1,89 (s, 3 H), 1,47 (s, 3 H), 1,46 (s, 3 H), 1,24 (t,J = 7,6 Hz, 3 H). Un tratamiento con HCl etéreo y una concentración proporcionan 39 (0,22 g, 0,49 mmol, 45%), el que se obtiene en forma de un sólido blanco: ^{1}H NMR ($CDCl_3$+ CD_3OD gota) δ 7,37 (m, 3 H), 7,24 (m, 1 H), 6,71 (m, 2 H), 6,62 (m, 1 H), 3,98 (m, 2 H), 3,0 (dd,J = 4, 14,7 Hz, 1 H), 2,78-2,65 (m+q,J = 7,6 Hz, 4 H), 2,46 (m, 1 H),1,91 (s, 3 H), 1,84 (s, 3 H), 1,83 (s, 3 H), 1,26 (t,J = 7,6 Hz, 3 H); IR (reflectancia difusa) 3250, 3229, 3053, 2967, 2933, 2876, 2786, 2764, 1645, 1628, 1595, 1550, 1459, 1377, 1116 cm -1. MS (Cl)m/z(intensidad rel,) 405 (MH+,99), 407 (6), 406 (41), 405 (99),

453

387 (7), 259 (23), 176 (8), 164 (18), 148 (7), 147 (19), 77 (15).HRMS (ESI) calculado para $C_{23}H_{30}N_2O_2F_2+H_1$ 405,2353; se encontró 405,2369. El análisis calculado para $C_{23}H_{30}F_2N_2O_2$,HCl+ 0,5 H_2O: C, 61,39; H, 7,17; N, 6,23 encontró: C, 61,27; H, 7,07; N, 6,20.

EJEMPLO 78: Preparación de hidrocloruro de (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propilformamido 41

ESQUEMA 10



Paso 1. Preparación de formil imidazol 40

A una solución de ácido fórmico (0,76 mL, 20 mmol, 96%) en CH_2Cl_2 que se agita bajo nitrógeno, se le añade, en porciones, durante 10 min, 3,6 g (22 mmol) de carbonildiimidazol, y la mezcla se la deja agitando durante la noche. Se añade $MgSO_4$ anhidro, y después de varias horas la mezcla se filtra y concentra al vacío (nota: el formil imidazol es volátil y esta operación debe ser seguida con cuidado para maximizar el rendimiento) lo que proporciona 0,7 g de cristales tornasolados. El espectro NMR muestra la presencia de formil imidazol 40: ^{1}H NMR ($CDCl_3$) δ 9,15 (s, 1 H), 8,14 (s, 1 H), 7,53 (s, 1 H), 7,20 (s, 1 H). Los cristales también contienen imidazol (δ 7,71 (s,1H), 7,13 (s, 2H)) y la máxima intensidad relativa y los pesos moleculares relativos se utilizan para determinar el peso porcentual de formil imidazol en el producto.

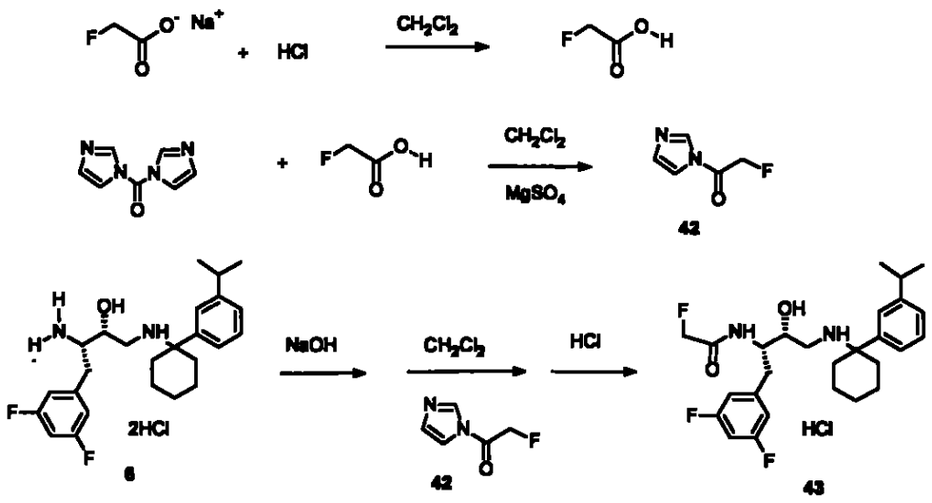
Paso 2. Preparación de hidrocloruro de (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil) ciclohexil]amino}propilformamido 41

459

A una solución de dihidrocloruro de 2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[1-(3-isopropilfenil) ciclohexil]amino}butan-2-ol 6 (209 mg, 0,43 mmol) en 4 mL de CH_2Cl_2 bajo nitrógeno se añade 125□L (0,9 mmol) de trietilamina. A esta mezcla se le añade 75 mg del sólido del Paso 1, que según lo determinado por el NMR contiene un 63% en peso de formil imidazol (47 mg, 0,49 mmol), y la solución se agita durante 20 min. Se añade metanol (5 mL), seguido de 2 mL de 1 N NaOH. La mezcla se concentra al vacío y se diluye con 1 N KH_2PO_4 y acetato de etilo. La fase orgánica se lava con 1 N $NaHCO_3$ y salmuera, y se seca sobre Na_2SO_4. Concentración y cromatografía sobre gel de sílice, eluyendo con 5% a 7,5 % de metanol (que contiene 1% de NH_4OH) en CH_2Cl_2 proporciona un aceite incoloro. Se añaden éter y HCl etéreo, y el precipitado tipo gel se concentra al vacío desde el etanol y después desde el acetato de etilo para proporcionar 176 mg (0,37 mmol, 85%) de hidrocloruro 41 en forma de un sólido blanco: ^{1}H NMR ($CDCl_3$+ gota de CD_3OD) δ 7,86 (s, 1 H), 7,39-7,28 (m, 4 H), 6,67 (m, 2 H), 6,60 (m, 1 H), 3,96 (m, 1 H), 3,79 (m, 1 H), 3,08 (dd, 1 H), 2,93 (m, 1 H), 2,7-2,5 (m, 4 H), 2,37 (dd, 1 H), 2,05 (m, 2 H), 1,78 (m, 2 H), 1,6 (m, 1 H), 1,45-1,3 (m, 3 H), 1,25 (dd,J = 1,7 Hz, 6 H); MS (CI) m/z 445,3 (MH+).

EJEMPLO 79: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)-2-fluoroacetamida 43

ESQUEMA 11



Paso 1. Preparación de fluoroacetil imidazol 42

455

A un lodo de 1,2 g (12 mmol) de fluoroacetato de sodio en 25 mL de CH_2Cl_2 se añade, agitando al matraz, 1 mL (12 mmol) de HCl concentrado (nota: esta operación debe realizarse dentro de una campana eficiente; ¡el ácido fluoroacético es altamente tóxico!). Se añade al matraz una cucharilla de $MgSO_4$ anhidro, y se filtra el contenido, enjuagando el papel de filtro con 15 mL de CH_2Cl. El combinado de lo filtrado y lo lavado se coloca bajo nitrógeno y se añade, en porciones durante 20 min, 1,3 g (8 mmol) de carbonildiimidazol a la mezcla agitada. Un análisis NMR de una alícuota tomada 40 minutos después indica que la reacción es casi completa. Después de 1 hora, se añade una cucharilla de $MgSO_4$, y la mezcla se deja bajo agitación durante la noche. Se filtra y concentra para eliminar la mayor parte del CH_2Cl_2 lo que resulta en 1,6 g de un aceite amarillo pálido. El espectro NMR indica la presencia de CH_2Cl_2, ácido fluoroacético, imidazol, y fluoroacetil imidazol 42: ^{1}H NMR ($CDCl_3$) δ 8,26 (s, 1 H), 7,53 (s, 1 H), 7,15 (s, 1 H), 5,40 (d,J = 47 Hz, 2 H). La integración revela que el aceite tiene un 28% de fluoroacetil imidazol en peso 42 (0,45 g, 3,5 mmol, 44%). El aceite se diluye con CH_2Cl_2 para elaborar una solución que es 0,2 M en 42.

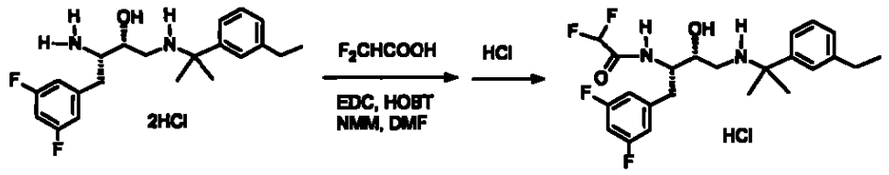
Paso 2. Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)-2-fluoroacetamida 43

Se añade dihidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[1-(3-isopropilfenil) ciclohexil] amino}butan-2-ol 6 (0,64 mmol) a 1 N NaOH y acetato de etilo. La fase orgánica se lava con 1N NaOH, salmuera, y después se seca sobre Na_2SO_4 y se concentra a 265 mg de un aceite incoloro. Esta base libre se disuelve en 3 mL de CH_2Cl_2 bajo nitrógeno y se le añade 3,2 mL (0,64 mmol) de una solución 0,2 M de fluoroacetil imidazol 42 en CH_2Cl_2. La mezcla se agita durante 5 min, y después se añaden una solución acuosa 1N KH_2PO_4 y acetato etilo. La fase orgánica se lava con 1N KH_2PO_4, 1N $NaHCO_3$, y salmuera, se seca sobre Na_2SO_4, y se concentra. Cromatografía sobre gel de sílice, eluyendo con 5 % metanol (que contiene 2% de NH_4OH) en CH_2Cl_2 proporciona un aceite incoloro. Se añaden éter y HCl etéreo, y los disolventes se eliminan al vacío para producir 256 mg (0,50 mmol, 78%) de hidrocloruro 43 en forma de un sólido blanco: ^{1}H NMR ($CDCl_3$) δ 9,85 (m, 1 H), 8,0 (m, 1 H), 7,51 (s, 1 H), 7,37 (m, 2 H), 7,27 (m, 1 H), 6,80 (d,J = 7 Hz, 1 H), 6,68 (m, 2 H), 6,63 (m, 1 H), 4,63 (d,J = 47 Hz, 2 H), 4,16 (m, 1 H), 4,10 (m, 1 H), 2,98-2,93 (m, 2 H), 2,77-2,64 (m, 4 H), 2,35-2,2 (m, 3 H), 1,80 (m, 2 H), 1,59 (m, 1 H), 1,44-1,25 (m, 3 H), 1,28 (d,J = 7 Hz, 6 H); MS (CI) m/z 477,4 (MH+).

EJEMPLO 80: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil] amino}-2-hidroxipropil)-2,2-difluoroacetamida 44

456

ESQUEMA 12



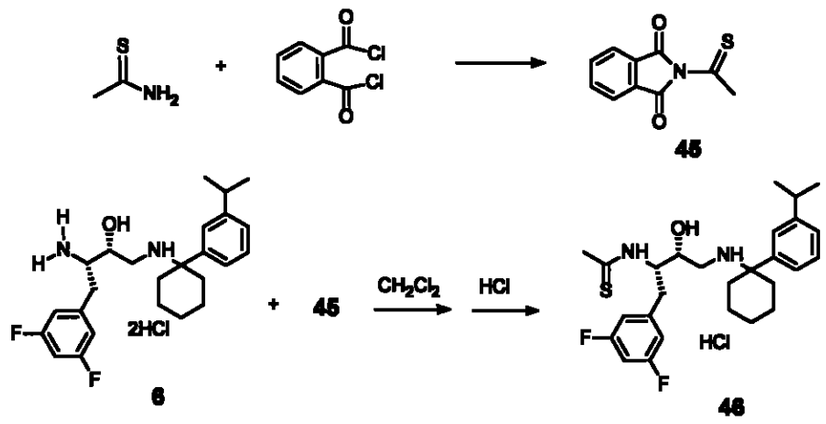
38 44

Ácido difluoroacético (40 □L, 0,63 mmol) se combina con hidrocloruro de 1-(3-dimetilamino-propil)-3-etilcarbodiimido (EDC, 120 mg, 0,63 mmol) y hidrato de 1-hidroxi- benzotriazol (HOBT, 85 mg, 0,63 mmol) en 2 mL de DMF seco bajo nitrógeno. Después de agitar durante 1 hora, se añade una mezcla del compuesto 38 (200 mg, 0,46 mmol) y 100 □L (0,91 mmol) de N-metilmorfolina en 2 mL de DMF seco. La mezcla de reacción se deja agitando durante 1,5 horas, y después se templa con 1 N KH_2PO_4 y acetato de etilo. La fase orgánica se lava con 1 N KH_2PO_4, 1 N $NaHCO_3$, y salmuera. Se seca sobre Na_2SO_4, se concentra, y se cromatografía sobre gel de sílice. Elución con 6% metanol (que contiene 1% de NH_4OH) en CH_2Cl_2 proporciona un aceite incoloro, y después de la concentración desde HCl etéreo se obtienen 125 mg (0,26 mmol, 57%) de hidrocloruro 44 en forma de un sólido blanco: ^{1}H NMR ($CDCl_3$) δ 9,9 (m, 1 H), 8,1 (m, 1 H), 7,35 (m, 4 H), 7,23 (d,J = 7 Hz, 1 H), 6,66-6,58 (m, 3 H), 5,95 (t,J = 54 Hz, 1 H), 4,6 (v br, 1 H), 4,37 (m, 1 H), 4,10 (m, 1 H), 2,89 (dd,J = 5,14 Hz, 1 H), 2,80-2,66 (m+q,J = 7,6 Hz, 4 H), 2,34 (m, 1 H), 1,87 (s, 6 H), 1,26 (t,J = 7,6 Hz, 3 H); MS (CI) m/z 441,3 (MH+).

EJEMPLO 81: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil) ciclohexil]amino}propil)etanotioamida 46

457

ESQUEMA 13



Paso 1. Preparación de tioacetil-N-ftalimida 1

Se suspende tioacetamida (1,9 g, 25 mmol) en 40 mL de CH_2Cl_2 y se enfría en un baño de hielo bajo nitrógeno. Se añade dicloruro de ftaloilo (3,6 mL, 25 mmol) lentamente durante 10 min por medio de una jeringa mientras se agita la mezcla. La mezcla se vuelve una solución clara de color naranja transitoriamente, finalmente depositando un precipitado. Después de agitar durante 40 h, la mezcla se concentra al vacío (¡en la campana!). El sólido coral aceitoso se tritura con hexanos. En cuestión de minutos los hexanos de la lejía matriz forman un precipitado, que es filtrado para proporcionar 0,2 g de un sólido coral claro: ^{1}H NMR ($CDCl_3$) δ 7,99 (m, 2 H), 7,86 (m, 2 H), 3,08 (s, 3 H). Los sólidos residuales que quedan tras la trituración con hexanos son triturados aún más con éter y después con CH_2Cl_2. Los líquidos madre combinados se concentran a alrededor de 3 g de un sólido rojo aceitoso, que se cromatografía sobre gel de sílice, utilizando una elución con 10% a 20% de acetato de etilo en heptano. Las fracciones rojas contienen un producto (concentrado como un sólido coral, 0,77 g) con la misma retención TLC (R_f = 0,32, 20% acetato de etilo en heptano) que el sólido coral que precipita de los hexanos. La recuperación total es 0,97 g, 4,7 mmol, 19%.

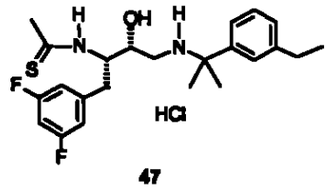
Paso 2. Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil) ciclohexil]amino}propil)etanotioamida 46

A 164 mg (0,39mmol) de la base libre preparada a partir de dihidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[1-(3-isopropilfenil) ciclohexil] amino}butan-2-ol 6 y disuelta en 3 mL de

458

CH_2Cl_2 bajo nitrógeno, enfriada en un baño de hielo, se añade tioacetil-N-ftalimida sólida 45 (80 mg, 0,39 mmol). La mezcla se agita durante 20 min y después se añaden 3 mL de metanol y 3 mL de 1N NaOH. La mezcla se toma en acetato de etilo y se lava dos veces con 1N NaOH, una vez con agua, y una vez con salmuera. Se seca sobre Na_2SO_4, se concentra, y se cromatografía sobre gel de sílice, utilizando elución con 4% metanol (que contiene 2% NH_4OH) en CH_2Cl_2. Las fracciones que contienen el producto se concentran en forma de un aceite incoloro, que se disuelve en éter y se trata con HCl etéreo. La concentración proporciona 97 mg (0,19 mmol, 49%) de hidrocloruro 46 en forma de un sólido blanco: ^{1}H NMR (gota de $CDCl_3$+ CD_3OD) δ 7,42-7,37 (m, 2 H), 7,29 (m, 2 H), 6,73 (m, 2 H), 6,62 (m, 2 H), 4,67 (m, 1 H), 4,10 (m, 1 H), 3,11 (dd,J = 5,14 Hz, 1 H), 2,96 (hept,J = 7 Hz, 1 H), 2,83 (m, 1 H), 2,65-2,4 (m, 4 H, obscurecido por disolvente), 2,38 (s, 3 H), 2,07 (m, 2 H), 1,78 (m, 2 H), 1,59 (m, 1 H), 1,44-1,35 (m, 3 H), 1,28 (d,J = 7 Hz, 6 H); MS (CI) m/z 475,3 (MH+).

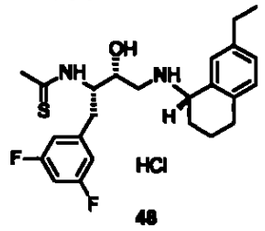
EJEMPLO 82: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil]amino}-2-hidroxipropil)etanotioamida 47



47

Siguiendo esencialmente el procedimiento descrito para el Ejemplo 81, el compuesto 38 (220 mg, 0,5 mmol) se convierte en el compuesto 47 del título, el que se obtiene en forma de sólido blanco (79 mg, 0,17 mmol, 34%): MS (CI) m/z 421,3 (MH+).

EJEMPLO 83: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}-2-hidroxipropil)etanotioamida 48

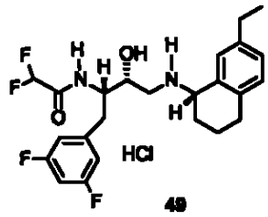


48

459 460

Siguiendo esencialmente el procedimiento descrito en el EJEMPLO 81, dihidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}butan-2-ol (0,71 mmol) se convierte en el compuesto del título 48 (158 mg, 0,34 mmol, 47%), que se obtiene en forma de sólido blanco: ^{1}H NMR ($CDCl_3$) δ 9,5 (br s, 1 H), 9,1 (d, 1 H), 7,95 (br , 1 H), 7,39 (s, 1 H), 7,15-7,07 (m, 2 H), 6,73 (m, 2 H), 6,60 (m, 1 H), 4,77 (m, 1 H), 4,47 (m, 1 H), 4,34 (m, 1 H), 3,0 (d,J = 7 Hz, 2 H), 2,97 (m, 1 H), 2,73 (m, 3 H), 2,61 (q,J = 7,5 Hz, 2 H), 2,53 (s, 3 H), 2,15 (m, 1 H), 2,02 (m, 1 H), 1,87 (m, 1 H), 1,79 (m, 1 H), 1,23 (t,J = 7,5 Hz, 3 H); IR (reflectancia difusa) 3194, 3029, 2964, 2932, 2872, 1627, 1597, 1459, 1439, 1420, 1384, 1153, 1119, 982, 847 cm -1. MS (CI)m/z(intensidad rel,) 433 (MH+,24), 221 (36), 184 (51), 176 (27), 174 (49), 172 (99), 159 (49), 156 (27), 77 (31), 60 (27), 58 (52). HRMS (ESI) calculado para $C_{24}H_{30}N_2OSF_2$+H_1 433,2125; se encontró 433,2114. Análisis calculado para $C_{24}H_{30}F_2N_2OS$,HCl+ H_2O: C, 59,19; H, 6,83; N, 5,75; Cl, 7,28; S, 6,58; se encontró: C, 59,84; H, 6,70; N, 5,88; Cl, 6,91; S, 6,40.

EJEMPLO 84: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}-2-hidroxipropil)-2,2-difluoroacetamida 49

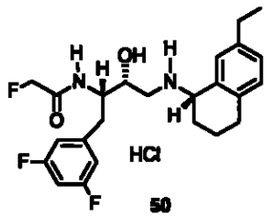


49

Utilizando métodos análogos a los anteriormente descritos, dihidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}butan-2-ol (0,33 mmol) se convierte en el compuesto del título 49 (88 mg, 0,18 mmol, 54%), que se obtiene en forma de sólido blanco: ^{1}H NMR ($CDCl_3$) δ 7,36 (s, 1 H), 7,12 (m, 2 H), 6,71 (m, 2 H), 6,64 (m, 1 H), 5,81 (t,J = 54 Hz, 1 H), 4,46 (m, 1 H), 4,18 (m, 1 H), 4,07 (m, 1 H), 3,12 (m, 2 H), 2,77 (m, 4 H), 2,63 (q,J = 7,5 Hz, 2 H), 2,2 (m, 1 H), 2,05 (m, 1 H), 1,96 (m, 1 H), 1,86 (m, 1 H), 1,23 (t,J = 7,5 Hz, 3 H); MS (CI) m/z 453,5 (MH+).

EJEMPLO 85: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}-2-hidroxipropil)-2-fluoroacetamida 50

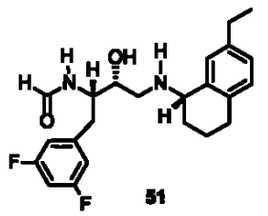
466



50

Utilizando métodos análogos a los anteriormente descritos, dihidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}butan-2-ol (0,0,71 mmol) se convierte en el compuesto del título 50 (248 mg, 0,53 mmol, 74%), que se obtiene en forma de sólido blanco: ^{1}H NMR ($CDCl_3$) δ 9,85 (br, 1 H), 8,41 (br, 1 H), 7,45 (s, 1 H), 7,09 (m, 2 H), 6,97 (d,J = 8,6 Hz, 1 H), 6,68 (m, 2 H), 6,62 (m, 1 H), 4,70 (dq,J ~ 50,11 Hz, 2 H), 4,48 (m, 1 H), 4,29 (m, 1 H), 4,16 (m, 1 H), 3,1-3,0 (m, 2 H), 2,83-2,69 (m, 4 H), 2,59 (q,J = 7,5 Hz, 2 H), 2,21 (m, 1 H), 2,02 (m, 2 H), 1,78 (m, 1 H), 1,21 (t,J = 7,5 Hz, 3 H); MS (CI) m/z 435,3 (MH+).

EJEMPLO 86: Preparación de (1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}-2-hidroxipropilformamida 51

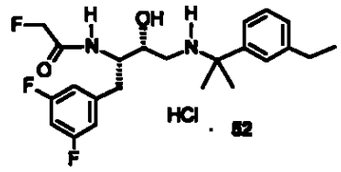


51

Utilizando métodos análogos a los descritos anteriormente, pero sin elaborar la sal HCl, dihidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[(1S)-7-etil-1,2,3,4-tetrahidronaftaleno-1-il]amino}butan-2-ol (0,0,31 mmol) se convierte en el compuesto del título 51 (70 mg, 0,17 mmol, 56%), que se obtiene en forma de sólido blanco, ^{1}H NMR ($CDCl_3$) δ 8,11 (s, 1 H), 7,16 (s, 1 H), 7,03 (s, 2 H), 6,76 (m, 2 H), 6,67 (m, 1 H), 5,83 (d,J = 9 Hz, 1 H), 4,25 (m, 1 H), 3,74 (m, 1 H), 3,53 (m, 1 H), 3,03 (dd,J = 4,8, 14,4 Hz, 1 H), 2,90-2,69 (m, 5 H), 2,61 (q,J = 7,6 Hz, 2 H), 1,85 (m, 3 H), 1,76 (m, 1 H), 1,23 (t,J = 7,6 Hz, 3 H); MS (CI) m/z 403,3 (MH+). Un rastro de doblete NMR(J = 11,8 Hz) aparece en δ 7,73, lo que se atribuye tentativamente a una forma del producto ciclada intramolecularmente en la solución de deuterocloroformo.

461

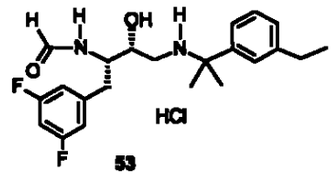
EJEMPLO 87: Preparación de hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil] amino}-2-hidroxipropil)-2-fluoroacetamida **52**



52

Utilizando métodos análogos a los anteriormente descritos, el compuesto **38** (150 mg, 0,34 mmol) se convierte en el compuesto del título **52** (80 mg, 50%), que se obtiene en forma de sólido blanco: ^{1}H NMR ($CDCl_3$) δ 9,95 (br, 1 H), 8,37 (br m, 1 H), 7,39-7,34 (m, 3 H), 7,23 (d,J = 7 Hz, 1 H), 6,94 (d,J = 8 Hz, 1 H), 6,67 (m, 2 H), 6,60 (m, 1 H), 4,68 (dq,J = 47, 14 Hz, 2 H), 4,27 (m, 1 H), 4,16 (m, 1 H), 2,97 (dd, 1 H), 2,80 (m, 2 H), 2,70 (q,J = 7,6 Hz, 2 H), 2,38 (m, 1 H), 1,88 (s, 3 H), 1,87 (s, 3 H), 1,27 (t,J = 7,6 Hz, 3 H); MS (CI) m/z 423,3 (MH+).

EJEMPLO 88: Preparación de hidrocloruro de (1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil] amino}-2-hidroxipropilformamida **53**

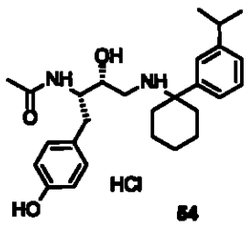


53

Utilizando métodos análogos a los anteriormente descritos, hidrocloruro de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-{[1-(3-etilfenil)-1-metiletil]amino}butan-2-ol **38** (0,60 mmol) se convierte en el compuesto del título **53** (130 mg, 50%), que se obtiene en forma de sólido blanco: ^{1}H NMR (gota de $CDCl_3$+ CD_3OD) δ 7,95 (s, 1 H), 7,39-7,31 (m, 3 H), 7,24 (d,J = 7 Hz, 1 H), 6,71 (m, 2 H), 6,62 (m, 1 H), 4,05 (m, 1 H), 3,95 (m, 1 H), 3,07 (dd, 1 H), 2,80 (m, 1 H), 2,70 (q,J = 7,6 Hz, 2 H), 2,6 (m, obscurecido, 1 H), 2,47 (m, 1 H), 1,83 (s, 3 H), 1,82 (s, 3 H), 1,26 (t,J = 7,6 Hz, 3 H); MS (CI) m/z 391,3 (MH+). El espectro NMR de la base libre en deuterocloroformo puro muestra un pequeño doblete (J = 11,6 Hz) en δ 7,58 lo que se atribuye tentativamente a una forma del producto ciclada intramolecularmente.

EJEMPLO 89: Preparación de hidrocloruro de N-((1S,2R)-2-hidroxi-1-(4-hidroxibencil)-3-{[1-(3-isopropilfenil) ciclohexil]amino}propil)acetamida **54**

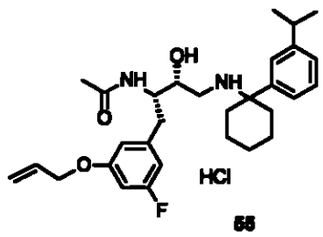
462



54

Utilizando métodos análogos a los anteriormente descritos, (1S)-2-(4-hidroxifenil)-1-[(2S)-oxiran-2-il]etilcarbamato de terc-butilo(0,78 mmol) se convierte en el compuesto del título **54** (70 mg, 0,15 mmol, 19%, 3 pasos), que se obtiene en forma de sólido blanco: ^{1}H NMR ($CDCl_3$+ gota de CD_3OD) δ 7,49 (s, 1 H), 7,39 (d,J = 4,6 Hz, 2 H), 7,28 (m, 1 H), 6,91 (d,J = 8 Hz, 2 H), 6,69 (d,J = 8 Hz, 2 H), 3,97 (m, 1 H), 3,90 (m, 1 H), 2,96 (hept,J = 7 Hz, 1 H), 2,83 (dd, 1 H), 2,62 (m, 4 H), 2,45 (m, 1 H), 2,13 (m, 2 H), 1,89 (s, 3 H), 1,78 (m, 2 H), 1,58 (m, 1 H), 1,45-1,3 (m, 3 H), 1,27 (d,J = 7 Hz, 6 H); MS (CI) m/z 439,3 (MH+).

EJEMPLO 90: Preparación de hidrocloruro de N-((1S,2R)-1-[3-(aliloxi)-5-fluorobencil]-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)acetamida **55**

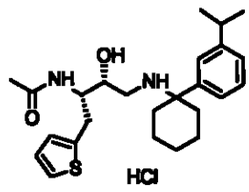


55

Utilizando métodos análogos a los anteriormente descritos, (1S)-2-[3-(aliloxi)-5-fluorofenil]-1-[(2S)-oxiran-2-il]etilcarbamato de terc-butilo (0,61 mmol) se convierte en el compuesto del título **55** (0,31 mmol, 51%, 3 pasos), que se obtiene en forma de sólido blanco: ^{1}H NMR ($CDCl_3$ + gota de CD_3OD) δ 7,42-7,27 (m, 4 H), 6,54 (m, 1 H), 6,48 (m, 1 H), 6,45 (m, 1 H), 6,05-5,98 (m, 1 H), 5,39 (m, 1 H), 5,28 (m, 1 H), 4,48 (m, 2 H), 3,95 (m, 1 H), 3,77 (m, 1 H), 2,96 (m, 2 H), 2,60 (m, 4 H), 2,4 (m, obscurecido, 1 H), 2,1 (m, 2 H), 1,81 (s+m, 5 H), 1,6 (m, 1 H), 1,45-1,3 (m, 3 H), 1,27 (d,J = 7 Hz, 6 H); MS (CI) m/z 497,4 (MH+).

EJEMPLO 91: Preparación de hidrocloruro de N-[(1S,2R)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}-1-(tien-2-ilmetil)propil]acetamida **56**

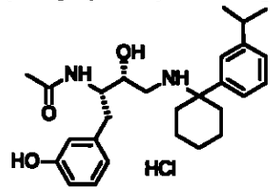
463



58

Utilizando métodos análogos a los anteriormente descritos, (1S)-1-[(2S)-oxiran-2-il]-2-tien-2-iletilcarbamato de terc-butilo (0,92 mmol) se convierte en el compuesto del título 56 (0,51 mmol, 55%, 3 pasos), que se obtiene en forma de sólido blanco: ^{1}H NMR ($CDCl_3$) δ 9,8 (br, 1 H), 8,03 (br, 1 H), 7,47 (s, 1 H), 7,37 (m, 2 H), 7,26 (m, 1 H), 7,21 (m, 1 H), 7,0 (br, 1 H), 6,95 (m, 1 H), 6,90 (d,J = 5 Hz, 1 H), 4,15 (m, 1 H), 3,96 (m, 1 H), 3,9 (v br, 1 H), 2,96 (hept,J = 7 Hz, 1 H), 2,86 (m, 2 H), 2,7-2,55 (m, 3 H), 2,24 (m, 3 H), 2,00 (s, 3 H), 1,8-1,7 (m, 2 H), 1,59 (m, 1 H), 1,45-1,3 (m, 3 H), 1,28 (dd,J = 1,7, 7 Hz, 6 H); MS (Cl) m/z 429,3 (MH+).

EJEMPLO 92: Preparación de hidrocloruro de N-((1S,2R)-2-hidroxi-1-(3-hidroxibencil)-3-{[1-(3-isopropilfenil) ciclohexil]amino}propil)acetamida 57

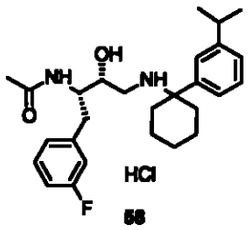


57

Utilizando métodos análogos a los anteriormente descritos, (1S)-2-[3-(benciloxi)fenil]-1-[(2S)-oxiran-2-il]etilcarbamato de terc-butilo (1,0 mmol) se convierte en el compuesto del título 57 (0,28 mmol, 28%, 4 pasos), obtenido en forma de un sólido incoloro tipo vidrio que puede ser pulverizado en un polvo beige: ^{1}H NMR ($CDCl_3$+ CD_3OD gota) δ 7,43 (s, 1 H), 7,37 (m, 2 H), 7,28 (m, 1 H), 7,08 (t,J = 7,7 Hz, 1 H), 6,78 (s, 1 H), 6,69 (d,J = 8 Hz, 1 H), 6,57 (d,J = 7,5 Hz, 1 H), 4,03 (m, 1 H), 3,75 (m, 1 H), 2,97 (m, 2 H), 2,65 (m, 4 H), 2,43 (m, 1 H), 2,12-2 (m, 2 H), 1,85 (s, 3 H), 1,78 (m, 2 H), 1,59 (m, 1 H), 1,45-1,3 (m, 3 H), 1,27 (d,J = 7 Hz, 6 H); MS (Cl) m/z 439,3 (MH+).

EJEMPLO 93: Preparación de hidrocloruro de N-((1S,2R)-1-(3-fluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil) ciclohexil]amino}propil)acetamida 58

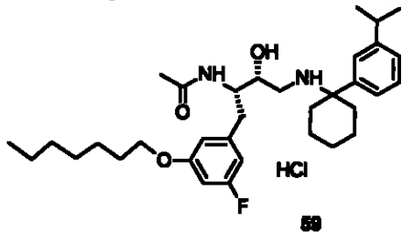
464



58

Utilizando métodos análogos a los anteriormente descritos, (1S)-2-(3-fluorofenil)-1-[(2S)-oxiran-2-il]etilcarbamato de terc-butilo(0,82 mmol) se convierte en el compuesto del título 58 (0,37 mmol, 45%, 3 pasos), obtenido en forma de sólido blanco:
^{1}H NMR ($CDCl_3$+ CD_3OD gota) δ 7,45 (s, 1 H), 7,4-7,35 (m, 2 H), 7,28 (m, 1 H), 7,20 (m, 1 H), 6,93 (m, 1 H), 6,88 (m, 2 H), 4,00 (m, 1 H), 3,87 (m, 1 H), 2,96 (m, 2 H), 2,7-2,6 (m, 4 H), 2,39 (m, 1 H), 2,11 (m, 2 H), 1,88 (s, 3 H), 1,79 (m, 2 H), 1,59 (m, 1 H), 1,45-1,3 (m, 3 H), 1,27 (d,J = 7 Hz, 6 H); MS (CI) m/z 441,5 (MH+).

EJEMPLO 94: Preparación de hidrocloruro de N-((1S,2R)-1-(3-(heptiloxi)-5-fluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)acetamida 59

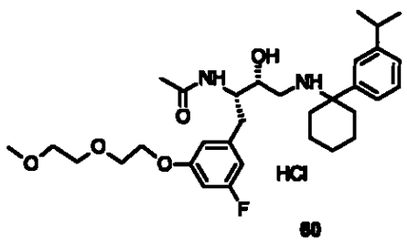


59

Utilizando métodos análogos a los descritos anteriormente, se hace reaccionar hidrocloruro de N-((1S,2R)-1-(3-hidroxi-5-fluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil] amino}propil)acetamida 11 (0,4 mmol) con 1-bromoheptano para proporcionar el compuesto del título 59 (0,14 mmol, 34%) en forma de un vidrio que puede ser pulverizado en un sólido blanquecino: ^{1}H NMR ($CDCl_3$+ gota de CD_3OD) δ 7,49 (s, 1 H), 7,37 (m, 2 H), 7,27 (m, 1 H), 6,51 (s, 1 H), 6,45 (s, 1 H), 6,43 (s, 1 H), 4,05 (m, 1 H), 3,98 (m, 1 H), 3,88 (t,J = 6,5 Hz, 2 H), 2,96 (hept,J = 7 Hz, 1 H), 2,84 (m, 1 H), 2,6 (3H obscurecido por el disolvente), 2,36 (m, 1 H), 2,16 (m, 2 H), 2,01 (s, 3 H), 1,85-1,75 (m, 4 H), 1,58 (m, 1 H), 1,5-1,26 (m, 18 H), 0,89 (t,J = 6,6 Hz, 3 H); MS (CI) m/z 555,5 (MH+).

EJEMPLO 95: Preparación de hidrocloruro de N-((1S,2R)-1-(3-(2-(2-metoxietoxi)etoxi)-5-fluorobencil)-2-hidroxi-3-{[1-(3-isopropilfenil)ciclohexil]amino}propil)acetamida 60

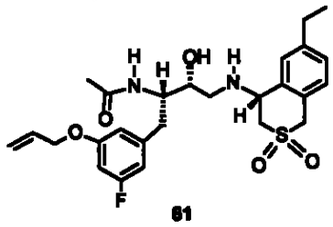
965



60

Utilizando métodos análogos a los descritos anteriormente, se hace reaccionar el compuesto 11 (0,4 mmol) con 1-bromo-2-(2-metoxietoxi)etano para proporcionar el compuesto del título 60 (0,21 mmol,52%) en forma de un sólido blanco higroscópico: ^{1}H NMR ($CDCl_3$) δ 9,4 (br, 1 H), 8,5 (br, 1 H), 8,32 (br, 1 H), 7,54 (s, 1 H), 7,38 (m, 2 H), 7,26 (m, 1 H), 6,56 (s, 1 H), 6,47 (m, 2 H), 4,34 (v br, agua H), 4,1 (m, 4 H), 3,83 (m, 2 H), 3,70 (m, 2 H), 3,58 (m, 2 H), 3,38 (s, 3 H), 2,96 (hept,J = 7 Hz, 1 H), 2,8-2,6 (m, 5 H), 2,4-2,2 (m, 3 H), 2,15 (s, 3 H), 1,80 (m, 2 H), 1,6 (m, 1 H), 1,5-1,3 (m, 3 H), 1,27 (d,J = 7 Hz, 6 H); MS (CI) m/z 559,5 (MH+).

EJEMPLO 96: Preparación de N-((1S,2R)-1-[3-(aliloxi)-5-fluorobencil]-3-{[(4R)-6-etil-2,2-dióxido-3,4-dihidro-1H-isotiocromeno-4-il]amino}-2-hidroxipropil)acetamida 61

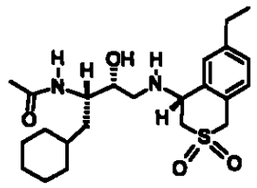


61

Utilizando métodos análogos a los anteriormente descritos, se hace reaccionar (1S)-2-[3-(aliloxi)-5-fluorofenil]-1-[(2S)-oxiran-2-il]etilcarbamato de terc-butilo (0,37 mmol) con (4R)-6-etil-3,4-dihidro-1H-isotiocromeno-4-amina 2,2-dióxido (0,78 mmol) y , luego, utilizando métodos análogos a los anteriormente descritos (excepto que no se forma la sal HCl), el producto se convierte en el compuesto del título 61 (0,16 mmol, 43%), que se obtiene en forma de un sólido blanco: ^{1}H NMR ($CDCl_3$) δ 7,22-7,19 (m, 2 H), 7,13 (m, 1 H), 6,57 (m, 1 H), 6,51 (m, 2 H), 6,06-5,99 (m, 1 H), 5,75 (br, 1 H), 5,41 (d,J = 17 Hz, 1 H), 5,30 (d,J = 12 Hz, 1 H), 4,67 (d,J = 15 Hz, 1 H), 4,50 (m, 2 H), 4,26 (m, 1 H), 4,17 (d,J = 15 Hz, 1 H), 4,1 (m, 1 H), 3,66 (m, 2 H), 3,48 (m, 1 H), 3,36 (dd, 1 H), 2,90 (m, 2 H), 2,78 (m, 2 H), 2,67 (q,J = 7,6 Hz, 2 H), 1,91 (s, 3 H), 1,25 (t,J = 7,6 Hz, 3 H); MS (CI) m/z 505,4 (MH+).

466

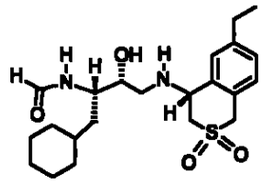
EJEMPLO 97: Preparación de N-{(1S,2R)-1-(ciclohexilmetil)-3-{[(4R)-6-etil-2,2-dióxido-3,4-dihidro-1H-isotiocromeno-4-il]amino}-2-hidroxipropil}acetamida 62



62

Utilizando métodos análogos a los anteriormente descritos, se hace reaccionar (1S)-2-ciclohexil-1-[(2S)-oxiran-2-il]etilcarbamato de terc-butilo (0,91 mmol) con (4R)-6-etil-3,4-dihidro-1H-isotiocromeno-4-amina 2,2-dióxido (1,15 mmol), y el producto (0,63 mmol, 69%) es recuperado por cromatografía sobre gel de sílice, utilizando elución con 3% metanol (que contiene 1 % NH_4OH) en CH_2Cl_2. De este material, 0,31 mmol se convierte adicionalmente, utilizando métodos análogos a los anteriormente descritos, (excepto que no se forma la sal HCl) en el compuesto del título 62 (0,21 mmol, 67%), que se obtiene en forma de un sólido blanco: MS (CI) m/z 437,3 (MH+).

EJEMPLO 98: Preparación de (1S,2R)-1-(ciclohexilmetil)-3-{[(4R)-6-etil-2,2-dióxido-3,4-dihidro-1H-isotiocromeno-4-il]amino}-2-hidroxipropilformamida 63

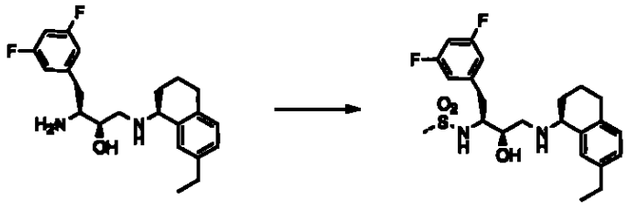


63

Utilizando métodos análogos a los anteriormente descritos, se hace reaccionar (1S)-2-ciclohexil-1-[(2S)-oxiran-2-il]etilcarbamato de terc-butilo (0,91 mmol) con (4R)-6-etil-3,4-dihidro-1H-isotiocromeno-4-amina 2,2-dióxido (1,15 mmol), y el producto (0,63 mmol, 69%) es recuperado por cromatografía sobre gel de sílice, utilizando elución con 3% metanol (que contiene 1 % NH_4OH) en CH_2Cl. De este material, se desprotege 0,0,26 mmol con TFA, utilizando métodos análogos a los anteriormente descritos (excepto que no se forma la sal HCl), y se convierte en el compuesto del título 63 (0,19 mmol, 73%, 2 pasos), que se obtiene en forma de un sólido blanco: MS (CI) m/z 423,3 (MH+)

467

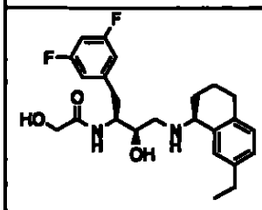
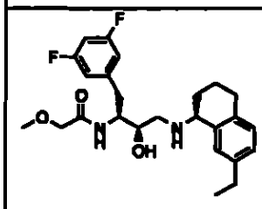
Ejemplo 99: Preparación de N-[(1*S*, 2*R*)-1-(3,5-Difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-metanosulfonamida (64)



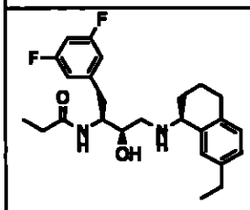
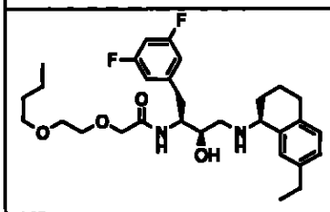
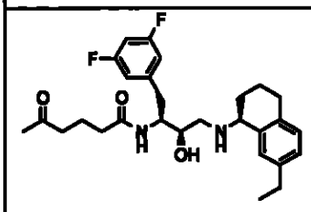
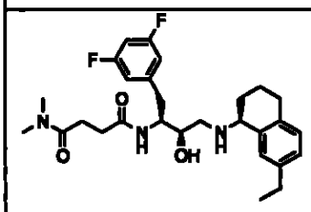
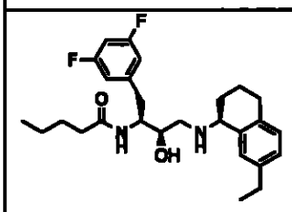
64

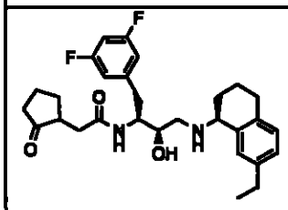
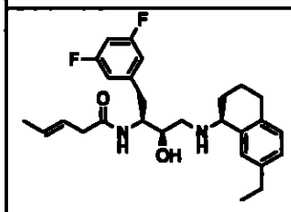
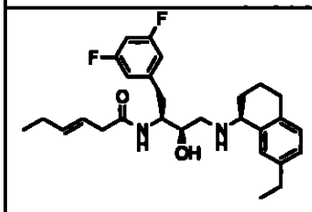
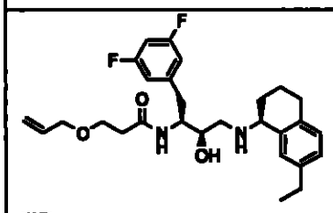
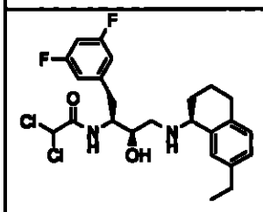
Se trató una muestra de 30 mg de la amina inicial en 1 mL de diclorometano con 33 uL de trietilamina. Se añadió una solución de 6 uL de cloruro de metanosulfonil en 0,5 mL de diclorometano y la solución se dejó bajo agitación durante la noche. Se evaporó el disolvente y se aisló el producto por medio de HPLC de fase inversa. Un análisis de espectroscopia de masa dio m/z = 453,2.

Los compuestos 65-78 son sintetizados de forma análoga, sustituyendo el cloruro de metanosulfonilo con diversos reactivos.

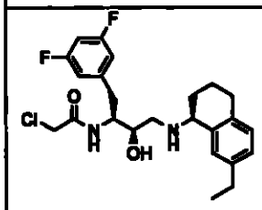
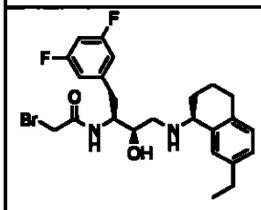
Estructura	Nombre	Espec. De Masa
 (65)	N-[(1*S*,2*R*)-1-(3,5-Difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxipropil]-2-hidroxi-acetamida	432,8
 (66)	N-[(1*S*,2*R*)-1-(3,5-Difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-2-metoxi-acetamida	446,9

468

Estructura	Nombre	Espec. De Masa
 (67)	N-[(1*S*,2*R*)-1-(3,5-Difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-propionamida	430,9
 (68)	2-(2-Butoxi-etoxi)-N-[(1*S*,2*R*)-1-(3,5-difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-acetamida	532,9
 (69)	Ácido 5-Oxo-hexanoico[(1*S*,2*R*)-1-(3,5-difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-amida	486,9
 (70)	N-[(1*S*,2*R*)-1-(3,5-Difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]- N',N'-dimetil-succinamida	501,9
 (71)	Ácido Pentanoico[(1*S*,2*R*)-1-(3,5-difluoro-bencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-amida	458,9

Estructura	Nombre	Espec. De Masa
 (72)	N-[(1*S*,2*R*)-1-(3,5-Difluorobencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-2-(2-oxo-ciclopentil)-acetamida	498,9
 (73)	Ácido Pent-3-enoico [(1*S*,2*R*)-1-(3,5-difluoro-bencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-amida	456,9
 (74)	Ácido Hex-3-enoico [(1*S*,2*R*)-1-(3,5-difluoro-bencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-amida	470,9
 (75)	3-Aliloxi-N-[(1*S*,2*R*)-1-(3,5-difluoro-bencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-propionamida	486,9
 (76)	2,2-Dicloro-N-[(1*S*,2*R*)-1-(3,5-difluoro-bencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-acetamida	485,7

470

Estructura	Nombre	Espec. De Masa
 (77)	2-Cloro-N-[(1*S*,2*R*)-1-(3,5-difluoro-bencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-acetamida	451,7
 (78)	2-Bromo-N-[(1*S*,2*R*)-1-(3,5-difluoro-bencil)-3-((1*S*)-7-etil-1,2,3,4-tetrahidro-naftaleno-1-ilamino)-2-hidroxi-propil]-acetamida	495,7

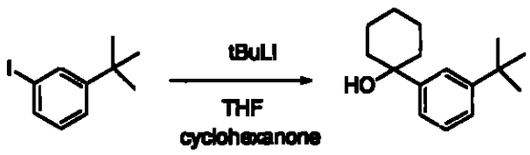
EJEMPLO 100:

A. Preparación de 1-*terc*-butil-3-lodo-benzeno a partir de 3-(*terc*-butil)anilina

Se añadió poco a poco 3-(*terc-butil*)anilina (Oakwood, 6,0 g, 40,21mmol) a una solución fría de 12 N HCl (24,5 mL) mientras ésta se agitaba sobre un baño de hielo/acetona en un matraz de tres cuellos con base redonda equipado con un termómetro. Se añadió una solución 2,9M de nitrito de sodio (16 mL) por medio de un embudo agregado al matraz de reacción, a una tasa tal de mantener la temperatura por debajo de 2°C. La solución se agitó durante 30 min antes de que se la añada al matraz de reacción que contenía una solución 4,2M de yoduro de potasio (100 mL). La mezcla reacciónante se dejó bajo agitación durante toda la noche al tiempo que alcanzaba la temperatura ambiente. La mezcla después fue extraída con una solución hexano/éter (1:1) seguida de un lavado con H_2O (2X), 0,2N ácido cítrico (2X) y NaCl saturado. La fase orgánica se separó, secó (Na_2SO_4) y concentró bajo presión reducida. El residuo fue purificado por cromatografía flash (100% Hexano) para obtener el intermediario de iodo deseado (8,33g, 80%): ^{1}H NMR ($CDCl_3$, 300 MHz) □ 1,34 (s, 9H), 7,07 (t,J = 8,0 Hz, 1H), 7,39(d,J = 8,0 Hz, 1H), 7,55(d,J = 8,0 Hz, 1H), 7,77 (t,J = 2,0 Hz, 1H).

471

B. Preparación de 1-(3-*terc-butil*-fenil)-ciclohexanol a partir de 1-*terc-Butil*-3-iodo-benzeno



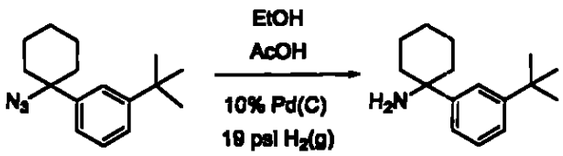
1-*terc-Butil*-3-iodo-benzeno(8,19g, 31,49mmol) en THF anhídrido (35mL) fue enfriado a –78°C. Se añadió una solución de 1,7M *terc-butil* litio y la mezcla de reacción se dejó bajo agitación bajo una entrada de N_2 (g) durante 2 h. Se añadió una solución de ciclohexanona en THF anhídrido (5mL) y la mezcla de reacción se dejó bajo agitación durante 1 h antes de ser transferida a un baño a 0°C por 1 h y de calentarse a temperatura ambiente durante 1 h. La reacción fue extinguida con H_2O y extraída con éter. La capa orgánica fue separada, secada ($NaSO_4$) y concentrada bajo presión reducida. El residuo fue purificado por cromatografía flash (100% $CHCl_3$) para obtener el alcohol deseado (4,73g, 65%): espec. de masa (CI) 215,2 (M-OH).

C. Preparación de 1-(1-azida-ciclohexil)3-terc-butil-benzeno a partir de 1-(3-*terc-butil*-fenil)-ciclohexanol

1-(3-*terc-butil*-fenil)-ciclohexanol (3,33g, 14,34mmol) en cloroformo seco (75mL) fue enfriado a 0°C bajo una entrada de N_2 (g). Se añadió azida de sodio (2,89g, 44,45mmol) seguido de una adición por goteo de ácido trifluoroacético (5,5mL, 71,39mmol). La mezcla de reacción se dejó bajo agitación a temperatura ambiente durante la noche y después se la partición entre H_2O y éter. Se retiró la capa acuosa y se lavó la mezcla con H_2O seguida de 1,0N NH_4OH. La capa orgánica fue separada, secada (Na_2SO_4), y concentrada bajo presión reducida. El residuo fue purificado por cromatografía flash (100% hexano) para obtener la azida deseada (0,50g, 14%): espec. de masa (CI) 215,2 ($M-N_3$).

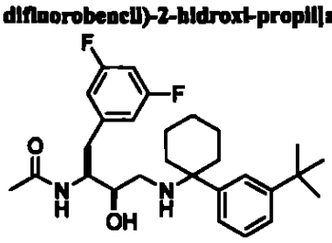
D. Preparación de 1-(3-*terc-butil*-fenil)-ciclohexilamina a partir de 1-(1-azida-ciclohexil)3-terc-butil-benzeno

472



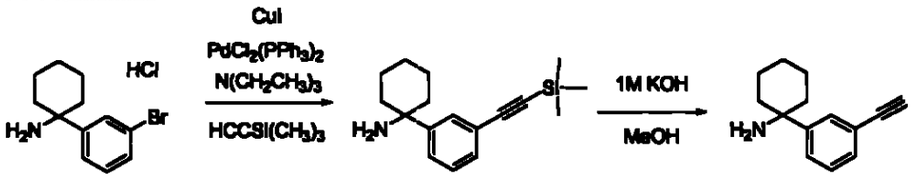
A una solución de 1-(1-azida-ciclohexil)-3-*terc-butil* benzeno disuelta en etanol (5mL) se añadió ácido acético (0,5mL) y 10% paladio sobre carbono (0,10g, 0,94mmol). La mezcla de reacción se colocó en el hidrogenador a 19 psi durante 3,5 horas y después fue filtrada a través de Celite y enjuagada con etanol. El filtrado se recogió, concentró bajo presión reducida, y se particionó entre EtOAc y 1N NaOH. Se separó la capa acuosa y se lavó la mezcla con H_2O. La capa orgánica fue separada, secada (Na_2SO_4), y concentrada bajo presión reducida. El producto crudo se utilizó sin ninguna purificación adicional: espec. de masa (CI) 215,2 (M-NH_2).

E. Preparación de (1*S*,2*R*)-*N*-[3-[1-(3-*terc-butil*-fenil)ciclohexilamina]-1-(3,5-difluorobencil)-2-hidroxi-propil]acetamida (79)



El producto del paso D es transformado en el producto anterior utilizando métodos análogos a otros descritos en la aplicación. Espec. de masa: (CI) 473,2 (M+H).

F. Preparación de 1-(3-etinilfenil)ciclohexilamina a partir de 1-(3-bromo-fenil)-ciclohexilamina

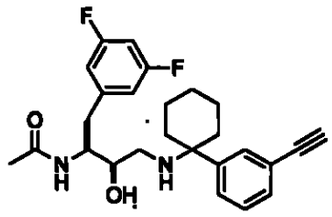


1-(3-Bromo-fenil)-ciclohexilamina (Pharmacia, 1,04 g, 4,09 mmol) fue purificada y después disuelta en trietilamina (20 mL, 143mol) antes de la adición de diclorobis(trifenilfosfina) paladio(II) (0,119 g, 0,170 mmol) y yoduro de cobre (0,040 g, 0,211 mmole). La mezcla de

473

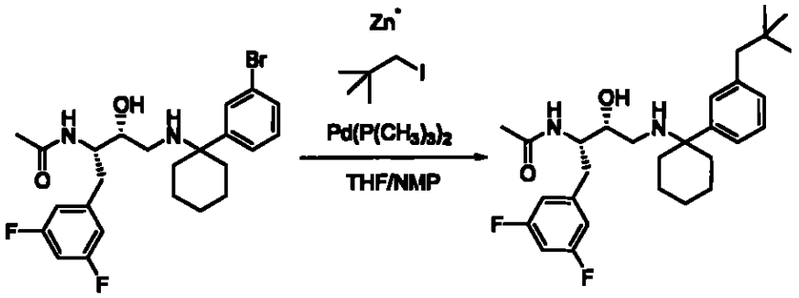
reacción se calentó al punto de reflujo y a tal punto se añadió trimetilsililacetileno (0,85 mL, 6,01 mmole) por medio de una jeringa. Después de refluir durante 3h, la mezcla de reacción fue enfriada a temperatura ambiente antes de ser particionada entre EtOAc y $NaHCO_3$ (aq) saturada. La fase acuosa se recogió y extrajo con EtOAc (3X). Las fases orgánicas entonces fueron recogidas y lavadas con NaCl (aq) saturada, separadas, secadas (Na_2SO_4) y concentradas bajo presión reducida. El producto crudo fue utilizado sin ninguna purificación adicional.
El intermediario de trimetilsilil fue disuelto en metanol (5mL) y 1 N KOH (6 mL) y agitado a temperatura ambiente durante 5,5 h. La mezcla de reacción fue entonces particionada entre EtOAc y $NaHCO_3$ (aq) saturada. La capa orgánica fue separada, secada (Na_2SO_4), y concentrada bajo presión reducida. El residuo fue purificado por cromatografía flash (5%MeOH, 94,5% $CHCl_2$, 0,5% NH_4OH) para obtener la amina deseada (0,35g, 31%): espec. de masa (CI) 183,1 (M-16).

G. Preparación de (1*S*,2*R*)-*N*-{1-(3,5-difluorobencil)-3-[1-(3-(etilfenil)ciclohexilamino]-2-hidroxi-propil}acetamida (80)



El producto del paso F es transformado en el producto anterior utilizando métodos análogos a otros descritos en la aplicación. Análisis espectrométrico de masa: (CI) 441,2 (M+H).

H. Preparación de (1*S*,2*R*)-*N*-(1-(3,5-difluorobencil)-3-{1-[3-(2,2-dimetilpropil)fenil]ciclohexilamino}-2-hidroxipropil)acetamida (81)

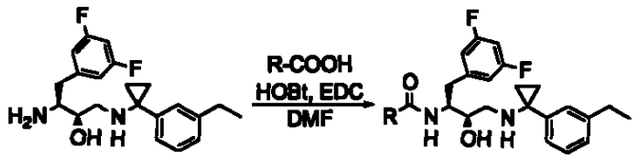


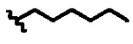
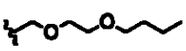
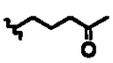
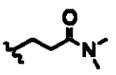
474

El producto deseado se prepara utilizando métodos análogos a otros descritos en la aplicación. Espec. de masa: (CI) 487,2 (M+H), 509 (M+Na).

EJEMPLO 101:

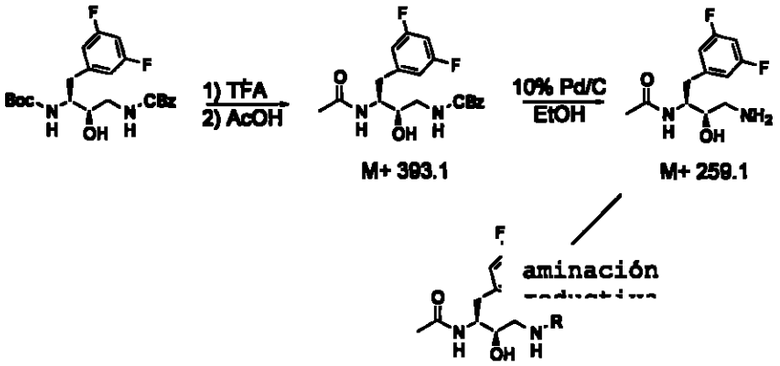
A. Una síntesis de los siguientes inhibidores se llevó a cabo utilizando esencialmente las mismas condiciones de acoplamiento descritas anteriormente en el Esquema I, excepto por la variante en el uso de los materiales iniciales de ácido carboxílico descritos más abajo.

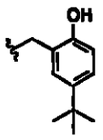
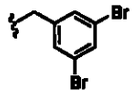


	MH+		
R = 	445.2	(*1S, 2R*) Pentanoic acid {1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide	(82)
	473.3	(*1S, 2R*) Heptanoic acid {1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide	(83)
	485.3	(*1S, 2R*) 2-Cyclohexyl-*N*-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-acetamide	(84)
	519.2	(*1S, 2R*) 2-(2-Butoxy-ethoxy)-*N*-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-acetamide	(85)
	473.2	(*1S, 2R*) 5-Oxo-hexanoic acid {1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide	(86)
	488.2	(1S, 2R) *N*-{1-(3,5-Difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-*N',N'*-dimethyl-succinamide	(87)

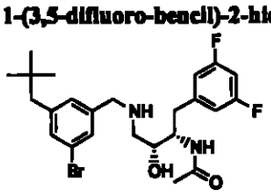
B. La preparación de derivativos de bencilamina disustituidos se realizó generalmente de la siguiente manera:

475



R =	M+		
	421.2	*(1S, 2R)* *N*-[3-(5-*tert*-Butyl-2-hydroxy-benzylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	(88)
	508.9	*(1S, 2R)* *N*-[3-(2,5-Dibromo-benzylamino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	(89)

Ejemplo 101a: Preparación de [(*1S,2R*) N-[3-[3-bromo-5-(2,2-dimetil-propil)-bencilamina]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida] (90)

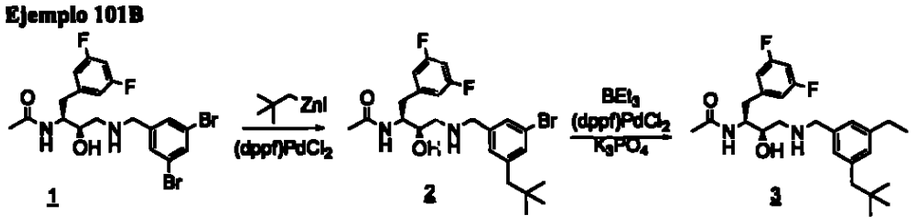


A dibromobencilamina (*1S,2R*) N-[3-(2,5-dibromo-bencilamina)-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida (0,504 g, 1,0 mM, 1 eq) se añadió una solución 0,5 M THF de yoduro de neopentilzinc (20 mL, 10 eq) y 0,082 g.(0,1 mM, 0,1 eq) de [1,1'-bis(difenilfosfino)ferroceno] dicloropaladio(II), complejo con diclorometano ($Pd(dppf)Cl_2$ CH_2Cl_2). La mezcla de reacción se dejó bajo agitación durante la noche a temperatura ambiente. La reacción fue extinguida con una solución acuosa saturada de NH_4Cl (20 mL) y extraída con acetato de etilo (3 x 30 mL). Las capas orgánicas combinadas fueron lavadas con salmuera, secadas y concentradas. [(*1S,2R*) N-[3-[3-Bromo-5-(2,2-dimetil-propil)-bencilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida] (90) fue purificado por HPLC, proporcionando 0,055 g (11%), ^1H NMR (300 MHz, DMSO-d_6) □ 8,60-9,00 (m, 1H), 7,88 (d,J = 8,7 Hz, 1H), 7,61 (s, 1H), 7,39 (s, 1H), 7,08 (s, 1H), 7,05 (t,J = 7,5 Hz, 1H), 6,93 (d,J = 6,9 Hz, 2H), 4,16 (bs, 2H), 3,85 (m,1H), 3,70 (m, 1H),

476

3,02 (m, 2H), 2,81 (m, 1H), 2,57 (m, 1H), 2,47 (s, 2H), 1,69 (s, 3H), 0,87 (s, 9H); ^{13}C NMR (300 MHz, DMSO-d_6) □ 170,0, 164,4, 164,2, 161,1, 160,9, 144,2, 142,9, 134,2, 133,9, 131,8, 131,0, 121,6, 112,9, 112,6, 102,2, 69,3, 53,5, 50,1, 49,1, 35,4, 32,1, 29,6, 23,0; MH+ (CI): 497,2.

Ejemplo 101B

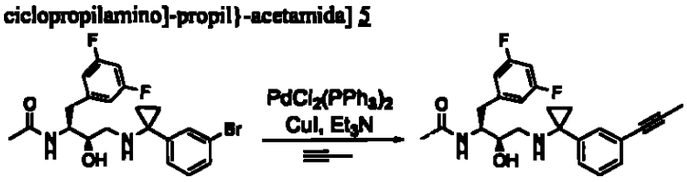


1 2 3

El compuesto (3) [(*1S,2R*) N-{1-(3,5-difluorobencil)-3-[3-(2,2-dimetilpropil)-5-etil-bencilamina]-2-hidroxipropil}-acetamida] fue preparado haciendo reaccionar el compuesto del Ejemplo 101A con BEt_3,un catalizador de paladio y fosfato de potasio. MH+ (CI): 447,2.

Ejemplo 101C

Preparación de [(*1S.2R*) N-{1-(3,5-difluorobencil)-2-hidroxi-3-[1-(3-prop-1-inil-fenil)-ciclopropilamino]-propil}-acetamida] 5



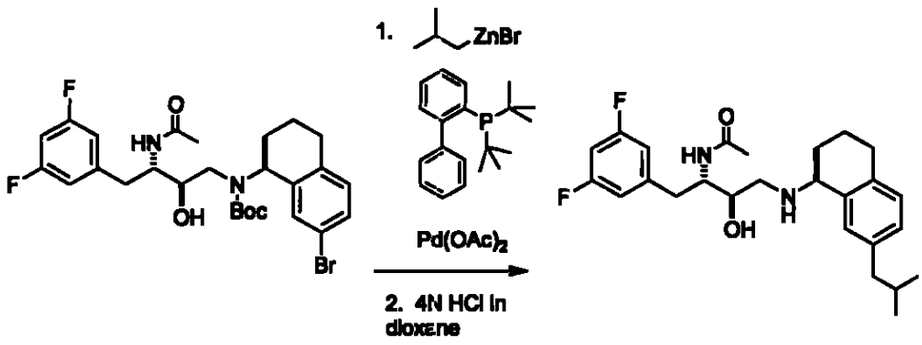
4 5

A una solución de (*1S.2R*) N-[3-[1-(3-bromo-fenil)-ciclopropilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida 4 (0,227 g.0,5 mM) en Et_3N (2 mL) y DMF (0,5 mL) se añadió $PdCl_2(PPh_3)_2$. La mezcla de reacción fue enfriada hasta –30°C y se hizo burbujear gas propeno en la mezcla durante 1 minuto. Se selló un tubo de reacción y la mezcla se agitó durante 2 min antes de que se añadiera CuI (0,001g). Tras agitar durante 10 min adicionales en un tubo sellado a temperatura ambiente el color de la mezcla de reacción cambió de amarillo a marrón oscuro. La reacción se calentó a 50°C durante 48 horas, se enfrió hasta temperatura ambiente, se filtró y se eliminó el disolvente. Purificado por HPLC; rendimiento 0,030g (15%); MH+ (CI): 413,2.

EJEMPLO 102

A. Preparación de N-(1*S.2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-[(1*S*)-(7-isobutil-1,2,3,4-tetrahidronaftaleno-1-ilamina)]-propil]-acetamida

977

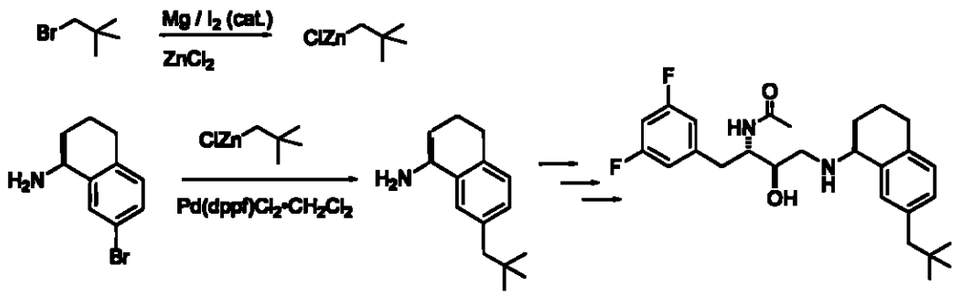


Acetato de paladio (II) (0,2 equiv, 0,07 mmol, 15,8 mg) y 2-(di-t-butilfosfino)bifenil (0,1 equiv, 0,035 mmol.10,5 mg) se disuelven en THF (2 mL) y son desoxigenados con una purga subsuperficial de N_2 (g) durante 5 minutos. Se añade bromuro (1 equiv, 0,352 mmol, 200 mg) en forma de sólido a esta solución, seguido de bromuro de isobutilo zinc (0,5 M solución en THF, 3 equiv, 1,1 mmol, 2,1 mL). La reacción se dejó bajo agitación durante toda la noche a la temperatura ambiente bajo una atmósfera de N_2 (g). Después de 12 horas, la reacción se particionó entre EtOAc y H_2O, se extrajo x3 en EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, secaron sobre Na_2SO_4, se filtraron y concentraron. Mediante cromatografía de columnas de SiO_2 con 30 → 50 % EtOAc en hexanos se obtuvo el producto protegido por Boc puro deseado. (148 mg, 77 % resultado) $M+Na^+$ (CI) = 567,2.

La eliminación del grupo Boc se consiguió disolviendo el compuesto anterior en 4N HCl en dioxano (1 mL) y agitando a temperatura ambiente durante 1 hora bajo una atmósfera de N_2 (g). La mezcla nebulosa blanca resultante se concentró para obtener el producto final. (100 mg, 85% resultado) ^{1}HNMR (CD_3OD): □ 7,3 (s, 1H), 7,15 (s, 2H), 6,9 (m, 2H), 6,8 (m, 1H), 4,6 (t, 1H), 4,05 (m, 1H), 3,9 (m, 1H), 3,2 (m, 2H), 3,0 (m, 1H, 2,8 (m, 2H), 2,7 (m, 2H), 2,5 (d, 2H), 2,2 (m, 2H), 2,0 (m, 1H), 1,85 (s, 3H), 1,85, (m, 1 H), 0,9 (m, 6H). $M+H^+$ (CI) = 445,2.

B. Preparación de *N*-(1*S*,2*R*)-{1-(3,5-difluoro-bencil)-3-[(1*S*)-7-(2,2-dimetilpropil)-1,2,3,4-tetrahidro-naftaleno-1-ilamina]-2-hidroxipropil}-acetamida

478

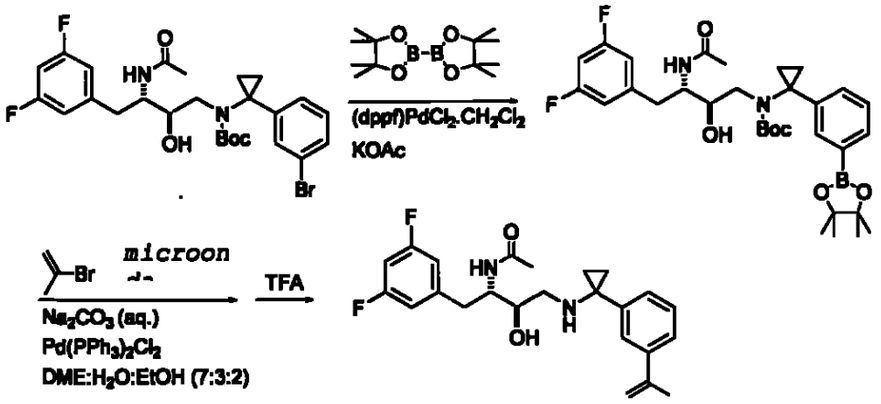


Se agitaron vigorosamente tiras de magnesio (1,5 equiv, 45 mmol, 1,1 g) y I_2 (catalítico) y se calentaron lentamente con una pistola de calor bajo N_2 (g) para activar el magnesio. El magnesio se enfrió hasta temperatura ambiente antes de la adición de una solución 0,5 M THF de $ZnCl_2$ (1 equiv, 30 mmol, 60 mL) seguido de bromuro de neopentilo (1,5 equiv, 45 mmol, 6,94 g, 5,8 mL). En cuestión de 5-10 minutos, la reacción se volvió una suspensión blanca. Finalmente, esta suspensión se volvió gris. La mezcla se calentó hasta
50 °C durante la noche seguido de 2 horas adicionales de calentamiento a reflujo. La suspensión gris se enfrió hasta la temperatura ambiente y se utilizó cruda para la siguiente reacción. Se supone que esta solución de cloruro de neopentilzinc tenía una concentración aproximada de 0,5 M.

A la amina de bromotetralina (1 equiv, 8 mmol, 1,71 g) se le añadió la suspensión cruda de cloruro de neopentilzinc (3 equiv, 24 mmol, 48 mL), seguida de $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0,05 equiv, 0,4 mmol, 330 mg). La reacción se dejó bajo agitación a temperatura ambiente bajo N_2 (g) durante la noche. La suspensión se volvió rápidamente amarilla, y finalmente se volvió de tonos violáceos durante la noche. Después de 12 h, la reacción se enfrió con NH_4Cl (aq) y se extrajo x3 con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, secaron sobre Na_2SO_4, se filtraron y concentraron. Usando cromatografía de columnas de SiO_2 con 2 → 10 % MeOH en CH_2Cl_2 se obtuvo la tetralinaneopentilamina deseada. (1,5 g, rendimiento del 86%) ^{1}HNMR ($CDCl_3$): δ7,15 (s,1H), 6,95 (m, 2H), 3,95 (m, 1H), 2,8 (m, 2H), 2,4 (s, 2H), 2,0 (m, 2H), 1,7 (m, 2H), 1,6 (amplio s, 2H), 1,0 (s, 9H); M-NH_2^+ (CI) = 201,2.

El compuesto final se sintetizó vía una apertura de epóxido, desprotección del grupo protector, y la acetilación como se ha descrito anteriormente: M+H^+ (CI) = 459,2.

C. Preparación de *N*-(1*S*.2*R*)-{1-(3,5-difluorobencil)-2-hidroxi-3-[1-(3-isopropenil-fenil)-ciclopropilamina]-propil}-acetamida

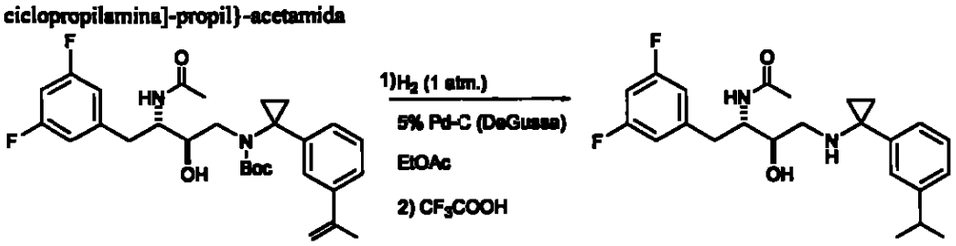


A un matraz se añadieron acetato de potasio (5 equiv, 8,8 mmol, 0,864 g), $(dppf)PdCl_2 \cdot CH_2Cl_2$ (0,04 equiv, 0,0704 mmol, 57,5 mg), y reactivo diboro (1,15 equiv, 2,03 mmol, 0,515g), seguido de bromuro (1 equiv, 1 g, 1,76 mmol) y DMF (7 mL).La mezcla se desoxigenó por medio de una purga subsuperficial N_2 (g) y se agitó a 80°C bajo N_2 (g) durante la noche. En cuanto se empezó el calentamiento, la mezcla de reacción se volvió marrón. Después de 18 h, la mezcla de la reacción se particionó entre EtOAc y H_2O, y se extrajo x3 con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, y se filtraron antes de eliminar el disolvente al vacío. Una columna rápida de SiO_2 con 20→50% EtOAc en hexanos proporcionó el éster borónico puro, (0,75 g, rendimiento del 69%) ^{1}HNMR (CD_3OD): □ 7,6 (t, 1H), 7,25 (m, 1H), 7,1 (m, 1H), 7,8 (dd, 2H), 6,6 (m, 1H), 4,05 (m, 1H), 3,8 (m, 1H), 3,5 (m, 2H), 2,9 (m, 2H), 1,8 (s, 3H), 1,4 (s, 9H), 1,2 (m, 12 H), 1,2 (m, 4 H). $M+Na^+$ (Cl) = 623,2.

El éster de boro (1 equiv, 0,167 mmol, 100 mg) seguido de $Pd(PPh_3)_2Cl_2$ (0,1 equiv, 0,017 mmol, 11,7 mg), 2-bromopropeno (1,2 equiv, 0,2 mmol, 24,2 mg, 17,8 □L), 2M Na_2CO_3 (aq) (1,5 equiv, 0,25 mmol, 0,125 mL), y finalmente 7:3:2 DME:$H_2$0:EtOH (0,7 mL) fueron colocados en un recipiente de reacción equipado con una varilla para agitar. El recipiente se selló y la mezcla de reacción se preagitó durante 15 s antes de ser puesta en el microondas a 160 °C durante 7 minutos a un Nivel de Absorción Normal y con Tiempo de Retención Fijado activado. (Se utilizó un reactor de microondas de *Personal Chemistry*). La mezcla de reacción se particionó entre EtOAc y H_2O, y se extrajo x3 con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, y se filtraron antes de la eliminación del disolvente al vacío. La purificación por medio de una columna de SiO_2 operada con 10→35% EtOAc en hexanos proporcionó el compuesto de estireno puro protegido por Boc. (45,9 mg, rendimiento del 53%) $M+Na^+$ (Cl) = 537,2

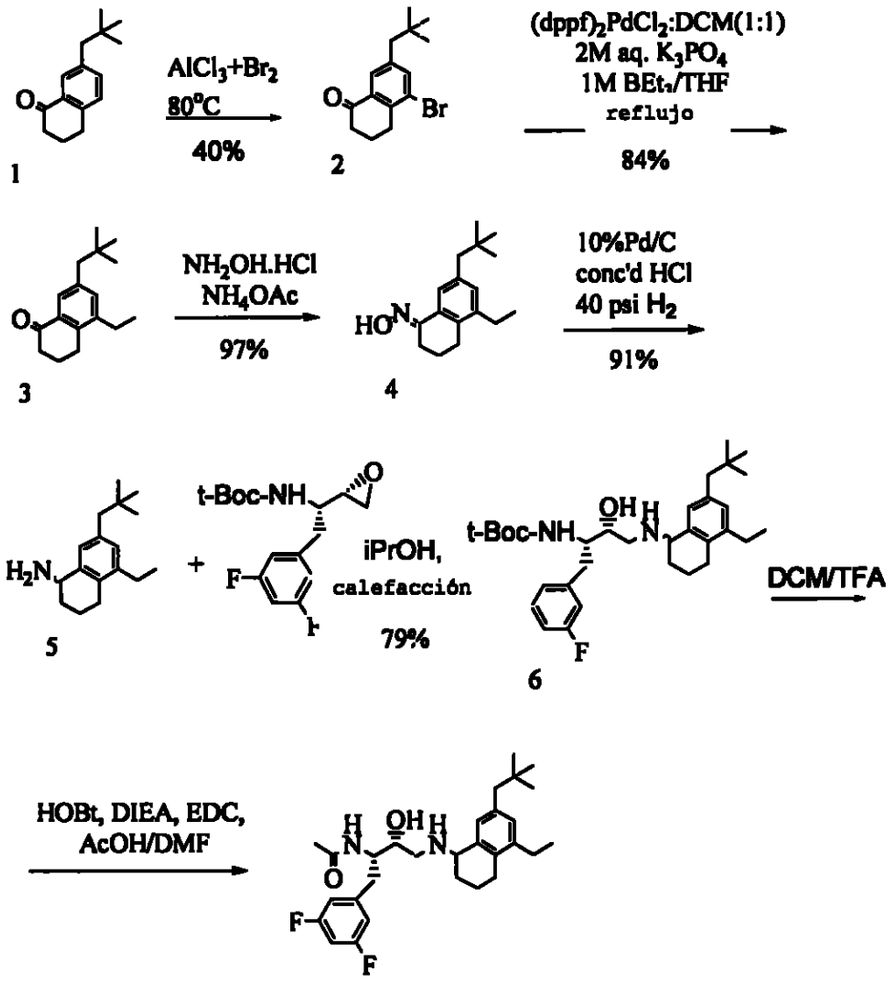
La eliminación del grupo Boc se consiguió tratando el compuesto protegido mencionado anteriormente con 1:4 TFA:CH_2Cl_2 a 0°C. La mezcla de reacción se agitó durante 2 h a 0°C, y después se concentró para obtener el producto deseado. La purificación HPLC proporcionó el producto puro deseado (7 mg, rendimiento del 36%): $M+H^+$ (CI) = 415,2.

D. Preparación de *N*-(1*S*,2*R*)-{1-(3,5-difluorobencil) -2-hidroxi-3-[1-(3-isopropilfenil)-ciclopropilamina]-propil}-acetamida



La amina Boc (1 equiv, 0,1 mmol, 55,4 mg) se disolvió en EtOAc antes de la adición del catalizador 5% Pd-C DeGussa (en una cantidad no medida). El aire se evacuó del matraz antes de que se aplicara un tubo de N_2 (g). La mezcla se agitó durante 4 h a temperatura ambiente Y, en ese momento, mediante ensayos HPLC-MS se determinó que la reacción era completa. La filtración a través de tierra de diatomeas seguida por la eliminación del disolvente mediante vacío resultó en el material reducido crudo limpio. (56,7 mg, cuantitativo) $M+H^+$ (CI) = 517,3.
La eliminación del grupo Boc se consiguió disolviendo el compuesto anterior en 50:50 TFA:CH_2Cl_2 y agitando a temperatura ambiente durante 1 hora bajo una atmósfera de N_2 (g). La solución resultante se concentró para proporcionar el producto final. (41,6 mg, cuantitativa): ^1H NMR (CD_3OD) δ 7,4 (s, 1H), 7,25 (m, 3H), 6,7 (m, 2H), 6,6 (m, 1H), 4,0 (m, 1H), 3,9 (m, 1H), 2,9 (m, 4H), 2,7 (m, 1H), 1,8 (s, 3H), 1,2 (d, 6 H), 1,2 (m, 4H). $M+H^+$ (CI) = 417,2.

EJEMPLO 103



1 2 3 4 5 6

PASO 1:

A 2,33 g (17,5 mmole, 2,5 eq.) de cloruro de aluminio se añadió en gotas 1,51 g (7 mmole) de 7-neopentiltetralina (1) calentado a 80° C, y se añadió bromo en gotas (0,43 mL, 8,4 mmole) durante 15 minutos. La mezcla de reacción se agitó 15 minutos más y se vertió en una mezcla de 2,8 ml de HCl concentrado y 21 g de hielo, se diluyo con 50 ml de agua, se extrajo con éter x3 y lavó con agua x2, se secó con sulfato de sodio anhidro, se separó del disolvente y se hizo pasar

482

por una columna flash resultando en 0,83 g (40%) de 2 en forma de sólido: TLC (10% EtOAc/Hexano) R_f = 0,48; MH+ (Cl) 295,0 (^{79}Br).

Paso 2:

La transferencia mediada por paladio del grupo etilo al bromuro de arilo se ha descrito anteriormente para obtener el compuesto 3. Rendimiento: 84%; MH+ (Cl) 245,2.

Paso 3:

La formación de la oxima se llevó a cabo como se ha descrito anteriormente para obtener el compuesto 4. Rendimiento: 97%; MH+ (Cl) 260,2.

Paso 4:

La reducción de la oxima a amina se consiguió como se ha descrito anteriormente para obtener el compuesto 5. Rendimiento: 91%; MH+ (Cl) 229,2.

Paso 5:

La apertura de epóxido se realizó como se ha descrito anteriormente. Rendimiento: 79%; MH+ (Cl) 545,3.

Paso 6:

La desprotección del Boc y acetilación se realizó como se ha descrito anteriormente. La mezcla diastereoisomérica resultante se purificó en HPLC de fase inversa para obtener los dos isómeros de :

N-(1*S*,2*R*)-{1-(3,5-difluorobencil)-3-[7-(2,2-dimetilpropil)-5-etil-1,2,3,4-tetrahidronaftalen-1-ilamina]-2-hidroxipropil}acetamida,

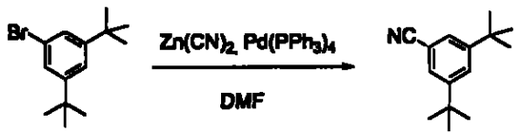
Isómero 1: MH+ (Cl) 487,3.

Isómero 2: MH+ (Cl) 487,3.

EJEMPLO 104: SÍNTESIS DE DERIVADOS 3,5-DISUSTITUIDOS DE BENCILAMINA

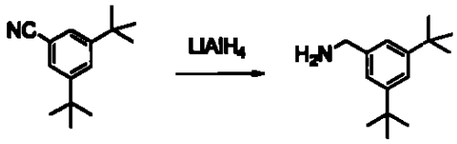
A. 3,5-di-*terc-butil*benzonitrilo a partir de 3,5-di-*terc-butil*bromobenceno.

483



De acuerdo con el procedimiento detallado en Dudley, D. A. et al. J. Med. Chem. 2000, *43*, 4063-4070, se disolvió 3,5-di-*terc-butil*bromobenzeno (Lancaster, 2,65 g, 9,8 mmol) en DMF seco (20 mL) a temperatura ambiente, se añadieron cianuro de Zinc(II)(680 mg, 0,6 equiv, 5,8 mmol) y tetrakis(trifenilfosfina) paladio (0) (900 mg, 0,08 equiv, 0,78 mmol), y la mezcla se calentó hasta 100 °C durante 22 h. La mezcla de reacción se dejó enfriar entonces hasta alcanzar la temperatura ambiente, se diluyó con agua (50 mL), y se extrajo con EtOAc (x2 100 mL). Las capas orgánicas combinadas se lavaron (salmuera, 50 mL), secaron ($MgSO_4$), filtraron y concentraron bajo presión reducida. El sólido crudo se purificó por cromatografía flash (R_f = 0,68 en 10% EtOAc/hexanos) para dar 1,46 g del 3,5-di-*terc-butil*benzonitrilo deseado en forma de sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7,64 (s, 1H), 7,48 (d,J = 1,8 Hz, 2H), 1,33 (s, 18H); espec. de masa (CI): 175,1.

B. 3,5-di-terc-butilbencilamina

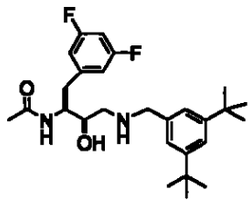


A 3,5-di-*terc*-butilbenzonitrilo (863 mg, 4,02 mmol) en THF seco (10 mL) a 0 °C se le añadió hidruro de litio y aluminio (304 mg, 8,0 mmol) en una porción. La mezcla de reacción se calentó hasta alcanzar la temperatura ambiente durante 2 horas, momento en que la reacción se extinguió (0,2 mL agua, seguida de 0,2 mL de una solución de hidróxido de potasio al 15% y 0,6 mL agua). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora, luego se filtró a través de tierra de diatomeas (elución de CH_2Cl_2). Luego se concentró el filtrado y se lo utilizó en la siguiente reacción sin ninguna purificación adicional: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7,33 (s, 1H), 7,16 (d,J = 1,8 Hz, 2H), 3,86 (s, 2H), 1,33 (s, 18H); espec. de masa (CI): 203,2 (M-NH_2).

La amina libre se hizo reaccionar en forma adicional para formar el producto final como se ha descrito anteriormente.

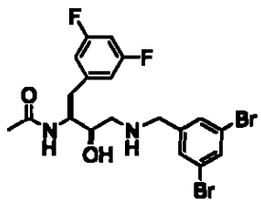
C. *N*-[(1*S*,2*R*)-3-(3,5-di-*terc-butil*-bencilamina)-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida

484



^{1}H NMR (300 MHz, $CDCl_3$) □ 7,36 (s, 1H), 7,16 (d,J = 1,4 Hz, 2H), 6,90 (d,J = 8,8 Hz, 1H), 6,70 (d,J = 6,2 Hz, 2H), 6,61 (tt,J = 9,0, 2,0 Hz, 1H), 4,22-4,10 (m, 1H), 4,03 (br s, 1H), 3,80 (d,J = 12,9 Hz, 1H),.3,74 (d,J = 12,9 Hz, 1H), 3,72-3,60 (m, 1H), 2,90-2,65 (m, 4H), 1,85 (s, 3H), 1,32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,5, 162,8 (dd,J = 248,2, 13,0 Hz, 2C), 151,0, 142,1 (t,J = 9,1 Hz, 1C), 137,3, 122,6, 121,5, 111,9 (dd,J = 16,9, 7,5 Hz, 2C), 101,8 (t,J = 25,3 Hz, 1C), 70,1, 54,2, 53,6, 50,7, 36,1, 34,7, 31,4, 23,2; MH+ (Cl): 461,3.

D. *N*-[(1S,2R)-3-(3,5-dibromobencilamina)-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida



El inhibidor del título se obtuvo por medio de aminación reductiva utilizando el aldehído comercialmente disponible sobre el intermediario de alcohol de amino Boc, seguido de desprotección y acetilación como se ha descrito anteriormente: ^{1}H NMR (300 MHz, $CDCl_3$) □ 7,56 (t,J = 1,5 Hz, 1H), 7,40 (d,J = 1,5 Hz, 2H), 6,74 (d,J = 6,2, 1,8 Hz, 2H), 6,68 (tt,J = 9,0, 2,2 Hz, 1H), 5,63 (d,J = 8,9 Hz, 1H), 4,20-4,05 (m, 1H), 3,78 (d,J = 13,9 Hz, 1H), 3,71 (d,J = 13,9 Hz, 1H), 3,51 (q,J = 5,3 Hz, 1H), 2,99 (dd,J = 14,3, 4,7 Hz, 1H), 2,82 (dd,J = 14,3, 8,7 Hz, 1H), 2,67 (d,J = 3,0 Hz, 2H), 1,93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,4, 163,0 (dd,J = 248,2, 13,0 Hz, 2C), 143,9, 141,7 (t,J = 9,1 Hz, 1C), 132,8, 129,8, 123,0, 112,0 (dd,J = 16,9, 7,5 Hz, 2C), 102,2 (t,J = 25,3 Hz, 1C), 70,7, 52,9, 52,8, 50,5, 36,1, 23,3; MH+ (Cl): 505,0 (^{79}Br X 2).

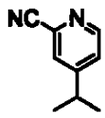
485

EJEMPLO 105: SÍNTESIS DE DERIVADOS DE PIRIDINA



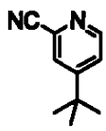
De acuerdo con el método de Ornstein, P. L. et al. *J. Med. Chem.* 1991, *34*, 90-97, *N*-óxido de 4-cloropiridina (Aldrich, 10,5 g, 81,2 mmol) se combinó en cloruro de metileno seco (50 mL) con cianotrimetilsilano (14,0 mL, 105 mmol) y cloruro de *N,N*-dimetilcarbamoilo (7,5 mL, 81,5 mmol) a temperatura ambiente. Esta mezcla se agitó a temperatura ambiente durante 24 horas, después de lo cual se concentró bajo presión reducida, y el residuo se filtró a través de sílice (elución de CH_2Cl_2) para dar 8,4 g de producto en forma de un sólido cristalino blanco: ^{1}H NMR (300 MHz, $CDCl_3$) □ 8,64 (d,J = 5,3 Hz, 1H), 7,72 (d,J = 1,7 Hz, 1H), 7,56 (dd,J = 5,3, 1,7 Hz, 1H); MH+ (CI): 139,0 (^{35}Cl).

A. 2-ciano-4-isopropilpiridina



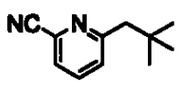
2-Ciano-4-isopropilpiridina se sintetizó de acuerdo con el método de Ornstein, P. L. et al. J. Med. Chem. 1991,*34*, 90-97: MH+ (CI): 147,1.

B. 2-Ciano-4-*terc-butil*piridina



2-Ciano-4-*terc-Butil*piridina se sintetizó de acuerdo con el método de Ornstein, P. L. et al. J. Med. Chem. 1991, *34*, 90-97: ^{1}H NMR (300 MHz, $CDCl_3$) □ 8,60 (d,J = 5,3 Hz, 1H), 7,68 (d,J = 1,5 Hz, 1H), 7,49 (dd,J = 5,3, 1,9 Hz, 1H), 1,33 (s, 9H); MH+ (CI): 161,1.

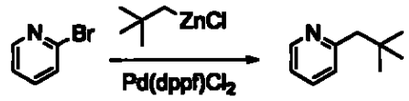
C. 2-ciano-6-neopentilpiridina



486

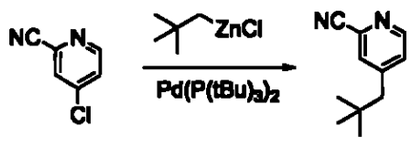
2-Ciano-6-neopentilpiridina se sintetizó a partir de 2-neopentilpiridina de acuerdo con el método de Ornstein, P. L. et al. J. Med. Chem. 1991,*34*, 90-97: R_f = 0,62 in 20% EtOAc/hexanos; MH+ (CI): 175,1.

D. 2-neopentilpiridina a partir de 2-bromopiridina



Se preparó una solución de cloruro de neopentilzinc de acuerdo con el método de Negishi, E.-I. et al. *Tetrahedron Lett*, 1983, *24*, 3823-3824. Se añadió bromuro de neopentil (2,83 mL, 22,5 mmol) a una suspensión de cloruro de zinc(II)(0,5 M en THF, 30 mL, 15,0 mmol) y magnesio (Aldrich, pequeñas tiras, 560 mg, 22,5 mmol) a 50 °C. Esta suspensión se agitó a 50 °C durante 18,5 horas. Se dejó enfriar a la suspensión resultante hasta alcanzar la temperatura ambiente y se utilizó sin ninguna purificación adicional en la reacción siguiente. Se añadieron 2-bromopiridina (Aldrich, 0,48 mL, 5,0 mmol) y [1.1'bis(difenilfosfino)ferroceno]dicloropaladio(II) complejo con diclorometano (1:1) (Aldrich, 200 mg, 0,25 mmol) a la suspensión de cloruro de neopentilzinc. La suspensión resultante se agitó a temperatura ambiente durante 21 horas, después de lo cual se añadió una solución de cloruro de amonio saturado (25 mL). La mezcla se extrajo con acetato de etilo (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), filtraron y concentraron bajo presión reducida. El residuo se disolvió en cloruro de metileno, y se lavó con 1 N HCl. La capa acuosa se separó, basificada con 10 N NaOH (aq), y se extrajo con CH_2Cl_2. La capa orgánica se secó (Na_2SO_4), filtró y concentró bajo presión reducida para obtener 2-neopentilpiridina en forma de aceite: R_f = 0,33 en 5% MeOH/CH_2Cl_2.

E. 2-ciano-4-neopentilpiridina

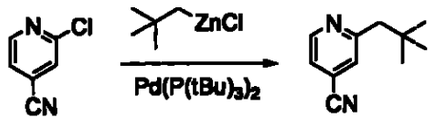


Esto se realizó de acuerdo con el método de Dai, C. and Fu, G. *J. Am. Chem. Soc.* 2001, *123*, 2719-2724. A yoduro de neopentilo (2,0 mL, 15,1 mmol) en THF seco (10 mL) en un recipiente de reacción de tapón de rosca de 100 mL a la temperatura ambiente se añadió una suspensión de

487

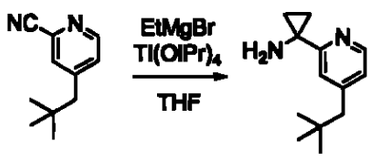
zinc Rieke (5 g en 100 mL THF, 20 mL, 15,3 mmol). Esta suspensión oscura se agitó durante 30 min, después de lo cual se añadió *N*-metilpirrolidinona (22 mL). Después de 15 min, se añadieron bis(tri-*terc*-*butil*)fosfinopaladio(0) (Strem, 747 mg, 1,46 mmol) y 4-cloro-2-cianopiridina (1,4 g, 10 mmol). El recipiente se taponó y la mezcla se calentó hasta alcanzar 100 °C durante 24 h. Se dejó enfriar la mezcla hasta alcanzar la temperatura ambiente, luego se añadió 1 N HCl acuosa (50 mL), y esto se extrajo con dietil éter (4 X 80 mL). Los extractos orgánicos combinados se secaron (Na_2SO_4), filtraron y concentraron, El residuo crudo se purificó por filtración a través de un pequeño tapón de sílice (elución de 20% éter/hexanos) para obtener 600 mg del 2-ciano-4-neopentilpiridina: R_f = 0,25 en 20% Et_2O/hexanos; MH+ (CI): 175,1.

F. 4-ciano-2-neopentilpiridina



El método para la síntesis de 2-ciano-4-neopentilpiridina se utilizó para convertir 2-cloro-4-cianopiridina (Oakwood) en 4-ciano-2-neopentilpiridina: R_f = 0,47 en 10% EtOAc/hexanos; ^1H NMR (300 MHz, $CDCl_3$) □ 8,73 (dd,J = 4,9, 0,7 Hz, 1H), 7,55-7,40 (m, 2H), 2,75 (s, 2H), 0,96 (s, 9H); MH+ (CI): 175,1.

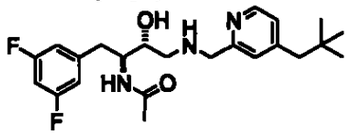
G. 2-cicloalquilamino-4-neopentilpiridina



A una solución de 2-ciano-4-neopentilpiridina (380 mg, 2,2 mmol) en THF seco (6 mL) a temperatura ambiente se añadió isopropróxido de titanio (IV) (0,7 mL, 2,4 mmol) seguido por bromuro de magnesio (1,0 M in THF, 4,3 mL, 4,3 mmol) al tiempo que se agitaba vigorosamente. Después de 30 min, se añadió 1 mL de agua. La mezcla de reacción templada se agitó a temperatura ambiente durante 30 min, después se filtró a través de tierra de diatomeas (elución de 10% iPrOH/$CHCl_3$). El filtrado se concentró bajo presión reducida. El residuo crudo se purificó por medio de cromatografía flash (R_f = 0,26 en 10% MeOH/CH_2Cl_2) para dar 166 mg del producto deseado en forma de aceite: MH+ (CI): 205,1.

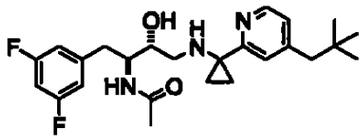
488

H. *N*-((1*S*,2*R*)-1-(3,5-difluorobencil)-3-{[4-(2,2-dimetilpropil)piridina-2-ilmetil]amino}-2-hidroxipropil) acetamida



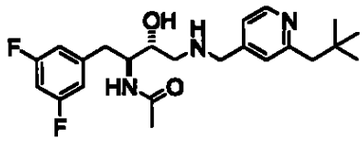
Al 2-aminometil-4-neopentilpiridina utilizado en la síntesis se accedió a partir de 2-ciano-4-neopentilpiridina por métodos de reducción conocidos en este campo: ^{1}H NMR (300 MHz, $CDCl_3$) □ 8,39 (d,J = 5,0 Hz, 1H), 7,03-6,92 (m, 2H), 6,72 (app d,J = 6,3 Hz, 2H), 6,63 (tt,J = 9,0, 2,2 Hz, 1H), 6,44 (d,J = 9,0 Hz, 1H), 4,25-4,10 (m, 1H), 3,93 (s, 2H), 3,72-3,62 (m, 1H), 2,94 (dd,J = 14,3, 4,7 Hz, 1H), 2,88-2,70 (m, 3H), 2,48 (s, 2H), 1,87 (s, 3H), 0,91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,3, 162,8 (dd,J = 248,2, 13,0 Hz, 2C), 157,7, 149,8, 148,3, 142,3 (t,J = 9,1 Hz, 1C), 124,62, 124,56, 112,0 (dd,J = 16,9, 7,4 Hz, 2C), 101,8 (t,J = 25,1 Hz, 1C), 71,0, 54,1, 52,9, 51,5, 49,5, 35,7, 31,7, 29,3, 23,1; MH+ (CI): 420,2.

I. *N*-((1*S*,2*R*)-1-(3,5-difluorobencil)-3-{1-[4-(2,2-dimetilpropil)piridina-2-il]ciclopropilamino}-2-hidroxipropil) acetamida



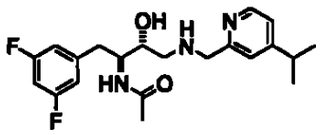
^{1}H NMR (300 MHz, $CDCl_3$)□ 8,35 (d,J = 5,1 Hz, 1H), 6,89 (dd,J = 5,1, 1,0 Hz, 1H), 6,80 (s, 1H), 6,73 (dd,J = 6,2, 2,0 Hz, 2H), 6,64 (tt,J = 9,0, 2,0 Hz, 1H), 5,93 (d,J = 9,2 Hz, 1H), 4,22-4,07 (m, 1H), 3,72 (s, 2H), 3,50 (dt,J = 6,6, 3,3 Hz, 1H), 2,96 (dd,J = 14,3, 4,6 Hz, 1H), 2,90-2,70 (m, 3H), 2,46 (s, 2H), 1,88 (s, 3H), 1,16 (d,J = 2,4 Hz, 4H), 0,90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,0, 163,3 (dd,J = 248,2, 13,0 Hz, 2C), 162,2, 149,4, 147,5, 142,1 (t,J = 9,1 Hz, 1C), 123,2, 120,9, 112,0 (dd,J = 16,9, 7,4 Hz, 2C), 101,9 (t,J = 25,1 Hz, 1C), 71,1, 63,6, 53,4, 52,6, 49,7, 49,4, 42,7, 35,8, 31,7, 29,3, 23,2, 19,0, 18,5; MH+ (CI): 446,2.

J. *N*-((1*S*,2*R*)-1-(3,5-difluorobencil)-3-{[2-(2,2-dimetilpropil)piridina-4-ilmetil]-amino}-2-hidroxipropil) acetamida



Al 4-aminometil-2-neopentilpiridina se accedió por reducción de 4-ciano-2-neopentilpiridina por métodos conocidos en este campo: ^{1}H NMR (300 MHz, $CDCl_3$) □ 8,44 (d,J= 5,0 Hz, 1H), 7,07 (d,J = 5,0 Hz, 1H), 7,06 (s, 1H), 6,72 (d,J = 6,3 Hz, 2H), 6,64 (tt,J = 9,0, 2,2 Hz, 1H), 6,56 (d,J = 8,7 Hz, 1H), 4,25-4,10 (m, 1H), 3,82 (d,J = 14,4 Hz, 1H), 3,76 (d,J = 14,4 Hz, 1H), 3,62 (q,J = 5,0 Hz, 1H), 3,42 (br s, 2H), 2,93 (dd,J = 14,2, 4,9 Hz, 1H), 2,78 (dd,J = 14,2, 8,9 Hz, 1H), 2,73 (d,J = 4,8 Hz, 2H), 2,66 (s, 2H), 1,88 (s, 3H), 0,94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,4, 162,7 (dd,J = 248,2, 13,0 Hz, 2C), 160,2, 148,7, 148,0, 142,0 (t,J = 9,1 Hz, 1C), 123,9, 120,3, 111,8 (dd,J = 16,9, 7,5 Hz, 2C), 101,9 (t,J = 25,3 Hz, 1C), 70,5, 53,4, 52,6, 51,7, 50,8, 36,0, 31,9, 29,5, 23,1; MH+ (Cl): 420,2.

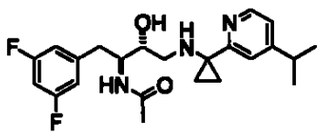
K. *N*-{(1*S*,2*R*)-1-(3,5-difluorobencil)-2-hidroxi-3-[(4-isopropilpiridina-2-ilmetil)-amino]propil}acetamida



^{1}H NMR (300 MHz, $CDCl_3$) □ 8,37 (d,J= 4,7 Hz, 1H), 7,10 (s, 1H), 7,06 (d,J = 5,2 Hz, 1H), 6,94 (d,J = 9,0 Hz, 1H), 6,72 (d,J = 6,3 Hz, 2H), 6,61 (tt,J = 9,0, 2,2 Hz, 1H), 4,77 (br s, 2H), 4,25-4,10 (m, 1H), 3,93 (s, 2H), 3,80-3,70 (m, 1H), 3,05-2,70 (m, 5H), 1,86 (s, 3H), 1,23 (d,J = 7,0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,4, 162,7 (dd,J = 248,2, 13,0 Hz, 2C), 158,8, 157,4, 148,9, 142,4 (t,J = 9,1 Hz, 1C), 120,9, 112,0 (dd,J = 16,9, 7,5 Hz, 2C), 101,7 (t,J = 25,3 Hz, 1C), 70,8, 54,0, 53,2, 51,6, 35,7, 33,5, 22,9; MH+ (Cl): 392,2.

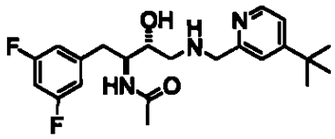
L. *N*-{(1*S*,2*R*)-1-(3,5-difluorobencil)-2-hidroxi-3-[1-(4-isopropilpiridin-2-il)-ciclopropilamino]propil}acetamida

490



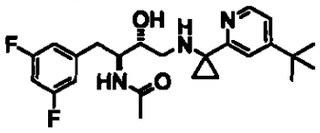
MH+ (Cl): 418,2.

M. *N*-[(1*S*,2*R*)-3-[(4-terc-butilpiridin-2-ilmetil)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida



^{1}H NMR (300 MHz, $CDCl_3$) □ 8,40 (d,J= 5,3 Hz, 1H), 7,22 (s, 1H), 7,19 (dd,J = 5,3, 1,7 Hz, 1H), 6,73 (d,J = 6,3 Hz, 2H), 6,65 (tt,J = 9,0, 2,2 Hz, 1H), 4,26 (br s, 2H), 4,25-4,10 (m, 1H), 3,94 (s, 2H), 3,77-3,67 (m, 1H), 3,05-2,70 (m, 4H), 1,88 (s, 3H), 1,30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,3, 162,8 (dd,J = 248,2, 13,0 Hz, 2C), 161,2, 157,9, 148,8, 142,4 (t,J = 9,1 Hz, 1C), 119,6, 119,5, 112,1 (dd,J = 16,9, 7,5 Hz, 2C), 101,8 (t,J = 25,3 Hz, 1C), 70,9, 54,3, 53,1, 51,7, 35,8, 34,7, 30,4, 28,7, 23,1; MH+ (Cl): 406,2.

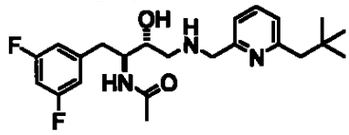
N. *N*-[(1*S*,2*R*)-3-[1-(4-terc-butilpiridina-2-il)ciclopropilamino]-1-(3,5-difluorobencil)-2-hidroxipropil] acetamida



^{1}H NMR (300 MHz, $CDCl_3$) □ 8,38 (d,J= 5,2 Hz, 1H), 7,15-7,05 (m, 2H), 6,73 (d,J = 6,3 Hz, 2H), 6,64 (tt,J = 9,0, 2,2 Hz, 1H), 5,88 (d,J = 9,1 Hz, 1H), 4,22-4,08 (m, 1H), 3,75 (br s, 2H), 3,50 (td,J = 6,5, 3,5 Hz, 1H), 2,99 (dd,J = 14,2, 4,5 Hz, 1H), 2,90-2,70 (m, 3H), 1,89 (s, 3H), 1,30 (s, 9H), 1,25-1,10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170,0, 162,9 (dd,J = 248,2, 13,0 Hz, 2C), 162,5, 160,8, 148,2, 142,1 (t,J = 9,1 Hz, 1C), 118,2, 115,6, 112,0 (dd,J = 16,9, 7,5 Hz, 2C), 101,9 (t,J = 25,3 Hz, 1C), 70,9, 52,6, 49,4, 43,1, 35,9, 34,8, 30,5, 23,2, 18,8, 18,7; MH+ (Cl): 432,2.

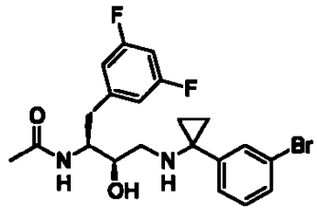
491

O. ***N*-((1*S*,2*R*)-1-(3,5-difluorobencil)-3-{[6-(2,2-dimetilpropil)piridin-2-ilmetil]-amino}-2-hidroxipropil) acetamida**

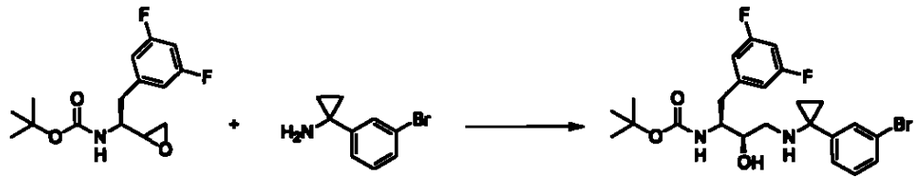


^{1}H NMR (300 MHz, $CDCl_3$) □ 7,56 (t,J= 7,6 Hz, 1H), 7,06 (d,J = 7,6 Hz, 1H), 7,02 (d,J = 7,6 Hz, 1H), 6,74 (dd,J = 6,3, 2,0 Hz, 2H), 6,64 (tt,J = 9,0, 2,2 Hz, 1H), 6,11 (d,J = 9,0 Hz, 1H), 4,25-4,10 (m, 1H), 3,92 (d,J = 1,2 Hz, 2H), 3,70-3,55 (m, 1H), 3,25 (br s, 1H), 2,93 (dd,J = 14,2, 4,9 Hz, 1H), 2,88-2,70 (m, 3H), 2,68 (s, 2H), 1,88 (s, 3H), 0,95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) □170,0, 162,8 (dd,J = 248,2, 13,0 Hz, 2C), 159,8, 157,6, 142,2 (t,J = 9,1 Hz, 1C), 136,3, 123,3, 119,6, 112,0 (dd,J = 16,9, 7,5 Hz, 2C), 101,9 (t,J = 25,3 Hz, 1C), 70,8, 54,2, 52,8, 51,6, 51,5, 35,7, 32,0, 29,5, 23,2; MH+ (Cl): 420,2.

EJEMPLO 106



Paso 1. Apertura del epóxido con 1-(3-bromofenil)ciclopropil amina



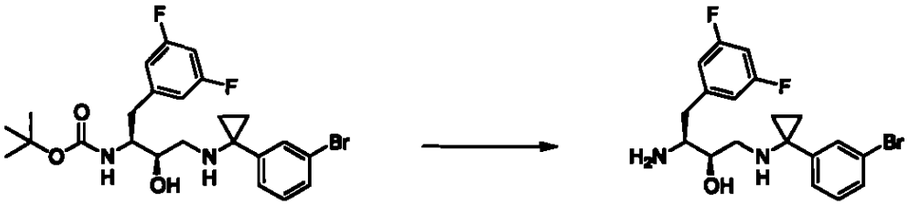
El N-BOC-1-(3-bromofenil)aminociclopropano (15,60 g, 50,2 mmol) se trató con 4N HCl en dioxano (50 mL) y se agitó durante 2 h. Los volátiles se evaporaron *in vacuo* y el residuo

492

se puso en 1N NaOH (250 mL). La mezcla se extrajo con dietil éter (2 x 200 mL). Los extractos de éter combinados se lavaron con salmuera (50 mL), se secaron (sulfato de sodio), después se filtraron y evaporaron *in vacuo* para proporcionar la base libre de aminas. La base libre de aminas se disolvió en 2-propanol (250 mL) y se añadió el epóxido (15,0 g, 50,2 mmol). La mezcla se calentó a reflujo durante 22 h y se dejó reposar a temperatura ambiente durante 3 d. El análisis por HPLC indicó que predominaba el producto deseado, y que alguna ciclopropilamina de origen permanecía sin reaccionar. El epóxido de origen se consumió. Se quitaron los volátiles *in vacuo* y se purificó el residuo mediante cromatografía por flash en gel de anhídrido silícico (eluido 2:1 hexano/acetato de etilo) para proporcionar el producto final (13,68 g, 53%).

LC-MS: [M+H] = 511, 513, Rt=2,31 min, Phenomenex Luna C18 (30 cm x 4,6 mm), 20-70% de CH_3CN/agua/ácido trifluoroacético al 0,1% en 2,33 min, tasa de flujo 1,5 mL/min.

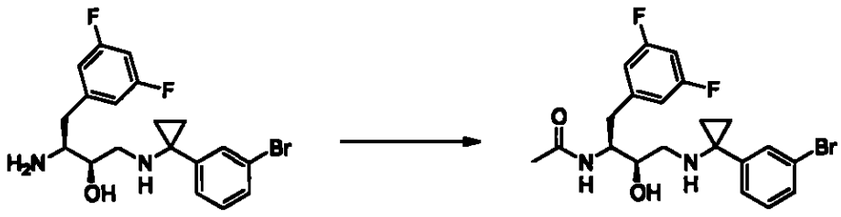
Paso 2. Preparación de S,R 1-(3,5-difluorobenzil)-3-[1-(3-bromofenil)ciclopropilamino)]-2-hidroxipropil amina.



La amina protegida por BOC (13,5 g, 26,7 mmol) se trató con 4N HCl en dioxano (30 mL). Se añadió metanol (15 mL) y la mezcla se volvió homogénea antes de depositar un precipitado. La mezcla se agitó durante 3 h antes de que se separaran los volátiles *in vacuo*. El residuo se puso en 1N NaOH (150 mL) y la mezcla se extrajo con dietil éter (3 x 100 mL). Los extractos combinados de éter se lavaron con salmuera (50 mL), se secaron (sulfato de magnesio), se filtraron y se evaporaron *in vacuo* para dar (3,5-difluorobenzil)-3-[1-(3-bromofenil)ciclopropil-amino)]-2-hidroxipropil amina (6,5 g). El material se utilizó directamente en el siguiente paso.

Paso 3. Preparación del compuesto (n°)

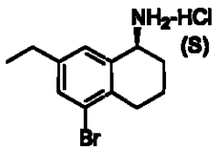
493



La diamina cruda del paso 2 (supuestamente alrededor de 26,7 mmol) se disolvió en diclorometano (250 mL). Se añadió ácido acético (1,53 mL, 1,60 g, 26,7 mmol), seguido de hidrato de 1-hidroxibenzotriazol (4,33 g, 32,0 mmol) y N-metilmorfolina (7,74 mL, 6,75 g, 66,7 mmol). La mezcla se enfrió en un baño de hielo y se añadió 1-(3-dimetil-aminopropil)3-etilcarbodiimidohidrocloruro (5,63 g, 29,4 mmol). La mezcla se agitó en un baño de hielo durante 2 h y después se calentó a temperatura ambiente durante 14 h. La mezcla se diluyó con agua (300 mL) y se extrajo con acetato de etilo (2 x 500 mL). Los extractos combinados se lavaron con bicarbonato sódico saturado acuoso (300 mL), agua (2 x 200 mL) y salmuera (100 mL); después se secaron (sulfato de sodio), se filtraron y se evaporaron *in vacuo* para proporcionar el producto deseado como un sólido blanco (11,75 g, 97%, Nota 1).

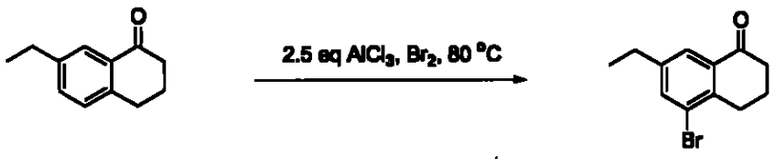
El análisis LC-MS indicó una pureza del 94%. LC-MS: [M+H] =453, 455, Rt=1,86 min, Phenomenex Luna C18 (30 cm x 4,6 mm), 20-70% CH_3CN/agua/ácido trifluoroacético al 0,1% en 2,33 min, tasa de flujo 1,5 mL/min.

EJEMPLO 107



A. Preparación de 5-bromo-7-etil-1-tetralona (nota 1)

994

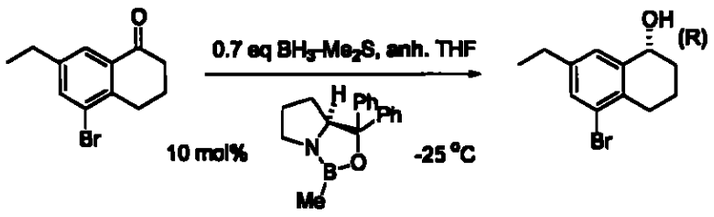


El método sintético se conoce en la técnica, pero aquí se describe brevemente. (Véase, por ejemplo, Cornelius, L.A.M. Combs, D.W., *Synthetic Communications* 1994, *24*, 2777-2788). Un matraz de tres bocas de 500 mL al que se le colocó un embudo adicional, un condensador de reflujo y un termómetro se cargó con cloruro de aluminio (11,23 g, 84,2 mmol) y se calentó a 70°C. Se añadió vía pipeta 7-etil-1-tetralona (5,9 g, 34 mmol). El lodo marrón resultante se agitó durante 5 min, antes de la adición gota a gota de bromo (6,5 g, 2,1 mL, 40 mmol) durante ~2 min. La mezcla se agitó durante 3 min, y después se sacó del baño de aceite. Se añadió 1N HCl (150 mL) helado y la mezcla se agitó hasta que se disolvieron los sólidos. La mezcla se extrajo con dietil éter (2 x 100 mL) y los orgánicos combinados se lavaron con agua (2 x 100 mL), se secaron (sulfato de sodio), se filtraron y se evaporaron *in vacuo* para dar una mezcla marrón oscuro del producto deseado y al menos un producto secundario dibromado. El producto se separó utilizando cromatografía flash con gel de anhídrido silícico (Biotage Flash 75, disolvente de elución 10/1 hexanos: MTBE) para producir 5-bromo-7-etil-1-tetralona (7,4 g, 75%).

El análisis LC-MS indicó la presencia de un producto de dibromo en co-elución con el producto deseado. Este material se tomó para el siguiente paso y se separó.

B. (R)-7-etil-5-bromotetralin-1-ol

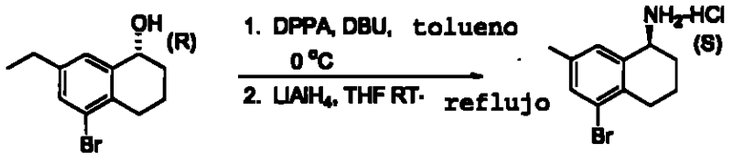
495



Este procedimiento es una adaptación de métodos conocidos en la técnica, (véase por ejemplo, Jones, T.K.; Mohan, J.J.; Xavier, L.C.; Blaclock, T.J.; Mathre, D.J.; Sohar, P.; Turner-Jones, E.T.; Reamer, R.A.; Roberts, F.E.; Grabowski, E.J.J. *J. Org. Chem.* 1991, 56, 763-769). Se colocó 7-etil-5-bromo-1-tetralona (7,45 g, 29,4 mmol) en un matraz de tres bocas con fondo redondo de 250 mL con un embudo de goteo, un termómetro, y una entrada de nitrógeno. La solución se enfrió a –20°C y se añadió 1M (S)-tetrahidro-1-metil-3,3-difenil-1H,3H-pirolo[1,2-c][1,3,2]oxazaborol en tolueno. (2,0 mL, 2,0 mmol, Fuente: Aldrich cat. # 45.770-1, "(S)-2-metil-CBS-oxazaborolidina". La utilización del S-auxiliar produce R-alcoholes. Jones, *et al*, indica que la utilización de 5 mol% de catalizador oxazaborolidina ofrece resultados comparables).

El embudo de goteo se cargó con una solución de borano-metilsulfuro (1,57 g, 1,95 mL, 20,1 mmol) en THF anhidro (55 mL, secado sobre tamices 4A). La solución de borano se añadió gota a gota durante 35 min manteniéndose la temperatura de reacción por debajo de –20°C. La mezcla se agitó durante 3 h de –15 a –20°C después de lo cual el análisis TLC indicó bajo consumo de la quetona. La mezcla se dejó calentar lentamente a ~15°C durante más de 16 h después de lo cual la reacción se templó mediante la adición cuidadosa de metanol (40 mL) a –15°C y se dejó calentar a temperatura ambiente y se agitó durante 16 h. Los volátiles se quitaron *in vacuo* y el residuo se purificó mediante cromatografía de gel de anhídrido silícico (Biotage Flash 65, disolvente de elución 10/1 hexanos: acetato de etilo) para producir (R)-7-etil-5-bromotetralin-1-ol (4,0 g, 53%).

C. **Hidrocloruro de (S)-7-etil-5-bromo-1,2,3,4-tetrahidro-1-naptilamina**



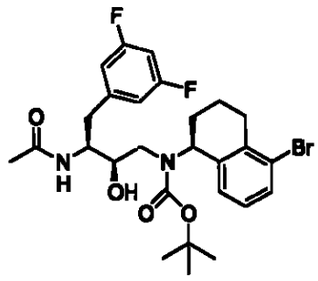
496

Este procedimiento es una adaptación de métodos de la técnica conocidos (por ejemplo, Rover, S., *et al*, *J. Med. Chem.* **2000**, *43*, 1329-1338. Una solución de (R)-7-etil-5-bromotetralin-1-ol (3,90 g, 15,3 mmol) en tolueno (35 mL) se enfrió en un baño de hielo y se trató con difenilfosforilazida (DPPA, 5,05 g, 3,9 mL, 18,3 mmol). Una solución de 1,8-diazabiciclo[5,4,0] undec-7-eno (DBU, 2,79 g, 2,74 mL, 18,3 mmol) en tolueno (15 mL) se añadió durante 20 min y la mezcla se agitó a 0°C durante 2 h y a temperatura ambiente durante 16 h. La mezcla se filtró a través de una almohadilla de gel de anhídrido silícico (eluido 6:1 hexanos/acetato de etilo) para quitar los precipitados y los volátiles se separaron *in vacuo* para dar un residuo oleaginoso de la S-azida cruda. Este material se utilizó directamente en el siguiente paso sin mayor caracterización.

La azida se disolvió en THF seco (50 mL) y se añadió gota a gota a temperatura ambiente a un lodo de hidruro alumínico de litio (0,7 g, 18 mmol) en THF seco (50 mL). La mezcla se agitó a temperatura ambiente durante 1 h y después se calentó a reflujo durante 1 h. La reacción se enfrió en un baño de hielo y se templó mediante sucesivas adiciones de agua (0,7 mL), NaOH al 15% acuoso (0,7 mL) y agua (2,1 mL). La mezcla resultante se agitó durante 1 h y luego se filtró a través de una almohadilla de Celite (dietil éter eluido). Se quitaron los volátiles *in vacuo* y el residuo se colocó en acetato de etilo (50 mL) y se trató con 4N HCl en dioxano (6 mL). El precipitado resultante se filtró (baño acetato de etilo), se recogió y se secó al vacío para dar hidrocloruro de (S)-7-etil-5-bromo-1,2,3,4-tetrahidro-1-naftilamina como un sólido blanco (2,9 g, 65%).

LC-MS: [M-NH2] = 237, 239, Rt = 6,34 min, Phenomenex Luna C18 (30 cm x 4,6 mm), CH_3CN al 5-20%/agua/ácido trifluoroacético al 0,1% en 3,33 min, tasa de flujo 1,5 mL/min.

EJEMPLO 108



997

Paso 1. Apertura del epóxido con (S)-7-bromo-1-aminotetralin para proporcionar el Compuesto nº: XX

Se preparó un lodo de hidrocloruro de (S)-7-bromol-amino tetralin (10,0 g, 38,1 mmol) en dietil éter (200 mL), se trató con 1N NaOH (50 mL) y la mezcla se agitó hasta que todos los sólidos se hubieron disuelto. Se separaron las capas y se extrajo la capa acuosa con dietil éter (2 x 50 mL). Los extractos combinados de éter se lavaron con salmuera (50 mL), se secaron (sulfato de magnesio), después se filtraron y evaporaron *in vacuo* para proporcionar la base libre de aminas.

La base libre de aminas se disolvió en 2-propanol (75 mL) y se añadió el epóxido (11,40 g, 38,0 mmol). La mezcla se calentó a reflujo durante 6 h y se dejó reposar a temperatura ambiente durante 3 días, lo que dio como resultado la formación del producto cristalizado. El producto se recogió vía filtración al vacío (10,81 g, 54%). La lejía madre se concentró y proporcionó un segundo lote de producto (0,86 g, 4%).

El análisis LC-MS indicó que ambos lotes eran puros en aproximadamente un 99%. LC-MS: [M+H] = 527, Rt= 2,34 min, Phenomenex Luna C18 (30 cm x 4,6 mm), CH_3CN al 20-70%/agua/ácido trifluoroacético al 0,1% en 2,33 min, tasa de flujo 1,5 mL/min.

Paso 2. Desprotección del Grupo Boc

La amina protegida por Boc del paso 1 (9,61 g, 18,3 mmol) se trató con 4N HCl en dioxano (25 mL). La mezcla se volvió homogénea antes de depositar un precipitado. La mezcla se agitó durante 2,5 h antes de que se quitaran los volátiles in vacuo. El residuo se puso en agua (100 mL) y se trató con NaOH acuoso al 50% (~12 mL). La mezcla se extrajo con dietil éter (2 x 200 mL). Los extractos combinados de éter se lavaron con salmuera (100 mL), se secaron (sulfato de magnesio), se filtraron y se evaporaron *in vacuo* para dar la base libre de diaminas. El material se utilizó directamente en el siguiente paso.

Paso 3. Acilación de amina N-terminal

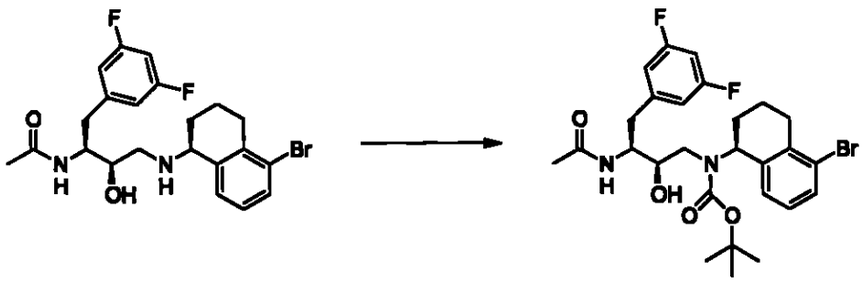
La diamina cruda del paso 2 (aproximadamente 18,31) se disolvió en diclorometano (200 mL). Se añadió N-metilmorfolina (5,03 4,63 g, 45,8 mmol), seguida de ácido acético (1,05 mL, 1,19 g, 18,3 mmol) e hidrato de 1-hidroxibenzotriazol (2,97 g, 22,0 mmol). La mezcla se enfrió

498

en un baño de hielo y se añadió 1-(3-dimetilaminopropi)-3-etilcarbodiimidohidrocloruro (3,59 g, 20,1 mmol). La mezcla se agitó en un baño de hielo durante 2 h y después se calentó a temperatura ambiente durante 16 h. La mezcla se diluyó con acetato de etilo (600 mL) y se lavó con agua (250 mL), bicarbonato sódico saturado acuoso(250 mL), agua (2 x 250 mL) y salmuera (150 mL). La solución se secó (sulfato de sodio), se filtró y se evaporó *in vacuo* para dar el producto deseado (8,51 g, 99%).

El análisis LC-MS indicó una pureza del 99%. LC-MS: [M+H] = 467, 469, Rt=1,94 min, Phenomenex Luna C18 (30 cm x 4,6 mm), CH_3CN al 20-70% /agua/ ácido trifluoroacético al 0,1% en 2,33 min, tasa de flujo 1,5 mL/min.

Paso 4.



El compuesto de partida (7,80 g, 16,7 mmol) se disolvió en diclorometano (150 mL). Se añadió di-terc-butildicarbonato (3,82 g, 17,5 mmol) y la mezcla se agitó durante 3 días.

La mezcla se concentró entonces *in vacuo* y el residuo se pasó a través de una almohadilla de gel de anhídrido silícico (eluido 1 L 2:1 hexanos/etilacetato, 0,5 L MeOH al 5%/diclorometano) para dar el producto deseado (8,52 g, 90%).

El análisis LC-MS indicó una pureza del 99%. LC-MS: [M+Na] = 589, 591, Rt= 5,12 min, Phenomenex Luna C18 (30 cm x 4,6 mm), CH_3CN al 20-70%/agua/ácido trifluoroacético al 0,1% en 2,33 min, tasa de flujo 1,5 mL/min.

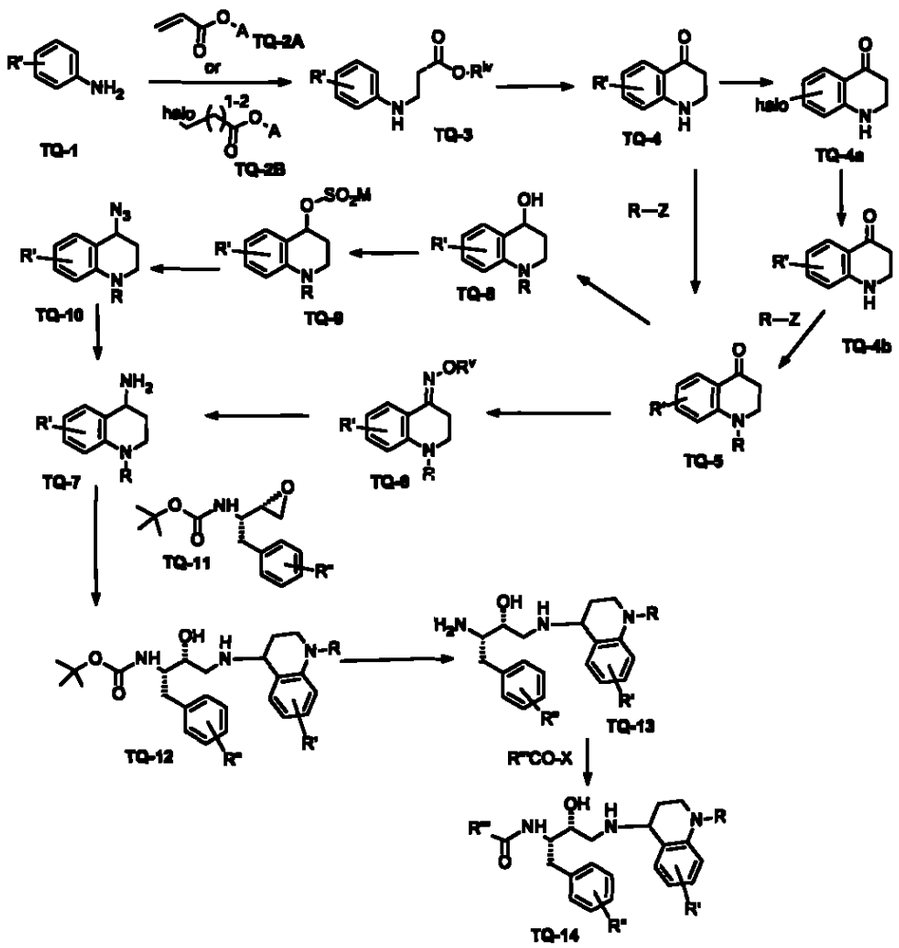
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Ejemplo 109 Derivados de tetrahidroquinolina

Los compuestos de la invención que contienen regiones de tetrahidroquinolina pueden producirse por métodos conocidos en la técnica. El siguiente esquema general (**Esquema AA**) puede resultar también útil para la síntesis de compuesto de tetrahidroquinolina.

ESQUEMA GENERAL AA



500

Descripción del esquema sintético general

La anilina TQ-1 se alquila con un haluro TQ-2B o acrilato TQ-2A para dar TQ-3. TQ-3 se trata entonces con un ácido fuerte o con un ácido de Lewis a temperaturas que varían desde 0°C hasta 140°C, preferiblemente con pentóxido de fósforo y ácido metanosulfónico a 130°C, para dar la quetona TQ-4. El nitrógeno de TQ-4 o bien se protege con un grupo de protección, muchos de los cuales se enumeran en *Protective Groups in Organic Synthesis*, Green y Wuts, 3ª edición, 1999, Wiley-Interscience, o bien se sustituye con un grupo alquilo, un grupo acilo, o un grupo sulfonilo, utilizando métodos bien conocidos por los expertos en la materia, utilizando R-Z, para dar la quetona protegida TQ-5. Una preparación alternativa de TQ-5 comienza con TQ-4 donde R' es hidrógeno. La halogenación con reactivos halogenantes como N-bromosuccinimida, N-yodosuccinimida, dibromatin y similares da como resultado TQ-4a donde R' es preferiblemente bromo o yodo. El tratamiento de TQ-4a bajo condiciones de acoplamiento cruzado como las descritas por Negishi (Tet. Lett. 1983, 3823), Huo (Org. Lett. 2003, 423) y reseñadas por Knochel (Tetrahedron 1998,8275) proporciona TQ-4b donde R' es alquilo. El ulterior tratamiento de TQ-4b con R-Z como se ha descrito más arriba da como resultado TQ-5.

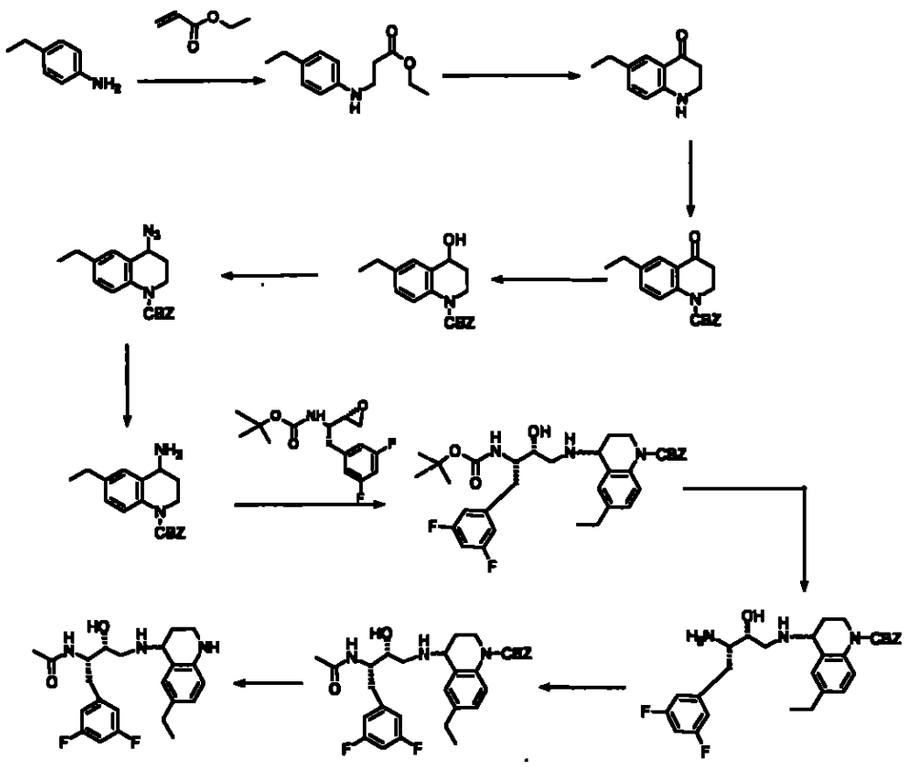
La quetona protegida TQ-5 se convierte entonces en la amina TQ-7 por varios métodos, cuya elección puede depender de la naturaleza del grupo R. En el primer método, TQ-5 se trata con una hidroxil amina en presencia de una base y una cantidad catalítica de ácido en disolventes como metanol, etanol, butanol y similares, a temperaturas que van desde la temperatura ambiente hasta la temperatura de reflujo del disolvente, para dar la oxima TQ-6. TQ-6 se reduce entonces a la amina TQ-7 utilizando un catalizador adecuado, preferiblemente paladio, en disolventes como metanol, etanol o acetato de etilo, bajo una manta de hidrógeno a presiones que van desde la atmosférica hasta 100 libras por pulgada cuadrada. Alternativamente, la quetona protegida TQ-5 se reduce a alcohol TQ-8 utilizando agentes reductores conocidos por los expertos en la materia, preferiblemente y en función de la naturaleza del grupo R utilizando borohidruro de sodio en metanol o etanol a temperaturas que van desde 0 a 100°C. El alcohol TQ-8 se convierte entonces en el éster de sulfonato TQ-9 con reactivos como cloruro de metanosulfonil o cloruro de toluenosulfonil utilizando métodos conocidos por los expertos en la materia. La sustitución del éster de sulfonato con azida utilizando, por ejemplo, azida de sodio en disolventes como diclorometano y DMF a temperaturas que van desde la temperatura ambiente hasta 120°C, da como resultado la azida TQ-10. La azida TQ-10 se reduce entonces a la amina T-7 utilizando, por

501

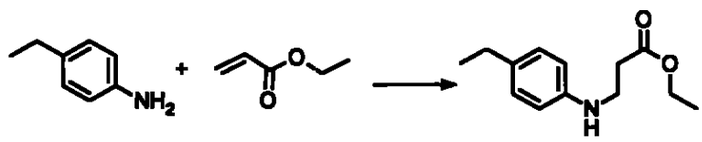
ejemplo, trimetilfosfina en disolventes como THF y similares a temperaturas entre 0°C hasta la temperatura de reflujo del disolvente. Se conocen otros métodos de reducción del grupo azida; la elección del agente reductivo dependerá de la naturaleza de los grupos R y R' y resultará conocida para los expertos en la materia y puede encontrarse en referencias como Smith and March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5ª ed., 2001, Wiley-Interscience. La amina TQ-7 se agita entonces en presencia del epóxido TQ-11 en preferiblemente, aunque no con carácter exhaustivo, disolventes alcohólicos como etanol, isopropilo, terc-butilo, o alcohol n-butilo, a temperaturas desde 50°C hasta la temperatura de reflujo del disolvente, para dar la Boc-amina TQ-12. La boc-amina TQ-12 se trata entonces con ácido fuerte como ácido trifluoroacético en disolventes no reactivos como diclorometano o con HCl seco en disolventes como éteres de dialquilo o disolventes alcohólicos a temperaturas que van desde la temperatura ambiente hasta 80°C para dar, tras un lavado con una base, la triamina TQ-13. La triamina TQ-13 se acila por medios bien conocidos para los expertos en la materia, por ejemplo condensación con un ácido carboxílico utilizando agentes de acoplamiento como EDC, DCC, HATU, o HBTU y similares. Los métodos preferidos son acilación con acil imidazol o acetilación con N,N-diacetilmetoxiamina para dar TQ-14.

A. Síntesis de N-{(1S,2R)-1-(3,5-difluorobencilo)-3-[(6-etil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hydroxipropil}acetamida.

502



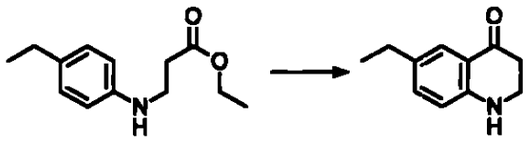
A1. Etil N-(4-etilfenil)-beta-alaninato



A una solución de 4-etil anilina (10,0 g) en ácido acético (25 mL) se añadió acrilato de etilo (10,8 g). La mezcla se calentó a 80°C durante 2 horas. Se añadió acrilato de etilo adicional (1,0 mL), y la mezcla se calentó de nuevo a 80°C durante 1 hora. La mezcla se dejó enfriar a temperatura ambiente y se removió durante 2 días. Se añadió hidróxido de sodio (8N) hasta obtener un pH de 9. La mezcla se dividió entre diclorometano y agua y los orgánicos combinados se lavaron una vez con 1N hidróxido de sodio, una vez con salmuera, se secaron con sulfato de sodio, se filtraron y se concentraron. La muestra se cromatografió utilizando un acetato de etilo al 20% en solución disolvente de heptano. Se obtuvo una mezcla del producto mono y di éster (19,5 g) (mezcla 1:1). MS(ESI+) para $C_{13}H_{19}NO_2$ *m/z* 221,99$(M+H)^+$.

503

A2. 6-etil-2,3-dihidroquinolin-4(1H)-ona



Una solución de pentóxido de fósforo (19,53 g) en ácido sulfónico de metano (200 mL) se calentó a 130°C. La mezcla se removió a 130°C durante una hora hasta que todo el pentóxido de fósforo se hubo disuelto. La mezcla se dejó enfriar durante 15 minutos y se añadió etil N-(4-etilfenil)-beta-alaninato (19,53 g de mezcla mono y di-éster). La mezcla se calentó a 130°C durante una hora y se dejó enfriar lentamente durante la noche. La mezcla se enfrió entonces en un baño de hielo y se añadió 10N hidróxido de sodio hasta alcanzar un pH de 9,5. Se añadió acetato de etilo a la mezcla para ayudar a disolver los sólidos. Los sólidos oscuros con aspecto gomoso restantes se disolvieron en metanol y se añadieron a la mezcla de etil acetato-hidróxido de sodio acuoso. Sólidos semi-cristalinos se precipitaron y se removieron mediante filtración a través de celite. El filtrado se lavó con agua, seguida de 1N hidróxido de sodio y salmuera, se secaron con sulfato de magnesio, se filtraron, y se concentraron. La cromatografía con gel de anhídrido silícico utilizando hidróxido de amonio al 0,25% en diclorometano resultó en fracciones mezcladas. Las fracciones mezcladas se combinaron y se recromatografiaron utilizando acetato de etiloal 30% en heptano. El material resultante se mejoró mediante la formación de la sal de hidrocloruro utilizando 2N HCl en éter. La sal se recogió mediante filtración y se lavó con heptano y se secó en un horno al vacío a 50°C durante la noche. La sal se dividió entonces entre diclorometano y 1N hidróxido de sodio. La capa orgánica se extrajo dos veces con diclorometano, se lavó con 1N hidróxido de sodio, se secó con sulfato de sodio, se filtró, y se concentró para dar 3,83 g del compuesto del título. MS(ESI+)para $C_{11}H_{13}NO$ *m/z* 175,96 $(M+H)^+$.

A3. Bencilo 6-etil-4-oxo-3,4-dihidroquinolina-1(2H)-carboxilato

A una solución de 6-etil-2,3-dihidroquinolin-4(1H)-ona (1,25 g) en THF (15 mL) se añadió bicarbonato sódico (0,84 g). Se añadió agua (5 mL) seguida de bencilo cloroformato (1,58 g) a la mezcla, y se removió a temperatura ambiente durante la noche. La reacción no se completó según lo determinado por TLC, de forma que se añadieron 0,60 g adicionales de $NaHCO_3$ a la mezcla y se removió a temperatura ambiente durante dos horas adicionales. La mezcla se concentró entonces bajo presión reducida y el residuo se dividió entre agua y acetato de etilo y la

504

capa orgánica se lavó con salmuera, se secó con sulfato de magnesio, se filtró, y se concentró. La cromatografía sobre gel de anhídrido silícico utilizando acetato de etilo al 25% en una solución disolvente de heptano dio 1,84 g del compuesto del título. MS(ESI+)para $C_{19}H_{19}NO_3$ *m/z* 310,03$(M+H)^+$.

A4. Bencilo 6-etil-4-hidroxi-3,4-dihidroquinolina-1(2H)-carboxilato

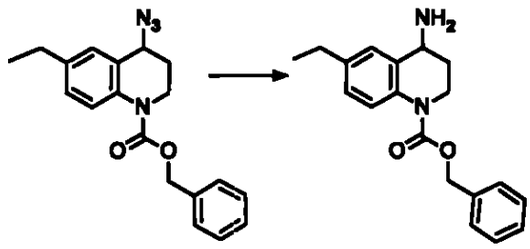
A una solución de bencilo 6-etil-4-oxo-3,4-dihidroquinolina-1(2H)-carboxilato (1,83 g) en EtOH (25 mL) se añadió $NaBH_4$ (0,67 g) por porciones durante quince minutos. La mezcla se removió a temperatura ambiente durante una hora y después se concentraron bajo presión reducida. El residuo se dividió entre acetato de etilo y agua y salmuera, se secó con sulfato de magnesio, se filtró, y se concentró. La cromatografía en gel de anhídrido silícico utilizando MeOH al 2% en solución disolvente de diclorometano con hidróxido de amonio al 0,5% dio como resultado 1,82 g del compuesto del título. ^{1}HNMR($CDCl_3$)δ 1,22(t, *J* = 8 Hz, 3H), 1,89 (s, 1H), 2,04(m, 2H), 2,61 (q, *J* = 8 Hz, 2H), 3,66 (m, 1H), 4,11 (m, 1 H), 4,74 (t, *J* = 4 Hz, 1 H), 5,25 (dd, *J* =12, 20 Hz, 2 H), 7,09 (dd, *J* = 2,9 Hz, 1 H), 7,21 (d, *J* = 2 Hz, 1 H), 7,35 (m, 5 H), 7,6 (d, *J* = 8 Hz, 1 H).

A5. Bencilo 4-azido-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato.

A una solución de bencilo 6-etil-4-hidroxi-3,4-dihidroquinolina-1(2H)-carboxilato (1,82 g) en diclorometano (15 mL) enfriado a 0°C se añadió N,N-diisopropiletilamina (3,1 mL), seguida de metanosulfonil cloruro (0,7 mL). Tras remover durante 1,5 horas, se quitó el disolvente bajo presión reducida. El residuo resultante se disolvió en 15 mL de DMF y se añadió azida de sodio (0,57 g). La mezcla se calentó a 60°C durante cinco horas y después se dejó enfriar a temperatura ambiente. La mezcla se templó con 1N HCl, y se extrajo tres veces con acetato de etilo. La capa de acetato de etilo se lavó con salmuera y bicarbonato de sodio en solución acuosa, se secó con sulfato de magnesio, se filtró y se concentró. El residuo se disolvió en diclorometano y se añadió carbón activado. El carbón se filtró utilizando un filtro de ayuda de celite y la solución resultante se concentró para dar 1,56 g del compuesto del título. ^{1}H NMR($CDCl_3$)δ 1,23(t, *J* = 8 Hz, 3H), 2,09 (m, 2H), 2,62 (q, *J* = 8 Hz, 2H), 3,67 (m, 1 H), 4,12 (m, 1 H), 4,58 (t, *J* = 4 Hz, 1 H), 5,24 (m, 2 H), 7,09 (d, *J* = 2 Hz, 1 H), 7,13 (dd, *J* = 2,9 Hz, 1 H), 7,35 (m, 5 H), 7,82 (d, *J* = 8 Hz, 1 H);

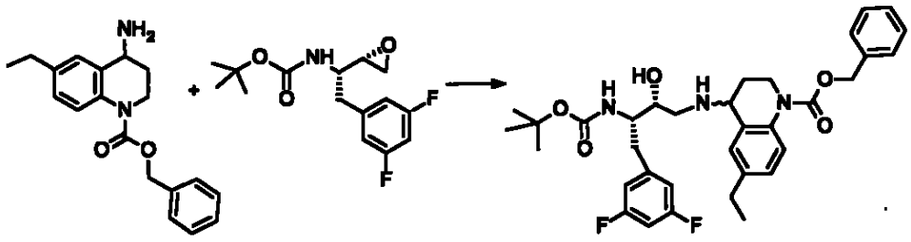
A6. Bencilo 4-amino-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato

505



A una solución de bencilo 4-azido-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato (1,56 g) en THF (20 mL) se añadió una solución 1M de trimetil fosfina en THF (5,1 mL) y la mezcla se removió a temperatura ambiente durante 2,25 horas. Se añadió agua a la mezcla (5 mL) y se calentó a 60°C durante tres horas. La mezcla se dejó enfriar lentamente durante la noche. La mezcla se concentró entonces bajo presión reducida y el residuo se templó con 1N HCl. La adición de acetato de etilo llevó a la formación de sólidos, que se recogieron mediante filtración. La lejía matriz se concentró bajo presión reducida y se añadió dietil éter. Los sólidos resultantes se recogieron de nuevo y se combinaron con los sólidos recogidos previamente. Los sólidos combinados se dividieron entre 1N NaOH y diclorometano. La capa orgánica se secó en sulfato de magnesio, se filtró, y se concentró para dar 0,51 g del producto del título. MS(ESI+)para $C_{19}H_{22}N_2O_2$ *m/z* 311,05$(M+H)^+$.

A7. Bencilo 4{[(2R,3S)-3-[(tert-butoxicarbonil)amino]-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3,4-dihidroquinolina-1(2H)-carboxilato.



A una solución de bencilo 4-amino-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato (0,51 g) en isopropanol (30 mL) se añadió el Ejemplo 134 (0,40 g) y la mezcla se calentó a 70°C durante 3,5 horas. 0,09 g adicionales del Ejemplo 134 se añadieron a la mezcla y se calentó de nuevo a 70°C durante cuatro horas. La mezcla se dejó enfriar lentamente a temperatura ambiente durante la noche. Se quitó el disolvente bajo presión reducida y el residuo se disolvió en etil acetato. La solución de acetato de etilo se lavó dos veces con 1N HCl, una vez con salmuera, se secó con sulfato de magnesio, se filtró, y se concentró. La cromatografía de gel de anhídrido silícico

506

utilizando MeOH al 2% en diclorometano con NH_4OH al 0,25% como sistema disolvente dio 0,76 g del compuesto del título. (75% de la producción). MS(ESI+) para $C_{34}H_{41}F_2N_3O_5$ *m/z* 610,51$(M+H)^+$.

A8. Bencilo 4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato.

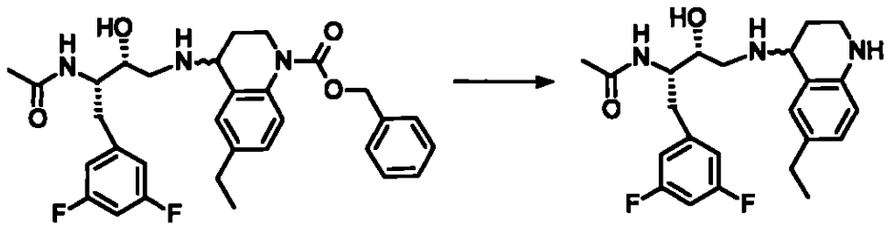
A una solución de bencilo 4-{[(2R,3S)-3-[(tert-butoxicarbonil)amino]-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3,4-dihidroquinolina-1(2H)-carboxilato (0,76 g) en MeOH (10 mL) se añadió 2N HCl en Et_2O (1,6 mL). La mezcla se removió a temperatura ambiente durante dos horas y se añadió 1,0 mL adicional de 2N HCl en Et_2O. La mezcla se removió durante cuatro horas más. La reacción aún no estaba completa, así que se añadieron 3,0 mL adicionales de HCl en Et_2O. La mezcla se removió durante dos horas y después se quitó el disolvente bajo presión reducida. El residuo se disolvió en acetato de etilo lavado dos veces con 1N NaOH, se secó con sulfato de magnesio, se filtró, y se concentró. Para la purificación se utilizó una columna de gel de anhídrido silícico utilizando MeOH al 4% en diclorometano con NH_4OH al 0,25% como solución disolvente y dio como resultado 0,44 g del compuesto del título. MS(ESI+) para $C_{28}H_{33}F_2N_3O_3$ *m/z* 510,36$(M+H)^+$.

A9. Bencilo 4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato.

A una solución de bencilo 4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato (0,43 g) en diclorometano (15 mL) se añadió N,N-diacetil-O-metilhidroxilamina (0,11 g). La mezcla se removió durante la noche a temperatura ambiente. Se añadieron entonces 0,10 g adicionales de N,N-diacetil-O-metilhidroxilamina y la mezcla se removió durante 6 horas. Otros 0,10 g de N,N-diacetil-O-metilhidroxilamina se añadieron y la mezcla se removió durante la noche y después se dividió entre diclorometano y 1N HCl y salmuera. La capa orgánica se secó con sulfato de magnesio, se filtró, y se concentró. Se utilizó una columna de gel de anhídrido silícico para la purificación utilizando MeOH al 4% en diclorometano con NH_4OH al 0,25% como solución disolvente y dio 0,35 g del compuesto del título. MS(ESI+) para $C_{31}H_{34}F_2N_3O_4$ *m/z* 552,32$(M+H)^+$.

A10. N-{(1S,2R)-1-(3,5-difluorobencilo)-3-[(6-etil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropil}acetamida.

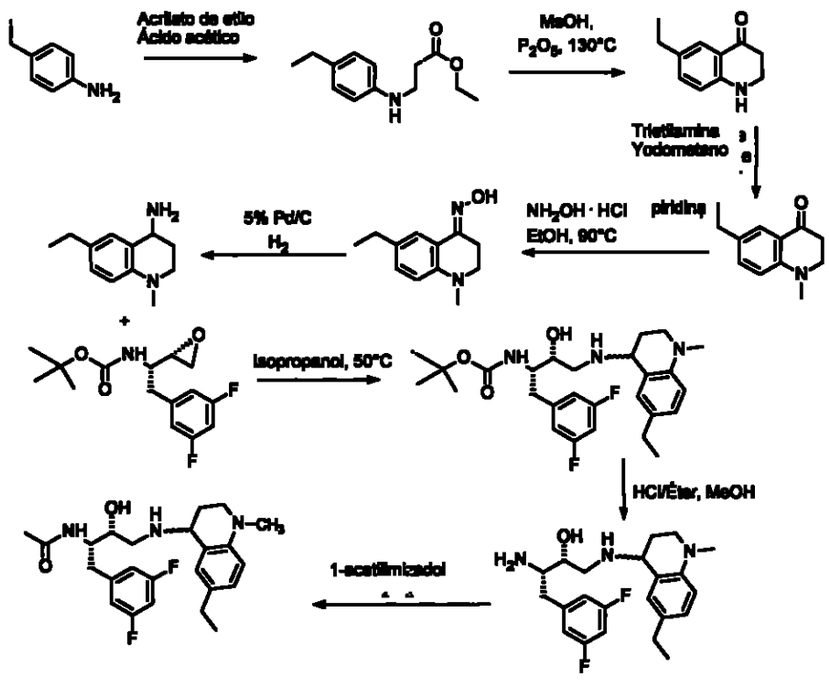
507



Se burbujeó nitrógeno por medio de una solución de bencilo4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-etil-3,4-dihidroquinolina-1(2H)-carboxilato (0,35 g), EtOH (25 mL), y ácido acético (0,75 mL). Se añadió paladio al 10% en carbono (0,29 g) a la mezcla y se agitó en un aparato de hidrogenación a 52 psi de hidrógeno durante 1,25 h. El catalizador se filtró utilizando celite y el filtrado se concentró bajo presión reducida. El residuo se dividió entre acetato de etilo, hidróxido de sodio acuoso (pH 10), y salmuera, y después se secó con sulfato de magnesio, se filtró, y se concentró. Se utilizó una columna de gel de anhídrido silícico utilizando MeOH al 6% en diclorometano con NH_4OH al 0,25% como solución disolvente y dio 0,04 g del compuesto del título. MS(ESI+) para $C_{23}H_{29}F_2N_3O_2$ *m/z* 418,31$(M+H)^+$.

A11.N-{(1S,2R)-1-(3,5-difluorobencilo)-3-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropil}acetamida.

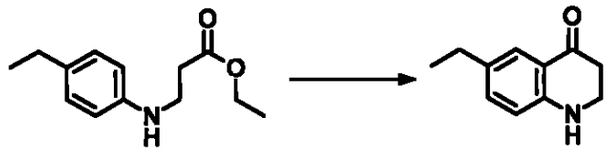
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A12. Etil N-(4-etilfenil)-beta-alaninato

A una solución de 4-etil anilina (10,00 g) en ácido acético (20 mL) se añadió acrilato de etilo (8,26). La mezcla se calentó a 70°C durante 3,5 horas. La mezcla se dejó enfriar a temperatura ambiente. La mezcla se dividió entre diclorometano y agua, y se extrajo tres veces. Los orgánicos combinados se lavaron una vez con salmuera, se secaron con sulfato de sodio, se filtraron, y se concentraron. La mezcla se llevó al segundo paso. MS(ESI+)para $C_{13}H_{19}NO_2$ *m/z* 223,1$(M+H)^+$.

A13. 6-etil-2,3-dihidroquinolin-4(1H)-ona



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Una solución de pentóxido de fósforo (11,14 g) en ácido sulfónico de metano (114 mL) se calentó a 130°C. La mezcla se removió a 130° durante una hora hasta que se hubo disuelto todo el pentóxido de fósforo. La mezcla se dejé enfriar durante 15 minutos, y se añadió etil N-(4-etilfenil)-beta-alaninato (11,14 g de mezcla mono y di-éster). La mezcla se calentó a 130°C durante 1,5 horas, y se dejó enfriar a temperatura ambiente. Luego, la mezcla se enfrió en un baño de hielo, y se añadió hidróxido de sodio al 50% hasta alcanzar un pH de 8. Los sólidos oscuros con aspecto de goma se disolvieron en MeOH, y se añadieron a la mezcla. Los sólidos empezaron a chocar, así que se filtraron con celite. Los líquidos se combinaron, se dividieron entre diclorometano y agua, y se extrajeron los orgánicos tres veces con diclorometano. Los orgánicos combinados se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron, y se concentraron. El producto se cromatografió utilizando acetato de etilo al 30% en una solución disolvente de heptano. Se recuperaron 4,10 g del producto del título. (28% de la producción por medio de los dos primeros pasos) MS(ESI+) para $C_{11}H_{13}NO$ *m/z* 176,00 $(M+H)^+$.

A14.6-etil-1-metil-2,3-dihidroquinolin-4(1H)-ona.

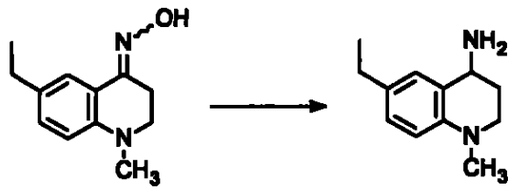
A una solución de 6-etil-2,3-dihidroquinolin-4(1H)-ona (1,00 g) en THF (25 mL) se añadió trietilamina (0,64 g) seguida de yodometano (0,89 g). La mezcla se reflujó a 70°C durante la noche. El disolvente se retiró bajo presión reducida, y el residuo se dividió entre bicarbonato de sodio en solución acuosa y diclorometano. Los orgánicos se extrajeron tres veces, se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron, y se concentraron. Se utilizó cromatografía para purificar el compuesto del título utilizando acetato de etiloal 40% en solución disolvente de heptano. Se recuperaron 0,32 g del producto del título. (30% de la producción). MS(ESI+) para $C_{12}H_{15}NO$ *m/z* 190,10 $(M+H)^+$.

A15.(4E)-6-etil-1-metil-2,3-dihidroquinolin-4(1H)-ona oxima.

A una solución de 6-etil-1-metil-2,3-dihidroquinolin-4(1H)-ona (0,32 g) en etanol (25 mL) se añadieron piridina (0,53 g) e hidrocloruro de hidroxilamina (0,59 g). La mezcla, acompañada de un condensador a reflujo se calentó a 90°C durante dos horas. La mezcla se enfrió a temperatura ambiente, y el disolvente se retiró bajo presión reducida. El residuo se repartió entre agua y diclorometano y los orgánicos se extrajeron tres veces. Los orgánicos combinados se lavaron una vez con salmuera, se secaron con sulfato de sodio, se filtraron y se concentraron. Se recuperaron 0,34 g del producto del título. (98% de la producción). MS(ESI+) para $C_{12}H_{16}N_2O$ *m/z* 205,02 $(M+H)^+$.

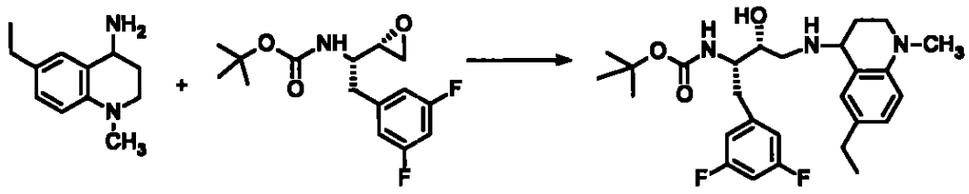
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A16. 6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-amina



(4E,Z)-6-etil-1-metil-2,3-dihidroquinolin-4(1H)-ona oxima (0,34 g), etanol (20 mL), y ácido acético (0,27 g) se combinaron en un matraz de hidrogenación y se desgasificaron con nitrógeno. Cuidadosamente se añadió a la mezcla (0,04 g) Paladio al 5% en carbono y la mezcla se desgasificó durante varios minutos más. La mezcla se formó en el aparato de hidrogenación, y se puso bajo 50 psi de hidrógeno. La mezcla se agitó durante cinco horas y media y se retiró de la máquina, pero no estaba completa de acuerdo con el TLC. La mezcla se desgasificó de nuevo, y se añadieron 0,10 g adicionales de paladio al 5% en carbono a la mezcla. El paladio en carbono se filtró utilizando celite, y los líquidos se concentraron bajo presión reducida. El residuo se dividió entre bicarbonato de sodio en solución acuosa y diclorometano, y los orgánicos se extrajeron tres veces. Los orgánicos combinados se secaron con sulfato sódico, se filtraron, y se concentraron. Se recuperaron 0,26 g del compuesto del título. (82% de la producción).

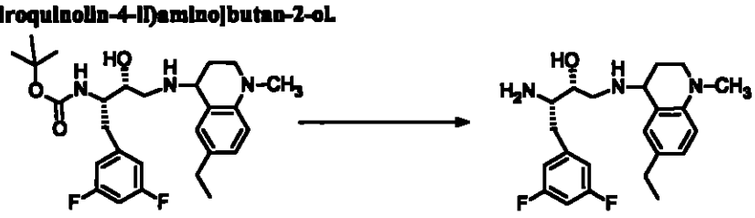
A17. tert-butil(1S,2R)-1-(3,5-difluorobencilo)-3-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropilcarbamato.



A una solución de 6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-amina (0,263 g) en isopropanol (20 mL) se añadió el Ejemplo 134 (0,276 g). La mezcla se calentó a 50° y se removió a esta temperatura durante la noche. La mezcla se dejó enfriar a temperatura ambiente, y se quitó el disolvente bajo presión reducida. El residuo se dividió entre 1N HCl y diclorometano, y los orgánicos se extrajeron tres veces. Los orgánicos combinados se secaron con sulfato de sodio, se filtraron, y se concentraron. Se recuperaron 0,412 g del producto del título. (91% de la producción). MS(ESI+) para $C_{27}H_{37}F_2N_3O_3$ *m/z* 490,59 $(M+H)^+$.

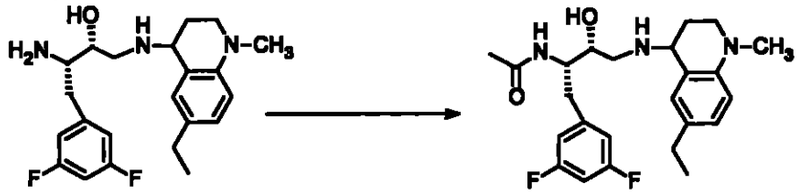
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A18. (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]butan-2-ol.



A una solución de tert-butil(1S,2R)-1-(3,5-difluorobencilo)-3-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropilcarbamato (0,412 g) en MeOH (5 mL) se añadió 2N HCl en Et_2O (2,1 mL).La mezcla se removió a temperatura ambiente durante quince minutos. A la mezcla se le quitó el disolvente bajo presión reducida. El residuo se dividió entre diclorometano y bicarbonato de sodio en solución acuosa , y el orgánico se extrajo tres veces, se lavó con salmuera, se secó con sulfato de sodio, se filtró, y se concentró. Se utilizó una columna de gel de anhídrido silícico para la purificación utilizando MeOH al 5% en diclorometano como solución disolvente. Se recuperaron 0,255 g del producto del título. (78% de la producción). MS(ESI+) para $C_{22}H_{29}F_2N_3O$ *m/z* 390,18 $(M+H)^+$.

A19. N-{(1S,2R)-1-(3,5-difluorobencilo)-3-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropil}acetamida.

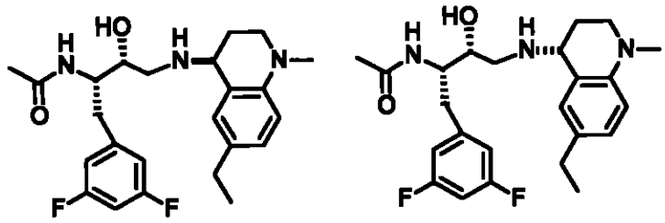


A una solución de (2R,3S)-3-amino-4-(3,5-difluorofenil)-1-[6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]butan-2-ol (0,218 g) en diclorometano (15 mL) se añadió 1-acetilimidazol (0,062 g). La mezcla se removió durante la noche a temperatura ambiente. La mezcla se dividió entre diclorometano y salmuera, y el orgánico se extrajo tres veces, se secó con sulfato de sodio, se filtró y se concentró. Se utilizó una columna de gel de anhídrido silícico para la purificación utilizando MeOH al 3% en diclorometano con NH_4OH al 0,5% como solución disolvente. El HPLC todavía indicaba la presencia de pequeñas cantidades del material original, así que la mezcla se lavó una vez con 1N HCl, se secó con sulfato de magnesio, se filtró, y se

512

concentró. Se recuperaron 0,115 g del producto del título. (48% de la producción). MS(ESI+) para $C_{24}H_{31}F_2N_3O_2$ *m/z* 432,18 $(M+H)^+$.

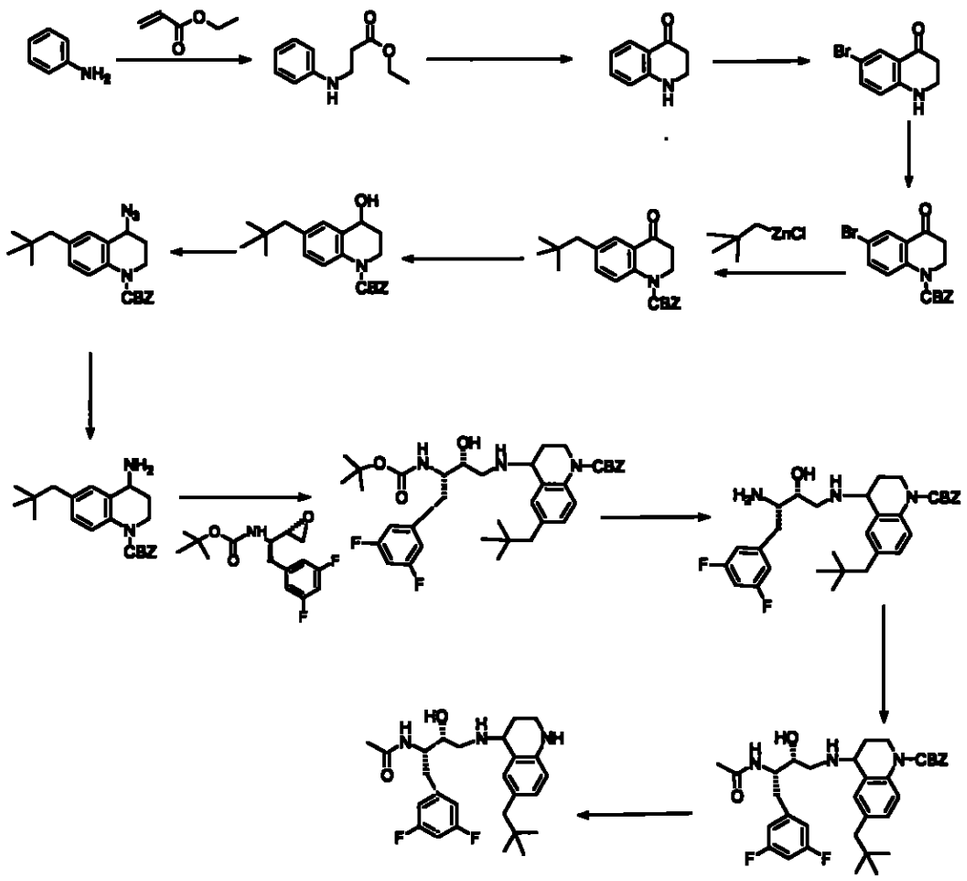
A20. N-((1S,2R)-1-(3,5-difluorobencilo)-3-{[(4S)-6-etil1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida y N-((1S,2R)-1-(3,5-difluorobencilo)-3-{[(4R)-6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida.



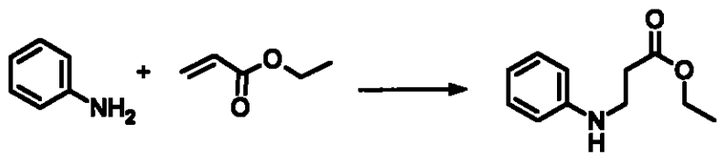
La cromatografía de gel de anhídrido silícico de aproximadamente 0,1 g de N-{(1S,2R)-1-(3,5-difluorobencilo)-3-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropil}acetamida utilizando metanol/diclorometano (8/92) con hidróxido de amonio al 0,1% dio como resultado 0,032 g de N-((1S,2R)-1-(3,5-difluorobencilo)-3-{[(4S)-6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida[R_f(MeOH/CH_2Cl_2/NH_4OH) = 0,40; MS(ESI+) para $C_{24}H_{31}F_2N_3O_2$ *m/z* 432,2 $(M+H)^+$]. La recromatografía de las fracciones mezcladas dio 0,011 g de una mezcla 9:1 de N-((1S,2R)-1-(3,5-difluorobencilo)-3-{[(4R)-6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida[R_f(MeOH/CH_2Cl_2/NH_4OH) = 0,35; MS(ESI+) para $C_{24}H_{31}F_2N_3O_2$ *m/z* 432,2(M+H)+] y N-((1S,2R)-1-(3,5-difluorobencilo)-3-{[(4S)-6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida.

B. Síntesis de N-{(1S-2R)-1-(3,5-difluorobencilo)-2-hidroxi-3-[(6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]propil}acetamida.

513



B.1. **Etil N-fenil-beta-alaninato**



A una solución de anilina (15,0 g) en ácido acético (25 mL) se añadió acrilato de etilo (17,7 g). La mezcla se calentó a 70ºC durante 5,5 horas. La mezcla se dejó entonces enfriar a temperatura ambiente y se removió durante la noche. Se añadió hidróxido de sodio (50% en agua) para conseguir un pH de 6. La mezcla se extrajo con dietil éter, se secó en sulfato de sodio, se filtró, y se concentró. La cromatografía en gel de anhídrido silícico utilizando acetato de etilo al 15% en heptano con solución disolvente de TFA al 0,25% dio 28,0 g de una mezcla de productos

514

mono y di-éster (1:1) que se llevaron al siguiente paso como una mezcla. MS(ESI+) para $C_{11}H_{15}NO_2$ *m/z* 193,99 $(M+H)^+$.

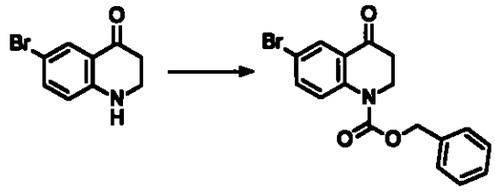
B.2. 2,3-dihidroquinolin-4(1H)-ona

Una solución de pentóxido de fósforo (20,0 g) en ácido sulfónico de metano (200 mL) se calentó a 130°. La mezcla se removió a 130° hasta que todo el pentóxido de fósforo se hubo disuelto. La mezcla se dejó enfriar durante 15 minutos, y se añadió etil N-fenil-beta-alaninato (28,0 g de mezcla). La mezcla se calentó a 130°C durante seis horas, y se dejó enfriar lentamente en el baño de aceite durante la noche. La mezcla se enfrió en un baño de hielo, y se añadió hidróxido de sodio al 50% hasta alcanzar un pH de 8. La mezcla se dividió entre Et_2O y el acuoso. Los sólidos empezaron a chocar, así que se filtraron a través de celite. Cuando el filtro se obturó, el líquido se trasvasó. Los sólidos se lavaron y se trasvasaron tres veces. La solución resultante se dividió entre Et_2O y agua, y se extrajo tres veces. El orgánico se lavó dos veces con salmuera, se secó con sulfato de magnesio, se filtró, y se concentró. Se utilizó una columna utilizando un acetato de etilo al 20-30% en gradiente de heptano. Se recuperaron 5,20 g del producto del título. (22% de la producción durante los dos primeros pasos). MS(ESI+) para C_9H_9NO *m/z* 147,96 $(M+H)^+$.

B.3. 6-bromo-2,3-dihidroquinolin-4(1H)-ona

A una solución de 2,3-dihidroquinolin-4(1H)-ona (2,94 g) en diclorometano (25 mL) se añadió N-bromosuccinamida (3,63 g). La mezcla se removió a temperatura ambiente durante 1,5 h y se dividió entre bicarbonato de sodio en solución acuosa y diclorometano. La capa orgánica se lavó con salmuera, se secó con sulfato de sodio, se filtró, y se concentró. El concentrado se cromatografió en gel de anhídrido silícico utilizando acetato de etilo al 35% en solución disolvente de heptano y dio 4,14 g del compuesto del título. MS(ESI-) para C_9H_8BrNO *m/z* 225,77 $(M-H)^-$.

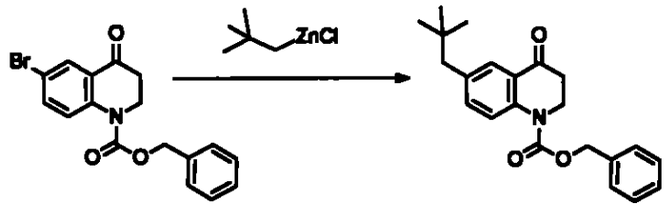
B.4. Bencilo 6-bromo-4-oxo-3,4-dihidroquinolina-1(2H)-carboxilato



515

A una solución de 6-bromo-2,3-dihidroquinolin-4(1H)-ona (3,76 g) en THF (30 mL) se añadió agua (10 mL) seguida de bicarbonato sódico (2,10 g) y finalmente, bencilo cloroformato (3,1 mL). La mezcla se removió a temperatura ambiente durante una hora, en cuyo momento se añadieron a la mezcla 5 mL adicionales de agua, 1,2 g de bicarbonato sódico, y 1,0 mL de bencilo cloroformato. Tras remover durante la noche a temperatura ambiente aún había material de origen, de modo que se añadieron a la mezcla 0,5 mL adicionales de agua, 0,5 g de bicarbonato sódico y 0,5 mL de bencilo cloroformato. La mezcla se dejó remover durante seis horas adicionales y luego se quitó el disolvente bajo presión reducida y el residuo se dividió entre dietil éter/acetato de etilo y agua. Las capas de orgánico combinado se secaron con sulfato de magnesio, se filtraron, y se concentraron. Los sólidos resultantes se recogieron, se lavaron con heptano, y se secaron para dar 5,24 g del compuesto del título. ^{1}H NMR ($CDCl_3$) δ 2,78 (t, J = 7 Hz, 2 H), 4,22 (t, J = 6 Hz, 2 H), 5,28 (s, 2H), 7,40 (m, 5H), 7,58 (dd, J = 2,9 Hz, 1 H), 7,75 (d, J = 9 Hz, 1 H), 8,10 (d, J = 2 Hz, 1 H).

B.5. Bencilo 6-neopentil-4-oxo-3,4-dihidroquinolina-1(2H)-carboxilato



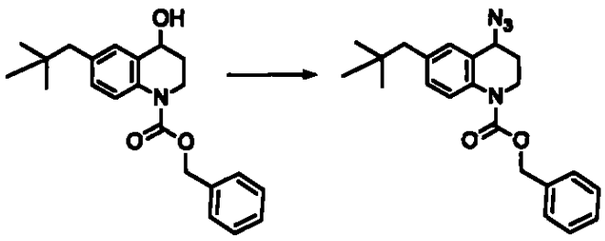
Bencilo 6-bromo-4-oxo-3,4-dihidroquinolina-1(2H)-carboxilato (3,10 g) y dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(II)aducto de diclorometano (0,35 g) se combinaron en un matraz de fondo redondo. La mezcla se puso en vacío alto y se purgó con nitrógeno. Una solución de 0,5 M de bromo(neopentil)cinc (55 mL) preparada utilizando el procedimiento de Negishi *et al. Tet. Lett.* 1983, *24*, 3823-3824, se añadió a la mezcla y se removió a temperatura ambiente durante dos días. La reacción no se había terminado, de modo que se añadieron 10 mL adicionales de la solución de bromo(neopentil)cinc y la mezcla se removió durante un día adicional. La mezcla se dividió entonces entre acetato de etilo y cloruro de amonio en solución acuosa, se secó con sulfato de magnesio, se filtró, y se concentró. La cromatografía de gel de anhídrido silícico utilizando acetato de etilo al 20% en solución disolvente de etano dio 2,17 g del compuesto del título. MS(ESI+) para $C_{22}H_{25}NO_3$ *m/z* 353,17 $(M+H)^+$.

B.6. Bencilo 4-hidroxi-6-neopentil-3,4-dihidroquinolina-1(2H)-carboxilato

516

A una solución de bencilo 6-neopentil-4-oxo-3,4-dihidroquinolina-1(2H)-carboxilato (2,17 g) en etanol (20 mL) se añadió borohidruro de sodio (0,70 g). La mezcla se removió a temperatura ambiente durante dos horas, después de lo cual se removió el etanol bajo presión reducida. El residuo se templó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó con sulfato de magnesio, se filtró, y se concentró para dar 2,13 g del compuesto del título. ^{1}H NMR ($CDCl_3$) δ 0,90 (s, 9 H), 1,80 (s, 1 H), 2,06 (m, 2 H), 2,45 (s, 2 H), 3,68 (m, 1 H), 4,12 (m, 1 H), 4,75 (t, J = 4 Hz, 1 H), 5,24 (dd, J = 12,17 Hz, 2 H), 7,02 (dd, J = 2,9 Hz, 1H), 7,12 (d, J = 2 Hz, 1 H), 7,35 (m, 5 H), 7,76 (d, J = 8 Hz, 1 H).

B.7. Bencilo 4-azido-6-neopentil-3,4-dihidroquinolina-1(2H)-carboxilato



A una solución de bencilo 4-hidroxi-6-neopentil-3,4-dihidroquinolina-1(2H)-carboxilato (2,05 g) en diclorometano (20 mL) removiendo en un baño de hielo se añadió N,N-diisopropiletilamina (3,1 mL) seguida de metanosulfonil cloruro (0,7 mL). Tras remover durante 1,5 horas, se quitó el disolvente bajo presión reducida y el residuo resultante se disolvió en 20 mL de DMF. Se añadió azida de sodio (0,57 g) y la mezcla se calentó a 60°C durante cinco horas y después se dejó enfriar a temperatura ambiente. La mezcla se templó con 1N HCl y se extrajo con acetato de etilo. Las capas orgánicas se lavaron dos veces con salmuera, se secaron con sulfato de magnesio, se filtraron, y se concentraron. El residuo se cromatografió en gel de anhídrido silícico utilizando acetato de etilo al 15% en solución disolvente de heptano para dar 1,90 g del compuesto del título. ^{1}H NMR ($CDCl_3$) δ 0,91 (s, 9 H), 2,09 (m, 2 H), 2,46 (s, 2 H), 3,66 (m, 1 H), 4,14 (m, 1 H), 4,58 (t, J = 4 Hz, 1 H), 4,24 (dd, J = 12,15 Hz, 2 H), 7,03 (d, J = 2 Hz, 1H), 7,06 (dd, J = 2,9 Hz, 1 H), 7,35 (m, 5 H), 7,86 (d, J = 8 Hz, 1 H).

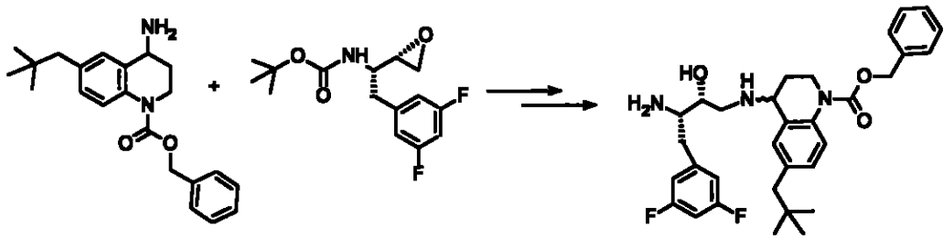
B.8. Bencilo 4-amino-6-neopentil-3,4-dihidroquinolina-1(2H)-carboxilato

A una solución de bencilo 4-azido-6-neopentil-3,4-dihidroquinolina-1(2H)-carboxilato (1,88 g) en THF (15 mL) se añadió una solución de 1M de trimetil fosfina en THF (5,5 mL) y la

517

mezcla se removió a temperatura ambiente durante cinco horas, después de lo cual se añadió agua a la mezcla (20 mL) y se calentó a 60ºC durante la noche. La mezcla se dejó enfriar a temperatura ambiente y se concentró bajo presión reducida. El residuo se templó con 1N HCl y se extrajo con etil acetato. Las capas orgánicas se lavaron con bicarbonato de sodio en solución acuosa, se secaron con sulfato de magnesio, se filtraron, y se concentraron. La cromatografía de gel de anhídrido silícico utilizando metanol al 2,5% en diclorometano con solución disolvente de hidróxido de amonio al 0,5% dio 1,46 g del compuesto del título. MS(ESI+) para $C_{22}H_{28}N_2O_2$ *m/z* 353,19 $(M+H)^+$.

B.9. Bencilo 4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hydroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato

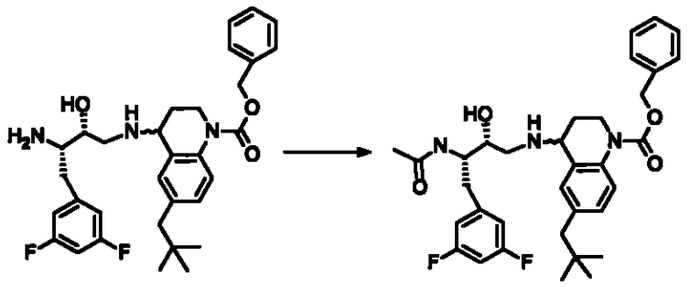


A una solución de bencilo 4-amino-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato (1.31 g) en isopropanol (25 mL), se añadió el Ejemplo 134 (0.75 g) y se calentó la mezcla a 90 °C durante 45 minutos. La temperatura se redujo a 60 °C y se dejó agitando toda la noche. A la mezcla se añadieron 0.36 g adicionales del Ejemplo 134 y se calentó a 80 °C durante cinco horas. Se procedió a enfriar la mezcla a temperatura ambiente y se eliminó el solvente bajo presión reducida. El residuo se dividió entre agua y acetato de etilo y las capas orgánicas se secaron con sulfato de magnesio, para luego filtrarlas y concentrarlas. Se pasó por una columna de sílica gel con el objeto de separar los diasteriómeros utilizando un gradiente de MeOH al 2-4% en diclorometano con 0.25% de NH_4OH como solvente. La primera fracción contenía una mezcla 70:30 de los diasteriómeros y la segunda fracción era una mezcla 50:50 de los diasteriómeros. Se extrajeron los grupos Boc disolviendo cada fracción en una cantidad mínima de diclorometano y añadiendo a cada una de las dos mezclas 15 mL de HCl 2N en éter. Las mezclas se agitaron por dos horas y se concentraron a presión reducida. A continuación se dividieron las mezclas entre hidróxido de sodio 1N y acetato de etilo, se secaron con sulfato de magnesio, se filtraron y concentraron hasta obtener 0.23 g de la mezcla 70:30 del compuesto en cuestión y 0.30 g de la mezcla 50:50. MS (ESI+) para el $C_{32}H_{39}F_2N_3O_3$ *m/z* 552.32 $(M+H)^+$ para la mezcla 70:30 y *m/z* 552.27 $(M+H)^+$ para la mezcla 50:50. Cada una de estas mezclas se llevó separadamente hasta el

518

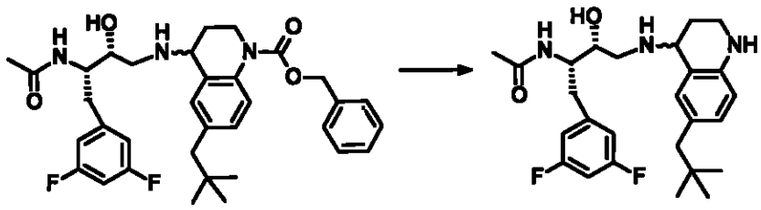
producto final. Los procedimientos a continuación ilustran ese proceso para la mezcla 70:30 exclusivamente.

B.10. Bencilo 4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato



A una solución de bencilo 4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato (0.226 g) en diclorometano (5 mL) se añadió N,N-diacetil-O-metilhidroxilamina (0.064 g). La mezcla se agitó durante el fin de semana a temperatura ambiente. El solvente se eliminó bajo presión reducida y el residuo se repartió entre HCl 1N y acetato de etilo, se secó con sulfato de magnesio, se filtró y concentró hasta obtener 0.243 g del compuesto en cuestión (rendimiento del 99%). MS (ESI+) para el $C_{34}H_{41}F_2N_3O_4$ *m/z* 594.31 $(M+H)^+$.

B.11. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]propil}acetamida



A una solución de bencilo 4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenilo)-2-hidroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato (0.242 g) en EtOH (30 mL), se añadió HCl 1N (1.0 mL) y 10% de paladio sobre carbono (0.030 g). La mezcla se desgasificó con N_2 durante cinco minutos. Toda la mezcla se colocó en un equipo de hidrogenación a 47 psi de H_2 y se agitó durante 4.5 horas. Se filtró el paladio utilizando Celita y

519

el solvente se concentró bajo presión reducida. El residuo se repartió entre agua y acetato de etilo y las capas orgánicas se lavaron con una solución acuosa de bicarbonato de sodio, se secaron con sulfato de magnesio, para luego filtrarlas y concentrarlas. Al pasarlas por una columna de sílica gel con 4% de MeOH en diclorometano como solvente y se obtuvieron 0.095 g del compuesto en cuestión. MS (ESI+) para el $C_{36}H_{33}F_3N_3O_2$ *m/z* 460.27 $(M+H)^+$.

CONJETURAS PREDECIBLES

Los compuestos mencionados en los **Ejemplos 109 (C-TT)** pueden producirse de acuerdo con los métodos análogos a los descritos arriba, al igual que los típicos conocidos.

Ejemplo No.	Nombre
C.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
D.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
E.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
F.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
G.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
H.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-7-fluoro-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
I.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-7-fluoro-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
J.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-7-fluoro-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
K.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-7-fluoro-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
L.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
M.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
N.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
O.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
P.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1-(2-hidroxietil)-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
Q.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-(2-hidroxietil)-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
R.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-(2-hidroxietil)-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
S.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-(2-hidroxietil)-6-neopentil-1,2,3,4-

524

520

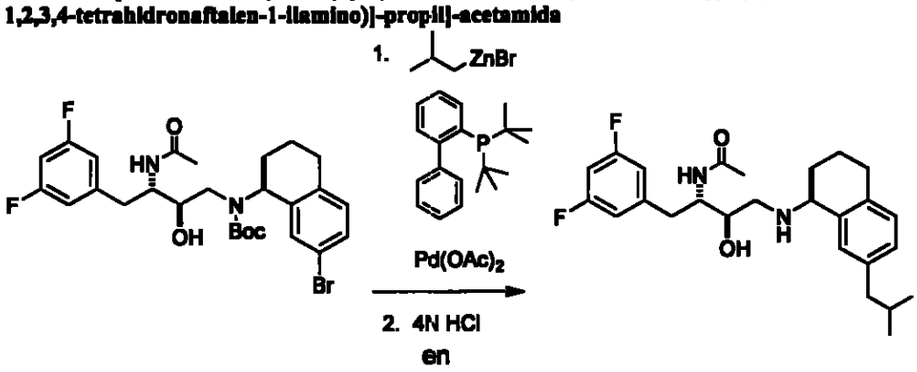
	tetrahidroquinolin-4-il]amino}propil)acetamida;
T.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
U.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
V.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hydroxipropil]acetamida;
W.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-tert-butil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
X.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1-(cianometil)-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
Y.	N-[(1S,2R)-3-{[(4S)-1-(cianometil)-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
Z.	N-[(1S,2R)-3-{[(4S)-1-(cianometil)-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
AA.	N-[(1S,2R)-3-{[(4S)-1-(cianometil)-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
BB.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1-hidroxi-2,2-dimetilpropil)-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
CC.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1-hidroxi-2,2-dimetilpropil)-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
DD.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-2,2-dimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
EE.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1,2,2-trimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
FF.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-1,4-dimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
GG.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-4-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
HH.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-4-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
II.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-1,4-dimetil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
JJ.	N-[(1S,2R)-3-[(6-tert-butoxi-1,2,3,4-tetrahidroquinolin-4-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
KK.	N-[(1S,2R)-3-[(6-tert-butoxi-4-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
LL.	N-[(1S,2R)-3-[(6-tert-butoxi-4,8-dimetil-1,2,3,4-tetrahidroquinolin-4-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
MM.	N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(4-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]propil}acetamida;
NN.	N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(4,8-dimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropil}acetamida;
OO.	N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(8-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]propil}acetamida;
PP.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(2-hidroxi-2-metilpropil)-8-metil-1,2,3,4-tetrahydroquinolin-4-il]amino}propil)acetamida;
QQ.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(2-hidroxi-2-metilpropil)-4-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
RR.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(2-hidroxi-2-metilpropil)-1,2,3,4-

521

	tetrahidroquinolin-4-il]amino}propil)acetamida;
SS.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(1-hidroxi-2,2-dimetilpropil)-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida; y
TT.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(1-hidroxi-2,2-dimetilpropil)-4-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida.

EJEMPLO 110

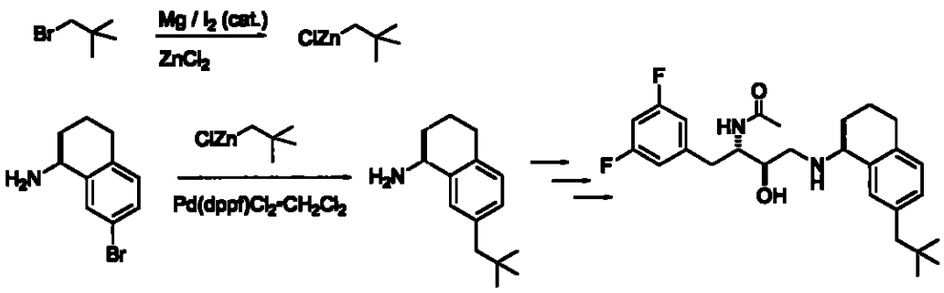
A. Preparación de N-(1*S*, 2*R*)-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-[(1*S*)-(7-isobutil-1,2,3,4-tetrahidronaftalen-1-ilamino)]-propil]-acetamida



Acetato de paladio (II) (0.2 equiv., 0.07 mmol, 15.8 mg) y 2-(di-t-butilfosfino)bifenil (0.1 equiv, 0.035 mmol, 10.5 mg) se disolvieron en THF (2 mL) y se desoxigenaron mediante purgado subsuperficial con N_2 (g) durante 5 minutos. A continuación se añadió el bromuro (1 equiv, 0.352 mmol, 200 mg) a esta solución en forma sólida, seguido por bromuro de zinc isobutilo (solución 0.5 M en THF, 3 equiv, 1.1 mmol, 2.1 mL). La reacción se agitó durante toda la noche a temperatura ambiente y bajo una atmósfera de N_2 (g). Después de transcurridas 12 horas, la reacción se repartió entre EtOAc y H_2O, y se extrajo 3x en EtOAc. Se procedió a lavar los extractos orgánicos combinados, secándolos posteriormente sobre Na_2SO_4 para luego filtrarlos y concentrarlos. Con la columna de cromatografía sobre SiO_2 con 30 → 50 % EtOAc en los hexanos, se produjo el producto deseado Boc, puro y protegido. (148 mg, rendimiento del 77 %) $M+Na^+$ (Cl) = 567.2

La eliminación del grupo Boc se logró disolviendo el compuesto anterior con HCl 4N en dioxano (1 mL) y agitando a temperatura ambiente durante 1 hora en una atmósfera de N_2 (g). La mezcla blanca turbia resultante se concentró para obtener el producto final. (100 mg, rendimiento del 85%) ^{1}HNMR (CD_3OD): δ 7.3 (s, 1H), 7.15 (s, 2H), 6.9 (m, 2H), 6.8 (m, 1H), 4.6 (t, 1H), 4.05 (m, 1H), 3.9 (m, 1H), 3.2 (m, 2H), 3.0 (m, 1H, 2.8 (m, 2H), 2.7 (m, 2H), 2.5 (d, 2H), 2.2 (m, 2H), 2.0 (m, 1H), 1.85 (s, 3H), 1.85, m, 1 H), 0.9 (m, 6H). $M+H^+$ (Cl) = 445.2

B. **Preparación de *N*-(1*S*, 2*R*)-{1-(3,5-Difluoro-bencil)-3-[(1*S*)-7-(2,2-dimetilpropil)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-2-hidroxipropil}-acetamida**



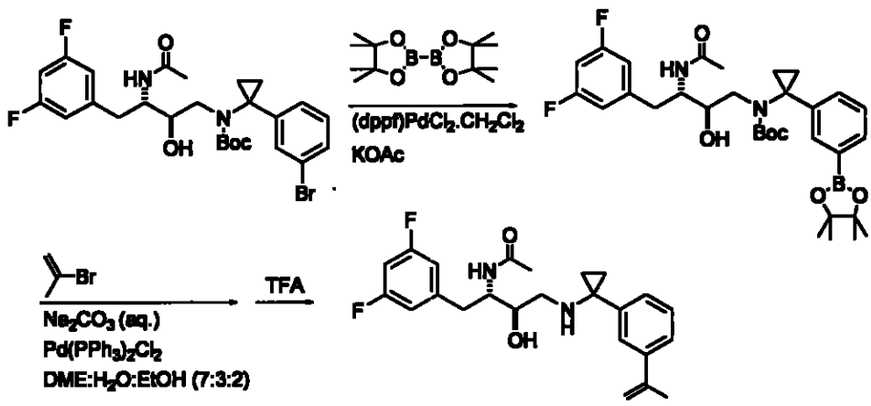
Se agitaron vigorosamente la escoria de magnesio (1.5 equiv, 45 mmol, 1.1 g) e I_2 (catalítico), procediendo a calentarlos suavemente con una pistola térmica bajo N_2 (g) para activar el magnesio. Se enfrió el magnesio a temperatura ambiente antes de añadir una solución de $ZnCl_2$ (1 equiv, 30 mmol, 60 mL) en THF 0.5 M seguido por bromuro de neopentilo (1.5 equiv, 45 mmol, 6.94 g, 5.8 mL). En cuestión de 5 a 10 minutos la reacción se tornó en una suspensión blanca. Eventualmente la suspensión adquirió un color gris. La mezcla se calentó a 50°C durante toda la noche, seguida por 2 horas adicionales de calentamiento a reflujo. Se enfrió la suspensión gris a temperatura ambiente y se utilizó cruda en la siguiente reacción. Se supuso que esta solución de cloruro de zincneopentilo tenía una concentración aproximada de 0.5 M.

A la amina bromotetralina (1 equiv, 8 mmol, 1.71 g) se añadió la suspensión cruda de cloruro de zincneopentilo (3 equiv, 24 mmol, 48 mL), seguido por el $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.05 equiv, 0.4 mmol, 330 mg). La reacción se agitó durante toda la noche a temperatura ambiente y bajo una atmósfera de N_2 (g). La suspensión rápidamente cambió a un color amarillo y durante la noche adquirió un color violeta. Después de 12 horas, la reacción se templó con NH_4Cl (ac) y se extrajo 3x con EtOAc. Se procedió a lavar con salmuera los extractos orgánicos combinados, secándolos posteriormente sobre Na_2SO_4 para luego filtrarlos y concentrarlos. Mediante cromatografía en columna sobre SiO_2 con 2 → 10 % de MeOH en CH_2Cl_2 se obtuvo el compuesto deseado neopentil tretalin amina. (1.5 g, rendimiento del 86%) ^{1}HNMR ($CDCl_3$): δ. 7.15 (s,1H), 6.95 (m, 2H), 3.95 (m, 1H), 2.8 (m, 2H), 2.4 (s, 2H), 2.0 (m, 2H), 1.7 (m, 2H), 1.6 (broad s, 2H), 1.0 (s, 9H); M-NH_2^+ (Cl) = 201.2.

El compuesto final se sintetizó mediante apertura epóxida, desprotección del grupo protector y acetilación tal como se describió previamente. M+H^+ (Cl) = 459.2.

523

C. Preparación de *N*-(1*S*, 2*R*)-{1-(3,5-Difluorobencil)-2-hidroxi-3-[1-(3-isopropenil-fenil)-ciclopropilamino]-propil}-acetamida

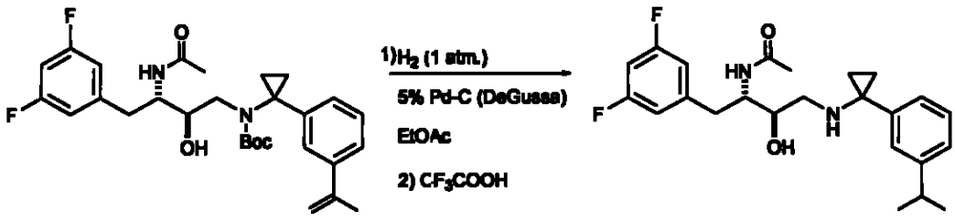


Al matraz se añadió acetato de potasio (5 equiv, 8.8 mmol, 0.864 g), (dppf)$PdCl_2$·CH_2Cl_2 (0.04 equiv, 0.0704 mmol, 57.5 mg), y diboro grado reactivo (1.15 equiv, 2.03 mmol, 0.515g), seguidos por el bromuro (1 equiv, 1 g, 1.76 mmol) y DMF (7 mL). La mezcla se desoxigenó mediante purgado subsuperficial con N_2 (g) y se agitó a 80°C bajo N_2 (g) de un día para otro. En cuanto se inició el calentamiento, la reacción cambió a un color pardo (marrón). Después de transcurridas 18 horas, la reacción se repartió entre EtOAc y H_2O, y se extrajo 3x con EtOAc. Los extractos orgánicos combinados se lavaron en salmuera, se secaron sobre Na_2SO_4 y se filtraron antes de eliminar el solvente en condiciones de vacío. Con una columna rápida de SiO_2 con 20→50% EtOAc en hexanos se obtuvo el éster borónico puro. (0.75 g, rendimiento del 69%) ^{1}HNMR (CD_3OD): δ 7.6 (t, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.8 (dd, 2H), 6.6 (m, 1H), 4.05 (m, 1H), 3.8 (m, 1H), 3.5 (m, 2H), 2.9 (m, 2H), 1.8 (s, 3H), 1.4 (s, 9H), 1.2 (m, 12 H), 1.2 (m, 4 H). $M+Na^+$ (CI) = 623.2

El éster del boro (1 equiv, 0.167 mmol, 100 mg) seguido por $Pd(PPh_3)_2Cl_2$ (0.1 equiv, 0.017 mmol, 11.7 mg), 2-bromopropeno (1.2 equiv, 0.2 mmol, 24.2 mg, 17.8 µl), 2M Na_2CO_3 (ac) (1.5 equiv, 0.25 mmol, 0.125 mL), y finalmente una mezcla 7:3:2 DME:$H_2$0:EtOH (0.7 mL) se colocaron en un vial para reacción equipado con una barra agitadora. El vial se selló y se procedió a preagitar la reacción durante 15 s antes de colocarla en microondas a 160 °C durante 7 minutos al nivel de absorción normal y con el tiempo de espera fijo activado. (Se utilizó un reactor personal químico de microondas). La reacción se repartió entre EtOAc y H_2O, y se extrajo 3x con EtOAc. Los extractos orgánicos combinados se lavaron en salmuera, se secaron

sobre Na_2SO_4 y se filtraron antes de eliminar el solvente en condiciones de vacío. La purificación se obtiene mediante una corrida en columna de SiO_2 con 10→35% EtOAc en hexanos obtuvieron el compuesto estireno Boc puro protegido. (45.9 mg, rendimiento del 53%) $M+Na^+$ (CI) = 537.2 El grupo Boc se eliminó con el tratamiento del anterior compuesto protegido con TFA:CH_2Cl_2 1:4 a 0°C. La reacción se agitó durante 2 h a 0°C y luego se concentró para obtener el producto deseado. Con la purificación por HPLC se obtuvo el producto deseado (7 mg, rendimiento del 36%): $M+H^+$ (CI) = 415.2

D. Preparación de *N*-(1*S*, 2*R*)-{1-(3,5-Difluorobencil)-2-hidroxi-3-[1-(3-isopropilfenil)-ciclopropilamino]-propil}-acetamida



La amina Boc (1 equiv, 0.1 mmol, 55.4 mg) se disolvió en EtOAc antes de añadirle el catalizador DeGussa Pd-C al 5% (esta cantidad no se midió). Se evacuó el aire del matraz antes de aplicar un balón de N_2 (g). La mezcla se agitó durante 4 h a temperatura ambiente. En este punto HPLC-MS determinó que la reacción había culminado. La filtración con tierra diatomácea seguida por la remoción del solvente con vacío produjo el material reducido crudo y limpio. (56.7 mg, cuantitativo) $M+H^+$ (CI) = 517.3.
La eliminación del grupo Boc se logró disolviendo el compuesto anterior con TFA:CH_2Cl_2 50:50 y agitando a temperatura ambiente durante 1 hora bajo una atmósfera de N_2 (g). La solución resultante se concentró para obtener el producto final. (41.6 mg, cuantitativo): ^{1}H NMR (CD_3OD) δ 7.4 (s, 1H), 7.25 (m, 3H), 6.7 (m, 2H), 6.6 (m, 1H), 4.0 (m, 1H), 3.9 (m, 1H), 2.9 (m, 4H), 2.7 (m, 1H), 1.8 (s, 3H), 1.2 (d, 6 H), 1.2 (m, 4H). $M+H^+$ (CI) = 417.2

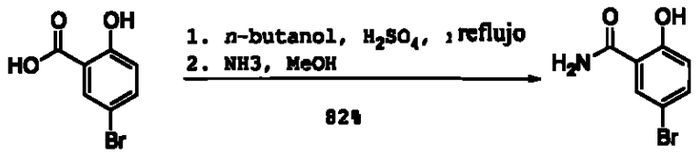
Ejemplo 111

Las reacciones se vigilaron y se evaluó la pureza con placas TLC sobre sílica gel GF, 250μ provenientes de Analtech, Inc., Newark, DE. La cromatografía de preparación a baja presión (flash) se efectuó sobre sílica gel 60 (malla 230-400 ASTM) proveniente de EM Science, Gibbstown, NJ. Los espectros del RMN protónico se recolectaron en un espectrómetro Bruker

525

Avance 400. Los desplazamientos químicos (δ) se dan en ppm, las constantes de acoplamiento (*J*) se miden en Hz. Se reportan absorbencias IR superiores a 1200 cm^{-1}. Todos los reactivos se obtuvieron de fuentes comerciales y se utilizaron sin purificación adicional. A no ser que se indique lo contrario, todos los solventes utilizados en la reacción se corrieron bajo una atmósfera inerte de nitrógeno en material de vidrio sobresecado. La cromatografía flash preparativa se realizó sobre sílica gel 60 (malla 230-240) suministrada por EM Science. El análisis HPLC se llevó a cabo en un sistema HP1100 (Agilent) con el siguiente gradiente lineal de 1.0 mL/min de TFA acuoso al 0.05% (A) y TFA al 0.05% en acetonitrilo (B): 0% B: 5 min: 60% B, 15 min: 90% B, 2 min: 0% B. Todos los solventes para cromatografía son grado HPLC. Si los materiales iniciales no se encuentran disponibles comercialmente, incluyendo los compuestos nuevos y los conocidos, se prepararon mediante métodos sintéticos conocidos. El compuesto HATU, que significa *N*-[(dimetilamino)-1-*H*-1,2,3-triazolo[4,5-b]pirindin-1-ilmetileno]-*N*-metilmetanaminio hexafluorofosfato *N*-óxido, se compró a PE Biosystems. Todas las sales de hidrocloruro se formaron añadiendo ácido clorhídrico etéreo a una solución etérea de amina, seguido por el proceso de concentración hasta llegar al compuesto seco.

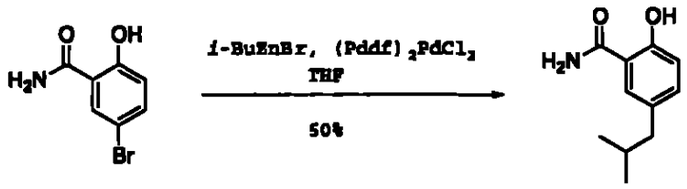
A. 5-bromo-2-hidroxibenzamida



A una solución agitada de ácido 5-bromosalicílico (30 g, 135.5 mmol) en *n*-butilalcohol (60 mL) se añadió H_2SO_4 (95.6%, 289 µL, 5.42 mmol) en un matraz de fondo redondo de 100 ml conectado con un condensador separador/de reflujo Dean-Stark que se llenó con 12 ml de *n*-butilalcohol. Después de calentar a reflujo durante 2 días, la reacción se enfrió hasta temperatura ambiente y se concentró obteniendo un aceite de color amarillo pálido. A esta mezcla se añadieron 50 mL de MeOH, seguido por NH_3 en MeOH (7 N, 116 mL) La reacción se agitó a temperatura ambiente durante otros 2 días y se vigiló por HPLC. Después de terminada la reacción, se concentró hasta obtener un sólido blanco. El sólido crudo se lavó con una pequeña cantidad de EtOAc y hexano para obtener 24 g del producto, un sólido blanco cristalino (rendimiento del 82%). ^1H NMR ($CDCl_3$) δ 12.15 (s, 1 H), 7.54 (m, 2 H), 6.97 (d, J = 12 Hz, 1 H), 6.00 (broad, 2 H).

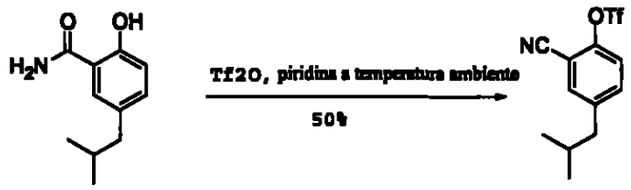
526

B. 2-hidroxi-5-isobutilbenzamida



A una solución previamente agitada de bromobenzamida (8.64 g, 40 mmol) en THF (100 mL) bajo argón se añadió [1,1'-Bis(difenilfosfino)ferroceno]dicloropaladio(II) (1.96 g, 2.4 mmol) seguido por *i*-BuZnBr (0.5 M, 200 mL). La mezcla reactiva se agitó a temperatura ambiente durante 4 días. La reacción se enfrió rápidamente en agua con HCl 1N y luego se concentró. El crudo resultante se diluyó con acetato de etilo, lavándolo luego en agua y salmuera, procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (5~10% de acetato de etilo: hexano) para obtener 4.63 g del producto isobutilbenzamida en forma de un sólido blancuzco (rendimiento del 60%). ^{1}H NMR ($CDCl_3$) δ 12.02 (s, 1 H), 7.24 (d, J = 8 Hz, 1 H), 7.12 (s, 1 H), 6.93 (d, J = 8 Hz, 1 H), 2.44 (d, J = 8 Hz, 2 H), 1.83 (m, 1 H), 0.93 (d, J = 8 Hz, 6 H).

C. 2-ciano-4-isobutilfenil trifluorometanosulfonato

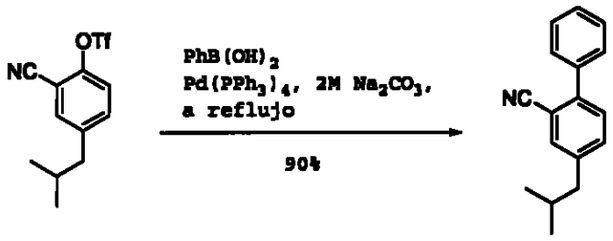


A 0 °C, a una solución previamente agitada del hidroxi-isobutilbenzamida (3.72 g, 19.3 mmol) en piridina (15 mL) bajo argón, se añadió anhídrido trifluorometanosulfónico (10.2 ml, 57.8 mmol). La mezcla reactiva eventualmente se calentó hasta temperatura ambiente y se agitó de un día para otro. El crudo resultante se diluyó con acetato de etilo, lavándolo luego con HCl 1N (x2), agua (x1) y salmuera (x1), procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida. El producto crudo se purificó mediante cromatografía en

527

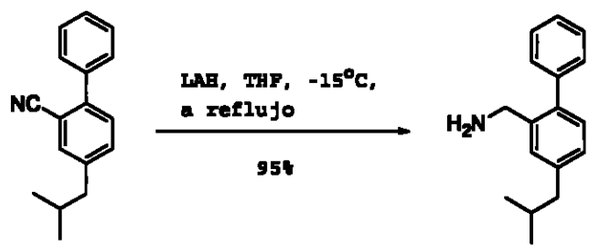
columna flash (5% de acetato de etilo: hexano) para obtener 2.66 g del producto deseado con la apariencia de un aceite transparente (rendimiento del 50%). ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.43 (d, J = 8 Hz, 1 H), 2.57 (d, J = 8 Hz, 2 H), 1.92 (m, 1 H), 0.97 (d, J = 4 Hz, 6 H).

D. 4-isobutil-1,1'-bifenil-2-carbonitrilo



A una solución previamente agitada del compuesto ciano (610 mg, 1.88 mmol), carbonato de sodio acuoso (2.0 M, 3.76 mmol) en DME (6 mL) se añadió tetraquis(trifenilfosfina) paladio(0) (109 mg, 0.094 mmol) seguido por ácido fenilborónico (280 mg, 2.26 mmol). La mezcla reactiva se calentó a reflujo de un día para otro y luego se enfrió a temperatura ambiente. La reacción se diluyó con acetato de etilo, lavándola posteriormente con agua y salmuera, procediendo luego a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (3% de acetato de etilo: hexano) para obtener 450 mg del producto de apariencia sólida cristalina (rendimiento del 90%). ^{1}H NMR ($CDCl_3$) δ 7.60 (m, 3 H), 7.54 (m, 2 H), 7.48 (m, 3 H), 2.60 (d, J = 8 Hz, 2 H), 1.96 (m, 1 H), 1.00 (d, J = 6 Hz, 6 H).

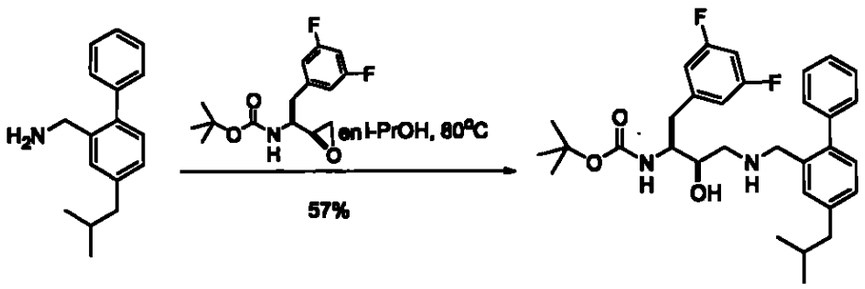
E. (4-isobutil-1,1'-bifenil-2-il)metilamina



528

A –15 °C, a una suspensión previamente agitada de LAH (171 mg, 4.5 mmol) en THF anhidro (2 mL) se añadió el compuesto bifenilciano (450 mg, 1.77 mmol) en THF (1 mL). La reacción se calentó eventualmente hasta temperatura ambiente de un día para otro y luego se mantuvo a reflujo durante 1 hora. La mezcla reactiva se enfrió hasta temperatura ambiente y luego se enfrió rápidamente con Na_2SO_4 acuoso saturado. La reacción se vertió en CH_2Cl_2 (10 mL) y luego se filtró. La precipitación se lavó varias veces con CH_2Cl_2. La solución orgánica se secó con sulfato de sodio, luego se concentró bajo presión reducida para obtener 400 mg del producto , un aceite amarillo pálido (rendimiento del 95%). ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 2 H), 7.44 (m, 3 H), 7.30 (s, 1 H), 7.20 (d, J = 8 Hz, 1 H), 7.14 (m, 1 H), 3.84 (s, 2 H), 2.58 (d, J = 8 Hz, 2 H), 1.93 (m, 1 H), 1.47 (s, 2 H), 1.00 (d, J = 4 Hz, 6 H); ESI-MS $[M+H^+]^+$ = 240.22.

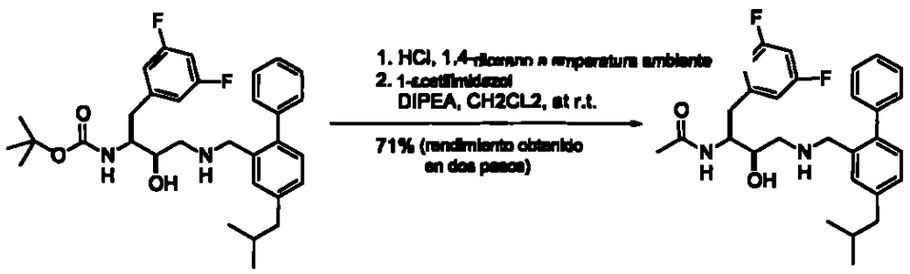
F. tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino} propilcarbamato



A una solución previamente agitada de bifenil amina (400 mg, 1.67 mmol) en *i*-propanol (10 mL) se añadió el Ejemplo 134 (nombre generado utilizando ACD Namepro versión 5.09) (336 mg, 1.12 mmol). La mezcla reactiva se calentó a 80 °C de un día para otro. La mezcla reactiva se concentró y purificó mediante cromatografía flash (2-5% MeOH: CH_2Cl_2) para obtener 510 mg del producto en forma de un sólido blanquecino (rendimiento del 57%). ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.38 (m, 3 H), 7.25 (s, 1 H), 7.21 (m, 1 H), 7.16 (m, 1 H), 6.76 (m, 2 H), 6.70 (m, 1 H), 4.55 (m, 1 H), 3.76 (m, 3 H), 3.34 (m, 1 H), 2.90 (m, 1 H), 2.78 (m, 2 H), 2.64 (m, 2 H), 2.55 (m, 3 H), 1.93 (m, 1 H), 1.40 (s, 9 H), 1.00 (d, 6 H); ESI-MS $[M+H^+]^+$ = 539.22.

G. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino}propil) acetamida

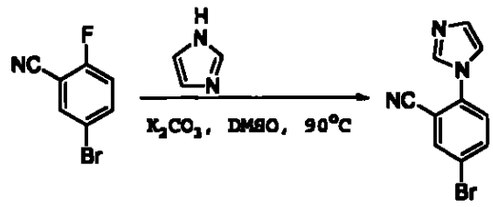
529



Paso 1: A una solución previamente agitada del material inicial (377 mg, 0.7 mmol) en MeOH (5 mL) se añadió HCl en 1,4-dioxano (4.0 M, 2 mL). Después de agitar a temperatura ambiente de un día al otro, la mezcla reactiva se concentró bajo presión reducida para obtener un sólido blanquecino que luego se usó sin purificarlo más.

Paso 2: A una solución previamente agitada de amina del paso 1 en CH_2Cl_2 (8 mL) se añadió DIPEA (304 µL, 1.75 mmol), y luego 1-acetilimidazol (86 mg, 0.77 mmol). La mezcla reactiva se agitó a temperatura ambiente de un día para otro, se enfrió rápidamente añadiéndole hidróxido de amonio al 50% y luego se diluyó con CH_2Cl_2. La capa orgánica se lavó con HCl 1N (x2), agua (x1), una solución acuosa de bicarbonato de sodio (x2) y salmuera (x1), procediendo a continuación a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (MeOH al 3-5%: CH_2Cl_2) para obtener 240 mg del producto en forma de un sólido blanquecino (rendimiento del 71%, en dos pasos). ^{1}H NMR ($CDCl_3$) δ 9.63 (b, 1 H), 8.48 (b, 1 H), 7.63 (s, 1 H), 7.46 (m, 3 H), 7.28 (m, 4 H), 6.74 (m, 2 H), 6.67 (m, 1 H), 4.24 (m, 1 H), 4.17 (m, 1 H), 4.05 (m, 2 H), 2.80 (m, 4 H), 2.57 (m, 3 H), 1.97 (m, 4 H), 0.97 (d, 6 H); ESI-MS $[M+H^+]^+$ = 481.35.

H. 5-bromo-2-(1H-imidazol-1-il)benzonitrilo



530

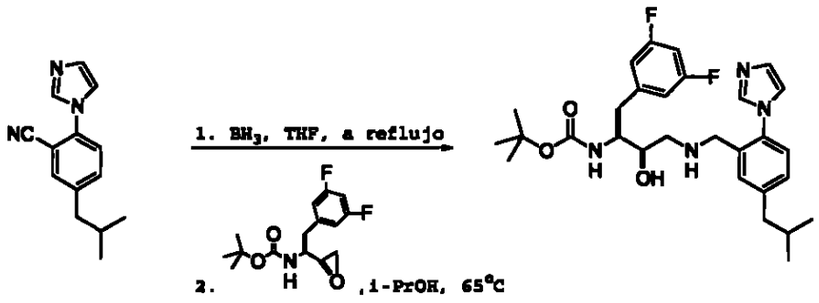
A una solución previamente agitada de 5-Bromo-2-fluorobenzonitrilo (2.5 g, 12.2 mmol) en DMSO (50 mL) se añadió K_2CO_3 (3.337 g, 24.4 mmol), y luego 1H-imidazol (996 mg, 14.64 mmol). La mezcla reactiva se calentó a 90°C de un día para el otro y se diluyó con agua. La mezcla reactiva se extrajo con EtOAC (x2). La capa orgánica se lavó con agua (x1) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida para obtener 2.97 g del imidazolilbenzonitrilo con apariencia de un sólido blanquecino (rendimiento del 98%). ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2 H), 7.90 (m, 1 H), 7.41 (d, J = 8 Hz, 1 H), 7.37 (s, 1 H), 7.32 (s, 1 H).

I. 2-(1H-Imidazol-1-il)-5-isobutilbenzonitrilo

A una solución previamente agitada del producto obtenido en (H) arriba (1.02 g, 4.11 mmol) en THF (5 mL) bajo argón se añadió [1,1'-Bis(difenilfosfino)ferroceno]dicloropaladio(II) (336 mg, 0.411 mmol) seguido por *i*-BuZnBr (0.5 M, 28.8 mL). La mezcla reactiva se agitó a temperatura ambiente de un día para otro. La reacción se enfrió en agua con HCl 1N y luego se concentró. El crudo resultante se diluyó con acetato de etilo, lavándolo luego en agua y salmuera, procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (50-100% de acetato de etilo: hexano) para obtener 870 g del producto con la apariencia de aceite pardo oscuro (rendimiento del 94%). ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1 H), 7.60 (s, 1 H), 7.53 (d, J = 8 Hz, 1 H), 7.40 (m, 2 H), 7.28 (m, 1 H), 2.60 (d, J = 8 Hz, 2 H), 1.93 (m, 1 H), 0.97 (d, 6 H); ESI-MS $[M+H^+]^+$ = 226.03.

J. tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(1H-imidazol-1-il)-5-isobutilbencil]amino} propilcarbamato

531

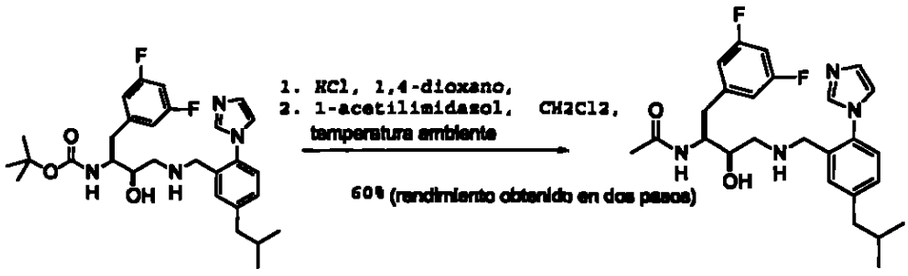


55%, (rendimiento obtenido en dos pasos)

Paso 1: A 0 °C, a una suspensión previamente agitada de BH_3 (1.5 M en THF, 4.9 mL) se añadió el producto imidazolil obtenido en (I) (722 mg, 3.2 mmol) en THF anhidro (8 mL). La reacción se calentó eventualmente hasta temperatura ambiente y luego se mantuvo a reflujo de un día para otro y posteriormente una vez más a reflujo durante 1 hora. La mezcla reactiva se enfrió hasta temperatura ambiente y luego se enfrió rápidamente con una solución acuosa de HCl 5N. La reacción se vertió en CH_2Cl_2 (10 mL), luego se lavó con bicarbonato de sodio acuoso saturado (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 2: A una solución previamente agitada de la amina del paso 1 en i-propanol (14 mL) se añadió (1S)-2-(3,5-difluorofenil)-1-[(2S)-oxiran-2-yl]etilcarbamato (509 mg, 1.7 mmol). La mezcla reactiva se calentó a 65 °C de un día para otro. La mezcla reactiva se concentró y purificó mediante cromatografía flash (MeOH 5-20%: CH_2Cl_2) para obtener 537 mg del producto en forma de un sólido blanquecino (rendimiento del 55%, en dos pasos). ESI-MS $[M+H^+]^+ = 529.35$.

K. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(1H-imidazol-1-il)-5-isobutilbencil]amino}propil) acetamida



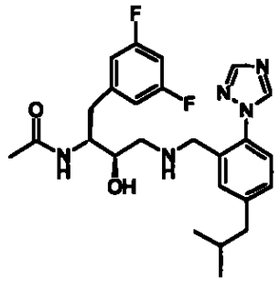
60% (rendimiento obtenido en dos pasos)

532

Paso 1: A una solución previamente agitada del producto obtenido en (J) (303 mg, 0.57 mmol) en MeOH (2 mL) se añadió HCl en 1,4-dioxano (4.0 M, 0.86 mL). Después de agitar a temperatura ambiente de un día para el otro, la mezcla reactiva se concentró bajo presión reducida para obtener un sólido blancuzco. La reacción se volvió a disolver en CH_2Cl_2, luego se lavó con bicarbonato de sodio acuoso saturado (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 2: A una solución previamente agitada de la amina obtenida en el paso 1 en CH_2Cl_2 (8 mL) [se añadió] 1-acetilimidazol (71 mg, 0.63 mmol). La mezcla reactiva se agitó a temperatura ambiente de un día para otro, se enfrió rápidamente añadiéndole hidróxido de amonio al 50% y luego se diluyó con CH_2Cl_2. La capa orgánica se lavó con HCl 1N (x2), una solución acuosa de bicarbonato de sodio (x2) y salmuera (x1), procediendo a continuación a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (MeOH al 5-20%: CH_2Cl_2) para obtener 160 mg del producto en forma de un sólido blanquecino (rendimiento del 60%, en dos pasos). ESI-MS $[M+H^+]^+ = 471.33$.

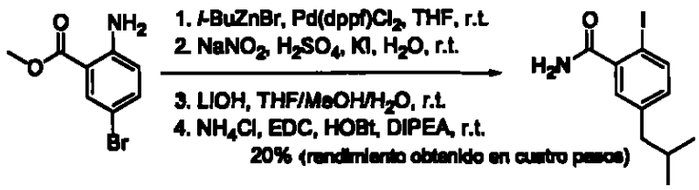
L. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[5-isobutil-2-(1H-1,2,4-triazol-1-il)bencil]amino}propil) acetamida



El compuesto anterior se puede sintetizar en forma análoga utilizando los materiales iniciales adecuados. The ESI-MS $[M+H^+]^+ = 472.0$

M. 2-Iodo-5-isobutilbenzamida

533



Paso 1: A una solución previamente agitada de metil 2-amino-5-bromobenzoato (5.77 g, 25 mmol) en THF (20 mL) bajo argón se añadió [1,1'-Bis(difenilfosfino)ferroceno] dicloropaladio(II) (2.04 g, 2.5 mmol) seguido por *i*-BuZnBr (0.5 M, 200 mL). La mezcla reactiva se agitó a temperatura ambiente de un día para otro. La reacción se enfrió rápidamente con HCl 1N y luego se concentró. El crudo resultante se diluyó con acetato de etilo, lavándolo luego en agua y salmuera, procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida sin más purificación.

Paso 2: A temperatura ambiente la amina del paso 1 se trató con H_2SO_4 al 5% (3.2 mL) y la reacción se calentó a 60 °C durante 5 – 10 minutos. La mezcla reactiva se enfrió hasta quedar helada y luego se añadió gota a gota $NaNO_2$ (1.87 g, 27 mmol) en H_2O (10 mL). Terminada la adición, la reacción se agitó a temperatura helada durante 15 – 20 minutos y luego se añadió KI (4.94 g, 29.7 mmol) en H_2O (20 mL). la reacción se agitó a temperatura ambiente de un día para el otro. Al siguiente día se extrajo la reacción con EtOAC (x3). La capa orgánica se lavó con salmuera (x1), se secó (con sulfato de sodio), se filtró y se concentró. El producto crudo se purificó mediante cromatografía flash (MeOH al 5-10%: CH_2Cl_2) para obtener 2 g del producto iodado.

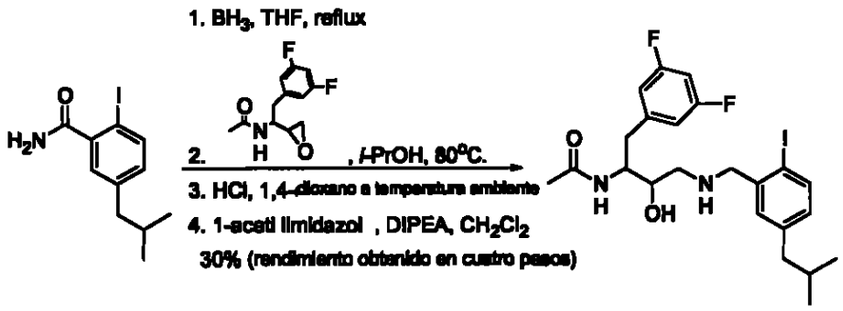
Paso 3: A una solución previamente agitada del producto iodado del paso 2 (6.6 g, 20.9 mmol) en una mezcla de solventes consistente en MeOH (30 mL), THF (30 mL) y agua (30 mL), se añadió $LiOH \cdot H_2O$ (4.4 mg, 104.5 mmol) a temperatura ambiente. Después de agitar durante 12 horas a temperatura ambiente, la mezcla reactiva se enfrió rápidamente con HCl 1N, se diluyó con CH_2Cl_2, se lavó con solución acuosa de bicarbonato de sodio (x1), agua (x2) y salmuera (x2), se secó sobre sulfato de sodio y se concentró bajo presión reducida. El producto crudo se usó en el siguiente paso sin más purificación.

Paso 4: A una solución previamente agitada de ácido obtenido en el paso 3 (2.8 g, 9.24 mmol) en DMF (60 mL) se añadió EDC (3.55 g, 18.5 mmol), HOBt (2.5 g, 18.5 mmol), diisopropiletilamina (8.04 mL, 46.2 mmol), y luego se agregó cloruro de amonio (1.49 g, 27.7 mmol) a temperatura ambiente. Después de agitar durante 10 horas a temperatura ambiente, la mezcla reactiva se vertió en agua. La solución acuosa se extrajo con acetato de etilo (x2) y se

534

recolectaron las capas orgánicas, se lavaron con agua (x2), HCl 1N (2), solución acuosa saturada de bicarbonato de sodio (x2) y salmuera (x2), se secó sobre sulfato de sodio y se concentró bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (EtOAC al 10-50%: CH_2Cl_2) para obtener 900 mg del producto en forma de un sólido blanquecino (rendimiento del 20%, en cuatro pasos). ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8 Hz, 1 H), 7.30 (s, 1 H), 6.95 (d, J = 8 Hz, H), 5.80 (b, 2 H), 2.47 (d, J = 6 Hz, 2 H), 1.87 (m, 1 H), 0.93 (2, H).

N. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-iodo-5-isobutilbencil)amino]propil}acetamida



Paso 1: A 0 °C, a una solución de BH_3 (1.5 M en THF, 9.3 mL) se añadió (1.838 g, 6.1 mmol) en THF anhidro (16 mL). La reacción se calentó eventualmente hasta alcanzar la temperatura ambiente y luego se mantuvo a reflujo de un día para otro y posteriormente una vez más a reflujo durante 1 hora. La mezcla reactiva se enfrió hasta llegar a temperatura ambiente y luego se enfrió rápidamente con una solución acuosa de HCl 5N. La reacción se vertió en CH_2Cl_2 (10 mL), luego se lavó con una solución acuosa de bicarbonato de sodio (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 2: A una solución previamente agitada de la amina del paso 1 en i-propanol (27 mL) se añadió (1S)-2-(3,5-difluorofenil)-1-[(2S)-oxiran-2-il]etilcarbamato (1.027 g, 3.43 mmol). La mezcla reactiva se calentó a 65 °C de un día para otro. La mezcla reactiva se concentró bajo presión reducida sin más purificación.

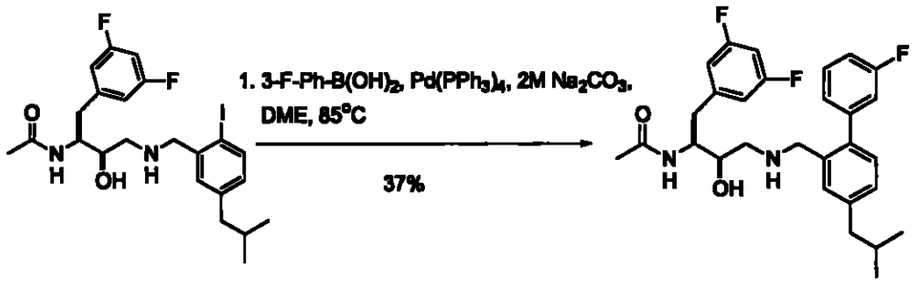
Paso 3: A una solución previamente agitada del compuesto crudo obtenido en el paso 2 en MeOH (10 mL) se añadió HCl en 1,4-dioxano (4.0 M, 5.6 mL). Después de agitar a temperatura ambiente de un día para el otro, la mezcla reactiva se concentró bajo presión reducida para obtener un sólido blanquecino. La reacción se volvió a disolver en CH_2Cl_2 , luego se lavó

535

con una solución acuosa saturada de bicarbonato de sodio (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 4: A una solución previamente agitada de amina del paso 3 en CH_2Cl_2 (60 mL) se añadió DIPEA (3.88 mL, 22.3 mmol), y luego 1-acetilimidazol (516 mg, 4.46 mmol). La mezcla reactiva se agitó a temperatura ambiente de un día para otro, se enfrió rápidamente añadiéndole hidróxido de amonio al 50% y luego se diluyó con CH_2Cl_2 . La capa orgánica se lavó con HCl 1N (x2), una solución acuosa saturada de bicarbonato de sodio (x2) y salmuera (x1), procediendo a continuación a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (MeOH al 3-5%: CH_2Cl_2) para obtener 1 mg del producto en forma de un sólido blancuzco (rendimiento del 30%, en cuatro pasos). ^1H NMR ($CDCl_3$) δ 7.76 (d, J = 9 Hz, 1 H), 7.14 (a, 1 H), 6.76 (m, 4 H), 5.97 (d, J = 3 Hz, 1 H), 4.20 (m, 1 H), 3.84 (m, 2 H), 3.63 (m, 1 H), 2.81 (m, 4 H), 2.46 (d, J = 6 Hz, 2 H), 1.88 (m, 4 H), 0.92 (d, 6 H).

O. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(3'-fluoro-4-isobutil-1,1'-bifenil-2-il)metil]amino}-2-hidroxipropil)acetamida



A una solución previamente agitada del producto obtenido en (N)(97 mg, 0.183 mmol), solución acuosa de carbonato de sodio (2.0 M, 0.403 mmol) en DME (1 mL) se añadió tetraquis(trifenilfosfina) paladio(0) (21 mg, 0.0183 mmol) seguido por ácido 3-fluoro-fenilborónico (64 mg, 0.458 mmol). La mezcla reactiva se calentó a reflujo de un día para otro y luego se enfrió a temperatura ambiente. La reacción se diluyó con CH_2Cl_2, lavándola posteriormente con agua y salmuera, procediendo luego a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (MeOH al 3-10%: CH_2Cl_2) para obtener 36 mg del producto en forma de un sólido blanco (rendimiento del 37%). ESI-MS $[M+H^+]^+$ = 499.32.

536

Los compuestos que se muestran en las secciones P-Z pueden sintetizarse utilizando métodos análogos a los descritos previamente.

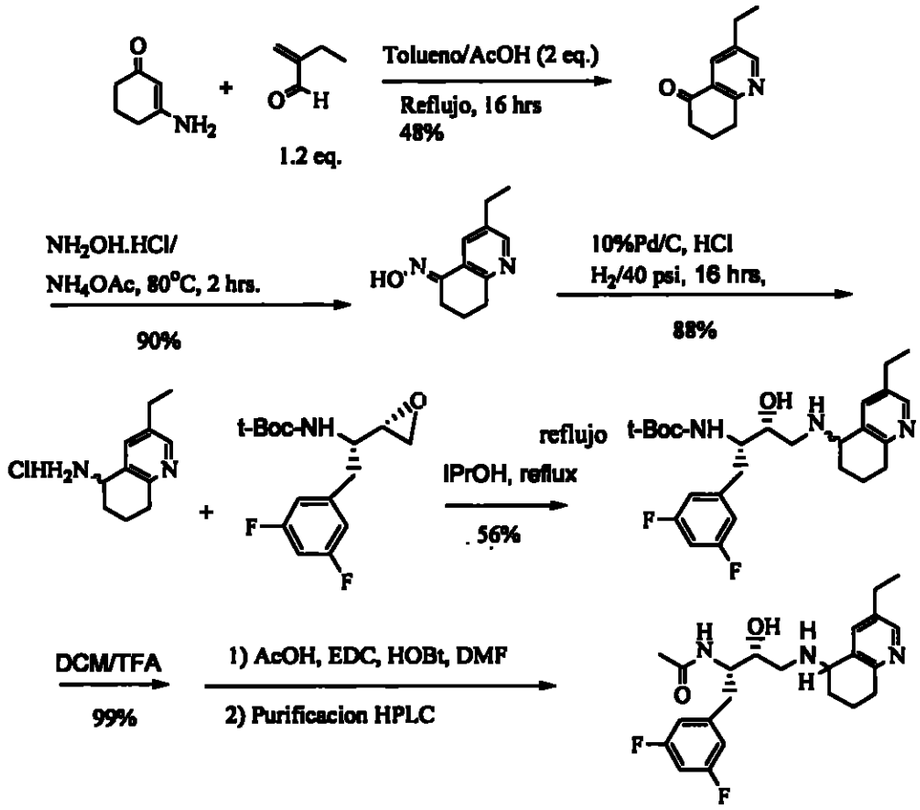
P. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino}propil) acetamida	ESI-MS $[M+H^+]^+$ = 481.35
Q. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(5-isobutil-2-piridin-3-ilbencil)amino]propil}acetamida	ESI-MS $[M+H^+]^+$ = 482.33
R. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(5-isobutil-2-piridin-4-ilbencil)amino]propil}acetamida	ESI-MS $[M+H^+]^+$ = 482.33
S. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4'-fluoro-4-isobutil-1,1'-bifenil-2-il)metil]amino}-2-hidroxipropil)acetamida	ESI-MS $[M+H^+]^+$ = 499.31
T. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(2'-fluoro-4-isobutil-1,1'-bifenil-2-il)metil]amino}-2-hidroxipropil)acetamida	ESI-MS $[M+H^+]^+$ = 499.32
U. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[5-isobutil-2-(6-metoxipiridin-3-il)bencil]amino}propil) acetamida	ESI-MS $[M+H^+]^+$ = 512.33
V. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(3'-hidroxi-4-isobutil-1,1'-bifenil-2-il)metil]amino}propil)acetamida	ESI-MS $[M+H^+]^+$ = 497.36
W. N-[(1S,2R)-3-{[(3'-acetil-4-isobutil-1,1'-bifenil-2-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamide	ESI-MS $[M+H^+]^+$ = 523.33
X. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[5-isobutil-2-(5-metoxipiridin-3-il)bencil]amino}propil) acetamida	ESI-MS $[M+H^+]^+$ = 512.30
Y. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(3-furil)-5-isobutilbencil]amino}-2-hidroxipropil)acetamida	ESI-MS $[M+H^+]^+$ = 471.32
Z. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(2-	ESI-MS

537

furil)-5-isobutilbencil]amino}-2-hidroxipropil)acetamida	$[M+H^+]^+$ = 471.32

Ejemplo 112

Véase Albright, J.D., *J. Heterocycl. Chem.*, 2000, *37*, 41-6 para obtener una referencia general sobre la preparación de los compuestos de piridil tetralina.



PASO 1:

A 5.5 g de 3-amino-2-ciclohexan-1-uno (49.5 mmole) y 5 g of 2-etil acroleina (59.4 mmole, 1.2 eq.) se añadieron 6 ml de ácido acético y 25 ml de tolueno. La mezcla reactiva se calentó a reflujo de un día para otro. La reacción se monitorizó mediante TLC para demostrar la formación de una nueva mancha con Rf = 0.73 (50% MeOH/DCM + 20% EtOH/Hexano.) Se sustrajo el solvente y el residuo se mezcló con tolueno, el cual se sustrajo nuevamente. El residuo se extrajo con DCM (2x), se lavó con $NaHCO_3$ saturado, se secó sobre sulfato de sodio anhidro y se concentró para obtener 9.38 g de un aceite crudo color canela oscuro. Este aceite se extrajo con

538

hexano caliente (2x of 125 ml). Los extractos se concentraron y secaron al vacío para obtener un sólido color canela claro. (4.13 g, 23.6 mmole, 48%). MH+ (ESI) = 176.1.

PASO 2:

La oxima se formó utilizando los procedimientos descritos en diferentes partes de la aplicación. El rendimiento fue del 90%; MH+ (ESI) = 191.1.

PASO 3:

La reducción de la oxima se llevó a cabo esencialmente siguiendo los procedimientos descritos en otras secciones de la aplicación. El rendimiento fue del 88%; MH+ (ESI) = 177.1.

PASO 4:

La sal del hidrocloruro de amina se obtuvo en su forma básica repartiéndola entre NaOH 1N y EtOAc. La solución básica libre se concentró luego y se usó en la reacción de apertura epóxida tal como se describió previamente: rendimiento del 56%; MH+ (ESI) = 476.2.

PASO 5:

La desprotección y acetilación del Boc se efectuó tal como se describió previamente. El procedimiento de HPLC de fase reversa fue efectivo en la resolución de los dos diasterómeros:

N-(1*S*, 2*R*)-[1-(3,5-Difluorobencil)-3-((5*S*)-3-etil-5,6,7,8-tetrahidroquinolin-5-ilamino)-2-hidroxipropil]-acetamida: MH+ (ESI) = 418.2.

N-(1*S*, 2*R*)-[1-(3,5-Difluorobencil)-3-((5*R*)-3-etil-5,6,7,8-tetrahidroquinolin-5-ilamino)-2-hidroxipropil]-acetamida: MH+ (ESI) = 418.2.

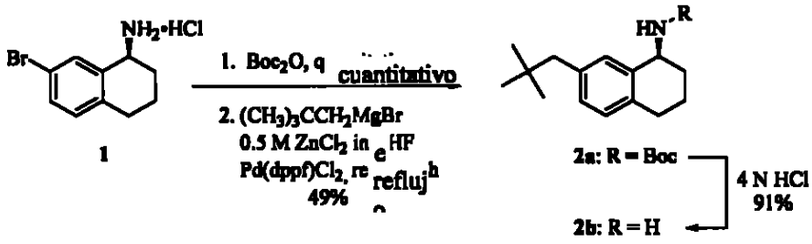
Ejemplo 113:

A. Síntesis de la Amina 2b

El compuesto (1), el cual se obtuvo fácilmente, se protegió y luego se enlazó, con mediación del paladio, con cloruro de *neo*-pentilzinc (generado in situ) para producir la tetralina *neo*-pentil **2a** sustituida (Esquema CC). La desprotección subsiguiente permitió obtener la amina intermedia **2b** en forma de la sal del hidrocloruro, la cual se usó en la construcción de objetivos adicionales (infra).

ESQUEMA CC

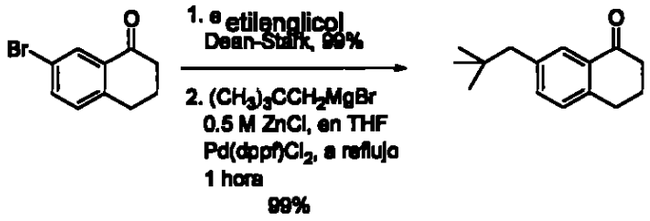
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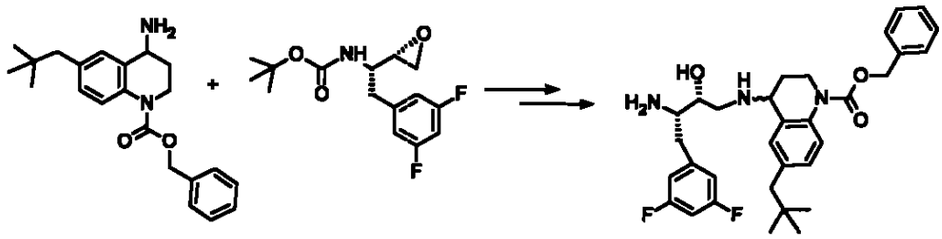
B. Síntesis de Tetralona 4

El compuesto 7-Bromotetralona (3) se protegió como dioxolano y luego experimentó reacción de acoplamiento con el cloruro de *neo*-pentilzinc (generado in situ) y catalizado con paladio para obtener, después de la fase acídica gradual, la tetralona *neo*-pentil 4 sustituida (Esquema DD). El compuesto (4) se envió a Pfizer Inc. el 6 de mayo de 2003.

ESQUEMA DD



B.9. Bencilo 4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hydroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato

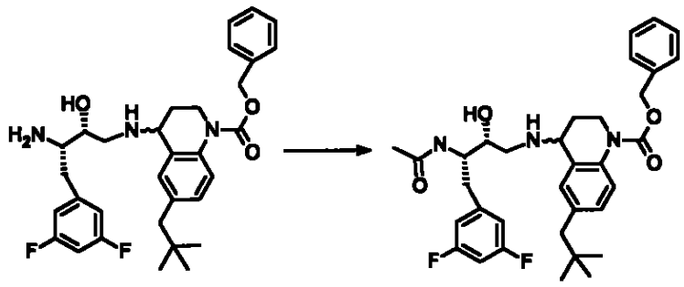


A una solución de Bencilo 4-amino-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato (1.31 g) en isopropanol (25 mL), se añadió el Ejemplo 134 (0.75 g) y se calentó la mezcla a 90 °C durante 45 minutos. La temperatura se redujo a 60 °C y se dejó agitando toda la noche. A la mezcla se añadieron 0.36 g adicionales del Ejemplo 134 y se calentó a 80 °C durante cinco horas. Se procedió a enfriar la mezcla a temperatura ambiente y se eliminó el solvente bajo presión reducida. El residuo se dividió entre agua y acetato de etilo y las capas orgánicas se secaron con

540

sulfato de magnesio, para luego filtrarlas y concentrarlas. Se pasó por una columna de sílica gel con el objeto de separar los diasteriómeros utilizando un gradiente de MeOH al 2-4% en diclorometano con 0.25% de NH_4OH como solvente. La primera fracción contenía una mezcla 70:30 de los diasteriómeros y la segunda fracción era una mezcla 50:50 de los diasteriómeros. Se extrajeron los grupos Boc disolviendo cada fracción en una cantidad mínima de diclorometano y añadiendo a cada una de las dos mezclas 15 mL de HCl 2N en éter. Las mezclas se agitaron por dos horas y se concentraron a presión reducida. A continuación se dividieron las mezclas entre hidróxido de sodio 1N y acetato de etilo, se secaron con sulfato de magnesio, se filtraron y concentraron hasta obtener 0.23 g de la mezcla 70:30 del compuesto en cuestión y 0.30 g de la mezcla 50:50. MS (ESI+) para el $C_{32}H_{39}F_2N_3O_3$ *m/z* 552.32 $(M+H)^+$ para la mezcla 70:30 y *m/z* 552.27 $(M+H)^+$ para la mezcla 50:50. Cada una de estas mezclas se llevó separadamente hasta el producto final. Los procedimientos a continuación ilustran ese proceso para la mezcla 70:30 exclusivamente.

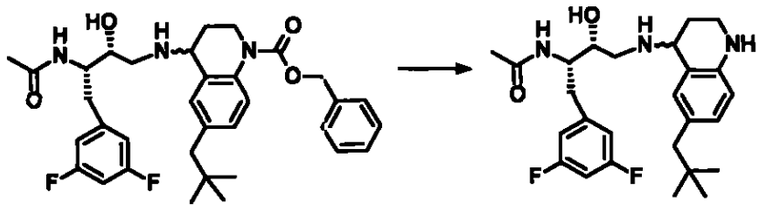
B.10. Bencilo 4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato



A una solución de Bencilo 4-{[(2R,3S)-3-amino-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato (0.226 g) en diclorometano (5 mL) se añadió N,N-diacetil-O-metilhidroxilamina (0.064 g). La mezcla se agitó durante el fin de semana a temperatura ambiente. El solvente se eliminó bajo presión reducida y el residuo se repartió entre HCl 1N y acetato de etilo, se secó con sulfato de magnesio, se filtró y concentró hasta obtener 0.243 g del compuesto en cuestión (rendimiento del 99%). MS (ESI+) para el $C_{34}H_{41}F_2N_3O_4$ *m/z* 594.31 $(M+H)^+$.

B.11. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]propil}acetamida

541



A una solución de Bencilo 4-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenilo)-2-hidroxibutil]amino}-6-neopentil-3,4-dihidroquinolin-1(2H)-carboxilato (0.242 g) en EtOH (30 mL), se añadió HCl 1N (1.0 mL) y 10% de paladio sobre carbono (0.030 g). La mezcla se desgasificó con N_2 durante cinco minutos. Toda la mezcla se colocó en un equipo de hidrogenación a 47 psi de H_2 y se agitó durante 4.5 horas. Se filtró el paladio utilizando Celita y el solvente se concentró bajo presión reducida. El residuo se repartió entre agua y acetato de etilo y las capas orgánicas se lavaron con una solución acuosa de bicarbonato de sodio, se secaron con sulfato de magnesio, para luego filtrarlas y concentrarlas. Al pasarlas por una columna de sílica gel con 4% de MeOH en diclorometano como solvente y se obtuvieron 0.095 g del compuesto en cuestión. MS (ESI+) para el $C_{28}H_{33}F_2N_3O_2$ *m/z* 460.27 $(M+H)^+$.

CONJETURAS

Los compuestos mencionados en los Ejemplos 109 (C-TT) pueden producirse de acuerdo con los métodos análogos a los descritos arriba, al igual que los típicos conocidos.

Ejemplo No.	Nombre
C.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
D.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
E.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
F.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
G.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
H.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-7-fluoro-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
I.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-7-fluoro-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
J.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-7-fluoro-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
K.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-7-fluoro-6-neopentil-1,2,3,4-

542

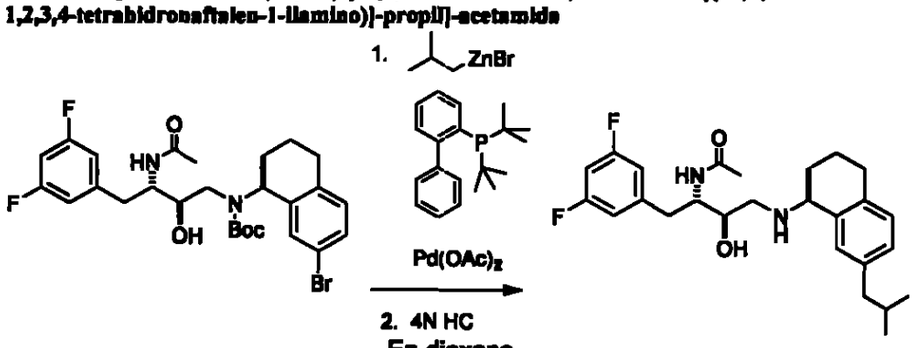
	tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
L.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
M.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
N.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
O.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
P.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1-(2-hidroxietil)-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
Q.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-(2-hidroxietil)-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
R.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-(2-hidroxietil)-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
S.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1-(2-hidroxietil)-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
T.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
U.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
V.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hydroxipropil]acetamida;
W.	N-[(1S,2R)-3-{[(4S)-1-acetil-6-tert-butil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
X.	N-[(1S,2R)-3-{[(4S)-6-tert-butil-1-(cianometil)-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
Y.	N-[(1S,2R)-3-{[(4S)-1-(cianometil)-6-isopropil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
Z.	N-[(1S,2R)-3-{[(4S)-1-(cianometil)-6-isobutil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
AA.	N-[(1S,2R)-3-{[(4S)-1-(cianometil)-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
BB.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1-hidroxi-2,2-dimetilpropil)-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
CC.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1-hidroxi-2,2-dimetilpropil)-1-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
DD.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-2,2-dimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
EE.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-1,2,2-trimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
FF.	N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-1,4-dimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}-2-hidroxipropil)acetamida;
GG.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-4-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
HH.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-4-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
II.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-1,4-dimetil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
JJ.	N-[(1S,2R)-3-[(6-tert-butoxi-1,2,3,4-tetrahidroquinolin-4-il)amino]-1-(3,5-difluorobencil)-

543

	2-hidroxipropil]acetamida;
KK.	N-[(1S,2R)-3-[(6-tert-butoxi-4-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
LL.	N-[(1S,2R)-3-[(6-tert-butoxi-4,8-dimetil-1,2,3,4-tetrahidroquinolin-4-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
MM.	N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(4-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]propil}acetamida;
NN.	N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(4,8-dimetil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropil}acetamida;
OO.	N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(8-metil-6-neopentil-1,2,3,4-tetrahidroquinolin-4-il)amino]propil}acetamida;
PP.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(2-hidroxi-2-metilpropil)-8-metil-1,2,3,4-tetrahydroquinolin-4-il]amino}propil)acetamida;
QQ.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(2-hidroxi-2-metilpropil)-4-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
RR.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(2-hidroxi-2-metilpropil)-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida;
SS.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(1-hidroxi-2,2-dimetilpropil)-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida; y
TT.	N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[6-(1-hidroxi-2,2-dimetilpropil)-4-metil-1,2,3,4-tetrahidroquinolin-4-il]amino}propil)acetamida.

EJEMPLO 110

A. Preparación de N-(1*S*, 2*R*)-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-[(1*S*)-(7-isobutil-1,2,3,4-tetrahidronaftalen-1-ilamino)]-propil]-acetamida



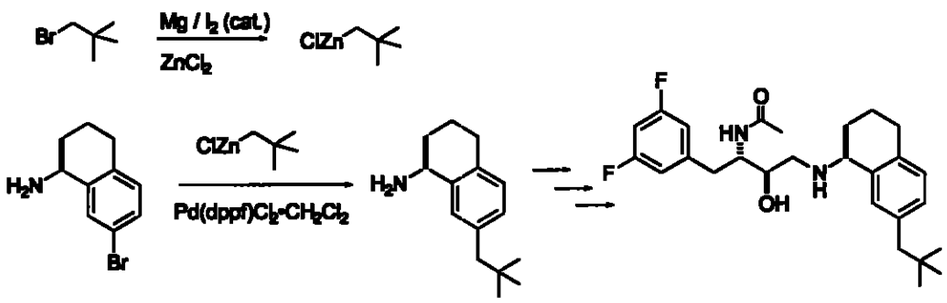
Acetato de paladio (II) (0.2 equiv., 0.07 mmol, 15.8 mg) y 2-(di-t-butilfosfino)bifenil (0.1 equiv, 0.035 mmol, 10.5 mg) se disolvieron en THF (2 mL) y se desoxigenaron mediante purgado subsuperficial con N_2 (g) durante 5 minutos. A continuación se añadió el bromuro (1 equiv, 0.352 mmol, 200 mg) a esta solución en forma sólida, seguido por bromuro de zinc isobutilo (solución 0.5 M en THF, 3 equiv, 1.1 mmol, 2.1 mL). La reacción se agitó durante toda la noche a temperatura ambiente y bajo una atmósfera de N_2 (g). Después de transcurridas 12 horas, la

544

reacción se repartió entre EtOAc y H_2O, y se extrajo 3x en EtOAc. Se procedió a lavar los extractos orgánicos combinados, secándolos posteriormente sobre Na_2SO_4 para luego filtrarlos y concentrarlos. Con la columna de cromatografía sobre SiO_2 con 30 → 50 % EtOAc en los hexanos, se produjo el producto deseado Boc, puro y protegido. (148 mg, rendimiento del 77 %) $M+Na^+$ (Cl) = 567.2

La eliminación del grupo Boc se logró disolviendo el compuesto anterior con HCl 4N en dioxano (1 mL) y agitando a temperatura ambiente durante 1 hora en una atmósfera de N_2 (g). La mezcla blanca turbia resultante se concentró para obtener el producto final. (100 mg, rendimiento del 85%) ^{1}HNMR (CD_3OD): δ 7.3 (s, 1H), 7.15 (s, 2H), 6.9 (m, 2H), 6.8 (m, 1H), 4.6 (t, 1H), 4.05 (m, 1H), 3.9 (m, 1H), 3.2 (m, 2H), 3.0 (m, 1H, 2.8 (m, 2H), 2.7 (m, 2H), 2.5 (d, 2H), 2.2 (m, 2H), 2.0 (m, 1H), 1.85 (s, 3H), 1.85, m, 1 H), 0.9 (m, 6H). $M+H^+$ (CI) = 445.2

B. Preparación de *N*-(1*S*, 2*R*)-{1-(3,5-Difluoro-bencil)-3-[(1*S*)-7-(2,2-dimetilpropil)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-2-hidroxipropil}-acetamida



Se agitaron vigorosamente la escoria de magnesio (1.5 equiv, 45 mmol, 1.1 g) e I_2 (catalítico), procediendo a calentarlos suavemente con una pistola térmica bajo N_2 (g) para activar el magnesio. Se enfrió el magnesio a temperatura ambiente antes de añadir una solución de $ZnCl_2$ (1 equiv, 30 mmol, 60 mL) en THF 0.5 M seguido por bromuro de neopentilo (1.5 equiv, 45 mmol, 6.94 g, 5.8 mL). En cuestión de 5 a 10 minutos la reacción se tornó en una suspensión blanca.

545

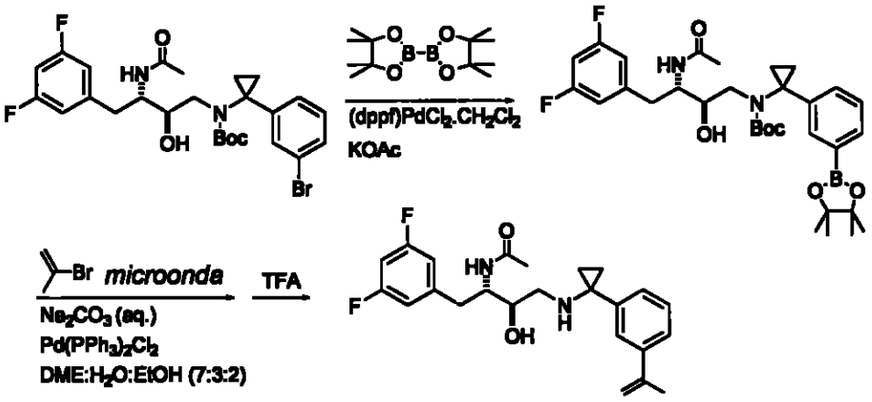
Eventualmente la suspensión adquirió un color gris. La mezcla se calentó a 50 °C durante toda la noche, seguida por 2 horas adicionales de calentamiento a reflujo. Se enfrió la suspensión gris a temperatura ambiente y se utilizó cruda en la siguiente reacción. Se supuso que esta solución de cloruro de zincneopentilo tenía una concentración aproximada de 0.5 M.

A la amina bromotetralina (1 equiv, 8 mmol, 1.71 g) se añadió la suspensión cruda de cloruro de zincneopentilo (3 equiv, 24 mmol, 48 mL), seguido por el $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.05 equiv, 0.4 mmol, 330 mg). La reacción se agitó durante toda la noche a temperatura ambiente y bajo una atmósfera de N_2 (g). La suspensión rápidamente cambió a un color amarillo y durante la noche adquirió un color violeta. Después de 12 horas, la reacción se templó con NH_4Cl (ac) y se extrajo 3x con EtOAc. Se procedió a lavar con salmuera los extractos orgánicos combinados, secándolos posteriormente sobre Na_2SO_4 para luego filtrarlos y concentrarlos. Mediante cromatografía en columna sobre SiO_2 con 2 → 10 % de *MeOH* en CH_2Cl_2 se obtuvo el compuesto deseado neopentil tretalin amina. (1.5 g, rendimiento del 86%) ^{1}HNMR ($CDCl_3$): §§7.15 (s,1H), 6.95 (m, 2H), 3.95 (m, 1H), 2.8 (m, 2H), 2.4 (s, 2H), 2.0 (m, 2H), 1.7 (m, 2H), 1.6 (broad s, 2H), 1.0 (s, 9H); M-NH_2^+ (CI) = 201.2.

El compuesto final se sintetizó mediante apertura epóxida, desprotección del grupo protector y acetilación tal como se describió previamente. M+H^+ (CI) = 459.2.

C. Preparación de *N*-(1*S*, 2*R*)-{1-(3,5-Difluorobencil)-2-hidroxi-3-[1-(3-isopropenil-fenil)-ciclopropilamino]-propil}-acetamida

546



Al matraz se añadió acetato de potasio (5 equiv, 8.8 mmol, 0.864 g), (dppf)$PdCl_2$·CH_2Cl_2 (0.04 equiv, 0.0704 mmol, 57.5 mg), y diboro grado reactivo (1.15 equiv, 2.03 mmol, 0.515g), seguidos por el bromuro (1 equiv, 1 g, 1.76 mmol) y DMF (7 mL). La mezcla se desoxigenó mediante purgado subsuperficial con N_2 (g) y se agitó a 80°C bajo N_2 (g) de un día para otro. En cuanto se inició el calentamiento, la reacción cambió a un color pardo (marrón). Después de transcurridas 18 horas, la reacción se repartió entre EtOAc y H_2O, y se extrajo 3x con EtOAc. Los extractos orgánicos combinados se lavaron en salmuera, se secaron sobre Na_2SO_4 y se filtraron antes de eliminar el solvente en condiciones de vacío. Con una columna rápida de SiO_2 con 20→50% EtOAc en hexanos se obtuvo el éster borónico puro. (0.75 g, rendimiento del 69%) ^{1}HNMR (CD_3OD): § 7.6 (t, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.8 (dd, 2H), 6.6 (m, 1H), 4.05 (m, 1H), 3.8 (m, 1H), 3.5 (m, 2H), 2.9 (m, 2H), 1.8 (s, 3H), 1.4 (s, 9H), 1.2 (m, 12 H), 1.2 (m, 4 H). M+Na^+ (Cl) = 623.2

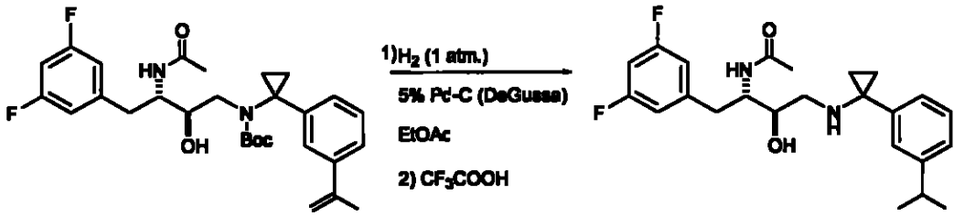
El éster del boro (1 equiv, 0.167 mmol, 100 mg) seguido por $Pd(PPh_3)_2Cl_2$ (0.1 equiv, 0.017 mmol, 11.7 mg), 2-bromopropeno (1.2 equiv, 0.2 mmol, 24.2 mg, 17.8 µl), 2M Na_2CO_3 (ac) (1.5 equiv, 0.25 mmol, 0.125 mL), y finalmente una mezcla 7:3:2 DME:$H_2$0:EtOH (0.7 mL) se colocaron en un vial para reacción equipado con una barra agitadora. El vial se selló y se procedió a preagitar la reacción durante 15 s antes de colocarla en microondas a 160 °C durante 7

547

minutos al nivel de absorción normal y con el tiempo de espera fijo (Fixed Hold Time) activado. (Se utilizó un reactor personal químico de microondas). La reacción se repartió entre EtOAc y H_2O, y se extrajo 3x con EtOAc. Los extractos orgánicos combinados se lavaron en salmuera, se secaron sobre Na_2SO_4 y se filtraron antes de eliminar el solvente en condiciones de vacío. La purificación se obtiene mediante una corrida en columna de SiO_2 con 10→35% EtOAc en hexanos obtuvieron el compuesto estireno Boc puro protegido. (45.9 mg, rendimiento del 53%) $M+Na^+$ (CI) = 537.2

El grupo Boc se eliminó con el tratamiento del anterior compuesto protegido con TFA:CH_2Cl_2 1:4 a 0°C. La reacción se agitó durante 2 h a 0°C y luego se concentró para obtener el producto deseado. Con la purificación por HPLC se obtuvo el producto deseado (7 mg, rendimiento del 36%): $M+H^+$ (CI) = 415.2

D. Preparación de *N*-(1*S*, 2*R*)-{1-(3,5-Difluorobencil)-2-hidroxi-3-[1-(3-isopropilfenil)-ciclopropilamino]-propil}-acetamida



La amina Boc (1 equiv, 0.1 mmol, 55.4 mg) se disolvió en EtOAc antes de añadirle el catalizador DeGussa Pd-C al 5% (esta cantidad no se midió). Se evacuó el aire del matraz antes de aplicar un balón de N_2 (g). La mezcla se agitó durante 4 h a temperatura ambiente. En este punto HPLC-MS determinó que la reacción había culminado. La filtración con tierra diatomácea seguida por la remoción del solvente con vacío produjo el material reducido crudo y limpio. (56.7 mg, cuantitativo) $M+H^+$ (CI) = 517.3.

548

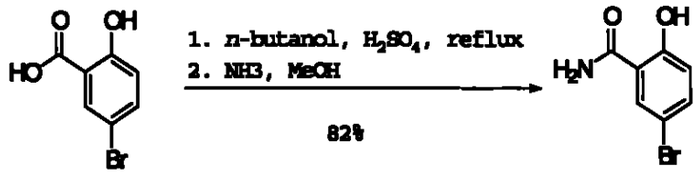
La eliminación del grupo Boc se logró disolviendo el compuesto anterior con TFA:CH_2Cl_2 50:50 y agitando a temperatura ambiente durante 1 hora bajo una atmósfera de N_2 (g). La solución resultante se concentró para obtener el producto final. (41.6 mg, cuantitativo): ^{1}H NMR (CD_3OD) § 7.4 (s, 1H), 7.25 (m, 3H), 6.7 (m, 2H), 6.6 (m, 1H), 4.0 (m, 1H), 3.9 (m, 1H), 2.9 (m, 4H), 2.7 (m, 1H), 1.8 (s, 3H), 1.2 (d, 6 H), 1.2 (m, 4H). $M+H^+$ (Cl) = 417.2

Ejemplo 111

Las reacciones se vigilaron y se evaluó la pureza con placas TLC sobre sílica gel GF, 250 µ provenientes de Analtech, Inc., Newark, DE. La cromatografía de preparación a baja presión (flash) se efectuó sobre sílica gel 60 (malla 230-400 ASTM) proveniente de EM Science, Gibbstown, NJ. Los espectros del RMN protónico se recolectaron en un espectrómetro Bruker Avance 400. Los desplazamientos químicos (δ) se dan en ppm, las constantes de acoplamiento (*J*) se miden en Hz. Se reportan absorbencias IR superiores a 1200 cm^{-1}. Todos los reactivos se obtuvieron de fuentes comerciales y se utilizaron sin purificación adicional. A no ser que se indique lo contrario, todos los solventes utilizados en la reacción se corrieron bajo una atmósfera inerte de nitrógeno en material de vidrio sobresecado. La cromatografía flash preparativa se realizó sobre sílica gel 60 (malla 230-240) suministrada por EM Science. El análisis HPLC se llevó a cabo en un sistema HP1100 (Agilent) con el siguiente gradiente lineal de 1.0 mL/min de TFA acuoso al 0.05% (A) y TFA al 0.05% en acetonitrilo (B): 0% B: 5 min: 60% B, 15 min: 90% B, 2 min: 0% B. Todos los solventes para cromatografía son grado HPLC. Si los materiales iniciales no se encuentran disponibles comercialmente, incluyendo los compuestos nuevos y los conocidos, se prepararon mediante métodos sintéticos conocidos. El compuesto HATU, que significa *N*-[(dimetilamino)-1-*H*-1,2,3-triazolo[4,5-b]pirindin-1-ilmetileno]-*N*-metilmetanaminio hexafluorofosfato *N*-óxido, se compró a PE Biosystems. Todas las sales de hidrocloruro se formaron añadiendo ácido clorhídrico etéreo a una solución etérea de amina, seguido por el proceso de concentración hasta llegar al compuesto seco.

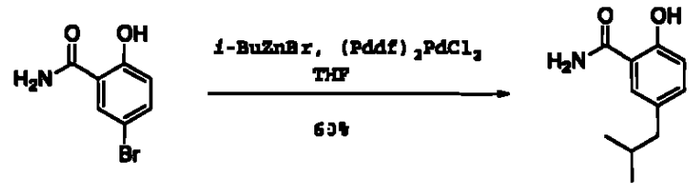
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A. 5-bromo-2-hidroxibenzamida



A una solución agitada de ácido 5-bromosalicílico (30 g, 135.5 mmol) en *n*-butilalcohol (60 mL) se añadió H_2SO_4 (95.6%, 289 µL, 5.42 mmol) en un matraz de fondo redondo de 100 ml conectado con un condensador separador/de reflujo Dean-Stark que se llenó con 12 ml de *n*-butilalcohol. Después de calentar a reflujo durante 2 días, la reacción se enfrió hasta temperatura ambiente y se concentró obteniendo un aceite de color amarillo pálido. A esta mezcla se añadieron 50 mL de MeOH, seguido por NH_3 en MeOH (7 N, 116 mL) La reacción se agitó a temperatura ambiente durante otros 2 días y se vigiló por HPLC. Después de terminada la reacción, se concentró hasta obtener un sólido blanco. El sólido crudo se lavó con una pequeña cantidad de EtOAc y hexano para obtener 24 g del producto , un sólido blanco cristalino (rendimiento del 82%). ^{1}H NMR ($CDCl_3$) δ 12.15 (s, 1 H), 7.54 (m, 2 H), 6.97 (d, J = 12 Hz, 1 H), 6.00 (broad, 2 H).

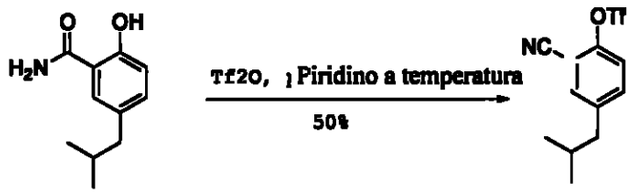
B. 2-hidroxi-5-isobutilbenzamida



550

A una solución previamente agitada de bromobenzamida (8.64 g, 40 mmol) en THF (100 mL) bajo argón se añadió [1,1'-Bis(difenilfosfino)ferroceno]dicloropaladio(II) (1.96 g, 2.4 mmol) seguido por *i*-BuZnBr (0.5 M, 200 mL). La mezcla de reacción se agitó a temperatura ambiente durante 4 días. La reacción se enfrió rápidamente en agua con HCl 1N y luego se concentró. El crudo resultante se diluyó con acetato de etilo, lavándolo luego en agua y salmuera, procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (5~10% de acetato de etilo: hexano) para obtener 4.63 g del producto isobutilbenzamida en forma de un sólido blanquecino (rendimiento del 60%). ^{1}H NMR ($CDCl_3$) δ 12.02 (s, 1 H), 7.24 (d, J = 8 Hz, 1 H), 7.12 (s, 1 H), 6.93 (d, J = 8 Hz, 1 H), 2.44 (d, J = 8 Hz, 2 H), 1.83 (m, 1 H), 0.93 (d, J = 8 Hz, 6 H).

C. 2-ciano-4-isobutilfenil trifluorometanosulfonato

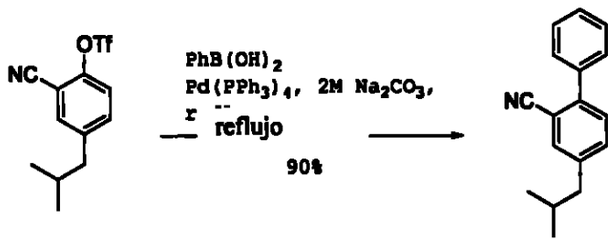


A 0 °C, a una solución previamente agitada del hidroxi-isobutilbenzamida (3.72 g, 19.3 mmol) en piridina (15 mL) bajo argón, se añadió anhídrido trifluorometanosulfónico (10.2 ml, 57.8 mmol). La mezcla de reacción eventualmente se calentó hasta temperatura ambiente y se agitó de un día para otro. El crudo resultante se diluyó con acetato de etilo, lavándolo luego con HCl 1N (x2), agua (x1) y salmuera (x1), procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida. El producto crudo se purificó mediante cromatografía en

551

columna flash (5% de acetato de etilo: hexano) para obtener 2.66 g del producto deseado con la apariencia de un aceite transparente (rendimiento del 50%). ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.43 (d, J = 8 Hz, 1 H), 2.57 (d, J = 8 Hz, 2 H), 1.92 (m, 1 H), 0.97 (d, J = 4 Hz, 6 H).

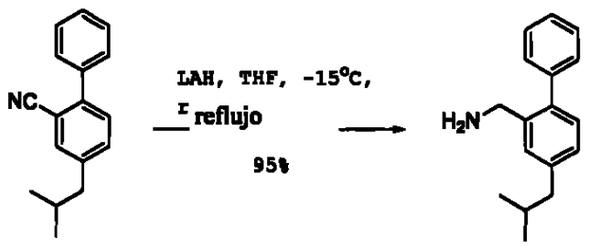
D. 4-isobutil-1,1'-bifenil-2-carbonitrilo



A una solución previamente agitada del compuesto ciano (610 mg, 1.88 mmol), carbonato de sodio acuoso (2.0 M, 3.76 mmol) en DME (6 mL) se añadió tetraquis(trifenilfosfina) paladio(0) (109 mg, 0.094 mmol) seguido por ácido fenilborónico (280 mg, 2.26 mmol). La mezcla de reacción se calentó a reflujo de un día para otro y luego se enfrió a temperatura ambiente. La reacción se diluyó con acetato de etilo, lavándola posteriormente con agua y salmuera, procediendo luego a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (3% de acetato de etilo: hexano) para obtener 450 mg del producto de apariencia sólida cristalina (rendimiento del 90%). ^{1}H NMR ($CDCl_3$) δ 7.60 (m, 3 H), 7.54 (m, 2 H), 7.48 (m, 3 H), 2.60 (d, J = 8 Hz, 2 H), 1.96 (m, 1 H), 1.00 (d, J = 6 Hz, 6 H).

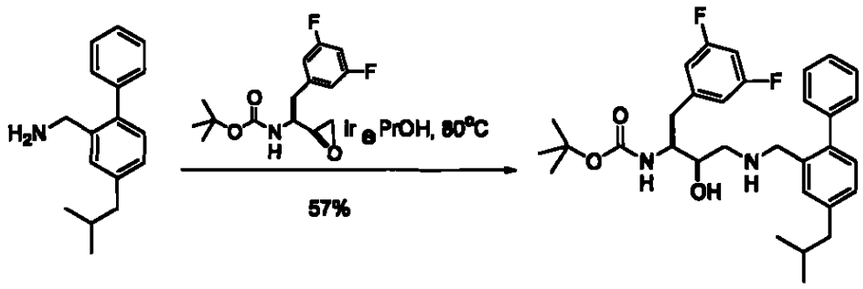
E. (4-isobutil-1,1'-bifenil-2-il)metilamina

552



A –15 °C, a una suspensión previamente agitada de LAH (171 mg, 4.5 mmol) en THF anhidro (2 mL) se añadió el compuesto bifenilciano (450 mg, 1.77 mmol) en THF (1 mL). La reacción se calentó eventualmente hasta temperatura ambiente de un día para otro y luego se mantuvo a reflujo durante 1 hora. La mezcla de reacción se enfrió hasta temperatura ambiente y luego se enfrió rápidamente con Na_2SO_4 acuoso saturado. La reacción se vertió en CH_2Cl_2 (10 mL) y luego se filtró. La precipitación se lavó varias veces con CH_2Cl_2.. La solución orgánica se secó con sulfato de sodio, luego se concentró bajo presión reducida para obtener 400 mg del producto, un aceite amarillo pálido (rendimiento del 95%). ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 2 H), 7.44 (m, 3 H), 7.30 (s, 1 H), 7.20 (d, J = 8 Hz, 1 H), 7.14 (m, 1 H), 3.84 (s, 2 H), 2.58 (d, J = 8 Hz, 2 H), 1.93 (m, 1 H), 1.47 (s, 2 H), 1.00 (d, J = 4 Hz, 6 H); ESI-MS $[M+H^+]^+$ = 240.22.

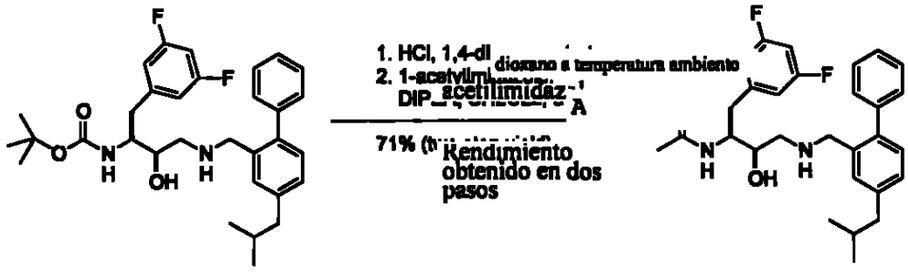
F. tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino} propilcarbamato



553

A una solución previamente agitada de bifenil amina (400 mg, 1.67 mmol) en *i*-propanol (10 mL) se añadió el Ejemplo 134 (nombre generado utilizando ACD Namepro versión 5.09) (336 mg, 1.12 mmol). La mezcla de reacción se calentó a 80 °C de un día para otro. La mezcla de reacción se concentró y purificó mediante cromatografía flash (2-5% MeOH: CH_2Cl_2) para obtener 510 mg del producto en forma de un sólido blanquecino (rendimiento del 57%). ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.38 (m, 3 H), 7.25 (s, 1 H), 7.21 (m, 1 H), 7.16 (m, 1 H), 6.76 (m, 2 H), 6.70 (m, 1 H), 4.55 (m, 1 H), 3.76 (m, 3 H), 3.34 (m, 1 H), 2.90 (m, 1 H), 2.78 (m, 2 H), 2.64 (m, 2 H), 2.55 (m, 3 H), 1.93 (m, 1 H), 1.40 (s, 9 H), 1.00 (d, 6 H); ESI-MS $[M+H^+]^+$ = 539.22.

G. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino}propil) acetamida

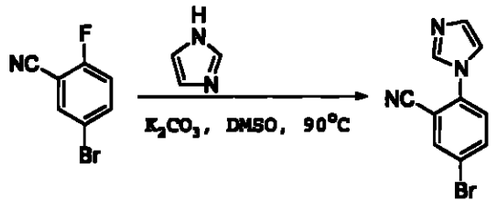


Paso 1: A una solución previamente agitada del material inicial (377 mg, 0.7 mmol) en MeOH (5 mL) se añadió HCl en 1,4-dioxano (4.0 M, 2 mL). Después de agitar a temperatura ambiente de un día al otro, la mezcla de reacción se concentró bajo presión reducida para obtener un sólido blanquecino que luego se usó sin purificarlo más.

554

Paso 2: A una solución previamente agitada de amina del paso 1 en CH_2Cl_2 (8 mL) se añadió DIPEA (304 µL, 1.75 mmol), y luego 1-acetilimidazol (86 mg, 0.77 mmol). La mezcla de reacción se agitó a temperatura ambiente de un día para otro, se enfrió rápidamente añadiéndole hidróxido de amonio al 50% y luego se diluyó con CH_2Cl_2 . La capa orgánica se lavó con HCl 1N (x2), agua (x1), una solución acuosa de bicarbonato de sodio (x2) y salmuera (x1), procediendo a continuación a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (MeOH al 3-5%: CH_2Cl_2) para obtener 240 mg del producto en forma de un sólido blanquecino (rendimiento del 71%, en dos pasos). ^{1}H NMR ($CDCl_3$) δ 9.63 (b, 1 H), 8.48 (b, 1 H), 7.63 (s, 1 H), 7.46 (m, 3 H), 7.28 (m, 4 H), 6.74 (m, 2 H), 6.67 (m, 1 H), 4.24 (m, 1 H), 4.17 (m, 1 H), 4.05 (m, 2 H), 2.80 (m, 4 H), 2.57 (m, 3 H), 1.97 (m, 4 H), 0.97 (d, 6 H); ESI-MS $[M+H^+]^+$ = 481.35.

H. 5-bromo-2-(1H-imidazol-1-il)benzonitrilo



A una solución previamente agitada de 5-Bromo-2-fluorobenzonitrilo (2.5 g, 12.2 mmol) en DMSO (50 mL) se añadió K_2CO_3 (3.337 g, 24.4 mmol), y luego 1H-imidazol (996 mg, 14.64 mmol). La mezcla de reacción se calentó a 90°C de un día para el otro y se diluyó con agua. La mezcla de reacción se extrajo con EtOAC (x2). La capa orgánica se lavó con agua (x1) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida para obtener 2.97 g of the imidazolilbenzonitrilo con apariencia de un sólido blanquecino (rendimiento

555

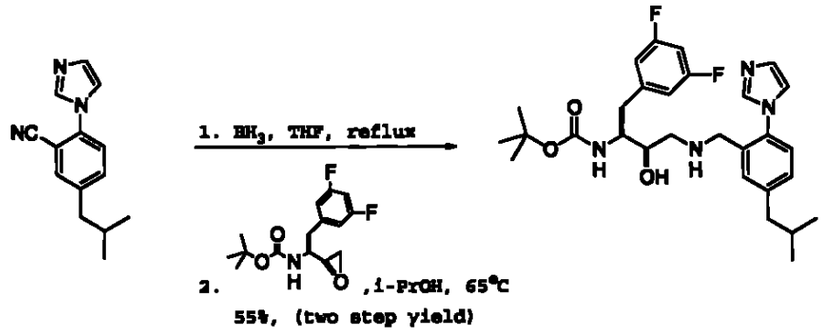
del 98%). ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2 H), 7.90 (m, 1 H), 7.41 (d, J = 8 Hz, 1 H), 7.37 (s, 1 H), 7.32 (s, 1 H).

I. 2-(1H-Imidazol-1-il)-5-isobutilbenzonitrilo

A una solución previamente agitada del producto obtenido en (H) arriba (1.02 g, 4.11 mmol) en THF (5 mL) bajo argón se añadió [1,1'-Bis(difenilfosfino)ferroceno]dicloropaladio(II) (336 mg, 0.411 mmol) seguido por *t*-BuZnBr (0.5 M, 28.8 mL). La mezcla de reacción se agitó a temperatura ambiente de un día para otro. La reacción se enfrió en agua con HCl 1N y luego se concentró. El crudo resultante se diluyó con acetato de etilo, lavándolo luego en agua y salmuera, procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna flash (50-100% de acetato de etilo: hexano) para obtener 870 g del producto con la apariencia de aceite pardo oscuro (rendimiento del 94%). ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1 H), 7.60 (s, 1 H), 7.53 (d, J = 8 Hz, 1 H), 7.40 (m, 2 H), 7.28 (m, 1 H), 2.60 (d, J = 8 Hz, 2 H), 1.93 (m, 1 H), 0.97 (d, 6 H); ESI-MS $[M+H^+]^+$ = 226.03.

J. tert-butil (1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(1H-imidazol-1-il)-5-isobutilbencil]amino} propilcarbamato

556

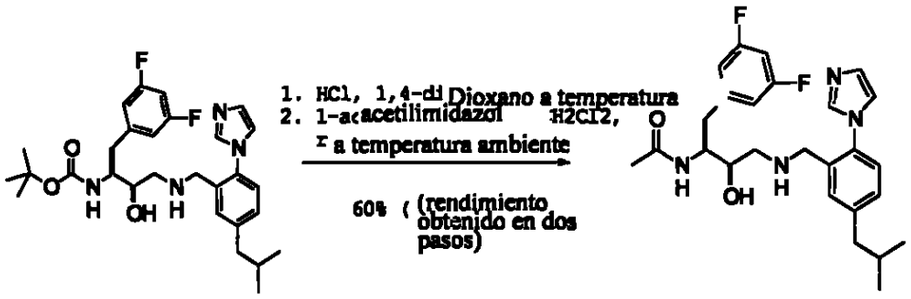


Paso 1: A 0 °C, a una suspensión previamente agitada de BH_3 (1.5 M en THF, 4.9 mL) se añadió el producto imidazolil obtenido en (I) (722 mg, 3.2 mmol) en THF anhidro (8 mL). La reacción se calentó eventualmente hasta temperatura ambiente y luego se mantuvo a reflujo de un día para otro y posteriormente una vez más a reflujo durante 1 hora. La mezcla de reacción se enfrió hasta temperatura ambiente y luego se enfrió rápidamente con una solución acuosa de HCl 5N. La reacción se vertió en CH_2Cl_2 (10 mL), luego se lavó con solución acuosa de bicarbonato de sodio saturado (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 2: A una solución previamente agitada de la amina del paso 1 en i-propanol (14 mL) se añadió (1S)-2-(3,5-difluorofenil)-1-[(2S)-oxiran-2-yl]etilcarbamato (509 mg, 1.7 mmol). La mezcla de reacción se calentó a 65 °C de un día para otro. La mezcla de reacción se concentró y purificó mediante cromatografía flash (MeOH 5-20%: CH_2Cl_2) para obtener 537 mg del producto en forma de un sólido blanquecino (rendimiento del 55%, en dos pasos). ESI-MS $[M+H^+]^+$ = 529.35.

K. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(1H-imidazol-1-il)-5-isobutilbencil]amino}propil) acetamida

557

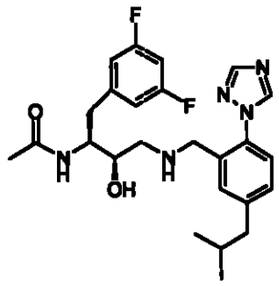


Paso 1: A una solución previamente agitada del producto obtenido en (J) (303 mg, 0.57 mmol) en MeOH (2 mL) se añadió HCl en 1,4-dioxano (4.0 M, 0.86 mL). Después de agitar a temperatura ambiente de un día para el otro, la mezcla de reacción se concentró bajo presión reducida para obtener un sólido blanquecino. La reacción se volvió a disolver en CH_2Cl_2, luego se lavó con solución acuosa de bicarbonato de sodio (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 2: A una solución previamente agitada de la amina obtenida en el paso 1 en CH_2Cl_2 (8 mL) [se añadió] 1-acetilimidazol (71 mg, 0.63 mmol). La mezcla de reacción se agitó a temperatura ambiente de un día para otro, se enfrió rápidamente añadiéndole hidróxido de amonio al 50% y luego se diluyó con CH_2Cl_2. La capa orgánica se lavó con HCl 1N (x2), una solución acuosa de bicarbonato de sodio saturado (x2) y salmuera (x1), procediendo a continuación a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (MeOH al 5-20%: CH_2Cl_2) para obtener 160 mg del producto en forma de un sólido blanquecino (rendimiento del 60%, en dos pasos). ESI-MS $[M+H^+]^+ = 471.33$.

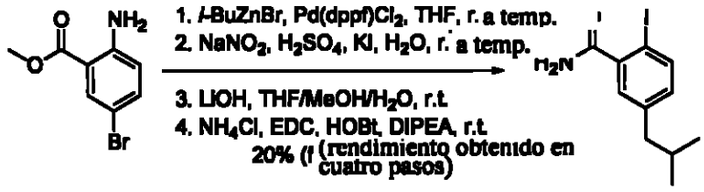
L. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[5-isobutil-2-(1H-1,2,4-triazol-1-il)bencil]amino}propil) acetamida

558



El compuesto anterior se puede sintetizar en forma análoga utilizando los materiales iniciales adecuados. The ESI-MS $[M+H^+]^+ = 472.0$

M. 2-Iodo-5-isobutilbenzamida



Paso 1: A una solución previamente agitada de metil 2-amino-5-bromobenzoato (5.77 g, 25 mmol) en THF (20 mL) bajo argón se añadió [1,1'-Bis(difenilfosfino)ferroceno] dicloropaladio(II) (2.04 g, 2.5 mmol) seguido por *i*-BuZnBr (0.5 M, 200 mL). La mezcla de reacción se agitó a temperatura ambiente de un día para otro. La reacción se enfrió rápidamente con HCl 1N y luego se concentró. El crudo resultante se diluyó con acetato de etilo, lavándolo luego en agua y salmuera, procediendo a continuación a secarlo con sulfato de sodio, filtrarlo y concentrarlo bajo presión reducida sin más purificación.

Paso 2: A temperatura ambiente la amina del paso 1 se trató con H_2SO_4 al 5% (3.2 mL) y la reacción se calentó a 60 °C durante 5 – 10 minutos. La mezcla de reacción se enfrió hasta quedar helada y luego se añadió gota a gota $NaNO_2$ (1.87 g, 27 mmol) en H_2O (10 mL).

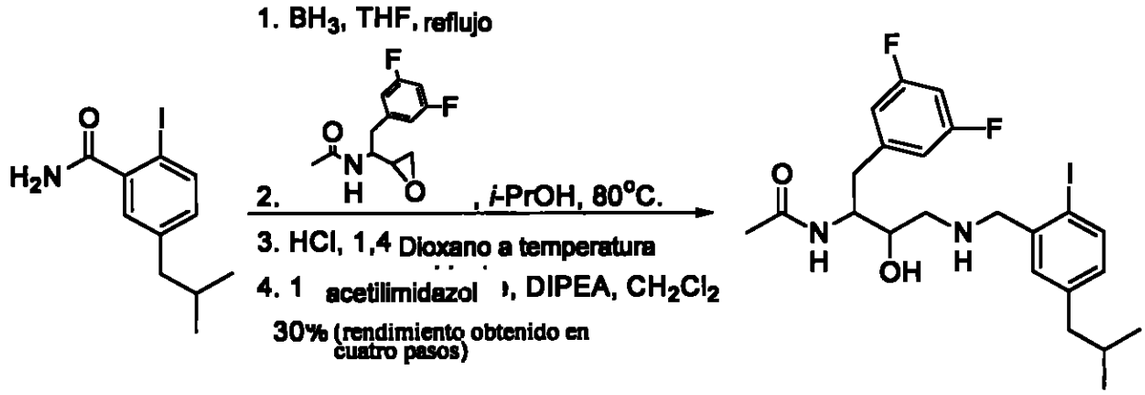
Terminada la adición, la reacción se agito a temperatura helada durante 15 – 20 minutos y luego se añadió KI (4.94 g, 29.7 mmol) en H_2O (20 mL). la reacción se agitó a temperatura ambiente de un día para el otro. Al siguiente día se extrajo la reacción con EtOAC (x3). La capa orgánica se lavó con salmuera (x1), se secó (con sulfato de sodio), se filtró y se concentró. El producto crudo se purificó mediante cromatografía flash (MeOH al 5-10%: CH_2Cl_2) para obtener 2 g del producto iodado.

Paso 3: A una solución previamente agitada del producto iodado del paso 2 (6.6 g, 20.9 mmol) en una mezcla de solventes consistente en MeOH (30 mL), THF (30 mL) y agua (30 mL), se añadió $LiOH•H_2O$ (4.4 mg, 104.5 mmol) a temperatura ambiente. Después de agitar durante 12 horas a temperatura ambiente, la mezcla de reacción se enfrió rápidamente con HCl 1N, se diluyó con CH_2Cl_2, se lavó con solución acuosa saturada de bicarbonato de sodio (x1), agua (x2) y salmuera (x2), se secó sobre sulfato de sodio y se concentró bajo presión reducida. El producto crudo se usó en el siguiente paso sin más purificación.

Paso 4: A una solución previamente agitada de ácido obtenido en el paso 3 (2.8 g, 9.24 mmol) en DMF (60 mL) se añadió EDC (3.55 g, 18.5 mmol), HOBt (2.5 g, 18.5 mmol), diisopropiletilamina (8.04 mL, 46.2 mmol), y luego se agregó cloruro de amonio (1.49 g, 27.7 mmol) a temperatura ambiente. Después de agitar durante 10 horas a temperatura ambiente, la mezcla de reacción se vertió en agua. La solución acuosa se extrajo con acetato de etilo (x2) y se recolectaron las capas orgánicas, se lavaron con agua (x2), HCl 1N (2), solución acuosa saturada de bicarbonato de sodio (x2) y salmuera (x2), se secó sobre sulfato de sodio y se concentró bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (EtOAC al 10-50%: CH_2Cl_2) para obtener 900 mg del producto en forma de un sólido blanquecino (rendimiento del 20%, en cuatro pasos). ^1H NMR ($CDCl_3$) δ 7.80 (d, J = 8 Hz, 1 H), 7.30 (s, 1 H), 6.95 (d, J = 8 Hz, H), 5.80 (b, 2 H), 2.47 (d, J = 6 Hz, 2 H), 1.87 (m, 1 H), 0.93 (2, H).

560

N. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-iodo-5-isobutilbencil)amino]propil}acetamida



Paso 1: A 0 °C, a una solución de BH_3 (1.5 M en THF, 9.3 mL) se añadió (1.838 g, 6.1 mmol) en THF anhidro (16 mL). La reacción se calentó eventualmente hasta temperatura ambiente y luego se mantuvo a reflujo de un día para otro y posteriormente una vez más a reflujo durante 1 hora. La mezcla de reacción se enfrió hasta temperatura ambiente y luego se enfrió rápidamente con una solución acuosa de HCl 5N. La reacción se vertió en CH_2Cl_2 (10 mL), luego se lavó con una solución acuosa saturada de bicarbonato de sodio (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 2: A una solución previamente agitada de la amina del paso 1 en i-propanol (27 mL) se añadió (1S)-2-(3,5-difluorofenil)-1-[(2S)-oxiran-2-il]etilcarbamato (1.027 g, 3.43 mmol). La mezcla de reacción se calentó a 65 °C de un día para otro. La mezcla de reacción se concentró bajo presión reducida sin más purificación.

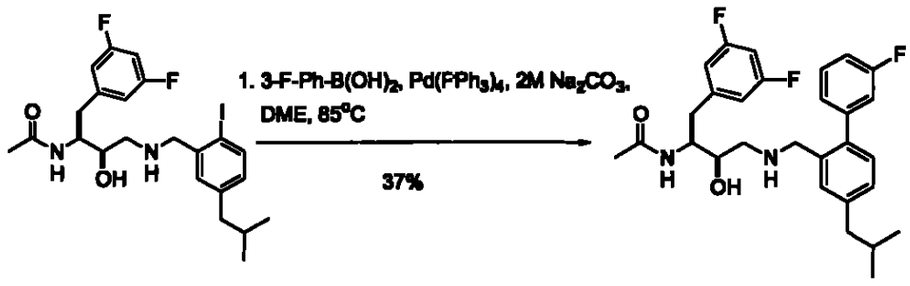
Paso 3: A una solución previamente agitada del compuesto crudo obtenido en el paso 2 en MeOH (10 mL) se añadió HCl en 1,4-dioxano (4.0 M, 5.6 mL). Después de agitar a temperatura ambiente de un día para el otro, la mezcla de reacción se concentró bajo presión reducida para obtener un sólido blanquecino. La reacción se volvió a disolver en CH_2Cl_2 , luego

561

se lavó con una solución acuosa de bicarbonato de sodio saturado (x2) y salmuera (x1), se secó con sulfato de sodio, se filtró y concentró bajo presión reducida sin más purificación.

Paso 4: A una solución previamente agitada de amina del paso 3 en CH_2Cl_2 (60 mL) se añadió DIPEA (3.88 mL, 22.3 mmol), y luego 1-acetilimidazol (516 mg, 4.46 mmol). La mezcla de reacción se agitó a temperatura ambiente de un día para otro, se enfrió rápidamente añadiéndole hidróxido de amonio al 50% y luego se diluyó con CH_2Cl_2 . La capa orgánica se lavó con HCl 1N (x2), una solución acuosa saturada de bicarbonato de sodio (x2) y salmuera (x1), procediendo a continuación a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (MeOH al 3-5%: CH_2Cl_2) para obtener 1 mg del producto en forma de un sólido blanquecino (rendimiento del 30%, en cuatro pasos). ^{1}H NMR ($CDCl_3$) δ 7.76 (d, *J* = 9 Hz, 1 H), 7.14 (s, 1 H), 6.76 (m, 4 H), 5.97 (d, *J* = 3 Hz, 1 H), 4.20 (m, 1 H), 3.84 (m, 2 H), 3.63 (m, 1 H), 2.81 (m, 4 H), 2.46 (d, *J* = 6 Hz, 2 H), 1.88 (m, 4 H), 0.92 (d, 6 H).

O. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(3'-fluoro-4-isobutil-1,1'-bifenil-2-il)metil]amino}-2-hidroxipropil)acetamida



A una solución previamente agitada del producto obtenido en (N)(97 mg, 0.183 mmol), solución acuosa de carbonato de sodio (2.0 M, 0.403 mmol) en DME (1 mL) se. añadió tetraquis(trifenilfosfina) paladio(0) (21 mg, 0.0183 mmol) seguido por ácido 3-fluoro-

562

fenilborónico (64 mg, 0.458 mmol). La mezcla de reacción se calentó a reflujo de un día para otro y luego se enfrió a temperatura ambiente. La reacción se diluyó con CH_2Cl_2, lavándola posteriormente con agua y salmuera, procediendo luego a secarla con sulfato de sodio, filtrarla y concentrarla bajo presión reducida. El producto crudo se purificó mediante cromatografía flash (MeOH al 3-10%: CH_2Cl_2) para obtener 36 mg del producto en forma de un sólido blanco (rendimiento del 37%). ESI-MS $[M+H^+]^+ = 499.32$.

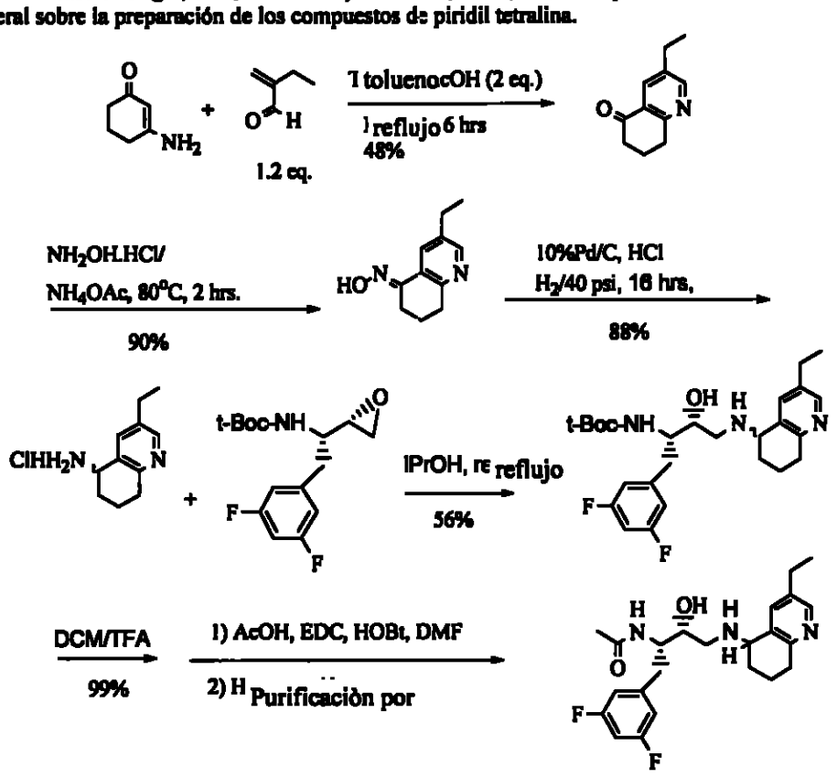
Los compuestos que se muestran en las secciones P-Z pueden sintetizarse utilizando métodos análogos a los descritos previamente.

P. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino}propil) acetamida	ESI-MS $[M+H^+]^+$ = 481.35
Q. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(5-isobutil-2-piridin-3-ilbencil)amino]propil}acetamida	ESI-MS $[M+H^+]^+$ = 482.33
R. N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(5-isobutil-2-piridin-4-ilbencil)amino]propil}acetamida	ESI-MS $[M+H^+]^+$ = 482.33
S. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4'-fluoro-4-isobutil-1,1'-bifenil-2-il)metil]amino}-2-hidroxipropil)acetamida	ESI-MS $[M+H^+]^+$ = 499.31
T. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(2'-fluoro-4-isobutil-1,1'-bifenil-2-il)metil]amino}-2-hidroxipropil)acetamida	ESI-MS $[M+H^+]^+$ = 499.32
U. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[5-isobutil-2-(6-metoxipiridin-3-il)bencil]amino}propil) acetamida	ESI-MS $[M+H^+]^+$ = 512.33
V. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(3'-hidroxi-4-isobutil-1,1'-bifenil-2-il)metil]amino}propil)acetamida	ESI-MS $[M+H^+]^+$ = 497.36
W. N-[(1S,2R)-3-{[(3'-acetil-4-isobutil-1,1'-bifenil-2-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamide	ESI-MS $[M+H^+]^+$ = 523.33
X. N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[5-isobutil-2-(5-metoxipiridin-3-il)bencil]amino}propil) acetamida	ESI-MS $[M+H^+]^+$ = 512.30
Y. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(3-furil)-5-isobutilbencil]amino}-2-hidroxipropil)acetamida	ESI-MS $[M+H^+]^+$ = 471.32
Z. N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(2-furil)-5-isobutilbencil]amino}-2-hidroxipropil)acetamida	ESI-MS $[M+H^+]^+$ = 471.32

563

Ejemplo 112

Véase Albright, J.D., *J. Heterocycl. Chem.*, **2000**, *37*, 41-6 para obtener una referencia general sobre la preparación de los compuestos de piridil tetralina.



PASO 1:

A 5.5 g de 3-amino-2-ciclohexan-1-uno (49.5 mmole) y 5 g of 2-etil acroleina (59.4 mmole, 1.2 eq.) se añadieron 6 ml de ácido acético y 25 ml de tolueno. La mezcla de reacción se calentó a reflujo de un día para otro. La reacción se vigiló mediante TLC para demostrar la formación de una nueva mancha con Rf = 0.73 (50% MeOH/DCM + 20% EtOH/Hexano.) Se sustrajo el solvente y el residuo se mezcló con tolueno, el cual se sustrajo nuevamente. El residuo se extrajo con DCM (2x), se lavó con $NaHCO_3$ saturado, se secó sobre sulfato de sodio anhidro y se concentró para obtener 9.38 g de un aceite crudo color canela oscuro. Este aceite se extrajo con hexano caliente (2x of 125 ml). Los extractos se concentraron y secaron al vacío para obtener un sólido color canela claro. (4.13 g, 23.6 mmole, 48%). MH+ (ESI) = 176.1.

564

PASO 2:

La oxima se formó utilizando los procedimientos descritos en diferentes partes de la aplicación. El rendimiento fue del 90%; MH+ (ESI) = 191.1.

PASO 3:

La reducción de la oxima se llevó a cabo esencialmente siguiendo los procedimientos descritos en otras secciones de la aplicación. El rendimiento fue del 88%; MH+ (ESI) = 177.1.

PASO 4:

La sal del hidrocloruro de amina se obtuvo en su forma básica repartiéndola entre NaOH 1N y EtOAc. La solución básica libre se concentró luego y se usó en la reacción de apertura epóxida tal como se describió previamente: rendimiento del 56%; MH+ (ESI) = 476.2.

PASO 5:

La desprotección y acetilación del Boc se efectuó tal como se describió previamente. El procedimiento de HPLC de fase reversa fue efectivo en la resolución de los dos diasterómeros:

N-(1*S*, 2*R*)-[1-(3,5-Difluorobencil)-3-((5*S*)-3-etil-5,6,7,8-tetrahidroquinolin-5-ilamino)-2-hidroxipropil]-acetamida: MH+ (ESI) = 418.2.
N-(1*S*, 2*R*)-[1-(3,5-Difluorobencil)-3-((5*R*)-3-etil-5,6,7,8-tetrahidroquinolin-5-ilamino)-2-hidroxipropil]-acetamida: MH+ (ESI) = 418.2.

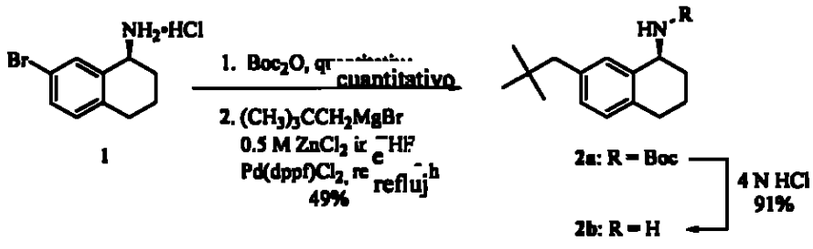
Ejemplo 113:

A. Síntesis de la Amina 2b

El compuesto (1), el cual se obtuvo fácilmente, se protegió y luego se enlazó, con mediación del paladio, con cloruro de *neo*-pentilzinc (generado in situ) para producir la tetralina *neo*-pentil **2a** sustituida (Esquema CC). La desprotección subsiguiente permitió obtener la amina intermedia **2b** en forma de la sal del hidrocloruro, la cual se usó en la construcción de objetivos adicionales (infra).

ESQUEMA CC

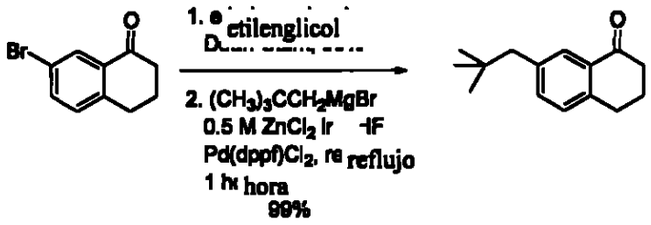
565



B. Síntesis de Tetralona 4

El compuesto 7-Bromotetralona (3) se protegió como dioxolano y luego experimentó reacción de acoplamiento con el cloruro de *neo*-pentilzinc (generado in situ) y catalizado con paladio para obtener, después de la fase acídica gradual, la tetralona *neo*-pentil 4 sustituida (Esquema DD). El compuesto (4) se envió a Pfizer Inc. el 6 de mayo de 2003.

Esquema DD

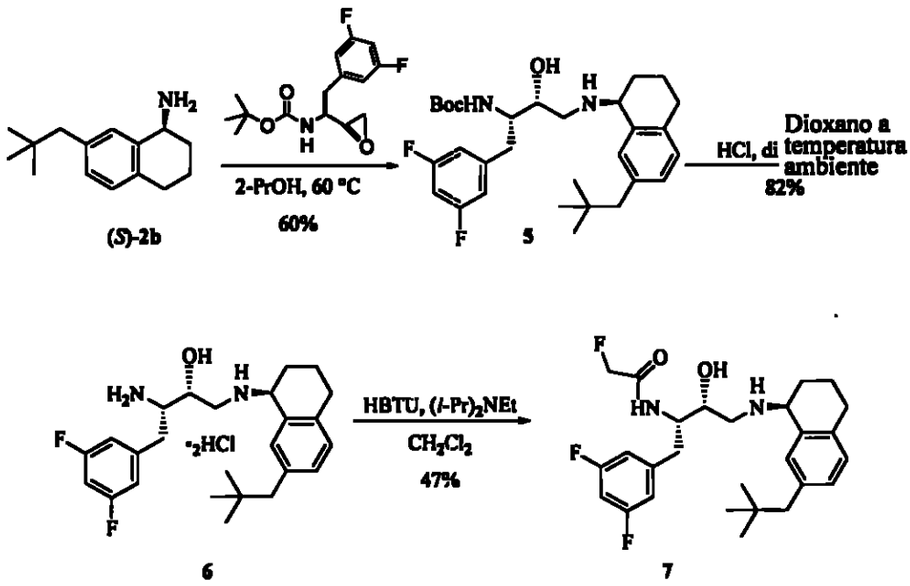


C. SÍNTESIS DEL COMPUESTO 7 DE TETRALINA

El acoplamiento de la amina tetralina enantioméricamente pura de la amina 2b con (1S)-2-(3,5-difluorofenil)-1-[(2S)-oxiran-2-il]etilcarbamato seguido por desprotección del Boc y acilación en presencia de HBTU produjo el compuesto final (7), predominantemente un diastereoisómero (Esquema EE)

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Esquema EE

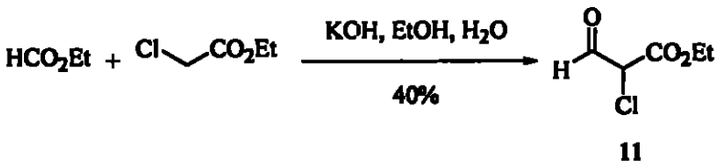


D. Síntesis de los tiazoles 18 y 20

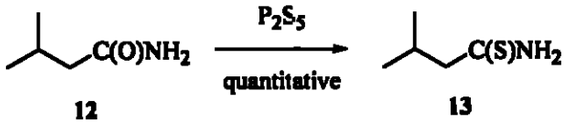
La condensación de Claisen del formiato de etilo y del cloroacetato de etilo produjo el éster 11 (Esquema FF). El tratamiento de la isovaleramida (12) con pentasulfuro de fósforo produjo 3-metil-tiobutiramida (13). La ciclización de 11 y 13 produjo el 5-carboetoxi-2-*iso*-butiltiazol (14)

567

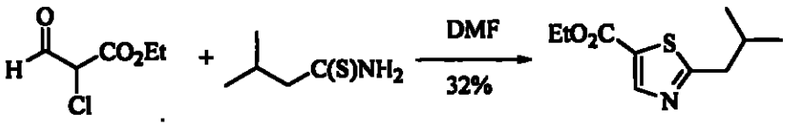
Esquema FF



11



12 13

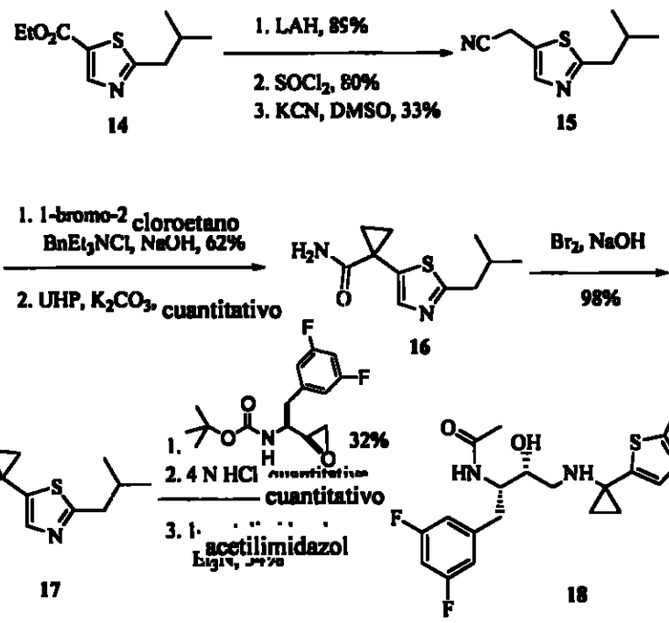


11 13 14

La reducción del éster 14 seguido por el tratamiento del alcohol resultante con cloruro de tionilo, seguido por sustitución nucleofílica con cianuro de potasio, produjo bencilnitrilo 15 (Esquema GG). La ciclopropanación de 15 seguida por hidrólisis produjo la amida 16. La reacción de Hoffman de 16 formó la amina 17. La N-alquilación de 17 seguida por desprotección y N-acetilación produjeron (18).

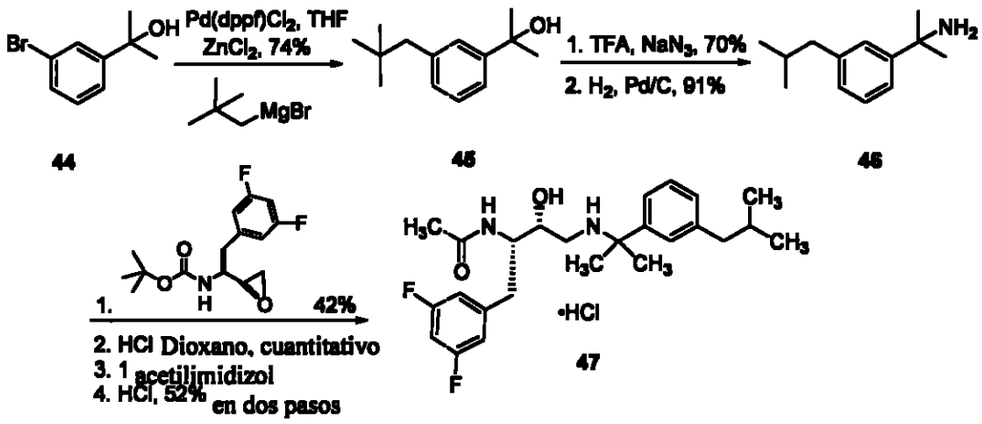
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Esquema GG



El acoplamiento con paladio del bromuro 44 con su *neo*-pentilzinc generado in situ produjo el alcohol 45 (Esquema HH). La conversión del alcohol 45 a la amida 46 se llevó a cabo en dos pasos. La apertura epóxida, más desprotección y posterior acetilación produjo (47).

Esquema HH



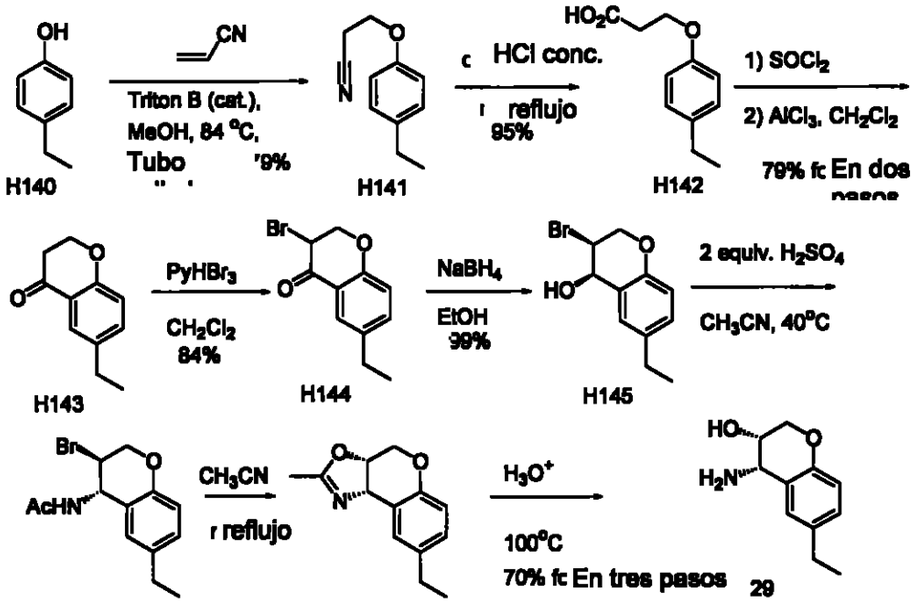
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E. SÍNTESIS DEL CROMÁN 32

La síntesis de aminocromán (29) se ilustra en el esquema II . En el esquema II, el fenol H140 sufrió la adición de Michael con acrilonitrilo para producir el nitrilo de H141. Las subsiguientes hidrólisis ácida produjo el ácido carboxílico de H142, el cual a su vez se convirtió al cloruro ácido y ciclizado intramulecularmente para dar cromona H143. La alfa bromination de la cetona H143 produjo bomeido H144, el cual se redujo con borohidruro de sodio para producir bromo alcohol H145. Utilizando las condiciones de la reacción de Ritters, H145 se transformó al alcohol amino racémico H146. Al final del esquema se encuentran los procedimientos experimentales más específicos.

Esquema II



Paso 1: Se agitó una mezcla de 4-etilfenol (H140, 26,69 g, 0.218 mol), acrilonitrilo (50 mL, 0.754 mol, 3.5 equiv), y tritón B (40 %p/p en metanol, 5 mL, 0.011 mol, 0.05 equiv) a 84 °C en un tubo sellado de un día para otro. La mezcla de reacción se diluyó con éter (300 mL) y el precipitado pardo (marrón) se retiró con filtración por succión. La solución de éter se lavó con una solución acuosa de hidróxido de sodio 2 M (2 x 100 mL), ácido clorhídrico 1 M (100 mL) y cloruro de sodio saturado, luego se secó (con sulfato de magnesio) y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, gradiente 10:1, y 6:1 hexanos/acetato de

570

etilo) produjo el nitrilo **H141** (30.17 g, 79%) en forma de un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.08 (m, 2H), 6.87-6.79 (m, 2H), 4.18 (t, *J*=6.4 Hz, 2H), 2.80 (t, *J*=6.4 Hz, 2H), 2.60 (q, *J*=7.6 Hz, 2H), 1.20 (t, *J*=7.6 Hz, 3H); ESI MS *m/z* 176 $[C_{11}H_{13}NO + H]^+$.

Paso 2: El nitrilo **H141** (30.17 g, 0.172 mol) se agitó con solución de ácido clorhídrico concentrado (100 mL, 1.20 mol, 7 equiv) a reflujo de un día para otro. Se formó un precipitado blanco a medida que la reacción avanzaba. La mezcla de reacción se enfrió a temperatura ambiente y el sólido se recolectó mediante filtración por succión. El filtrado aglutinado se lavó varias veces con agua fría y se secó en un horno de vacío a 50 °C durante 14 h. El ácido carboxílico **H142** se obtuvo en forma de un sólido blanco (31.79g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.08 (m,2H), 6.88-6.80 (m, 2H), 4.20 (t, *J*=6.3 Hz, 2H), 2.85 (t, *J*=6.3 Hz, 2H), 2.58 (q, *J*-7.6 Hz, 2H), 1.18 (t, *J*=7.6 Hz, 3H); ESI MS *m/z* 193 $[C_{11}H_{14}O_3 - H]$.

Paso 3: El ácido carboxílico **H142** (0.800 g, 4.12 mmol) se agitó con cloruro de tionilo (6 mL, 82.4 mmol, 20 equiv) a reflujo durante 2 h. El exceso de cloruro de tionilo se retiró bajo presión reducida. El cloruro de ácido obtenido de este modo se utilizó sin más purificación en la siguiente reacción.

Se añadió una porción de cloruro de aluminio (1.10 g, 8.24 mmol, 2 equiv) a una solución de cloruro de ácido indicada arriba en cloruro de metileno seco (50 mL) y la mezcla parda resultante se agitó a reflujo durante 14 horas para luego enfriarla a temperatura ambiente. La mezcla se vertió sobre hielo triturado en un vaso de precipitado, seguido por la adición de ácido clorhídrico 6 M (20 mL) y la posterior extracción con cloruro de metileno (3 x 40 mL). Los compuestos orgánicos combinados se lavaron con cloruro de sodio saturado, se secaron (con sulfato de magnesio) y se concentraron bajo presión reducida. La purificación por cromatografía flash (sílica, gradiente 10:1, y hexanos/acetato de etilo 6:1) produjo cromona **H143** (574 mg, 79%), siendo éste un aciete incoloro: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J*=2.2 Hz, 1H), 7.32 (dd, *J*=8.5, 2.2 Hz, 1H), 6.90 (d, *J*=8.5 Hz, 1H), 4.52 (t, *J*=6.5 Hz, 2H), 2,80 (t, *J*=6.5 Hz, 2H), 2.60 (q, *J*=7.6 Hz, 2H), 1.20 (t, *J*=7.6 Hz, 3H); ESI MS *m/z* 177 $[C_{11}H_{12}O_2+H]^+$.

Paso 4: Se añadió piridinio hidrobromuro perbromuro (743 mg, 2.32 mmol) a una solución de cromona **H143** (372 mg, 2.11 mmol) en cloruro de metileno seco (15 mL) y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se añadió agua (15 mL) a la mezcla y se separaron las capas. La capa acuosa se extrajo una vez más con cloruro de metileno (2 x 15 mL). Los compuestos orgánicos combinados se secaron (con sulfato de magnesio) y se concentraron bajo

571

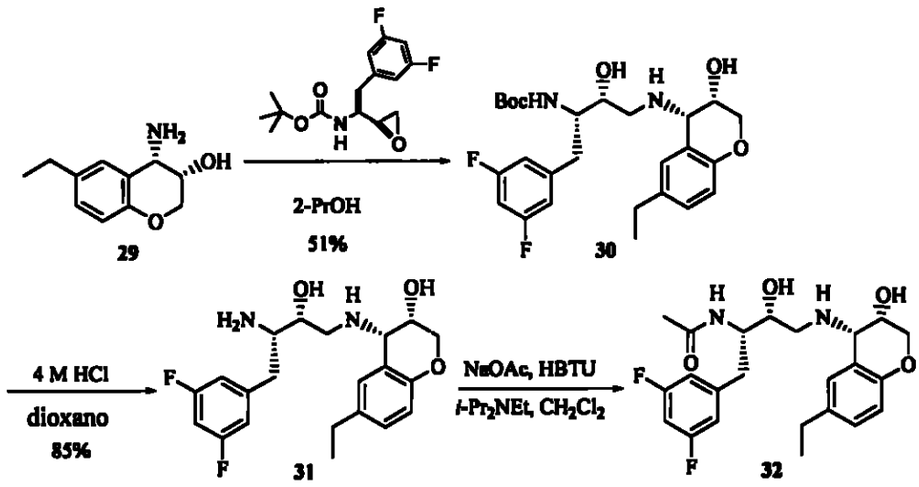
presión reducida. La purificación por cromatografía flash (sílica, gradiente 20:1, y hexanos/acetato de etilo 10:1) produjo bromocetona **H144** (450 mg, 84%) en forma de un aceite ligeramente amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J*=2.2 Hz, 1H), 7.39 (dd, *J*=8.5, 2.2 Hz, 1H), 6.97 (d, *J*=8.5 Hz, 1H), 4.68-4.52 (m, 3H), 2.62 (q, *J*=7.6 Hz, 2H), 1.22 (t, *J*=7.6 Hz, 3H); ESI MS *m/z* 255 $[C_{11}C_{11}BrO_2+H]^+$.

Paso 5: El borohidruro de sodio (99 mg, 2.61 mmol, equiv) se añadió a una solución de bromocetona **H144** (444 mg, 1.74 mmol) en etanol absoluto (15 mL) y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se enfrió rápidamente añadiéndole ácido clorhídrico 1 M (4 mL) y se eliminó gran parte del etanol mediante evaporación giratoria. El residuo se repartió entre agua y cloruro de metileno. La capa acuosa se extrajo aún más con cloruro de metileno. Los compuestos orgánicos combinados se secaron (con sulfato de sodio) y se concentraron bajo presión reducida. El bromo alcohol **H145** se obtuvo en forma de un sólido blanco (443 mg, 99%) y se utilizó en el siguiente paso sin purificación adicional: ^{1}H NMR (300 MHz, CD_3OD) δ 7.14 (d, *J*=1.5 Hz, 1H), 7.03 (dd, *J*=8.3, 1.5 Hz, 1H), 6.69 (d, *J*=8.3 Hz, 1H), 4.78 (d, *J*=3.2 Hz, 1H), 4.58-4.49 (m, 1H), 4.35-4.26 (m,2H), 2.56 (q, *J*=7.6 Hz, 2H), 1.16 (t, *J*=7.6 Hz, 2H), 1.16 (t, *J*=7.6 Hz, 3H).

Paso 6: El bromo alcohol del paso 5 **H145** (443 mg, 1.72 mmol) se disolvió en acetonitrilo anhidro (10 mL) y con una jeringa se añadió ácido sulfúrico concentrado (0.19 mL, 3.47 mmol). La mezcla de reacción se agitó a 40 °C durante 5 h y después se colocó a reflujo por 12 h. Se añadió agua (10 mL) y se retiró la mayor parte del acetonitrilo bajo presión reducida. Al residuo se añadió ácido clorhídrico 6 M (10 mL) y la mezcla resultante se agitó a reflujo durante 14 h. La mezcla de reacción se enfrió a temperatura ambiente y se colocó en baño de hielo. A esta mezcla se añadió hidróxido de sodio 6 M hasta obtener un pH de 12. Posteriormente se extrajo la mezcla con cloruro de metileno (3x 50 mL). Los compuestos orgánicos combinados se lavaron con cloruro de sodio saturado, se secaron (con sulfato de sodio) y se concentraron. La purificación por cromatografía flash (sílica, gradiente 20:1, y cloruro de metileno/metanol 10:1 y 1:1) produjo el amino alcohol (**H146**, 233 mg, 70%) en forma de un sólido blanco: mp 93-94 C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J*=1.5 Hz, 1H), 7.01 (dd, *J*=8.3, 1.5 Hz, 1H) 6.78 (d, *J*=8.3 Hz, 1H), 4.09 (d, *J*=11.5 Hz, 1H), 4.00-3.91 (m, 2H), 3.88-3.75 (m, 1H), 2.58 (q, *J*=7.6 Hz, 2H), 1.60 (br s, 3H) 1.20 (t, *J*=7.6 Hz, 3H); ESI MS *m/z* 194 $[C_{11}H_{15}NO_2+H]^+$; HPLC (método E) 96.7% (AUC), ^tR = 9.4 min.

572

Esquema II-a



El subsiguiente acoplamiento de aminocroman racémico **29** con el Ejemplo 134, seguido por desprotección del Boc y acilación en presencia de HBTU produjo (**32**), como una mezcla de diastereoisómeros (Esquema II-a) Abajo se describe un posible procedimiento para preparar el compuesto **32**.

Síntesis del compuesto (32)

Paso 1: A una solución de **29** (1.00 g, 5.18 mmol) en 2–propanol (60 mL) se añadió el Ejemplo 134 (1.40 g, 4.71 mmol) y la mezcla de reacción se calentó a 50 °C durante 17 h y luego a 80 °C por 1 h. La mezcla de reacción se enfrió a temperatura ambiente y el solvente se retiró bajo presión reducida. El residuo se repartió entre cloruro de metileno (20 mL) y agua (20 mL). La fase acuosa se extrajo con cloruro de metileno (10 mL), la fase orgánica combinada se lavó sucesivamente con ácido clorhídrico 0.5 N (10 mL), bicarbonato de sodio saturado (10 mL) y cloruro de sodio (10 mL), se secó (con sulfato de sodio), se filtró y concentró bajo presión reducida. El producto crudo se purificó por cromatografía flash (sílica, cloruro de metileno/metanol 95:5) para obtener el amino alcohol **30** (1.30 g, 51%) en forma de un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.42–7.38 (m, 1H), 7.20–6.96 (m, 1H), 6.78–6.62 (m, 5H), 4.64–4.58 (m, 1H), 4.56–4.20 (m, 1H), 4.18–4.08 (m, 2H), 3.90–3.48 (m, 4H), 3.16–2.70 (m,

573

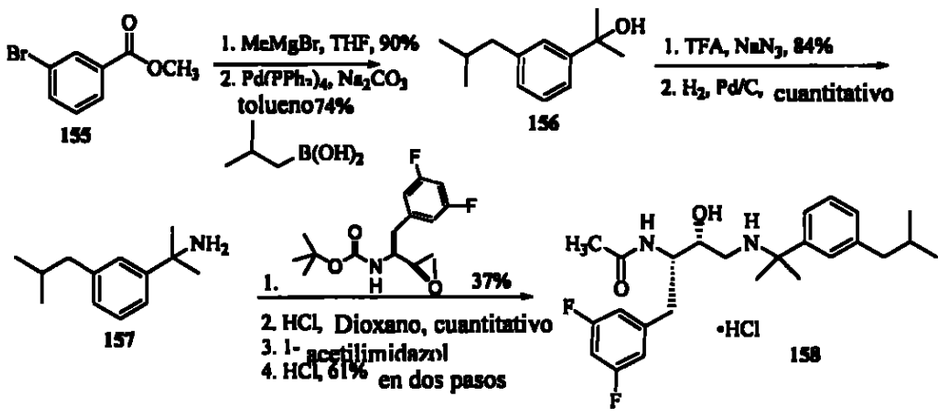
5H), 2.64–2.50 (m, 2H), 1.50–1.30 (s, 9H), 1.23–1.18 (m, 3H); ESI MS m/z 493 [$C_{26}H_{34}F_2N_2O_5$ + H].

Paso 2: A una solución de amino alcohol 30 (0.47 g, 0.95 mmol) en dioxano (20 mL) a temperatura ambiente se añadió cloruro de hidrógeno (4.77 mL, solución 4 M en dioxano, 19.09 mmol) y la mezcla de reacción se agitó durante 17 h. A continuación se concentró la mezcla de reacción bajo presión reducida y el residuo se trituró con éter dietílico para obtener la amina 31 (0.38 g, 85%) en forma de un sólido blanco: ^{1}H NMR (300 MHz, CD_3OD) § 7.40 (s, 1H), 7.19–7.17 (m, 1H), 7.05–6.83 (m, 5H), 4.71–4.69 (m, 1H), 4.44–4.40 (m, 2H), 4.19–4.08 (m, 3H), 3.78 (br s, 1H), 3.78–3.52 (m, 1H), 3.49–3.47 (m, 1H), 3.34–3.30 (m, 1H), 3.12–3.01 (m 2H), 2.98–2.63 (m, 4H), 1.30–1.17 (m, 3H); ESI MS m/z 393 [$C_{21}H_{26}F_2N_2O_3$ + H].

Paso 3: A una suspensión de acetato de sodio (0.67 g, 0.82 mmol), diisopropiletilamina (0.71 mL, 4.09 mmol) y HBTU (0.31 g, 0.82 mmol) en cloruro de metileno (5 mL) se añadió una solución adicional de amina 31 (0.38 g, 0.82 mmol), diisopropiletilamina (0.71 mL, 4.09 mmol) en cloruro de metileno (5 mL) y la mezcla combinada se agitó a temperatura ambiente durante 24 h. Se añadió agua (30 mL) y la fase acuosa se extrajo con cloruro de metileno adicional (5 mL). La fase orgánica combinada se lavó sucesivamente con ácido clorhídrico 0.5 N (10 mL) y cloruro de sodio saturado (10 mL), luego se secó (con sulfato de sodio), se filtró y concentró bajo presión reducida. La purificación mediante HPLC de preparación (Método G) produjo ALB 15297 (32, 55 mg, 4%) en forma de una espuma blanca: punto de fusión 95–97 °C; IR (ATR) 3254, 2966, 1657, 1627, 1596 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) § 7.34–7.28 (m, 1H), 7.17–7.14 (m, 1H), 6.88–6.75 (m, 5H), 4.56–4.54 (m, 1H), 4.39–4.34 (m, 1H), 4.16–4.04 (m, 3H), 3.90–3.85 (m, 1H), 3.77–3.62 (m, 1H), 3.54–3.10 (m, 5H), 2.71–2.57 (m, 3H), 1.85–1.82 (m, 3H), 1.28–1.16 (m, 3H); ESI MS m/z 435 [$C_{23}H_{28}F_2N_2O_4$+ H]; HPLC (Método F) 94.1 (AUC), t_R=11.1, 11.5 min (3:2 mezcla de diastereoisómeros).

575
574

Esquema JJ



F. Síntesis del Acetato 158

Al añadir reactivo Grignard de metilo al éster 155 seguido por acoplamiento con ácido borónico 2-metilpropilo se produjo el alcohol 156 (Esquema JJ). La conversión del alcohol a la azida y su reducción arrojaron la amina 157. La apertura epóxida, más la remoción del grupo protector, la acetilización y la formación de la sal del ácido clorhídrico produjeron (158).

Métodos generales de HPLC

Método A: Columna Phenomenex Luna C18(2), 150 × 4.6 mm, 5µ

A: 0.05% TFA en 95:5 H_2O/CH_3CN; B: 0.05% TFA en 5:95 H_2O/CH_3CN

Gradiente: 10–90% B en 15 min; flujo 1.0 mL/min

Detección: 254 nm

Método B: Columna Phenomenex Luna C18(2), 150 × 4.6 mm, 5µ

A: 0.05% TFA en 95:5 H_2O/CH_3CN; B: 0.05% TFA en 5:95 H_2O/CH_3CN

Gradiente: 30-100% B en 15 min; flujo 1.0 mL/min

Detección: 254 nm

Método C: Columna Phenomenex Synergi Max-RP, 150 × 4.6 mm, 4µ

A: H_2O; B: CH_3CN

Gradiente: 30-100% B en 15 min; flujo 1.0 mL/min

Detección: 220 nm

576

575

Método D: Columna Phenomenex Luna C18(2), 150 × 4.6 mm, 4µ
A: 95:5 H_2O/CH_3CN; B: 5:95 H_2O/CH_3CN
Gradiente: 40-100% B en 15 min; flujo 1.0 mL/min
Detección: 254 nm

Método E: Columna Phenomenex Luna C18(2), 150 × 4.6 mm, 4µ
A: 95:5 H_2O/CH_3CN; B: 5:95 H_2O/CH_3CN
Gradiente: 1-99% B en 15 min; flujo 1.0 mL/min
Detección: 254 nm

Método F: Columna Phenomenex Luna C18(2), 150 × 4.6 mm, 5µ
A: 0.05% TFA en 95:5 H_2O/CH_3CN; B: 0.05% TFA en 5:95 H_2O/CH_3CN
Gradiente: 10–90% B en 15 min; flujo 1.0 mL/min
Detección: 225 nm

EJEMPLO 114

A. Síntesis del bromuro de *Neo*-Pentilmagnesio

En un matraz de bola con tres bocas y acoplado con un embudo adicional, condensador de agua y barra de agitación magnética, se agregaron escorias de magnesio (10.0 g, 413.8 mmol), iodo (100 mg), y fragmentos de vidrio. La mezcla se calentó vigorosamente en condiciones de vacío y agitación durante 20 minutos. Se procedió a enfriar el matraz a temperatura ambiente y luego se le introdujo argón y las escorias de magnesio se agitaron durante 0.5 h adicionales. A continuación se incorporó al matraz éter dietílico (65 mL) y el embudo adicional con una solución de bromuro de *neo*-pentilo (20.0 g, 132.4 mmol) en éter dietílico (100 mL). Luego se añadió bromuro de *neo*-pentilo (2.5 g, 16.55 mmol) directamente a la mezcla de reacción y la solución se tibió suavemente con una pistola térmica para iniciar la reacción. Una vez iniciada la reacción, el contenido del embudo adicional se añadió gota por gota durante el transcurso de 1 h para mantener un reflujo suave. Se añadió una porción de otra alícuota de bromuro de *neo*-pentilo (2.5 g, 16.55 mmol) a la mezcla de reacción seguido por la adición gota a gota de 1,2-dibromoetano (14.3 mL, 165.5 mmol) durante el transcurso de 1 h. El gas etano generado se retiró del matraz con un flujo constante de nitrógeno. La mezcla de reacción se calentó a reflujo durante 24 h y se enfrió a temperatura ambiente, produciendo una solución negra. El sólido suspendido se dejó asentar y la solución arriba del residuo sólido correspondía a bromuro de *neo*-pentilmagnesio

575
576

(alrededor de 1.0 M en éter, 165.5 mmol), la cual se usó en subsiguientes reacciones de acoplamiento.

B. Síntesis de la Amina 2b

Paso 1: Se añadió una porción de di-*tert*-butil dicarbonato (5.45 g, 25.0 mmol) a temperatura ambiente a una solución del compuesto (1) (5.05 g, 19.23 mmol) y *N,N*-diisopropiletilamina (10.0 mL, 57.7 mmol) en acetonitrilo (32 mL) y la mezcla de reacción se agitó a temperatura ambiente durante 36 h. Se retiró el solvente bajo presión reducida y el residuo se repartió entre acetato de etilo y bicarbonato de sodio saturado. Las fases fueron separadas y la fase orgánica se lavó con agua, cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y luego se concentró bajo presión reducida para producir la amina protegida deseada (7.38 g, cuantitativa) en forma de un sólido ceroso que se usó en el siguiente paso sin más purificación: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.47 (s, 1H), 7.28–7.24 (m, 1H), 6.94 (d, J = 8.2 Hz, 1H), 4.77 (m, 2H), 2.72–2.66 (m, 2H), 2.04–2.00 (m, 1H), 1.83–1.72 (m, 3H), 1.44 (s, 9H).

Paso 2: Una solución de bromuro de *neo*-pentilmagnesio preparada arriba (115.4 mL) se añadió gota a gota a temperatura ambiente a una solución de cloruro de zinc (115.4 mL, 0.5 M en tetrahidrofurano, 57.7 mmol) durante un período de 40 min. Después de la adición de Grignard la mezcla de reacción se agitó durante 0.5 h produciendo una suspensión heterogénea blanca. Se añadió una porción del complejo [1,1'-Bis(difenilfosfino)ferroceno]dicloropaladio(II) con diclorometano (1:1) (1.60 g, 1.92 mmol) seguido por la adición gota a gota durante 20 min. de una solución de la amina protegida preparada en el paso 1 (7.38 g, 19.23 mmol) en tetrahidrofurano (20 mL) arrojando una mezcla de reacción de color amarillo. La mezcla de reacción se agitó a temperatura ambiente durante 0.5 h y luego se calentó a reflujo durante 2 h produciendo una solución parda. La mezcla de reacción se enfrió a temperatura ambiente y se enfrió rápida y cuidadosamente con ácido clorhídrico al 10% (100 mL) y la mezcla se agitó a temperatura ambiente de un día para otro. La mezcla de reacción se diluyó con éter dietílico y se separaron las fases. La fase orgánica se lavó a continuación con agua, cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida para producir un semisólido de color pardo. La purifiación por cromatografía flash (sílica, hexanos/acetato de etilo 19:1) produjeron la amina 2a protegida (3.0 g, 49%) con aspecto de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.08 (s, 1H), 6.98–6.90 (m, 2H), 4.82–4.75 (m, 2H), 2.76–2.69 (m, 2H), 2.43 (s, 2H), 2.04–1.97 (m, 1H), 1.84–1.80 (m, 3H), 1.47 (s, 9H), 0.88 (m, 9H); ESI MS *m/z* 318 $[C_{20}H_{31}NO_2 + H]^+$.

577

Paso 3: A una solución de amina 2a (3.00 g, 9.45 mmol) en 1,4-dioxano (25 mL) se añadió a temperatura ambiente una solución de ácido clorhídrico (23.5 mL, 4 N en 1,4-dioxano, 94.5 *mmol*) y la mezcla de reacción se agitó a temperatura ambiente de un día para otro produciendo un precipitado blanco. La filtración al vacío arrojó la amina 2b (2.15 g, 91%) en forma de un sólido blanco: ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) § 7.21 (s, 1H), 7.08–7.02 (m, 2H), 4.43 (m, 1H), 3.01–2.76 (m, 5H), 2.48 (s, 2H), 2.19–2.12 (m, 2H), 1.96–1.87 (m, 2H), 0.90 (m, 9H); ESI MS *m/z* 201 $[C_{13}H_{20}]^+$.

C. Síntesis de Tetralona 4

Paso 1: Una solución de tetralona 3 (5.0 g, 22.21 mmol) en benceno (100 mL) conteniendo etilenglicol (5.0 mL, 88.8 mmol) y ácido *p*-toluensulfónico monohidratado (420 mg, 2.22 mmol) se calentó a reflujo en un aparato de Dean–Stark durante 24 h. La mezcla de reacción se enfrió a temperatura ambiente, se concentró bajo presión reducida y el residuo resultante se repartió entre acetato de etilo y agua. Las fases se separaron y la fase orgánica se lavó con cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida para producir el dioxolano deseado (5.97 g, 99%) con la apariencia de un aceite dorado: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.57 (d, J = 2.0 Hz, 1H), 7.32 (dd, J = 8.2, 2.0 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 4.23–4.07 (m, 4H), 2.73–2.72 (m, 2H), 2.04–1.94 (m, 4H).

Paso 2: Una solución de bromuro de *neo*-pentilmagnesio preparada arriba (60 mL) se añadió gota a gota a temperatura ambiente durante 20 min. a una solución de cloruro de zinc (60 mL, 0.5 M en tetrahidrofurano, 30.0 mmol). Después de la adición de Grignard, la mezcla de reacción se agito durante 0.5 h y produjo una suspensión heterogénea blanca. Se añadió una porción del complejo [1,1'-Bis(difenilfosfino)ferroceno]dicloropaladio(II) con diclorometano (1:1) (816 mg, 1.0 mmol) seguido por la adición gota a gota de una solución del dioxolano preparado en el paso 1 (2.69 g, 10.0 mmol) en tetrahidrofurano (20 mL) arrojando una mezcla de reacción de color amarillo, la cual procedió a calentarse a reflujo durante 1 h para producir una solución parda. La mezcla de reacción se enfrió a temperatura ambiente y se enfrió rápida y cuidadosamente con ácido clorhídrico al 10% (100 mL) y la mezcla se agitó a temperatura ambiente de un día para otro. La mezcla de reacción se diluyó con éteréter dietílico y se separaron las fases. La fase orgánica se lavó a continuación con agua, cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida para producir un aceite negro. La purificación por cromatografía flash (sílica, hexanos/acetato de etilo 19:1) produjeron el compuesto (4) (2.17 g, 99%) con aspecto de un aceite amarillo: IR (ATR) 3359, 2957, 1762, 1686, 1521, 1236, 1126, 1076, 1053, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) § 7.79 (s, 1H), 7.26–7.22 (m, 1H), 7.15 (m,

579
578

1H), 2.96–2.92 (m, 2H), 2.67–2.62 (m, 2H), 2.50 (s, 2H), 2.17–2.08 (m, 2H), 0.89 (s, 9H); ESI MS *m/z* 217 $[C_{15}H_{20}O + H]^+$; HPLC: (Método D) >99% (AUC), t_R = 13.30 min.

D. Síntesis del compuesto (7)

Paso 1: A una solución de 2b (0.22 g, 5.18 mmol) en 2–propanol (10 mL) se añadió el Ejemplo 134 (0.31 g, 1.03 mmol) y la mezcla de reacción se calentó a 50 °C durante 17 h. La mezcla se dejó enfriar luego a temperatura ambiente y el solvente se retiró bajo presión reducida. El residuo resultante se repartió entre cloruro de metileno (20 mL) y agua (20 mL). La fase acuosa se extrajo con cloruro de metileno (10 mL), la fase orgánica combinada se lavó sucesivamente con ácido clorídrico 0.5 N (10 mL), bicarbonato de sodio saturado (10 mL) y cloruro de sodio (10 mL), se secó (con sulfato de sodio), se filtró y concentró bajo presión reducida. El producto crudo se purificó por cromatografía flash (sílica, cloruro de metileno/metanol 95:5) para obtener el amino alcohol 5 (0.32 g, 60%) el cual se dejo sin caracterización adicional: ESI MS *m/z* 517 $[C_{30}H_{42}F_2N_2O_3 + H]$.

Paso 2: A una solución de amino alcohol 5 (0.32 g, 0.61 mmol) en dioxano (5 mL) a temperatura ambiente se añadió cloruro de hidrógeno (1.50 mL, solución 4 M en dioxano, 6.18 mmol) y la mezcla de reacción se agitó durante 17 h. A continuación se concentró la mezcla reactiva bajo presión reducida y el residuo se trituró con éteréter dietílico para obtener la amina 6 (0.25 g, 85%) en forma de un sólido blanco que no se purificó ni caracterizó más: ESI MS *m/z* 417 $[C_{25}H_{36}Cl_2F_2N_2O + H]$.

Paso 3: A una suspensión de fluoroacetato de sodio (0.04 g, 0.82 mmol), *N,N*-diisopropiletilamina (0.23 mL, 1.41 mmol) y HBTU (0.17 g, 0.47 mmol) en cloruro de metileno (2 mL) se añadió una solución de amina 6 (0.23 g, 0.47 mmol), *N,N*-diisopropiletilamina (0.15 mL, 0.94 mmol) en cloruro de metileno (5 mL) y la mezcla combinada se agitó a temperatura ambiente durante 24 h. Se añadió agua (20 mL) y la fase acuosa se extrajo con cloruro de metileno adicional (5 mL). La fase orgánica combinada se lavó sucesivamente con ácido clorídrico 0.5 N (10 mL) y cloruro de sodio saturado (10 mL), luego se secó (con sulfato de sodio), se filtró y concentró bajo presión reducida. La purificación mediante HPLC de preparación (Método B) produjo el compuesto (7) (106 mg, 47%) en forma de un sólido blanco: punto de fusión ; IR (ATR) 3324, 2957, 1659, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) § 7.29 (s, 1H), 7.12–6.95 (m, 2H), 6.82–6.55 (m, 4H), 4.93–4.83 (m, 1H), 4.81–4.67 (m, 1H), 4.27–4.18 (m, 1H), 3.75–3.74 (m, 1H), 3.57–3.52 (m, 1H), 3.10–3.04 (m, 1H), 2.94–2.67 (m, 5H), 2.48 (s, 2H), 1.98–1.75 (m, 4H), 1.60–1.40 (br s, 2H), 0.93 (s, 9H); ESI MS *m/z* 476 $[C_{27}H_{35}F_3N_2O_2 + H]$; HPLC (Method C) >99% (AUC), t_R = 8.60 min.

579

E. Síntesis del 5-Carboetoxi-2-*iso*-butiltiazol (14)

Paso 1: Una solución de formiato de etilo (38 mL, 470 mmol) y cloroacetato de etilo (44 mL, 416 mmol) en éteréter dietílico (200 mL) se añadió a una solución helada de etóxido de potasio (33.5 g, 400 mmol) en alcohol etílico/éteréter dietílico 1:2 (300 mL). La suspensión resultante se agitó a temperatura ambiente de un día para otro. El sólido se filtró, se lavó con éteréter dietílico y se disolvió en agua (200 mL). La solución se enfrío en un baño helado y se acidificó hasta un pH de 4 con ácido clorhídrico concentrado. Se extrajo la solución con éter dietílico y la capa orgánica se lavó con cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida para dar el formilcloroacetato (11, 24.2 g, 40%), cuyo aspecto era el de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99–4.19 (m, 2H), 4.08 (s, 1H), 3.64–3.57 (m, 1H), 1.35–1.18 (m, 3H).

Paso 2: Se añadió pentasulfuro de fósforo (3.8 g, 10.9 mmol) en porciones a una solución de isovaleramida (12, 10 g, 99 mmol) en éteréter dietílico (400 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y luego se filtró. El filtrado se concentró bajo presión reducida produciendo isovalerotioamida (13, 11.60 g, cuantitativa) en forma de un aceite amarillo: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 1H), 9.12 (s, 1H), 2.33 (d, J = 7.3 Hz, 2H), 2.17–2.12 (m, 1H), 0.86 (d, J = 8.4 Hz, 6H).

Paso 3: Una solución de 13 (11.60 g, 98.97 mmol) y 11 (9.98 g, 66.31 mmol) en *N,N*-dimetilformamida (40 mL) se calentó a 95 °C de un día para otro. La mezcla de reacción se enfrió a 0 °C y se añadió agua fría (100 mL). La mezcla de reacción se ajustó a pH 8 añadiendo lentamente bicarbonato de sodio sólido y se extrajo con éteréter dietílico. La capa orgánica se lavó con agua, cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, hexanos/acetato de etilo 90:10) produjeron 5-carboetoxi-2-*iso*-butiltiazol (14, 4.53 g, 32%) con aspecto de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (q, J = 7.2 Hz, 2H), 2.90 (d, J = 7.2 Hz, 2H), 2.15 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 6.7 Hz, 6H).

F. Síntesis del compuesto (18)

Paso 1: A una solución helada de hidruro de litio y aluminio (18.7 mL, 1.0 M en tetrahidrofurano, 18.7 mmol) se añadió a una solución de 14 (2.0 g, 9.37 mmol) en tetrahidrofurano (3 mL). La mezcla de reacción se agitó a 0 °C durante 0.5 h y después de un día para otro a temperatura ambiente. La mezcla de reacción se enfrió rápidamente en esta secuencia: agua (1 mL), hidróxido de sodio al 15% (1 mL) y agua (1 mL). La mezcla resultante se secó (con sulfato de sodio), se

580

filtró y se concentró bajo presión reducida para obtener el alcohol deseado (1.43 g, 89%) cuyo aspecto era el de un aceite amarillo claro: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 4.81 (s, 2H), 2.83 (d, J = 7.2 Hz, 2H), 2.71 (s, 1H), 2.10 (m, 1H), 0.98 (d, J = 6.7 Hz, 6 Hz).

Paso 2: A una solución helada del alcohol preparado en el paso 1 (1.3 g, 7.6 mmol) en cloruro de metileno (5 mL) se añadió cloruro de tionilo (5.53 mL, 76 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y luego se evaporó bajo presión reducida. El residuo se neutralizó con bicarbonato de sodio saturado y luego se repartió en agua y cloruro de metileno. La capa orgánica se lavó con cloruro de sodio saturado, se añadió trietilamina, y se procedió a secar la solución resultante (sulfato de sodio), se filtró, y se concentró bajo presión reducida para dar el cloruro deseado (1.15 g, 80%) con el aspecto de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 4.78 (s, 2H), 2.85 (d, J = 7.2 Hz, 2H), 2.10 (m, 1H), 0.99 (d, J = 6.7 Hz, 6H).

Paso 3: A una solución del cloruro preparado en el paso 2 (1.15 g, 6.1 mmol) en sulfóxido de dimetilo (5 mL) se añadió cianuro de potasio (475 mg, 7.3 mmol). La mezcla de reacción se agitó a temperatura ambiente de un día para otro y luego se repartió entre agua y acetato de etilo. La fase orgánica se lavó a continuación con cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida para producir un aceite negro. La purificación por cromatografía flash (sílica, hexanos/acetato de etilo 66:34) produjeron el nitrilo 15 (363 mg, 33%) con apariencia de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 3.89 (s, 2H), 2.85 (d, J = 7.2 Hz, 2H), 2.10 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H).

Paso 4: A una mezcla de 15 (367 mg, 2.04 mmol), 1-bromo-2-cloroetano (2.5 mL, 30.5 mmol), y cloruro de benciltrietilamonio (14 mg, 0.06 mmol) a 50 °C se añadió una solución al 50% de hidróxido de sodio (3.6 mL). La mezcla de reacción se agitó a 50 °C durante 1 h, se dejó enfriar hasta temperatura ambiente y luego se repartió entre agua y cloruro de metileno. La fase orgánica se lavó a continuación con cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida para producir un aceite negro. La purificación por cromatografía flash (sílica, hexanos/acetato de etilo 66:34) produjo el ciclopropilbencilnitrilo deseado (260 mg, 62%) con la apariencia de un aceite amarillo pálido: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 2.81 (d, J = 7.2 Hz, 2H), 2.05 (m, 1H), 1.77 (m, 2H), 1.43 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H).

Paso 5: A una solución del nitrilo preparado en el paso 4 (250 mg, 1.21 mmol) en acetona/agua 1:1 (2 mL) se añadió carbonato de potasio (17 mg, 0.12 mmol) y peróxido de úrea-hidrógeno (456 mg, 4.85 mmol). La mezcla de reacción se agitó a temperatura ambiente de un día para otro. La acetona se evaporó bajo presión reducida y el residuo se diluyó con agua. Se recogió por filtración la amida 16 deseada (270 mg, cuantitativo). Este compuesto se usó en el siguiente paso sin caracterización adicional.

581

Paso 6: A una solución helada de hidróxido de sodio (228 mg, 5.7 mmol) en agua (2.5 mL) se añadió bromuro (94 µL, 1.84 mmol) gota a gota. Después de agitar por 5 min. a 0 °C, se añadió en una porción la amida 16 (336 mg, 1.5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 20 min y luego se calentó a 75 °C por 5 h. A continuación se diluyó la mezcla con agua y se extrajo con cloruro de metileno. La capa orgánica se lavó a continuación con cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida para producir un sólido amarillo. La purificación por cromatografía flash (sílica, cloruro de metileno/metanol 95:5) produjo la amina 17 (288 mg, 98%) con apariencia de un sólido amarillo pálido: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 1H), 2.79 (d, J = 7.2 Hz, 2H), 2.08 (m, 1H), 1.13 (m, 1H), 1.06–0.97 (m, 8H).

Paso 7: Una solución de amina 17 (150 mg, 0.76 mmol) y el Ejemplo 134 (206 mg, 0.68 mmol) en 2-propanol (2 mL) se calentó a 70 °C de un día para otro. La mezcla de reacción se enfrió hasta temperatura ambiente y luego se repartió entre agua y cloruro de metileno. La capa orgánica se lavó con cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, cloruro de metileno/metanol 95:5) produjo la amina *N*-alquilada (108 mg, 32%) con apariencia de un sólido amarillo: ESI MS *m/z* 496 $[C_{25}H_{33}F_2N_3O_3S + H]^+$.

Paso 8: Se añadió cloruro de hidrógeno (2.0 mL, 4 N en 1,4-dioxano, 8 mmol) a temperatura ambiente a una solución de la amina preparada en el paso 7 (108 mg, 0.22 mmol) en 1,4-dioxano (1 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 h y luego se concentró bajo presión reducida para dar 19 (103 mg, cuantitativo) con la apariencia de un sólido amarillo: ESI MS *m/z* 396 $[C_{20}H_{27}F_2N_3OS + H]^+$.

Paso 9: A una solución helada de 19 (103 mg, 0.22 mmol) y trietilamina (129 µL, 0.92 mmol) en cloruro de metileno (2 mL) se añadió 1-acetilimidazol (24 mg, 0.22 mmol). La mezcla de reacción se agitó a temperatura ambiente de un día para otro y luego se repartió entre agua y cloruro de metileno. La capa orgánica se lavó con cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, cloruro de metileno/metanol 95:5) produjo el compuesto (18) (51 mg, 54%) con apariencia de un sólido blanquecino: punto de fusión IR (ATR) 3330, 2960, 1647, 1595, 1529, 1458, 1112, 980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.74–6.63 (m, 3H), 5.52 (d, J = 9.1 Hz, 1H), 4.08–4.10 (m, 1H), 3.43–3.41 (m, 1H), 2.98–2.96 (m, 1H), 2.98–2.70 (m, 5H), 2.10–2.00 (m, 1H), 1.89 (s, 3H), 1.06–0.96 (m, 10H); ESI MS *m/z* 438 $[C_{22}H_{29}F_2N_3O_2S + H]^+$; HPLC (Method E) 98.1% (AUC), t_R = 11.45 min. Anal. Calcd for $C_{22}H_{29}F_2N_3O_2S$: C, 60.39; H, 6.68; N, 9.60. Encontró: C, 60.10; H, 6.73; N, 9.57.

582

G. Síntesis del compuesto (47)

Paso 1: A una solución agitada de bromuro de zinc *neo*-pentilo (20.93 mL, 0.5 M en éteréter dietílico, 10.47 mmol), preparado como se describió anteriormente, se añadió cloruro de zinc (20.93 mL, 0.5 M en éteréter dietílico, 10.47 mmol). La mezcla de reacción se agitó durante 1 h y luego se añadió $Pd(dppf)Cl_2$ (285 mg, 0.349 mmol). La mezcla de reacción se agitó por 5 min y luego se añadió bromuro 44 (750 mg, 3.49 mmol) y la mezcla se agitó de un día para otro. La mezcla de reacción se repartió entre acetato de etilo y cloruro de amonio saturado. La capa orgánica se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, hexanos/acetato de etilo 5:1) produjo el alcohol 45 (590 mg, 74%) con apariencia de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.31 (d, J = 7.2 Hz, 1H), 7.25 (obs m, 2H), 6.98 (d, J = 7.2 Hz, 1H), 2.51 (s, 2H), 1.58 (s, 6H), 0.90 (s, 9H).

Paso 2: A una solución helada de 45 (590 mg, 2.60 mmol) y azida de sodio (338 mg, 5.20 mmol) en cloruro de metileno (12 mL) se añadió ácido trifluoroacético (2.37 g, 20.80 mmol) en cloruro de metileno (5 mL) durante 1 h. A la mezcla de reacción se le agregó agua (3 mL) seguida por una proporción 1:1 agua/hidróxido de amonio concentrado (6 mL) y luego se diluyó con acetato de etilo. La capa orgánica se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, hexanos/acetato de etilo 9:1) produjo una azida (420 mg, 70%) con apariencia de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.27 (obs m, 2H), 7.21–6.98 (m, 2H), 2.53 (s, 2H), 1.63 (s, 6H), 0.91 (s, 9H).

Paso 3: Una mezcla de la azida del paso 2 (420 mg, 1.82 mmol) y Pd/C al 10% se agitó bien bajo una atmósfera de hidrógeno durante 5 h a 45 psi. La mezcla de reacción se filtró a través de tierra diatomácea y se concentró bajo presión reducida para producir la amina 46 (340 mg, 91%) con apariencia de un aceite amarillo. Esta amina se utilizó sin ninguna purificación ni caracterización adicionales.

Paso 4: Una mezcla de la amina 46 (340 mg, 1.66 mmol) y el Ejemplo 134 (496 mg, 1.66mmol) se calentó a 60 °C de un día para otro. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, cloruro de metileno/metanol/hidróxido de amonio concentrado 97:3:1) produjo la amina (350 mg, 42%) con apariencia de una espuma blanca: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.24–7.11 (m, 4H), 6.85–6.79 (m, 3H), 4.52 (m, 1H), 3.74 (m, 1H), 3.36 (m, 1H), 2.84 (m, 1H), 2.48 (m, 3H), 1.82 (m, 1H), 1.53 (s, 5H), 1.36 (s, 9H), 0.91 (d, J = 7.2 Hz, 9H).

Paso 5: A una solución agitada de la amina del paso 4 (350 mg, 0.694 mmol) en dioxano (3 mL) se añadió ácido clorhídrico (0.69 mL, 4 N en dioxano, 2.78 mmol). La mezcla de reacción se

583

agitó por 72 h y luego se concentró bajo presión reducida para obtener la sal del hidrocloruro (370 mg, cuantitativo), la cual se utilizó sin purificación ni caracterización adicionales.

Paso 6: A una mezcla agitada de la sal del paso 5 (150 mg, 0.32 mmol) y trietilamina (144 mg, 1.43 mmol) en cloruro de metileno (5 mL) se añadió 1-acetilimidazol (35 mg, 0.32 mmol). La mezcla de reacción se agitó de un día para otro y luego se repartió entre agua y cloruro de metileno. La capa orgánica se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, cloruro de metileno/metanol/hidróxido de amonio concentrado 9.5:1:1) produjo un sólido blanco: El sólido se disolvió en metanol (1 mL) y luego se añadió ácido clorhídrico (1 mL, 1 N en éter dietílico, 1 mmol). La solución resultante se concentró bajo presión reducida para obtener ALB 16810 (47, 80 mg, 52%) con la apariencia de un sólido blanco: IR (ATR) 3253, 2953, 1725, 1622 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) § 9.35 (br s, 1H), 9.01 (br s, 1H), 7.92 (d, J = 7.4 Hz, 1H), 7.39–7.29 (m, 3H), 7.17 (d, J = 7.4 Hz, 1H), 7.01–6.97 (m, 1H), 6.91–6.84 (m, 2H), 5.82 (d, J = 5.9 Hz, 1H), 3.82–3.67 (m, 2H), 2.98 (m, 1H), 2.65 (m, 1H), 2.49 (d, J = 7.2 Hz, 2H), 2.48 (m, 2H), 1.87 (m, 1H), 1.74 (s, 6H), 1.61 (s, 3H), 0.86 (s, 9H); ESI MS *m/z* 447 [$C_{26}H_{36}F_2N_2O_2$ + H]$^+$; HPLC (Method B) >99% (AUC), t_R = 8.92 min.

H. Síntesis del compuesto (158)

Paso 1: A una solución helada y agitada del éster **155** (4.64 g, 21. 57 mmol) en tetrahidrofurano (100 mL) se añadió bromuro de metilmagnesio (25.16 mL, solución 3.0 M en éter dietílico, 75.48 mmol). La mezcla reactiva se calentó hasta temperatura ambiente y se agitó de un día para otro. La mezcla de reacción se enfrió rápidamente añadiéndole cloruro de amonio saturado y diluido con éter dietílico. La capa orgánica se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purifiación por cromatografía flash (sílica, hexanos/acetato de etilo 6:1) produjo un alcohol (3.72 g, 90%) con apariencia de un aceite transparente: ^1H NMR (300 MHz, $CDCl_3$) § 7.67 (s, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.21 (m, 1H), 1.57 (s, 6H).

Paso 2: Una mezcla de alcohol del paso 1 (1.68 g, 7.82 mmol), ácido 2-metiylpropilborónico (1.19 g, 11.73 mmol), y carbonato de sodio (13.69 mL, 2 M aq, 27.38 mmol) se desgasificó con nitrógeno durante 20 min. Se añadió tetraquis(trifenilfosfina)paladio(0) (450 mg, 0.391 mmol) y la mezcla de reacción se calentó a reflujo de un día para otro. La mezcla de reacción se enfrió hasta temperatura ambiente, se filtró a través de tierra diatomácea y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, hexanos/acetato de etilo 4:1) produjo el alcohol **156** (1.11 g, 74%) con apariencia de un aceite transparente: ^1H NMR (300 MHz, $CDCl_3$)

584

§ 7.28–7.24 (m, 3H), 7.11 (d, J = 7.2 Hz, 1H), 2.48 (d, J = 6.1 Hz, 2H), 1.84 (m, 1H), 1.58 (s, 6H), 0.92 (d, J = 7.1 Hz, 3H).

Paso 3: A una solución helada y agitada del alcohol 156 (360 mg, 1.87 mol) y azida de sodio (244 mg, 3.75 mmol) en cloruro de metileno (10 mL) se añadió gota a gota ácido trifluoroacético (1,71 g, 14. 96 mmol) en cloruro de metileno (3 mL) durante 1 h. A la mezcla de reacción después de 1 h se le agregó agua (2 mL) y una solución 1:1 de hidróxido de amonio concentrado/agua (4 mL). La mezcla de reacción se diluyó con éter dietílico, se secó la capa orgánica (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, hexanos) produjo una azida (340 mg, 84%) con apariencia de un aceite transparente: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.28–7.24 (m, 4H), 2.50 (d, J = 6.1 Hz, 2H), 1.84 (m, 1H), 1.63 (s, 6H), 0.92 (d, J = 7.1 Hz, 3H).

Paso 4: Una mezcla de la azida del paso 3 (340 mg, 1.57 mmol) y Pd/C al 10% se agitó bien bajo una atmósfera de hidrógeno durante 2 h a 50 psi. La mezcla de reacción se filtró a través de tierra diatomáceа y se concentró bajo presión reducida para producir la amina 157 (300 mg, 91%) con apariencia de un aceite amarillo: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.28–7.24 (m, 4H), 2.49 (d, J = 6.1 Hz, 2H), 1.84 (m, 1H), 1.58 (s, 6H), 0.92 (d, J = 7.1 Hz, 3H).

Paso 5: Una solución de amina 157 (150 mg, 0.79 mmol) y el Ejemplo 134 (215 mg, 0.79 mmol) en 2-propanol (2 mL) se calentó a reflujo de un día para otro. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró bajo presión reducida. El residuo crudo se repartió entre cloruro de metileno y ácido clorhídrico 1 N. La capa orgánica se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (cloruro de metileno/metanol 8:1) produjo un alcohol (144 mg, 37%) con apariencia de una espuma blanca: ^{1}H NMR (300 MHz, $CDCl_3$) § 7.27–7.11 (m, 4H), 6.89–6.77 (m, 3H), 4.55 (m, 1H), 3.78 (m, 1H), 3.36 (m, 1H), 2.84 (m, 1H), 2.48 (m, 3H), 1.82 (m, 1H), 1.53 (s, 5H), 1.36 (s, 9H), 0.91 (d, J = 7.2 Hz, 3H).

Paso 6: Una mezcla del alcohol del paso 5 (144 mg, 0.29 mmol) y ácido clorhídrico (2.20 mL, solución 4 N en dioxano, 8.81 mmol) en dioxano (1 mL) se dejó agitando de un día para otro. La mezcla de reacción se concentró bajo presión reducida para obtener la sal del dihidrocloruro (136 mg, cuantitativo) con apariencia de una espuma blanca: ^{1}H NMR (300 MHz, DMSO-d_6) § 9.91 (br s, 1H), 9.36 (br s, 1H), 8.11 (br s, 4H), 7.54–6.98 (m, 7H), 6.28 (m, 1H), 4.12 (br s, 1H), 3.10–2.74 (m, 4H), 2.47 (d, J = 6.8 Hz, 2H), 1.91 (m, 1H), 1.72 (s, 6H), 0.87 (d, J = 7.1 Hz, 6H).

Paso 7: A una mezcla agitada de la sal del paso 6 (136 mg, 0.29 mmol) y trietilamina (135 mg, 1.33 mmol) en cloruro de metileno (5 mL) se añadió 1-acetilimidazol (33 mg, 0.29 mmol). La mezcla de reacción se agitó de un día para otro y luego se repartió entre agua y cloruro de

585

metileno. La capa orgánica se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica, cloruro de metileno/metanol/hidróxido de amonio concentrado 9.5:1:1) produjo un sólido blanco: El sólido se disolvió en metanol (1 mL) y luego se añadió ácido clorhídrico (1 mL, 1 N en éter dietílico, 1 mmol). La solución resultante se concentró bajo presión reducida para obtener el compuesto (158) (85 mg, 61%) con la apariencia de un sólido blanco: ^{1}H NMR (300 MHz, DMSO-d_6) § 9.45 (br s, 1H), 9.03 (br s, 1H), 7.95 (d, J = 7.4 Hz, 1H), 7.41–7.35 (m, 3H), 7.19 (d, J = 7.4 Hz, 1H), 7.01–6.97 (m, 1H), 6.91–6.84 (m, 2H), 5.82 (d, J = 5.9 Hz, 1H), 3.82–3.67 (m, 2H), 2.98 (m, 1H), 2.65 (m, 1H), 2.49 (d, J = 7.2 Hz, 2H), 2.48 (m, 2H), 1.87 (m, 1H), 1.74 (s, 6H), 1.61 (s, 3H), 0.86 (d, J = 6.5 Hz, 3H); ESI MS m/z 433 [$C_{25}H_{34}F_2N_2O_2$ + H]$^+$; HPLC (Method A) >99% (AUC), t_R = 10.45 min.

Ejemplo 115: La invención también incluye compuestos de indol y fluoreno, tales como los compuestos ejemplificados de las Tablas YY y ZZ.

Tabla 115.YY (Fluorenos)

Compuesto	DATOS MS	ESTRUCTURA
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-7-fluoro-9H-fluoren-9-il)amino]-2-hidroxipropil}acetamida	$C_{27}H_{27}F_3N_2O_2$ + H$^+$ requiere 547, y se encontraron 547	
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isobutil-9H-fluoren-9-il)amino]propil}acetamida	$C_{29}H_{32}F_2N_2O_2$ + H$^+$ requiere 479, y se encontraron 479	
N-[(1S,2R)-3-[(2-bromo-9-metil-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{26}H_{25}BrF_2N_2O_2$ + H$^+$ requiere 557, y se encontraron 557	
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(1-etilpropil)-9H-fluoren-9-il]amino}-2-hidroxipropil)acetamida	$C_{30}H_{34}F_2N_2O_2$ + H$^+$ requiere 491, y se encontraron 491	
N-[(1S,2R)-3-[(2-ciclopentil-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{30}H_{32}F_2N_2O_2$ + H$^+$ requiere 493, y se encontraron 493	
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-9-metil-9H-fluoren-9-il)amino]-2-hidroxipropil}acetamida	$C_{28}H_{30}F_2N_2O_2$ + H$^+$ requiere 465, y se encontraron 465	
N-[(1S,2R)-3-[(2-ciclohexil-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{31}H_{34}F_2N_2O_2$ + H$^+$ requiere 505, y se encontraron 505	
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(dimetilamino)-9H-fluoren-9-il]amino}-2-hidroxipropil)acetamida	$C_{27}H_{29}F_2N_3O_2$ + H$^+$ requiere 466, y se encontraron 466	
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-6-fluoro-9H-fluoreno-9-il)amino]-2-	$C_{27}H_{27}F_3N_2O_2$ + H$^+$ requiere 467, y se	

586

Compuesto	DATOS MS	ESTRUCTURA
hidroxipropil}acetamida	encontraron 467	
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(metoximetil)-9H-fluoren-9-il]amino}propil)acetamida.	$C_{27}H_{28}F_2N_2O_3 + H^+$ requiere 469, y se encontraron 469	
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-etil-5-(trifluorometil)-9H-fluoren-9-il]amino}-2-hidroxipropil)acetamida	$C_{28}H_{27}F_5N_2O_2 + H^+$ requiere 519, y se encontraron 519	
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(3-metilbutil)-9H-fluoren-9-il]amino}propil)acetamida	$C_{30}H_{34}F_2N_2O_2 + H^+$ requiere 493, y se encontraron 493	
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isopropil-9H-fluoren-9-il)amino]propil}acetamida	$C_{28}H_{30}F_2N_2O_2 + H^+$ requiere 465, y se encontraron 465	
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-neopentil-9H-fluoren-9-il)amino]propil}acetamida.	$C_{30}H_{34}F_2N_2O_2 + H^+$ requiere 493, y se encontraron 493	
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isopropenil-9H-fluoren-9-il)amino]propil}acetamida	$C_{28}H_{28}F_2N_2O_2 + H^+$ requiere 463, y se encontraron 463	
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(isopropilamino)-9H-fluoren-9-il]amino}propil)acetamida	$C_{28}H_{31}F_2N_3O_2 + H^+$ requiere 480, y se encontraron 480	
N-[(1S,2R)-3-[(2-cloro-7-etil-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{27}H_{27}ClF_2N_2O_2 + H^+$ requiere 543, y se encontraron 543	
N-[(1S,2R)-3-{[2-(tert-butilamino)-9H-fluoren-9-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{29}H_{33}F_2N_3O_2 + H^+$ requiere 494, y se encontraron 494.	
N-[(1S,2R)-3-{[2-(tert-butilamino)-9H-fluoren-9-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{29}H_{33}F_2N_3O_2 + H^+$ requiere 494, y se encontraron 494	
N-[(1S,2R)-3-{[2-(tert-butilamino)-9H-fluoren-9-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{29}H_{33}F_2N_3O_2 + H^+$ requiere 494, y se encontraron 494	
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-morfolin-4-il-9H-fluoren-9-il)amino]propil}acetamida	$C_{29}H_{31}F_2N_3O_3 + H^+$ requiere 508, y se encontraron 508	
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(neopentilamino)-9H-fluoren-9-il]amino}propil)acetamida	$C_{30}H_{35}F_2N_3O_2 + H^+$ requiere 508, y se encontraron 508	

Tabla 115.YY (Indoles)

Compuesto	DATOS MS
N-[(1S,2R)-3-{[(5-bromo-2,3-dihidro-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{21}H_{24}BrF_2N_3O_2 + H^+$ requiere 468, y se encontraron 468
N-[(1S,2R)-3-{[(5-bromo-1-etil-2,3-	$C_{23}H_{28}BrF_2N_3O_2 + H^+$ requiere

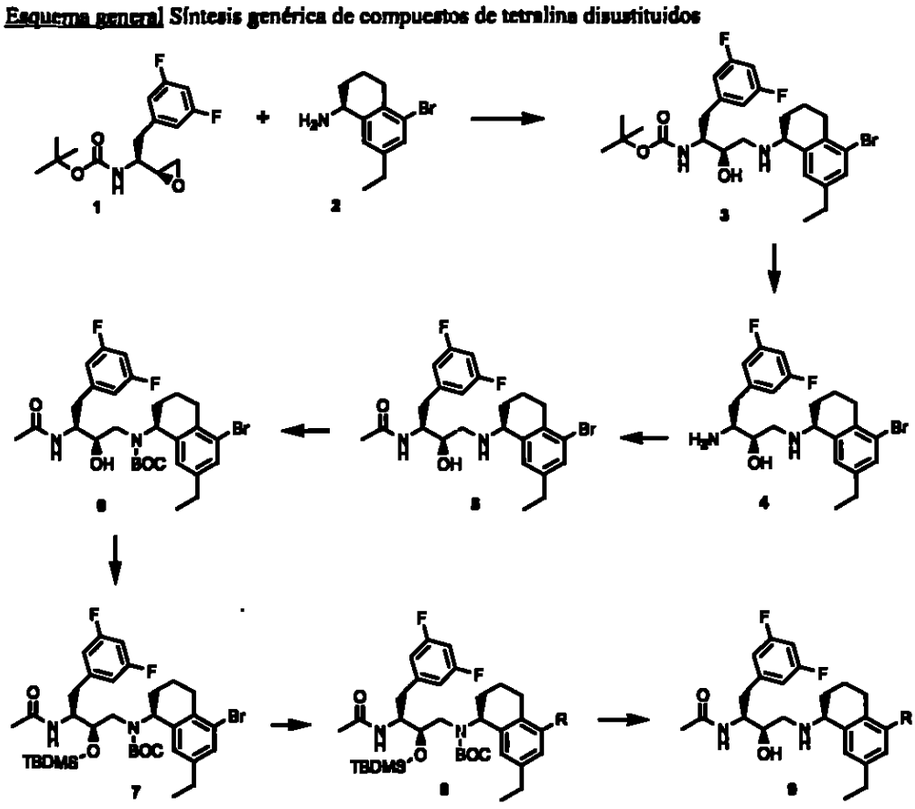
587

Compuesto	DATOS MS
dihidro-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	498, y se encontraron 498
N-[(1S,2R)-3-{[(1,5-dietil-2,3-dihidro-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{25}H_{33}F_2N_3O_2$ + H^+ rquiere 446, y se encontraron 446
N-[(1S,2R)-3-{[(1-bencil-5-isobutil-2,3-dihidro-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{32}H_{39}F_2N_3O_2$ + H^+ requiere 536, y se encontraron 536
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(5-isobutil-2,3-dihidro-1H-indol-7-il)metil]amino}propil)acetamida	$C_{25}H_{33}F_2N_3O_2$ + H^+ rquiere 446, y se encontraron 446
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(5-isobutil-1-propil-2,3-dihidro-1H-indol-7-il)metil]amino}propil)acetamida	$C_{28}H_{39}F_2N_3O_2$ + H^+ requiere 488, y se encontraron 488
N-[(1S,2R)-3-{[(1-butil-5-isobutil-2,3-dihidro-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{29}H_{41}F_2N_3O_2$ + H^+ requiere 502, y se encontraron 502
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(5-isobutil-1-isopropil-2,3-dihidro-1H-indol-7-il)metil]amino}propil)acetamida	$C_{28}H_{39}F_2N_3O_2$ + H^+ requiere 488, y se encontraron 488
N-[(1S,2R)-3-{[(1-alil-5-isobutil-2,3-dihidro-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{28}H_{37}F_2N_3O_2$ + H^+ requiere 486, y se encontraron 486
N-[(1S,2R)-3-{[(1-bencil-5-isobutil-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{32}H_{37}F_2N_3O_2$ + H^+ requiere 534, y se encontraron 534
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(5-isobutil-1H-indol-7-il)metil]amino}propil)acetamida	$C_{25}H_{31}F_2N_3O_2$ + H^+ requiere 444, y se encontraron 444
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(5-isobutil-1-propil-1H-indol-7-il)metil]amino}propil)acetamida	$C_{28}H_{37}F_2N_3O_2$ + H^+ requiere 486, y se encontraron 486
N-[(1S,2R)-3-{[(1-butil-5-isobutil-1H-indol-7-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida	$C_{29}H_{39}F_2N_3O_2$ + H^+ requiere 500, y se encontraron 500

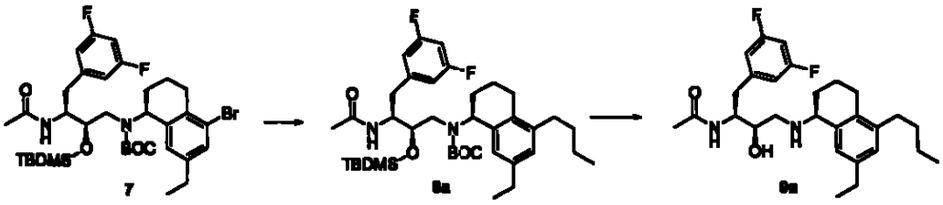
588

Ejemplos 116-118: El Esquema general de abajo se puede usar para sintetizar los componentes publicados y descritos en los Ejemplos 116-118 sin limitar el ámbito de la invención.

Esquema general Síntesis genérica de compuestos de tetralina disustituidos



EJEMPLO 116. SÍNTESIS DE N-[(*1S, 2R*)-3-((1*S*)-5-BUTIL-7-ETIL-1,2,3,4-TETRAHIDRO-NAFTALEN-1-ILAMINO)-1-(3,5-DIFLUOROBENCIL)-2-HIDROXI-PROPIL]-ACETAMIDA



589

A. La preparación de [(*1S, 2R*)-3-((1*S*)-5-Bromo-7-etil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-1-(3,5-difluoro-bencil)-2-hidroxipropil]-tert-butil éster del ácido carbámico 3

Una solución de *N*-BOC-epóxido 1 (869mg, 2.91mmol) y el bromo-sustituido 1-amino-tetrahidronaftaleno 2 (783 mg, 2.91 mmol) en 10 mL de isopropanol, se calienta a 80°C durante 6 horas. Después de culminada la reacción, la mezcla se enfría y el producto 3 se cristaliza a partir de la solución en bruto y se recolecta por filtración. Los cristales se lavan con etanol frío. Después de aplicar vacío para retirar trazas de los compuestos volátiles, la reacción produce alrededor de 995 mg de 3 ($[M+H]^+$ =552.8).

B. Preparación de (3*S*, 2*R*)-3-Amino-1-((1*S*)-5-bromo-7-etil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-4-(3,5-difluoro-fenil)-butan-2-ol 4

E compuesto 3 (995 mg) se disuelve en 10 mL de CH_2Cl_2 anhidro seguido por la adición de 10 mL de ácido trifluoroacético (anhidro). La solución se deja quieta por 90 min y luego se retiran los compuestos volátiles con un chorro de nitrógeno. El compuesto se desaliniza por extracción entre acetato de etilo, 10 mL, y solución acuosa de bicarbonato de sodio , 20 mL. La fase de acetato de etilo se lava una segunda vez con bicarbonato de sodio saturado. La fase orgánica a continuación se seca con $MgSO_4$ (anhidro), se filtra y se evaporaron los compuestos volátiles produciendo 865 mg de 4 ($[M+H]^+$ =452.8).

C. Preparación de N-[(*1S, 2R*)-3-((1*S*)-5-Bromo-7-etil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-1-(3,5-difluorobencil)-2-hidroxipropil]-acetamida 5

A una solución de diamina 4 (350 mg, 0.77 mmol) en 5 mL de CH_2Cl_2 anhidro, se añade HOBt (125mg, 0.93mmol), *N*-metil-morfolina (0.17mL, 1.55mmol) y ácido acético glacial (46.4mg, 0.773).

Esta solución se enfrió a 0°C *vía* baño de hielo y luego se añadió EDC-HCl (1-[3-(Dimetilamino)propil]-3-etilcarbodiimida clorhidrato, 163 mg, 0.85 mmol) y una barra de agitación. La reacción se agitó a 0°C durante 12 horas. Después de calentar hasta temperatura ambiente, el solvente se retiró con un chorro de N_2 y el residuo se lavó entre acetato de etilo y solución acuosa de bicarbonato de sodio saturado. La fase de acetato de etilo se secó con $MgSO_4$ (anhidro), se filtró y luego se retiró el solvente mediante evaporación giratoria y gran cantidad de vacío para producir 295mg de los compuestos 5 ($[M+H]^+$ =494.8).

D. Preparación de [(3S, 2R)-3-Acetilamino-4-(3,5-difluorofenil)-2-hidroxibutil]-((1*S*)-5-bromo-7-etil-1,2,3,4-tetrahidronaftalen-1-il)-tert-butil éster del ácido carbámico 6

590

A una solución de amina 5 (295 mg, 0.6 mmol) en 5 mL de THF anhidro se añadió *N,N'*-diisopropiletilamina (0.35 mL, 1.2 mmol) y di-*t*-butil dicarbonato (145 mg, 0.66 mmol). La solución se agita de un día para otro seguido por la eliminación del solvente con un chorro de nitrógeno. El producto se aisla lavando primero el residuo entre acetato de etilo (10 mL) y bisulfato de sodio 1N (20 mL). La capa de acetato de etilo se lavó a continuación contra solución acuosa de bicarbonato de sodio saturado (20 mL). La fase de acetato de etilo se secó con $MgSO_4$ (anhidro), se filtró y luego se retiró el solvente mediante evaporación giratoria y gran cantidad de vacío para producir 354.4 mg de 6 ($[M+H]^+$ =594.5).

E. Preparación de [(*1S, 2R*)-3-Acetilamino-2-(tert-butil-dimetil-silaniloxi)-4-(3,5-difluorofenil)-butil]-((1*S*)-5-bromo-7-etil-1,2,3,4-tetrahidro-naftalen-1-il)-tert-butil éster del ácido carbámico 7

A una solución de cloruro de *t*-butildimetilsilil (105 mg, 0.66 mmol) e imidazol (102 mg, 1.5 mmol) en dimetilformamida anhidra (3 mL) se añade 6 (354 mg, 0.6 mmol) y la solución se dejó agitando a temperatura ambiente durante 16 horas. El DMF se elimina *vía* evaporación giratoria. El residuo resultante se disuelve en acetato de etilo y se lava contra bisulfato de sodio 1N y luego con solución acuosa de bicarbonato de sodio saturado. El acetato de etilo se secó con $MgSO_4$ sólido, se filtró y se evaporaron los compuestos volátiles *vía* evaporación giratoria y gran cantidad de vacío. El producto 7 produjo M+H = 731.2 y se utilizó en los acoplamientos catalizados con paladio sin ninguna purificación adicional.

F. **PREPARACIÓN DE [(*1S, 2R*)-3-ACETILAMINO-2-(TERT-BUTILDIMETILSILANILOXI)-4-(3,5-DIFLUOROFENIL)-BUTIL]-((1*S*)-5-BUTIL-7-ETIL-1,2,3,4-TETRAHIDRO-NAFTALEN-1-IL)-TERT-BUTIL ÉSTER DEL ÁCIDO CARBÁMICO 8A**

El proceso a continuación se efectúa en una cámara de atmósfera inerte rellena de nitrógeno. A una solución de 7 (73 mg, 0.1 mmol) en 0.1 mL de THF anhidro se añadió una solución de $Pd(OAc)_2$ (2.25 mg, 0.01 mmol) y 2-(*di-t*-butilfosfino)bifenilo (5.9 mg, 0.01 mmol) en 0.1 mL de THF anhidro. La reacción se inició añadiendo bromuro de butilzinc (0.5M in THF, 0.5 mL, 0.25 mmol). La reacción se agitó durante 16 horas, y a continuación se eliminó el solvente con un chorro de nitrógeno. El residuo se redisolvió en metanol (1 mL) para su purificación por HPLC en fase reversa. El producto butilado 8a ($[M+H]^+$ = 709.1) se obtuvo en forma de aceite después de evaporado el solvente (evaporación giratoria y gran cantidad de vacío).

591

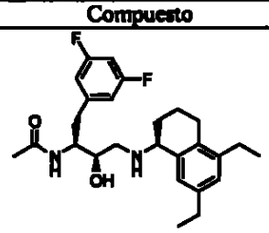
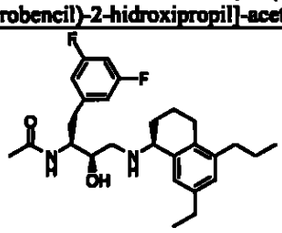
G. Preparación de N-[(*1S, 2R*)-3-((1*S*)-5-Butil-7-etil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-1-(3,5-difluorobencil)-2-hidroxipropil]-acetamida **9a**

A una solución de **8a** en 1 mL de CH_2Cl_2 se añadió 1mL de ácido trifluoroacético anhidro. Después de 1 hora, los compuestos volátiles se eliminaron con un chorro de N_2 seguido por gran cantidad de vacío para producir **9a** ($[M+H]^+ = 472.8$).

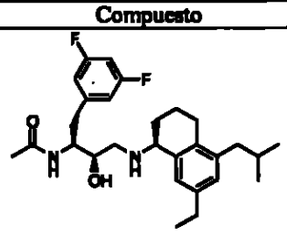
EJEMPLO 117. Procedimiento general para la preparación de los compuestos 9

Los compuestos **8** se prepararon a partir de los compuestos **7** siguiendo el procedimiento utilizado en la preparación de **8a** (G, arriba), excepto que el bromuro de butilzinc utilizado en la preparación de **8a** fue reemplazado con otros reactivos de zinc tal como se indica en la Tabla 117.A. Los grupos protectores se eliminaron de los compuestos intermedios **8** tal como se describió para la preparación de **9a** a partir de **8a**.

TABLA 117.A

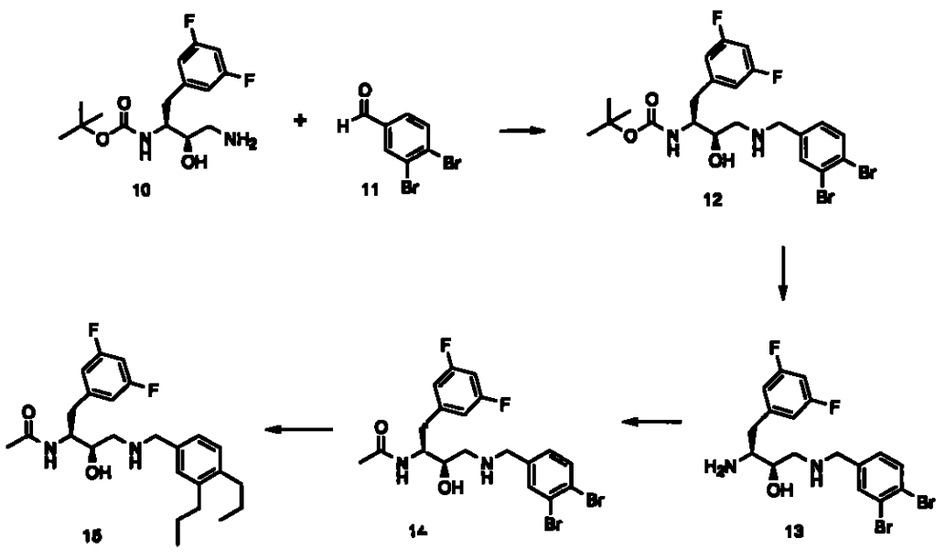
Compuesto	Reactivo	*m/z* $(M+H)^+$
 N-[(*1S, 2R*)-3-((1*S*)-5,7-Dietil-1,2,3,4-tetrahidronaftalen-1-ilamino)-1-(3,5-difluorobencil)-2-hidroxipropil]-acetamida	Et_2Zn (Dietilzinc)	444.8
 N-[1-((*1S, 2R*)-3,5-Difluorobencil)-3-((1*S*)-7-etil-5-propil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-2-hidroxipropil]-acetamida	PrZnBr (Bromuro de propilzinc)	458.8

592

Compuesto	Reactivo	*m/z* $(M+H)^+$
 N-[(*1S, 2R*)-1-(3,5-Difluorobencil)-3-((1*S*)-7-etil-5-isobutil-1,2,3,4-tetrahidronaftalen-1-ilamino)-2-hidroxipropil]-acetamida	*i*-BuZnBr (Bromuro de isobutilzinc)	472.8

EJEMPLO 118.
El esquema general 118 representa una ruta sintética que puede usarse para sintetizar el Compuesto 15.

Esquema 118



A. Preparación de [(1*S*,2*R*)-3-(3,4-Dibromobencilamino)-1-(3,5-difluorobencil)-2-hidroxipropil] tert-butil éster del ácido carbámico 12

El 3,4-dibromobenzaldehido disponible comercialmente (250mg, 0.95 mmol) y N-BOC-diamina 10 (250 mg, 0.79 mmol), se disolvieron conjuntamente en 10 mL de ácido acético al 10% en THF. Después de dejar la solución quieta a temperatura ambiente durante 30 min., se añadieron 1.7g (~3.8mmol) de MP-cianoborohidruro (un cianoborohidruro metilpoliestireno trietilamonio de Argonaut Corporation). La suspensión se agitó durante 3 h utilizando un agitador de órbita (J-

593

Kem). Posteriormente se filtró la suspensión y luego se eliminó el solvente por evaporación giratoria. El residuo se disolvió en metanol y luego se dividió en 10 alícuotas para su fraccionamiento por HPLC en fase reversa. Las fracciones que contienen el compuesto puro 12 se combinan y se procede a eliminar los compuestos volátiles por evaporación giratoria y/o aplicando vacío. El análisis de espectrometría de masas del producto final 12 produjo $[M+H]^+$ = 564.7.

B. PREPARACIÓN DE (3*S*,2*R*)-3-AMINO-1-(3,4-DIBROMO-BENCILAMINO)-4-(3,5-DIFLUOROFENIL)-BUTAN-2-OL 13

El compuesto 13 se preparó a partir del compuesto 12 utilizando el procedimiento descrito arriba para la preparación de 4 partiendo de 3. El análisis por espectrometría de masas produjo m/z = 464.8.

C. Preparación de N-[(1*S*,2*R*)-3-(3,4-Dibromobencilamino)-1-(3,5-difluorobencil)-2-hidroxi-propil]-acetamida 14

El compuesto 14 se preparó a partir del compuesto 13 utilizando el procedimiento descrito arriba para la preparación de 5 partiendo de 4. El análisis por espectrometría de masas produjo m/z = 506.8.

D. Preparación de N-[(1*S*,2*R*)-1-(3,5-Difluorobencil)-3-(3,4-dipropilbencilamino)-2-hidroxipropil]-acetamida 15

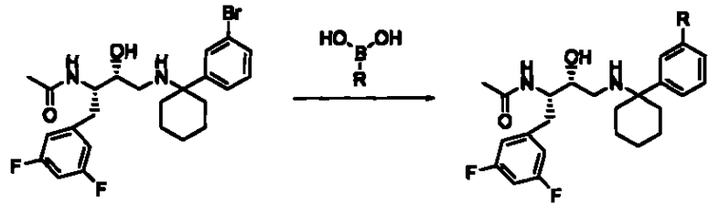
La preparación de 15 a partir de 14 se efectuó utilizando el procedimiento descrito arriba para la preparación de 8a partiendo de 7 excepto que se usó bromuro de propilzinc en lugar de bromuro de butilzinc. El análisis de espectrometría de masas del producto 13 produjo $[M+H]^+$ = 432.9).

EJEMPLO 119

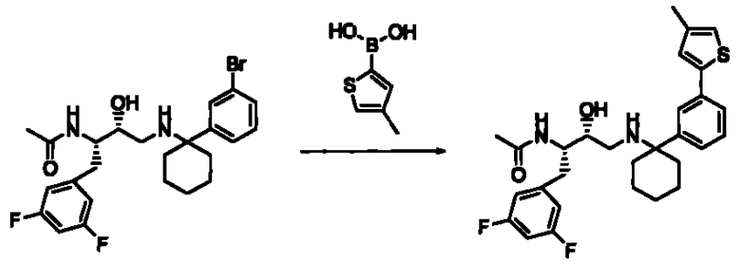
Los compuestos de la invención que comprende las fracciones ciclohexil pueden sintetizarse siguiendo el Esquema general 119.

594

Esquema 119



A. N-(*1S, 2R*)-(1-(3,5-Difluoro-bencil)-2-hidroxi-3-{1-[3-(4-metil-tiofen-2-il)-fenil]-ciclohexilamino}-propil)-acetamida



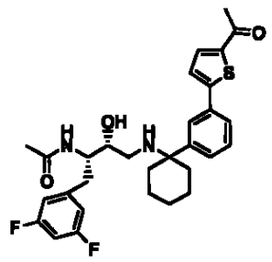
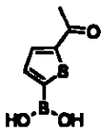
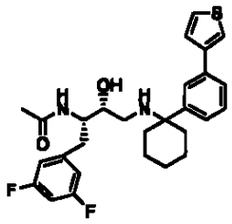
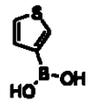
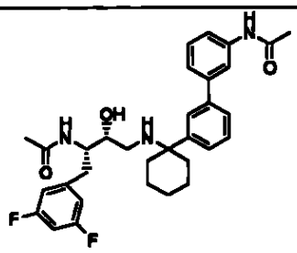
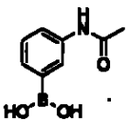
Acetato de paladio ($Pd(OAc)_2$) (0.82 mgs, 10 mol. % p/p) y se añadió Bifenil-2-il-di-tert-butil-fosfano (2.16 mgs, 20 mol. % p/p) al reactor (Recipiente 1). N-(*1S, 2R*)-[3-[1-(3-Bromo-fenil)-ciclohexilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida (0.09075 mM) se colocó en otro reactor (Recipiente 2) y se disolvió en 200 mL DME. Se añadió ácido 4-Metiltiofeno-2-borónico y Fluoruro de Potasio (KF) (3 eq., 6.33 mgs) en un reactor separado y se disolvieron en 200 µL DME (Recipiente 3). Los solventes en los Recipientes 2 y 3 se añaden al Recipiente 1 en presencia de nitrógeno. El Recipiente 1 se agitó de un día para otro a temperatura ambiente. La reacción se concentró posteriormente con vacío. El material en bruto se purificó por HPLC de preparación. Las fracciones de producto se recolectaron y concentraron con vacío. MS (ESI+) for $C_{29}H_{34}F_2N_2O_2S$ *m/z* 513.0 $(M+H)^+$

B. Compuestos adicionales.

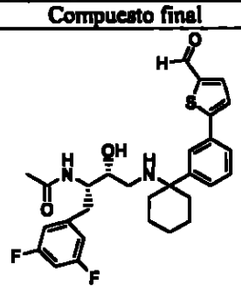
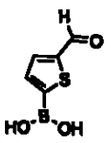
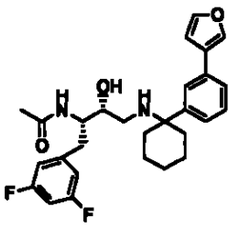
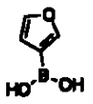
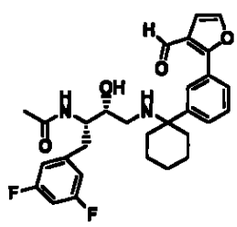
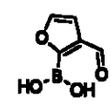
Todos los compuestos en la **Tabla 119.A** se pueden sintetizar siguiendo el mismo procedimiento aplicado en la síntesis de N-(*1S,2R*)-(1-(3,5-Difluoro-bencil)-2-hidroxi-3-{1-[3-(4-metil-thiofen-2-il)-fenil]-ciclohexilamino}-propil)-acetamida; sin embargo, en lugar del ácido 4-metiltiofeno-2-borónico, se pueden utilizar los reactivos indicados al lado de los productos finales.

595

Tabla 119.A

Compuesto final	Reactivo	*m/z* $(M+H)^+$
 *N-(1S,2R)*-[3-{1-[3-(5-Acetyl-thiophen-2-yl)-phenyl]-cyclohexylamino}-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	 5-Acetyl-2-thiophene-2-boronic acid	540.8
 *N-(1S,2R)*-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-[1-(3-thiophen-3-yl-phenyl)-cyclohexylamino]-propyl}-acetamide	 Thiophene-3-boronic acid	498.8
 *N-(1S,2R)*-[3-[1-(3'-Acetylamino-biphenyl-3-yl)-cyclohexylamino]-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-acetamide	 3-Acetamidobenzene boronic acid	549.9

596

Compuesto final	Reactivo	*m/z* $(M+H)^+$
 *N-(1S,2R)*-(1-(3,5-Difluoro-benzyl)-3-{1-[3-(5-formyl-thiophen-2-yl)-phenyl]-cyclohexyl-amino}-2-hydroxy-propyl)-acetamide	 5-Formyl-2-thiophene boronic acid	526.8
 *N-(1S,2R)*-(1-(3,5-Difluoro-benzyl)-3-[1-(3-furan-3-yl-phenyl)-cyclohexylamino] -2-hydroxy-propyl)-acetamide	 3-Furan-boronic acid	482.9
 *N-(1S,2R)*-(1-(3,5-Difluoro-benzyl)-3-{1-[3-(3-formyl-furan-2-yl)-phenyl]-cyclohexyl-amino}-2-hydroxy-propyl)-acetamide	 3-Formylfuran-2-boronic acid	510.8

Ejemplo 120.

A. Paso 1. 5-Bromo-2-iodobenzamida

597

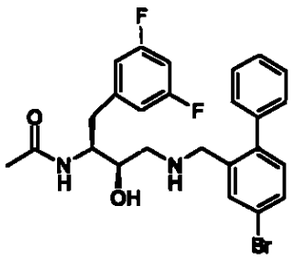
Al ácido 5-bromo-2-iodobenzóico (20g, 61.2 mmol) en una mezcla 1:1 de diclorometano y dimetilformamida (200 mL) se añadió HATU (25g, 65.8 mmol), y la solución se agitó durante 2 min. Se añadió exceso de cloruro de amonio (20 g) y la mezcla heterogénea se agitó por 1 h. Se agregó hidróxido de amonio (20 mL) produciendo un precipitado blanco. El precipitado se filtró y lavó con acetato de etilo. La solución se diluyó con acetato de etilo, se lavo con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado, y cloruro de sodio saturado, se secó (con sulfato de magnesio), se filtró y concentró bajo presión reducida resultando en la formación de un precipitado blanco. El sólido se filtró para obtener el compuesto principal (14.4 g). ESI MS *m/z* 327.0 $[M + H]^+$.

Paso 2. (4-Bromo-1,1'-bifenil-2-il)metilamina

A una solución previamente agitada de 5-bromo-2-iodobenzamida (14.1 g, 43.3 mmol), ácido fenil borónico (5.3 g, 43.3 mmol), y carbonato de potasio (24.4 g, 176.8 mmol) en dimetilformamida (rociando con nitrógeno, 100 mL), se añadió paladio(0) tetraquis(trifenilfosfina) (2.6 g, 2.2 mmol). La reacción se mantuvo a reflujo de un día para otro bajo N_2. La solución parda se enfrió y filtró a través de Celita. La solución se diluyó en acetato de etilo y agua y luego se repartió. La capa orgánica se lavó con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado y cloruro de sodio saturado, se secó (sulfato de magnesio), se filtró y posteriormente se concentró bajo presión reducida hasta quedar un alquitrán. Por cromatografía flash (sílica, 50% de acetato de etilo/hexano) produjo un sólido color canela (2.4 g). La bifenilamida se disolvió en tetrahidrofurano (20 mL), y se añadió lentamente BH_3-THF (1N, 20 mL, 20 mmol). La reacción se mantuvo a reflujo de un día para otro bajo N_2. La reacción se enfrió hasta 0°C y se enfrió rápidamente con acetato de etilo resultando en la generación de gas. Después de terminada la generación de gas, los compuestos orgánicos se lavaron con agua, bicarbonato de sodio saturado, cloruro de sodio saturado, se secaron (con sulfato de sodio), se filtraron y posteriormente concentraron para obtener el compuesto principal con apariencia de un semisólido de color gris (2.4 g). ESI MS *m/z* 262.0/264.0 $[M + H]^+$.

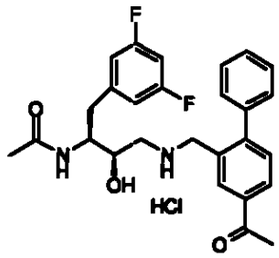
Paso 3. N-[(1S,2R)-3-{[(4-Bromo-1,1'-bifenil-2-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil] acetamida

598



A una solución de (4-bromo-1,1'-bifenil-2-il)metilamina (2.4 g, 9.2 mmol) en isopropanol (50 mL) se añadió el Ejemplo 134 (1.8 g, 6.1 mmol), y la reacción se dejó a reflujo durante 2 h. La solución se concentró y el residuo se redisolvió en acetato de etilo, se lavó con ácido clorhídrico 1 N y cloruro de sodio saturado, se secó (con sulfato de sodio), se filtró y concentró posteriormente bajo presión reducida. El residuo (3.3 g) se redisolvió en metanol y se añadió ácido clorhídrico 4 N en dioxano (5 mL). La reacción se agitó durante 30 min y luego se concentró hasta obtener una espuma color canela (3.1 g). La sal se disolvió en diclorometano (25 mL) y diisopropiletilamina (4 mL, 23 mmol), y luego se añadió acetilimidazol (636 mg, 5.8 mmol). La reacción se agitó de un día para otro a temperatura ambiente. Los compuestos orgánicos se lavaron con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado y cloruro de sodio saturado, se secaron (sulfato de magnesio), se filtraron y posteriormente se concentraron bajo presión reducida. La purificación por cromatografía flash (sílica, metanol/diclorometano al 10%) produjo el compuesto principal (550 mg). ESI MS *m/z* 504.3 $[M + H]^+$. Una pequeña cantidad del producto se disolvió en éter, se precipitó con exceso de HCl 1N en éter y se concentró para dar la sal mono-HCl .

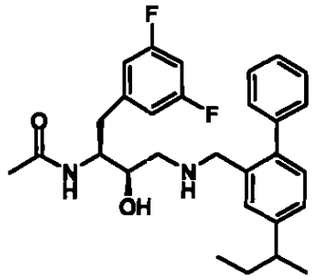
B. Paso 1. N-[(1S,2R)-3-{[(4-Acetil-1,1'-bifenil-2-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil] clorhidrato de acetamida



A N-[(1S,2R)-3-{[(4-bromo-1,1'-bifenil-2-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil] acetamida (120 mg, 0.24 mmol) en tolueno (1 mL) se añadió tributil(1-etoxivinil)estaño (100 µL, 0.28 mmol) y dicloruro de *bis*-trifenilfosfina paladio(II) (10 mg, 0.012 mmol), y la reacción se

calentó a 100°C por 3 h bajo N_2. La solución se enfrió hasta temperatura ambiente, se añadió ácido clorhídrico 1N (1 mL), y luego se agitó la mezcla durante 20 min. La mezcla se repartió y los compuestos orgánicos se lavaron con fluoruro de potasio saturado (ac.). La mezcla de reacción se secó (con sulfato de sodio), se filtró y se concentró bajo presión reducida. La purificación por cromatografía flash (sílica gel, metanol/cloruro de metileno al 8%) produjo un aceite. El residuo se disolvió en éter, se precipitó con exceso de HCL 1N en éter y se concentró para dar el compuesto principal (11 mg). ESI MS *m/z* 467.28 $[M + H]^+$.

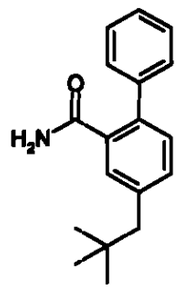
C. N-[(1S,2R)-3-{[(4-sec-Butil-1,1'-bifenil-2-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil] acetamida



A N-[(1S,2R)-3-{[(4-bromo-1,1'-bifenil-2-il)metil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil] acetamida (150 mg, 0.3 mmol) en THF (2 mL) se añadió fosfato de potasio 2M (0.65 mmol), tri-*sec* butilborano (1M en THF, 330 µL, 0.33 mmol), y dicloruro de *bis*-trifenilfosfina paladio(II) (3 mg, 0.003 mmol), y la reacción se calentó a reflujo durante 2 días. Se añadió tri-*sec* butilborano (1M en THF, 1.2 mL, 1.2 mmol), luego dicloruro de *bis*-trifenilfosfina paladio(II) (10 mg, 0.012 mmol), y la reacción se dejó a reflujo durante 16 h. La solución se diluyó en acetato de etilo y se lavó con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado y cloruro de sodio saturado. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. La cromatografía flash (metanol/diclorometano al 7%) produjo el compuesto principal. MS (ESI) $[M+H^+] = 481.34$.

D. Paso 1. 4-Neopentil-1,1'-bifenil-2-carboxamida

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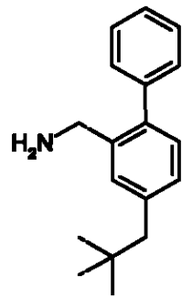


Al metil 5-bromo-2-iodobenzoato (4.41 g, 13 mmol), ácido fenilborónico (1.6 g, 13 mmol), carbonato de potasio (3.6 g, 26 mmol), y carbonato de cesio (4.2 g, 13 mmol) en DMF (50 mL, rociado con nitrógeno) se añadió paladio(0) tetraquis(trifenilfosfina) (751 mg, 0.65 mmol). La reacción se dejó a reflujó durante 16 h, se enfrió y lavó con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado y cloruro de sodio saturado. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El residuo se purificó por cromatografía flash (acetato de etilo/hexano al 5%) para producir metil 4-bromo-1,1'-bifenil-2-carboxilato (1.3 g). Al metil 4-bromo-1,1'-bifenil-2-carboxilato (500 mg, 1.72 mmol) y al $Pd(dppf)Cl_2$-CH_2Cl_2 (70 mg, 0.086 mmol) en THF (5 mL) se añadió lentamente cloruro de magnesio neopentilo 1M (5 mL, 5 mmol) a temperatura ambiente. La reacción se agitó de un día para otro y luego se enfrió rápidamente con agua. La reacción se diluyó en acetato de etilo, filtrando luego el sólido pardo resultante. La capa orgánica se lavó con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado y cloruro de sodio saturado. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El residuo se purificó por cromatografía flash (acetato de etilo/hexano al 1%) para producir un sólido amarillo (200 mg). El sólido se redisolvió en THF/metanol/agua 2:1:1 (8 mL) y se añadió hidróxido de litio monohidratado (60 mg, 1.4 mmol). La reacción se agitó durante 6 días y la solución se concentró hasta quedar seca. (Se añadieron 1.7 g de 4-bromo-1,1'-bifenil-2-carboxilato para preparar un total combinado de 1.8g de residuo producto de la hidrólisis). Los compuestos reunidos se redisolvieron en DMF (10 mL) y se añadieron diisopropiletilamina (3.7 mL, 21 mmol), HATU (4 g, 10.2 mmol) y cloruro de amonio (5 g). La reacción se agito durante 1 h. Se añadió hidróxido de amonio produciendo un precipitado blanco. El líquido se diluyó en acetato de etilo y luego se lavó con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado y cloruro de sodio saturado. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida hasta convertirse en un aceite negro. El residuo se purificó por cromatografía flash (acetato de etilo/hexano al 60%) para

601

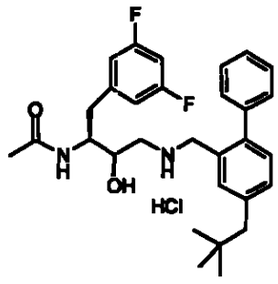
producir el compuesto principal con apariencia de un sólido color canela (210 mg) ESI MS *m/z* 268 $[M + H]^+$.

Paso 2. (4-Neopentil-1,1'-bifenil-2-il)metilamina



Al borano-THF (1M, 1.7 mL, 1.7 mmol) se añadió 4-neopentil-1,1'-bifenil-2-carboxamida (200 mg, 0.75 mmol), y la reacción se agitó a reflujo durante 16 h. La solución se dejó enfriar y luego se enfrió rápidamente con HCl 1N. La solución se basificó con bicarbonato de sodio saturado y el producto se extrajo entre acetato de etilo. Los compuestos orgánicos se lavaron con cloruro de sodio saturado, se secaron (sobre sulfato de sodio) y luego se concentraron al vacío para obtener el compuesto principal con la apariencia de un aceite (200 mg). ESI MS *m/z* 254.22 $[M + H]^+$.

Paso 3. N-((1S,2R)-1-(3,5-Difluorobencil)-2-hidroxi-3-{[(4-neopentil-1,1'-bifenil-2-il)metil]amino}propil) diacetamida, clorhidrato



A una solución de (4-Neopentil-1,1'-bifenil-2-yl)metilamina (200 mg, 0.8 mmol) en isopropanol (5 mL) se añadió el Ejemplo 134 (120 mg, 0.4 mmol), y la reacción se mantuvo a reflujo durante 2 h. La solución posteriormente se concentró y el residuo se disolvió en acetato de etilo, se lavó con ácido clorhídrico 1N y cloruro de sodio saturado, se secó (sobre sulfato de sodio), se filtró y

602

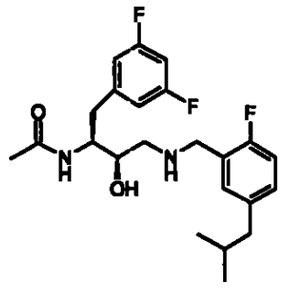
luego se concentró bajo presión reducida. El residuo se disolvió en metanol y se añadió ácido clorhídrico 4 N en dioxano (5 mL). La reacción se agitó durante 30 min y luego se concentró hasta obtener una espuma blanca (100 mg). La sal se disolvió en diclorometano (2 mL) y diisopropiletilamina (100 mL, 0.5 mmol), y luego se añadió acetilimidazol (30 mg, 0.3 mmol). La reacción se agitó durante 1 h a temperatura ambiente. Los compuestos orgánicos se lavaron con agua, ácido clorhídrico 1N, bicarbonato de sodio saturado y cloruro de sodio saturado, se secaron (sulfato de magnesio), se filtraron y posteriormente se concentraron bajo presión reducida. La purificación por cromatografía flash (sílica, metanol/diclorometano al 8%) produjo el compuesto principal (60 mg) en forma bruta.

El material se purificó por HPLC de preparación para obtener el compuesto deseado. El producto se disolvió en éter, se precipitó con exceso de HCL 1N en éter y se concentró para obtener la sal mono-HCl (6 mg). ESI MS *m/z* 495 $[M + H]^+$.

E. **Paso 1.** 2-Fluoro-5-isobutil-benzonitrilo

Al 5-bromo-2-fluorobenzonitrilo (2.3 g, 11.7 mmol) en THF (5 mL) se añadieron 0.5 M de bromuro de isobutilzinc (70 mL, 35 mmol), y luego $Pd(dppf)Cl_2$ (955 mg, 1.17 mmol), y la reacción se agitó durante 16 h a temperatura ambiente bajo N_2. La reacción se enfrió rápidamente con exceso de ácido clorhídrico acuoso (1N). Se añadió acetato de etilo y la solución se repartió. La capa orgánica se lavó con cloruro de sodio saturado. Por cromatografía flash (sílica, 4% de acetato de etilo/hexano) se produjo un sólido incoloro (1.3 g).

Paso 2

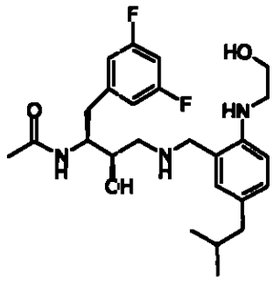


Al producto obtenido en el paso 1 (230 mg, 1.3 mmol) en THF (2 mL) se añadió lentamente borano-THF (1M, 3 mL, 3 mmol) a 0°C. La reacción se agitó durante 16 h a temperatura

603

ambiente. La solución se enfrió inicialmente y luego rápidamente con HCl 1N. La solución se basificó con bicarbonato de sodio saturado y el producto se extrajo en acetato de etilo. Los compuestos orgánicos se lavaron con cloruro de sodio saturado, se secaron (sobre sulfato de sodio) y luego se concentraron al vacío para obtener un aceite. El residuo se disolvió en isopropanol (2 mL), y se añadió el Ejemplo 134 (120 mg, 0.4 mmol) y la reacción se sometió a reflujo durante 3 h. Se añadió luego ácido clorhídrico 4 N en dioxano (5 mL), y la reacción se agitó por 1.5 h, para luego concentrarse y convertirse en una espuma blanca. El residuo se disolvió en diclorometano (5 mL) y diisopropiletilamina (678 mL, 3.9 mmol), y luego se añadió acetilimidazol (66 mg, 0.6 mmol). La reacción se agitó durante 30 min a temperatura ambiente. También se añadió acetilimidazol adicional (30 mg, 0.3 mmol). Los compuestos orgánicos se lavaron con agua, bicarbonato de sodio saturado y cloruro de sodio saturado, se secaron (sobre sulfato de magnesio), se filtraron y posteriormente se concentraron bajo presión reducida. La purificación por cromatografía flash (sílica, 8% metanol/diclorometano) produjo el compuesto principal (89 mg) con apariencia de un sólido blanco (89 mg). ESI MS *m/z* 423 $[M + H]^+$.

F. N-[(1S,2R)-1-(3,5-Difluorobencil)-2-hidroxi-3-({2-[(2-hidroxietil)amino]-5-isobutilbencil}amino)propil]acetamida



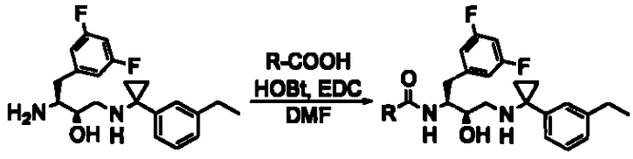
El 2-Fluoro-5-isobutil-benzonitrilo (533 g, 3 mmol) en etanolamina (5 mL) se calentó a 100°C durante 2 h en un tubo sellado. La reacción se diluyó en acetato de etilo y la capa orgánica se lavó con agua y cloruro de sodio saturado. La solución se secó (sobre sulfato de sodio), se filtró y se concentró hasta obtener un aceite. El residuo se redisolvió en THF (3 mL) y esta solución se añadió al borano-THF (9 mL) a 0°C. La reacción se agitó a temperatura ambiente durante 16 h. La solución se vertió sobre hielo y se añadió acetato de etilo. La parte orgánica se repartió y lavó con cloruro de sodio saturado, se secó (sobre sulfato de sodio), se filtró y se concentró hasta obtener un aceite (220 mg). El residuo se disolvió en isopropanol (5 mL), se añadió 2-Fluoro-5-isobutil-benzonitrilo (160 mg, 0.5 mmol) y la reacción se mantuvo a reflujo durante 2 h. La

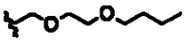
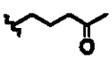
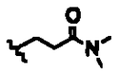
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reacción se enfrió y concentró posteriormente. La cromatografía flash (sílica, 8% metanol/diclorometano) produjo un aceite (108 mg). El residuo se trató con ácido clorhídrico 4 N en dioxano (5 mL) y la reacción se agitó durante 1 h para luego concentrarla hasta obtener un sólido blanco. El residuo se disolvió en diclorometano (5 mL) y diisopropiletilamina (108 mL, 3.9 mmol), y luego se añadió acetilimidazol (44 mg, 0.6 mmol). La reacción se agitó durante 30 min a temperatura ambiente. Los compuestos orgánicos se lavaron con agua, bicarbonato de sodio saturado y cloruro de sodio saturado, se secaron (sobre sulfato de magnesio), se filtraron y posteriormente se concentraron bajo presión reducida. La purificación por cromatografía flash (sílica, 8% metanol/diclorometano) produjo el compuesto principal (18 mg) con apariencia de un aceite (18 mg). ESI MS *m/z* 464.34 $[M + H]^+$.

EJEMPLO 121.

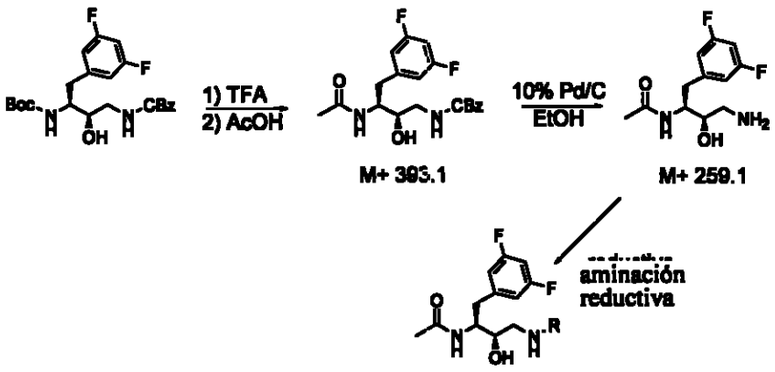
La síntesis de estos compuestos se realizó con condiciones de unión previamente descritas, excepto con la variación de materiales de origen de ácido carboxílico tal y como se señala más abajo.

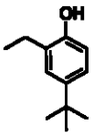
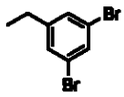


R =	MH+		
	445.2	(1S,2R) ácido pentanoico {1-(3,5-difluoruro-bencil)-3-[1-(3-etil-fenil)-ciclopropilamino]-2-hidroxi-propil}-amida	(82)
	473.3	(1S,2R) ácido heptanoico {1-(3,5-difluoruro-bencil)-3-[1-(3-etil-fenil)-ciclopropilamino]-2-hidroxi-propil}-amida	(83)
			(84)
	485.3	(1S,2R) 2-ciclohexil-N-{1-(3,5-difluoruro-bencil)-3-[1-(3-etil-fenil)-ciclopropilamino]-2-hidroxi-propil}-acetamida	(85)
	519.2	(1S,2R) 2-(2-butoxi-etoxi)-N-{1-(3,5-difluoruro-bencil)-3-[1-(3-etil-fenil)-ciclopropilamino]-2-hidroxi-propil}-acetamida	(86)
	473.2	(1S,2R) 5-oxo-ácido hexanoico{1-(3,5-difluoruro-bencil)-3-[1-(3-etil-fenil)-ciclopropilamino]-2-hidroxi-propil}-amida	(87)

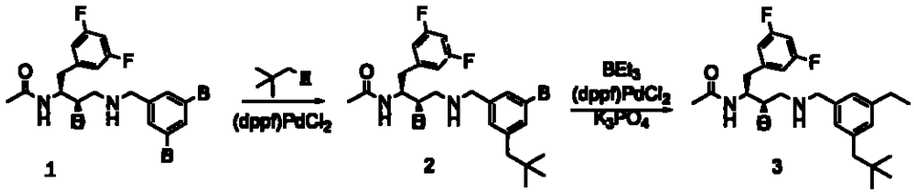
A. Preparación de derivados de bencilamina disustituida

605



R =	M+	
	421.2	(1S,2R) N-[3-(5-terc-butil-2-hidroxi-bencilamino)-1-(3,5-difluorobencil)-2-hidroxi-propil]-acetamida
	506.9	(1S,2R) N-[3-(2,5-dibromo-bencilamino)-1-(3,5-difluorobencil)-2-hidroxi-propil]-acetamida

B. Preparación de [(1S,2R) N-[3-[3-bromo-5-(2,2-dimetil-propil)-bencilamino]-1-(3,5-difluoro-bencil)-2-(hidroxi-propil]acetamida] 2 y [(1S,2R) N-{1-(3,5-difluoro-bencil)-3-[3-(2,2-dimetil-propil)-5-etil-bencilamino]-2-hidroxi-propil}-acetamida] 3



A la dibromobencilamina (1S,2R) N-[3-(2,5-dibromo-bencilamino)-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida 1 (0,504 g, 1,0 mM, 1 eq.) se añadió una solución de 0,5 M de THF yoduro de neopentilcinc (20 mL, 10 eq.) y (0,082 g, 0,1 mM, 0,1 eq.) de [1,1'-bis(difenilfosfino)ferroceno)dicloropaladio(II), complejo con diclorometano $Pd(dppf)Cl_2$ CH_2Cl_2]. Se removió una mezcla de reacción a temperatura ambiente durante la noche. El siguiente día se templó con solución saturada acuosa de NH_4Cl (20 mL) y se extrajo con acetato de etilo (3 x 30 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron y se concentraron. El producto resultante, 2, se purificó por HPLC; producción de 0,055 g (11%). ^1H NMR (300 MHz, DMSO-d_6) δ 8,60-9,00 (m, 1H), 7,88 (d, J = 8,7 Hz, 1H), 7,61 (s, 1H), 7,39 (s,

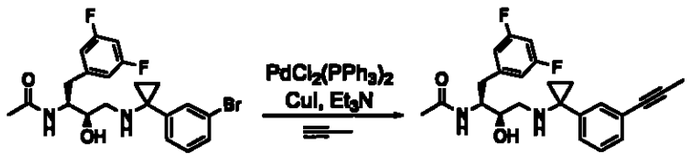
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1H), 7,08 (s, 1H), 7,05 (t, J = 7,5 Hz, 1H), 6,93 (d, J = 6,9 Hz, 2H), 4,16 (bs, 2H), 3,85 (m, 1H), 3,70 (m, 1H), 3,02 (m, 2H), 2,81 (m, 1H), 2,57 (m, 1H), 2,47 (s, 2H), 1,69 (s, 3H), 0,87 (s, 9H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 170,0, 164,4, 164,2, 161,1, 160,9, 144,2, 142,9, 134,2, 133,9, 131,8, 131,0, 121,6, 112,9, 112,6, 102,2, 69,3, 53,5, 50,1, 49,1, 35,4, 32,1, 29,6, 23,0; MH+ (CI): 497.2.

C. El compuesto 3 [(1S,2R) N-[1-(3,5-difluorobencil)-3-[3-(2,2-dimetilpropil)-5-etil-bencilamino]-2-hidroxipropil]-acetamida] se preparó mediante el método descrito anteriormente: MH+ (CI): 447.2.

D. Preparación de [(1S,2R) N-[1-(3,5-difluorobencil)-2-hidroxi-3-[1-(3-prop-1-inil-fenil)-ciclopropilamino[-propil}-acetamida] 5

A una solución de (1S,2R) N-[3-[1-(3-bromo-fenil)-ciclopropilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida 4 (0,227 g, 0,5 mM) en Et_3N (2 mL) y DMF (0,5 mL) se añadió $PdCl_2(PPh_3)_2$. Una mezcla de reacción se enfrió a –30°C y se burbujeó en ella gas propeno durante 1 minuto. Se cerró un tubo de reacción y la mezcla se removió durante 2 min. antes de que se añadiera CuI (0,001 g). Tras remover durante 10 min. adicionales en un tubo cerrado a temperatura ambiente el color de la mezcla de reacción cambió del amarillo al marrón oscuro. La reacción se calentó a 50°C durante 48 hrs., se enfrió a temperatura ambiente, se filtró y se le quitó el disolvente. Purificada por HPLC; producción de 0,030 g (15%); MH+ (CI): 413.2.

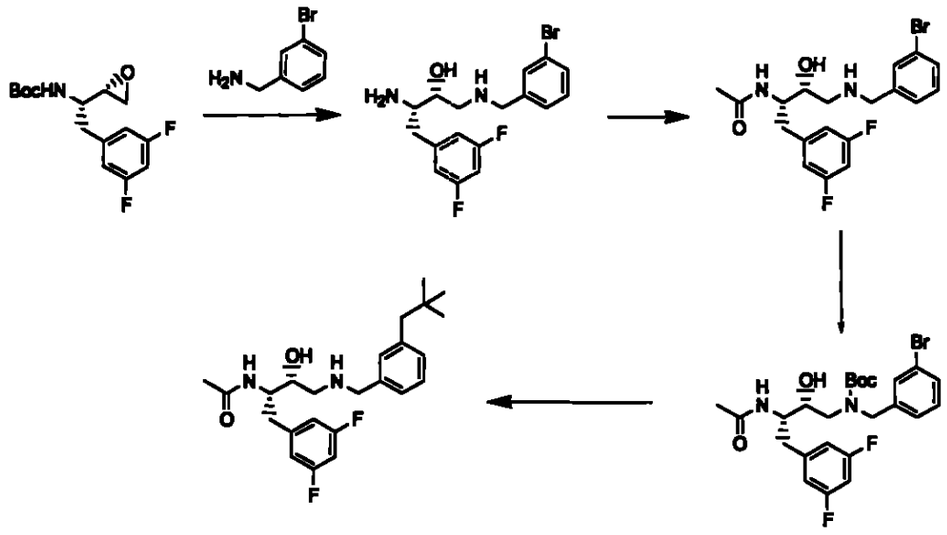


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EJEMPLO 122. Síntesis de N-(1S-2R)-{1-)(3,5-difluoro-bencil)-3-[3-(2,2-dimetil-propil)bencilamino]-2-hidroxi-propil)acetamida

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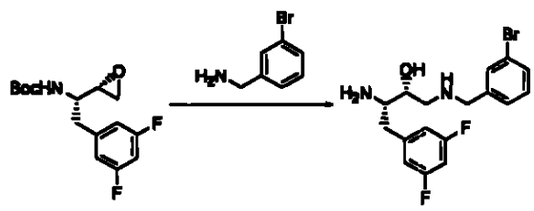
ESQUEMA GENERAL 122



A. 3-bromo-bencilamina

Una sal 3-bromo-bencilamina HCl (0,75 g) se disolvió en 10 mL de IPA al 15% en CH_2Cl_2. Se añadieron 7 gotas de 10N hidróxido de sodio (NaOH) y se removió durante 3 minutos. A la mezcla de reacción, se añadieron 5 mL de dH_2O y se removió durante 5 minutos. Se extrajo la capa de IPA/CH_2Cl_2. La capa acuosa se enjuagó con 10 mL de IPA al 15% en CH_2Cl_2. Todas las capas orgánicas se juntaron y se concentraron al vacío. MS (ESI+) para C_7H_8BrN *m/z* 186,3 $(M+H)^+$

B. (*1S,2R*)-3-amino-1-(3-bromobencilamino)-4-(3,5-difluorofenil)butan-2-ol



Se añadió (*1S, 2R*)-[2-(3,5-difluoro-fenil)-1-oxiranil-etil]-ácido carbámico terc-butil éster (0,32 g, 1,075 mM) a un tubo cerrado junto con 3-bromo-bencilamina (0,2 g, 1,075 mM). Se añadieron 2 mL de IPA al tubo cerrado. La mezcla de reacción se removió y calentó a 80°C durante 2 horas.

609
608

Una vez terminada la reacción, la mezcla de reacción se concentró por vacío. El producto se disolvió entonces en 750 mL de 4N HCl en dioxano. Se dejó reposar durante 1 hora y se concentró después vacío. MS (ESI+) para $C_{17}H_{19}BrF_2N_2O$ *m/z* 387,1 $(M+H)^+$

C. N-(*1S,2R*)-[3-(3-BROMOBENCILAMINO)-1-(3,5-DIFLUOROBENCIL)-2-HIDROXIPROPIL]ACETAMIDA

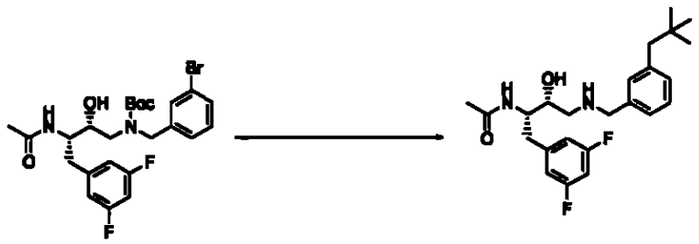
Se disolvió (*1S, 2R*)-3-amino-1-(3-bromo-bencilamino)-4-(3,5-difluoro-fenil)-butan-2-ol (0,348 g, 0,9040 mM) en 9 mL de CH_2Cl_2. Se añadió N-metilmorfolina (NMM)(0,4114 g, 4,0679 mM) a la mezcla de reacción. La mezcla de reacción se enfrió a 0°C y se removió durante 15 minutos. Se añadió lentamente ácido acético (0,057 g, 0,9944 mM) a la mezcla de reacción y se removió durante 5 minutos. Se añadió entonces HOBt (0,134 g, 0,9944 mM), después EDC (0,190 g, 0,9944 mM). La mezcla de reacción se removió a temperatura ambiente durante dos días. Una vez terminada la reacción, se retiró el disolvente por vacío. El material crudo se purificó en una columna de anhídrido silícico utilizando metanol al 10% en CH_2Cl_2. MS (ESI+) para $C_{19}H_{21}BrF_2N_2O_2$ *m/z* 427,2 $(M+H)^+$

D. **(*1S,2R*)-[3-acetilamino-4-(3,5-difluorofenil)-2-hidroxibutil]-(3-bromobencil)-ácido carbámico terc-butil éster**

SE DISOLVIÓ N-(*1S, 2R*)-[3-(3-BROMO-BENCILAMINO)-1-(3,5-DIFLUORO-BENCIL)-2-HIDROXI-PROPIL]-ACETAMIDA (0,10 G, 0,234 MM) EN CH_2CL_2 (2,3 ML, 0,1 M). LA REACCIÓN SE ENFRIÓ A 0°C. SE AÑADIÓ LENTAMENTE DICARBONATO DE DI-TERC-BUTILO (BOC_2O)(0,051 G, 0,234 MM) A LA REACCIÓN. SE DEJÓ REMOVER LA REACCIÓN A TEMPERATURA AMBIENTE DURANTE LA NOCHE. SE CONCENTRÓ DESPUÉS LA REACCIÓN POR VACÍO. MS (ESI+) PARA $C_{24}H_{29}BRF_2N_2O_4$ *M/Z* 529,1 $(M+H)^+$

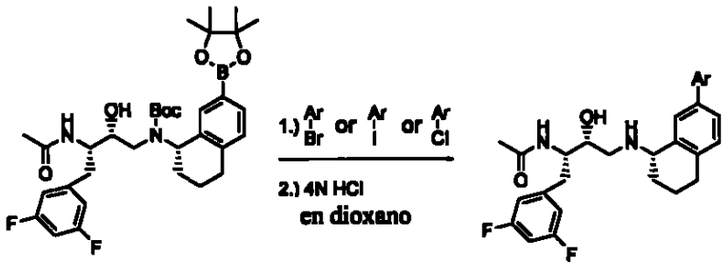
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E. N-(*1S,2R*)-{1-(3,5-DIFLUORO-BENCIL)-3-[3-(2,2-DIMETHIL-PROPIL)-BENCILAMINO]-2-HIDROXI-PROPIL}-ACETAMIDA



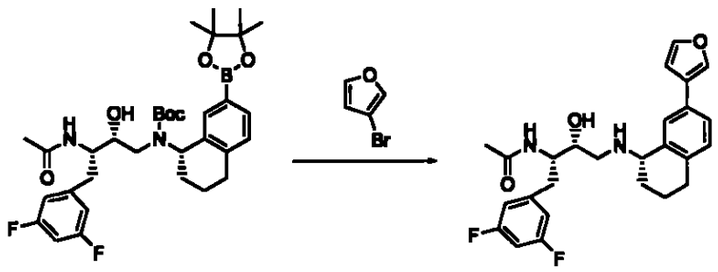
Se añadieron 1-yodo-2,2-dimetil-propano (1,5 eq., 0,0579 g, 0,2926 mM) y metal de cinc (1,6 eq., 0,0204 g, 0,3122 mM) a un tubo cerrado secado en el horno (con tabiques de goma para la parte superior). Se añadieron 2 mL de THF al tubo cerrado. La reacción se removió durante 30 minutos bajo nitrógeno. Se añadió 1-metil-2-pirrolidinona (secada con tamices moleculares) (0,43 mL) a la mezcla de reacción. Se añadieron a la mezcla de reacción bis(tri-t-butilfosfina) paladio [0] (0,15 eq., 0,0149 g, 0,02926 mM) y N-(*1S, 2R*)-[3-acetilamino-4-(3,5-difluoro-fenil)-2-hidroxi-butil]-(3-bromo-bencil)-ácido carbámico terc-butil éster (0,1029 g, 0,1951 mM). Se añadió la tapa de rosca al tubo cerrado. La reacción se calentó a 100ºC durante la noche. La mezcla de reacción se enfrió después a temperatura ambiente y se transfirió a un embudo de decantación. La mezcla de reacción se diluyó con 10 mL de acetato de etilo. La capa orgánica se lavó una vez con 7 mL de dH_2O y una vez con 7 mL de salmuera. La capa orgánica se secó con sulfato de magnesio, se filtró, y se concentró al vacío. El producto se disolvió entonces en 500 mL 4N HCl y se dejó reposar durante 1 hora. La reacción se concentró por vacío y se purificó por HPLC preparativo. MS (ESI+) para $C_{24}H_{32}F_2N_2O_2$ *m/z* 419,2 $(M+H)^+$

Ejemplo 123: Síntesis general para N-(*1S, 2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-(*1S*)-(1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida



610

Ejemplo 124: Síntesis general para N-(*1S, 2R*)-[1-(3,5-difluoro-bencil)-3-((*1S*)-7-furan-3-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-2-hidroxi-propil]-acetamida



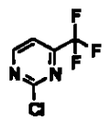
Se disolvieron 3-bromofurano (4,85 mgs, 0,033 mM) y Tetraquis(trifenil-fosfina)paladio [0] (3,81 mgs, 10 mol. %peso) en 300 mL 1,2-dimetoxietano (glima) (DME). Se añadieron 99 mL 2M Na_2CO_3 en dH_2O a la mezcla de reacción. Se añadió *N*-(*1S, 2R*)-[3-acetilamino-4-(3,5-difluoro-fenil)-2-hidroxi-butil]-[7-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-(*1S*)-1,2,3,4-tetrahidro-naftalen-1-il]- ácido carbámico terc-butil éster (20,28 mgs, 0,033 mM) a la mezcla de reacción y se removió a 90°C durante la noche. La mezcla de reacción se concentró al vacío y después se disolvió en 1,5 mL de metanol. La mezcla de reacción se purificó por HPLC preparativo. El producto aislado se concentró por vacío. El producto se disolvió en 500 mL de 4N HCl en dioxano y se dejó reposar a temperatura ambiente durante 30 minutos. Se concentró después la mezcla de reacción por vacío. MS (ESI+) para $C_{25}H_{28}F_2N_2O_3$ *m/z* 455,2 $(M+H)^+$

Todos los compuestos finales en la Tabla 124.A pueden sintetizarse utilizando el mismo procedimiento que el utilizado para N-(*1S, 2R*)-[1-(3,5-difluoro-bencil)-3-((*1S*)-7-furan-3-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-2-hidroxi-propil]-acetamida; sin embargo en lugar de 3-bromofuran, se utilizaron los reactivos enumerados al lado de los productos finales.

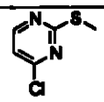
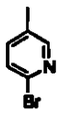
Tabla 124.A

Reactivo	Compuesto final	*m/z* $(M+H)^+$

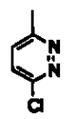
611

Reactivo	Compuesto final	*m/z* $(M+H)^+$
 3-Bromo-4-methyl-thiophene 3-bromo-4-metil-tiofeno	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(4-metil-tiofen-3-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	485.1
 5-Iodo-1-methyl-1*H*-imidazole 5-yodo-1-metil-1 *H*-imidazol	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(3-metil-3H-imidazol-4-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	469.2
 2-Bromo-pyrimidine 2-bromo-pirimidina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-pirimidin-2-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	467.2
 2-Chloro-4-trifluoromethyl-pyrimidine 2-cloro-4-trifluorometil-pirimidina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(4-trifluorometil-pirimidin-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	535,2
	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(2-metilsulfanil-pirimidin-4-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	513,2

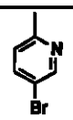
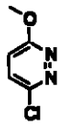
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Reactivo	Compuesto final	*m/z* $(M+H)^+$
 4-Chloro-2-methylsulfanyl-pyrimidine 4-cloro-2-metilsulfanil-pirimidina		
 5-Bromo-pyrimidine 5-bromo-pirimidina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-pirimidin-5-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	467,2
 2-Iodo-pyridine 2-yodo-piridina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-piridin-2-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	466,6
 2-Bromo-5-methyl-pyridine 2-bromo-5-metil-piridina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(5-metil-piridin-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	480,2
	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-piridin-3-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	466,2

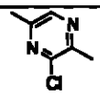
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Reactivo	Compuesto final	*m/z* $(M+H)^+$
 3-Iodo-pyridine 3-yodo-piridina		
 2-Bromo-3-methyl-pyridine 2-bromo-3-metil-piridina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(3-metil-piridin-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	480,3
 3-Chloro-6-methyl-pyridazine 3-cloro-6-metil-piridazina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(6-metil-piridazin-3-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	481,2
 4-Iodo-pyridine 4-yodo-piridina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-piridin-4-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	466,2
	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(6-metil-piridin-3-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	480,2

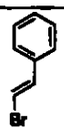
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Reactivo	Compuesto final	*m/z* $(M+H)^+$
 5-Bromo-2-methyl-pyridine 5-bromo-2-metil-piridina		
 3-Chloro-6-methoxy-pyridazine 3-cloro-6-metoxi-piridazina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(6-metoxi-piridazin-3-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	497,2
 3-Bromo-4-methyl-pyridine 3-bromo-4-metil-piridina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(4-metil-piridin-3-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	480,2
 2-Chloro-pyrazine 2-cloro-pirazina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-pirazin-2-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	467,2
	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(3,6-dimetil-pirazin-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-2-	495,3

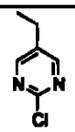
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Reactivo	Compuesto final	*m/z* $(M+H)^+$
 3-Chloro-2,5-dimethyl-pyrazine 3-cloro-2,5-dimetil-pirazina	hidroxi-propil}-acetamida	
 2-Bromo-5-methyl-thiophene 2-bromo-5-metil-tiofeno	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(5-metil-tiofen-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	485,2
 2-Bromo-furan 2-bromo-furan	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-furan-2-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-2-hidroxi-propil]-acetamida	455,2
 2-Bromo-thiazole 2-bromo-tiazol	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-tiazol-2-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	472,2
 3-Bromo-thiophene 3-bromo-tiofeno	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-tiofen-3-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	471,2

616

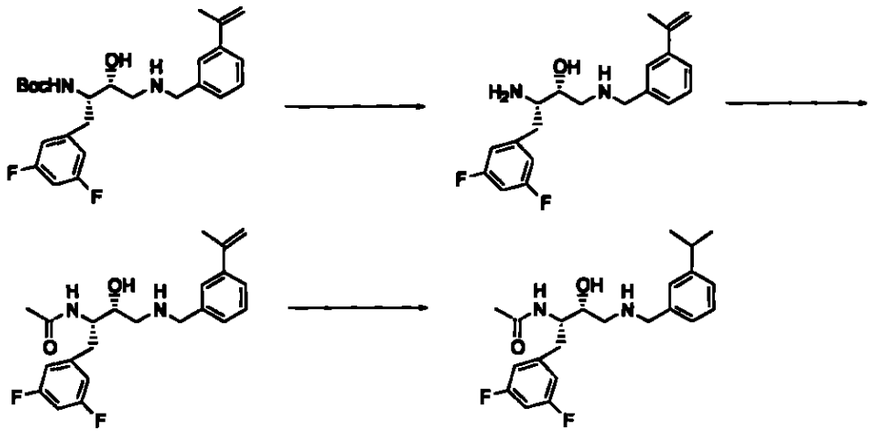
Reactivo	Compuesto final	*m/z* $(M+H)^+$
 (2-Bromo-vinyl)-benzene (2-bromo-vinil) benceno	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-estiril-3-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	491,2
 4-Iodo-3,5-dimethyl-isoxazole 4-yodo-3,5-dimetil-isoxazol	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(3,5-dimetil-isoxazol-4-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-2-hidroxi-propil}-acetamida	484,1
 2-Iodo-1-methyl-1*H*-Imidazole 2-yodo-1-metil-1*H*-imidazol	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(1-metil-1H-imidazol-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	469,2
 2-Bromo-thiophene 2-bromo-tiofeno	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-tiofen-2-il-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	471,2
	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(3-metil-tiofen-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	4852

617

Reactivo	Compuesto final	*m/z* $(M+H)^+$
 2-Bromo-3-methyl-thiophene 2-bromo-3-metil-tiofeno		
 2-Chloro-5-ethyl-pyrimidine 2-cloro-5-etil-pirimidina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(5-metil-pirimidin-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-2-hidroxi-propil}-acetamida	495,2
 2-Bromo-4-methyl-pyridine 2-bromo-4-metil-piridina	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-[7-(4-metil-piridin-2-il)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-propil}-acetamida	480,2
 2-Bromo-propene 2-bromo-propeno	N-(1S, 2R) -{1-(3,5-difluoro-bencil)-2-hidroxi-3-(1S)-(7-isopropenil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida	429,1

Ejemplo 125: Síntesis de N-(*1S, 2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-(3-isopropenil-bencilamino)-propil]-acetamida y N-(*1S,2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-(3-isopropil-bencilamino)-propil]-acetamida

618



A. (*1S,2R*)-3-amino-4-(3,5-difluoro-fenil)-1-(3-isopropenil-bencilamino)-butan-2-ol

Se disolvió (*1S,2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-(3-isopropenil-bencilamino)-propil]-ácido carbámico terc-butil éster en 6 mL de CH_2Cl_2 con 600 mL de TFA. La mezcla de reacción se removió durante 4 horas a temperatura ambiente. Se añadieron 15 mL de IPA al 15% en cloroformo a la mezcla de reacción y se lavó con 10 mL de bicarbonato sódico saturado ($NaHCO_3$ sat.) en dH_2O. La capa de $NaHCO_3$ sat. en dH_2O se enjuagó con IPA al 15% en cloroformo. Se combinaron todas las capas orgánicas y se secaron con carbonato de magnesio, se filtraron y se concentraron al vacío. MS (ESI+) para $C_{20}H_{24}F_2N_2O$ *m/z* 347,4 $(M+H)^+$

B. N-(*1S,2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-(3-isopropenil-bencilamino)-propil]-acetamida

Se disolvió (*1S, 2R*)-3-amino-4-(3,5-difluoro-fenil)-1-(3-isopropenil-bencilamino)-butan-2-ol (0,479 g, 0,1366 mM) en 13 mL de CH_2Cl_2. Se añadió N-metilmorfolina (NMM)(4,5 eq., 0,6148 mM) a la mezcla de reacción. La mezcla de reacción se enfrió a 0°C y se removió durante 15 minutos. Se añadió lentamente ácido acético (1,1 eq., 0,1502 mM) a la mezcla de reacción y se removió durante 5 minutos más. Se añadió entonces HOBt (1,1 eq., 0,1502 mM), después EDC (1,1 eq., 0,1502 mM). Se removió la reacción a temperatura ambiente durante la noche. Una vez terminada la reacción, se retiró el disolvente por vacío. Se aumentó el material crudo añadiendo 25 mL de acetato de etilo. Se lavó el acetato de etilo tres veces con 10 mL de $NaHCO_3$ sat. y se lavó una vez con 10 mL de salmuera. La capa orgánica se secó con sulfato de magnesio y se

620

619

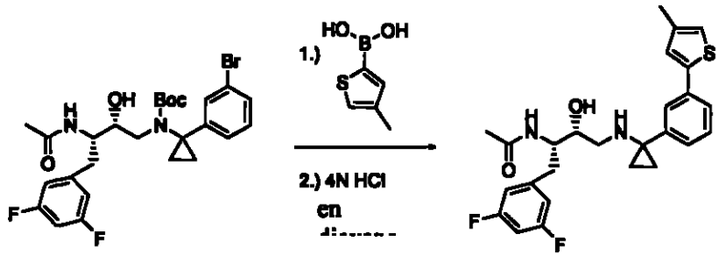
filtró. El disolvente orgánico se concentró entonces utilizando un vacío. El material crudo se purificó en gel de anhídrido silícico utilizando metanol al 5% en CH_2Cl_2. MS (ESI+) para $C_{22}H_{26}F_2N_2O_2$ *m/z* 389,5 $(M+H)^+$

C. N-(*1S,2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-(3-isopropil-bencilamino)-propil]-acetamida

Se disolvió N-(*1S,2R*)-[1-(3,5-difluoro-bencil)-2-hidroxi-3-(3-isopropenil-bencilamino)-propil]-acetamida (0,036 g) en 2 mL de metanol. Se añadió al vial Pd/C al 5% (0,004 g). la reacción se hidrógeno a 50 psi durante 4 horas. La mezcla de reacción se filtró y el filtrado se concentró utilizando un vacío. MS (ESI+) para $C_{22}H_{28}F_2N_2O_2$ *m/z* 391,4 $(M+H)^+$

Ejemplo 126:

N-(*1S,2R*)-(1-(3,5-difluoro-bencil)-2-hidroxi-3-{1-[3-(4-metil-tiofen-2-il)-fenil]-ciclopropilamino}-propil)-acetamida

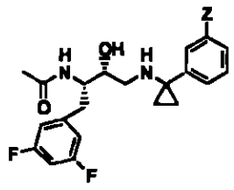


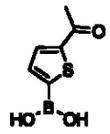
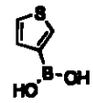
Se añadieron acetato de paladio ($Pd(OAc)_2$) (0,82 mgs, 10 mol. %peso) y bifenil-2-il-di-terc-butil-fosfano (2,16 mgs, 20 mol. %peso) al recipiente de reacción (Recipiente 1). El N-(*1S, 2R*)-[3-acetilamino-4-(3,5-difluoro-fenil)-2-hidroxi-butil]-[1-(3-bromo-fenil)-ciclopropil]- ácido carbámico terc-butil éster (13,88 mgs, 0,09075 mM) se colocó en un recipiente de reacción separado (Recipiente 2) y se disolvió en 200 mL de DME. Se añadieron 4-metiltiofeno-2-ácido borónico y fluoruro de potasio (KF) (3 eq., 6,33 mgs) en un recipiente de reacción separado y se disolvieron en 200 mL de DME (Recipiente 3). Los disolventes en los recipientes 2 y 3 se añadieron al recipiente 1 bajo nitrógeno. El recipiente 1 se removió durante la noche a temperatura ambiente. Se concentró después la reacción por vacío. Material crudo purificado por HPLC preparativo. Se recogieron fracciones de producto y se concentraron por vacío. El producto se disolvió entonces en 500 mL de 4N HCl en dioxano. Se dejó reposar durante 30

minutos a temperatura ambiente. Se concentró después la mezcla de reacción por vacío. MS (ESI+) para $C_{26}H_{28}F_2N_2O_3S$ *m/z* 471,2 $(M+H)^+$

Todos los compuestos en la Tabla 126.A pueden sintetizarse utilizando el mismo procedimiento general que el utilizado en la síntesis del Ejemplo 126, que representa: el derivado de ácido borónico que se utilizó, la masa del producto, y el nombre del producto.

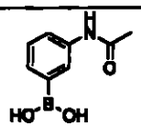
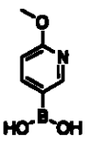
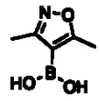
Tabla 126.A



Ejemplo nº	Z	*m/z* $(M+H)^+$	Producto
127	 5-Acetyl-2-thiophene-2-boronic acid 5-acetil-2-tiofeno-2-ácido borónico	499,2	N-(1S,2R)-[3-{1-[3-(5-acetil-tiofen-2-il)-fenil]-ciclopropilamino}-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida
128	 Thiophene-3-boronic acid Tiofeno-3-ácido borónico	457,2	N-(1S,2R)-{1-(3,5-difluoro-bencil)-2-hidroxi-3-[1-(3-tiofen-3-il-fenil)-ciclopropilamino]-propil}-acetamida
129		508,1	N-(1S,2R)-[3-[1-(3'-acetilamino-bifenil-3-il)-ciclopropilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida

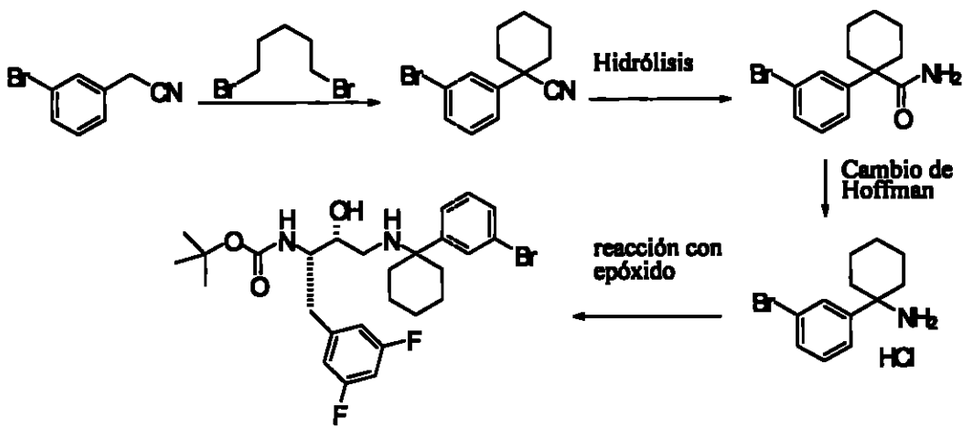
622

621

Ejemplo nº	Z	*m/z* $(M+H)^+$	Producto
	 3-Acetamidobenzene boronic acid 3-acetamidobenceno ácido borónico		
130	 2-Methoxy-5-pyridine bornonic acid 2-metoxi-5-piridina ácido borónico	482,3	N-(*1S,2R*)-(1-(3,5-difluoro-bencil)-2-hidroxi-3-{1-[3-(6-metoxi-piridin-3-il)-fenil]-ciclopropilamino}-propil)-acetamida
131	 3-Furan-boronic acid 3-furan-ácido borónico	441,2	N-(1S,2R)-{1-(3,5-difluoro-bencil)-3-[1-(3-furan-3-il-fenil)-ciclopropilamino]-2-hidroxi-propil}-acetamida
132	 3,5-Dimethyl isoxazole-4-boronic acid 3,5-dimetil isoxazol-4-ácido borónico	470,2	N-(1S,2R)-(1-(3,5-difluoro-bencil)-3-{1-[3-(3,5-dimetil-isoxazol-4-il)-fenil]-ciclopropilamino}-2-hidroxi-propil)-acetamida

622

Ejemplo 133:



Se obtuvo 3-bromobencilnitrilo de Kimera. Se obtuvo polvo de KOH de Oxechem. Otros reactivos eran de Aldrich.

Paso 1: 1-(3-bromofenil)ciclohexanecarbonitrilo

A un matraz de tres bocas con fondo redondo de 5 L equipado con entrada de N_2, sonda de temperatura, embudo adicional, y agitador mecánico se añadió 3-bromobencilnitrilo (297 g, 1,51 mol, 1,0 eq.) y THF (2,75 L). La solución clara se enfrió a 0-5°C por medio de un baño de hielo. Se pesó KO*t*Bu (374 g, 3,33 mol, 2,2 eq.) dentro de la guantera en un matraz con fondo redondo de 200 mL y se añadió a la solución clara fría poco a poco. La primera inyección (71,1 g) se añadió durante 30 segundos y se observó una temperatura inmediata exotérmica de 9°C junto con un cambio de color de una solución clara a una solución naranja/marrón. Tras esperar durante 15 min. para que la solución se enfriara a 5,1°C, se añadió la segunda inyección (96,0 g) y se observó una temperatura exotérmica de 6,5°C. Después de otros 15 min., se añadió la tercera inyección y se observó una temperatura exotérmica de 5°C. Después de otros 15 min., se añadió la cuarta y última inyección y se observó una temperatura exotérmica de 3,8°C. La solución naranja/marrón se removió en baño de hielo durante 30 min. a raíz de lo cual la solución se espesó. Si se añade cuidadosamente 1,5-dibromopentano (365,5 g, 1,56 mol, 1,05 eq.) a la mezcla naranja/marrón a un ritmo tal como para mantener la temperatura de reacción <15°C. La reacción cambiará de una solución a un lodo marrón y la temperatura exotérmica seguirá ascendiendo durante la adición. La adición exigió alrededor de 2 horas. El embudo de adición se enjuagó con THF (250 mL) y se añadió al lodo marrón. El baño de hielo se quitó después y el lodo se autocalentó a

623

temperatura ambiente mientras se mantenía la agitación media. Se sacó una muestra del lodo después de una hora removiendo. El GC indicaba la terminación con sólo exceso de 1,5-dibromopentano y producto. El lodo marrón claro se filtró entonces en una almohadilla de celite para quitar las sales. El pan se enjuagó con THF (aproximadamente 2 L) hasta quedar claro. Se añadió entonces hielo (aproximadamente 1 L en volumen) al filtrado burdeos y se removió a temperatura ambiente durante la noche. La mezcla se concentró entonces para quitar el THF y la resultante mezcla marrón bifásica se extrajo con EtOAc y solución saturada de NaCl. Las capas orgánicas naranjas se secaron con Na_2SO_4 anhidro, se filtraron y se enjuagaron con EtOAc. El filtrado naranja se concentró entonces hasta secarse para dar un aceite rojo. Se añadió EtOAc (100 mL) para redisolver al aceite. Removiendo a velocidad media, se añadió heptano (2 L) durante 1-2 min. a raíz de lo cual el aceite burdeos se pegó al fondo y a los lados del matraz. La solución amarilla se trasvasó entonces cuidadosamente desde el aceite pegajoso y se concentró hasta secarse para dar un aceite naranja claro (379,7 g, 95% de la producción). El GC de aceite naranja claro indicó exceso de 1,5-dibromopentano (2,8% área), producto (95,3% área), y otros 7 picos con menos de 0,5% área (total = 1,9% área).

<u>Condiciones del GC</u> 15m DB5 0,25 × 0,25 micron; Temp. Inic. = 75° C, Inic. Tiempo = 5 min, Ritmo = 15° C/min, Temp. Final = 275° C, Tiempo final = 2 min, Temp. Iny. = 275° C, Temp. det. = 250° C; 1,5-dibromopentano RT = 6,35 min, Prod. RT = 13,47 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7,62 (s, 1H), 7,45 (d, 2H), 7,26 (t, 1H), 2,14 (d, 2H), 1,74-1,88 (m, 6H), 1,26-1,29 (m, 2H). ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 143,63, 130,98, 130,40, 128,73, 124,41, 122,94, 122,07, 44,14, 37,23, 24,82, 23,46.

Paso 2: 1-(3-bromofenil)ciclohexanecarboxamida

Con agitador aéreo, se calentó a reflujo durante la noche una mezcla del producto crudo del paso 1, explicado más arriba, (380 g, 1207 mmol), KOH en polvo (720 g) y t-BuOH (2,5 L). Véase Hall, J.H.; Gisler, M.A. Un método sencillo para convertir nitrilo en amidas. Hidrólisis con hidróxido de potasio en alcohol terc-butílico. *J. Org. Chem.* **1976**, *41*, 3769-3770. Si se consideraba terminada mediante el análisis GC, se enfriaba con agua helada (enfriar lentamente para evitar la ruptura del cristal), se templaba con agua helada (1500 mL). La mezcla templada se extraía entonces con MTBE (3,5 L + 1,5 L). Las capas de MTBE se concentraban en un sólido amarillo, 390 g.

624

Condiciones del GC: 15m DB5 0,25 × 0,25 micron; Temp. Inic. = 75° C, Inic. Tiempo = 5 min, Ritmo = 15° C/min, Temp. Final = 275° C, Tiempo final = 2 min, Temp. Iny. = 275° C, Temp. det. = 250° C; RT del producto = 15,3 min.

Paso 3: hidrocloruro de 1-(3-bromofenil)ciclohexanamina,

El producto del paso 2, explicado más arriba (189 g, 603 mmol) se suspensió en t-BuOH caliente (1140 mL) a ~35°C, se añadió 3N NaOH (570 mL, 2,8 equiv.). La reacción se enfrió a 30°C. Se añadió NzOCl (380 mL, 13,6% peso, 1,4 equiv.) en una porción. La mezcla de reacción se enfrió a 26°C, después se empezó a calentar. Se añadió hielo directamente a la mezcla a temperatura controlada de <35°C. Se utilizó un total de 300 g de hielo. La generación de calor se paró después de 15 min. Todos los sólidos se habían disuelto en ese punto. Ensayada la capa orgánica a los 30 min., el GC indicó terminación. La mezcla se extrajo con 1100 mL de MTBE. La capa orgánica se combinó con la capa orgánica de una prueba paralela de la misma escala, y se filtró para quitar algunos ppt (precipitados) blancos (probablemente producto secundario de urea). Se extrajeron las capas acuosas con 300 mL de MTBE. Las capas combinadas de MTBE (aproximadamente 5 L) se trataron con 150 mL de HCl conc. (1,8 mol), se removieron durante 4 h, se enfriaron a 0°C y se filtraron. El sólido blanco se secó a 50°C para dar 180 g del 1er cultivo (52%) de material. El filtrado se trató con NaOH y $NaHSO_3$ hasta obtener un pH>12. La capa orgánica se concentró hasta formar un aceite. Este aceite se disolvió en 1 L de MTBE y se trató con 75 mL de HCl conc., se enfrió, se filtró y se secó para dar 140 g (40%) del producto deseado.Anal. Calcd para $C_{12}H_{16}BrN.HCl$: C, 49,59; H, 5,90; N, 4,82; Br, 27,49; Cl, 12,20; encontrado: C, 50,34; H, 6,23; N, 4,70; HRMS calcd para $C_{12}H_{16}BrN^+$ 253,0467, encontrado 253,0470.

Condiciones del GC: 15m DB5 0,25 × 0,25 micron; Temp. Inic. = 75° C, Inic. Tiempo = 5 min, Ritmo = 15° C/min, Temp. Final = 275° C, Tiempo final = 2 min, Temp. Iny. = 275° C, Temp. det. = 250° C; RT del producto = 12,9 min.

Paso 4: terc-butil-(1S,2R)-3-{[1-(3-bromofenil)ciclohexil]amino}-1-(3,5-difluorobencil)-2-hidroxipropilcarbamato,

625

El producto del paso 3, arriba indicado, (90 g, 310 mmol, 1,5 eq.) se convirtió en una base libre en 1000 mL de MTBE/400 mL de 2N NaOH. La capa de MTBE se separó, se lavó con salmuera. Se extrajeron las capas acuosas con 400 mL de MTBE. La capa combinada de MTBE se concentró (teóricos 78,3 g) para ofrecer la base libre

Se suspendieron 61,7 g. de epóxido (206 mmol, 1 eq., FW 299,3) y la base libre antedicha en 320 mL de t-BuOH (caliente). Se utilizaron un manto y una sonda/termómetro para calentar la mezcla en agitación a 80°C a un ritmo de 5°C/hora durante la noche. La mezcla se concentró en un evaporador rotatorio con condensador de 20°C. El aceite resultante se disolvió en MTBE (1 L), se lavó con 1N HCl (200 mL, después 100 mL x 5)(contiene el producto del paso 3, el primer lavado se hizo por separado rápidamente para evitar la colisión). Se extrajo la capa acuosa secuencialmente con MTBE (200 mL). La capa de MTBE se removió con 1N NaOH (500 mL) durante 30 min., después se separó. La capa de MTBE se lavó con salmuera y después se concentró hasta secarse. Recristalizada en MTBE/Heptano (150/900 mL). Filtrada a 0°C y lavada con heptano (150 mL x 2), secada a 45°C, 95,3 g (83,5%)

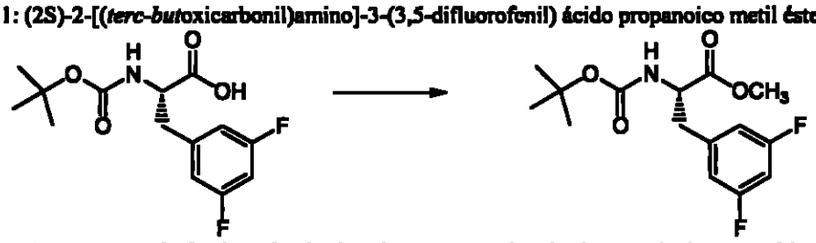
Los lavados de HCl (suspensión) se basificaron con NaOH al 50% (aproximadamente 50 g), se extrajeron con MTBE (400 mL + 200 mL). La capa de MTBE se tratró con HCl conc. (15 mL). La suspension resultante se enfrió y se filtró para dar la amina de origen sin reaccionar, el producto del paso 3, indicado arriba, 31,3 g (52%)

Condiciones del HPLC: Luna C18(2), 3 micron, min, 80:20 TFA al 0,1% en MeOH/0. TFA al 1% en agua; 10 min, RT del producto = 2.0 min.

Ejemplo 134

terc-butil (1S)-2-(3,5-difluorofenil)-1-[(2S)-oxiran-2-yl]etilcarbamato

Paso 1: (2S)-2-[(*terc-but*oxicarbonil)amino]-3-(3,5-difluorofenil) ácido propanoico metil éster

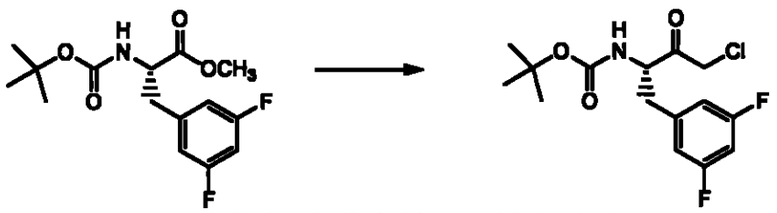


A un matraz de fondo redondo de 3 bocas y 1 L dotado de un agitador magnético, una entrada de nitrógeno y un termo-par se le añade (2S)-2-[(terc-butoxicarbonil)amino]-3-(3,5-difluorofenil)ácido propanoico (1, 40 g, 0,133 moles, 1 equivalente) seguido de THF (240 mL). Se añade monohidrato de hidróxido de litio (5,6 g, 0,133 moles, 1 equivalente) en una porción

626

única y se deja agitar durante 30 min, pasados los cuales se enfría el contenido a 0°. Una vez enfriado, se añade sulfato de dimetilo (12,6 mL, 0,133 moles, 1 equivalente) mediante una jeringa y luego se agita durante 30 min. Luego se calienta la mezcla hasta 50° y se la sigue (por HPLC) hasta que se alcanza una conversión del 90%. Entonces se enfría la mezcla por debajo de los 20° (forma sólida). Luego se vierte la mezcla en bicarbonato de sodio (200 mL), se agita durante 15 min, luego se extrae con metil *t*-butil éter (200 mL). Se separan las fases y se extrae la capa acuosa con metil *t*-butil éter (2 x 200 mL). Se lavan las fases orgánicas combinadas con agua (400 mL) se secan sobre sulfato de sodio, se filtran y concentran bajo presión reducida para dar un sólido. Luego se recristaliza este material desde hexanos para dar el compuesto del título, mp = 81°; NMR (DMSO-d_6) δ 7.51, 7.15-7.25, 4.43, 3.81, 3.00-3.26 y 1.49; CMR (DMSO-d_6) δ 172.43, 163.74, 161.20, 155.67, 142.58, 112.70, 120.23, 78.69, 54.71, 52.24, 39.25 y 28.37.

Paso 2 (1S)-3-cloro-1-(3,5-difluorobencil)-2-oxopropilcarbamato (III) de *terc*-butilo

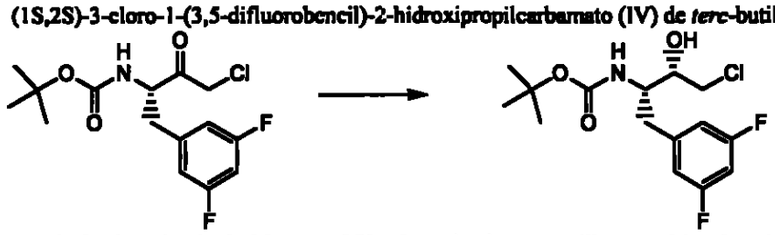


A un matraz de fondo redondo de 3 bocas y 1 L dotado de un agitador magnético, entrada de nitrógeno, termo-par y un embudo adicional se le añade (2S)-2-[(terc-butoxicarbonil)amino]-3-(3,5-difluorofenil)ácido propanoico metil éster (II, Paso 1, 10,0 g, 0,0317 moles, 1 equivalente) seguido de THF (175 mL) y luego enfriado a -78°. Una vez enfriada la mezcla, se añade una porción de iodoclorometano (9,25 mL, 0,127 moles, 4 equivalentes) mediante una jeringa. Se carga el embudo adicional con LDA (79 mL, 0,158 moles, 5 equivalentes, 2,0 M en heptano/THF) y se añade después gota a gota a la mezcla manteniendo la temperatura interna por debajo de -70°. Completada la adición, se agita el contenido durante 15 minutos, y luego se añade el ácido acético (47,2 mL, 0,824 moles, 26 equivalentes) gota a gota mediante el embudo de adición manteniendo la temperatura interna por debajo de -65°. Una vez realizada la adición, se agita la mezcla durante 15 minutos y luego se calienta hasta los 0° y se vierte en agua (500 mL), salina (500 mL) y metil *t*-butil éter (500 mL) luego se pasa a un embudo separador. Se separan las fases y se extrae la fase acuosa con metil *t*-butil éter (2 x 250 mL). Se lavan las fases orgánicas combinadas con bicarbonato de sodio saturado (500 mL), sulfito de sodio (500 mL) y agua (500 mL). Se seca la fase orgánica sobre

127

sulfato de sodio, se filtra y se concentra bajo presión reducida para dar un sólido. El sólido se recristaliza desde heptano/*i*-propil alcohol (10/1) para dar el compuesto del título, mp = 139°; NMR (DMSO-d_6) δ 7.47, 7.06-7.14, 4.78, 4.49, 3.20, 2.82 y 1.40; CMR (DMSO-d_6) δ 200.87, 163.74, 161.20, 142.74, 112.80, 102.13, 79.04, 58.97, 47.72, 34.95 y 28.30.

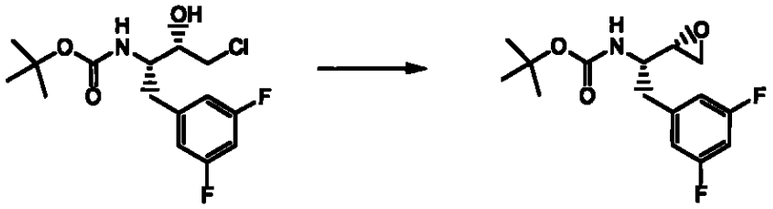
Paso 3 (1S,2S)-3-cloro-1-(3,5-difluorobencil)-2-hidroxipropilcarbamato (IV) de *terc*-butilo



A un matraz de fondo redondo de 3 bocas y 250 mL equipado con varilla magnética de agitar, entrada de nitrógeno y termo-par, se le añade (1S)-3-cloro-1-(3,5-difluorobencil)-2-oxopropilcarbamato(III) de *terc*-butilo (Paso 2, 4,4 g, 0,0132 moles, 1 equivalente) seguido de THF (20 mL) y etanol (30 mL), luego se enfría hasta -78°. Una vez enfriada la mezcla, se añade borohidruro de sodio (2,0 g, 0,0527 moles, 4 equivalentes) como sólido porción a porción durante 30 minutos manteniendo la temperatura interna por debajo de -70°. Completada la adición, se agita el contenido durante 2 hr a -78°, luego se calienta hasta 0° y se agita 1 hr más. La mezcla se enfría por la adición de bisulfato de potasio saturado (15 mL) y agua (15 mL). Se agita este compuesto acuoso durante 30 minutos a 20-25° y luego se concentra bajo presión reducida hasta llegar a la mitad de su volumen. Luego se enfría hasta 0° y se agita durante 30 min. Pasado este tiempo, los sólidos resultantes se recogen por filtración y se lavan con agua (2 x 50 mL) luego se secan bajo presión reducida a 50° para dar un producto crudo. Se ha observado una proporción sin/anti de 4-9:1. Se recristaliza el producto deseado desde hexanos/etanol (25/l) para dar el compuesto del título, , mp = 149°; NMR (DMSO-d_6) δ 6.89-7.16, 5.61, 3.64-3.83, 3.19, 2.69 y 1.41; CMR (DMSO-d_6) δ 163.67, 161.24, 155.44, 112.70, 101.55, 78.04, 72.99, 54.29, 48.24, 35.97 y 28.37.

Paso 4 (1S)-2-(3,5-difluorofenil)-1-[(2S)-oxiran-2-yl]etilcarbamato de terc-butilo

628



A un matraz de fondo redondo de 3 bocas y 250 mL equipado de varilla magnética agitadora, entrada de nitrógeno y termo-par, se añade (1S,2S)-3-cloro-1-(3,5-difluorobencil)-2-hidroxipropilcarbamato (IV) de *terc*-butilo (Paso 3, 3,5 g, 0,010 moles, 1 equivalente) seguido de etanol absoluto (60 mL) y se enfría a 0°. Se añade a esta mezcla hidróxido de potasio (0,73 g, 0,013 moles, 1,25 equivalentes) disuelto en etanol absoluto (10 mL) durante 1 hr y se calienta la suspensión resultante a 15-20° y se agita durante 1 hr. Luego se añade agua (100 mL) al contenido de la reacción y se agita durante 30 minutos. Se recogen los sólidos por filtración y se lavan con agua fría (2 x 25 mL) y luego se secan bajo presión reducida a 45° para dar el compuesto del título, mp = 133°; NMR (DMSO-d_6) δ 7.03, 3.61, 2.68-2.98 y 1.33; CMR (DMSO-d_6) δ 163.72, 161.29, 155.55, 143.35, 112.65, 101.80, 78.17, 53.42, 52.71, 44.90, 36.98 y 28.36.

El *anti*-diastereómero mp = 101°.

Ejemplo 135

Se preparan los siguientes compuestos de acuerdo esencialmente con los procedimientos establecidos en los ejemplos y esquemas anteriores..

N-[(1S,2R)-3-{[(1R)-5-(3-aminofenil)-7-etil-1,2,3,4-tetrahidronaftalen-1-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1R)-7-etil-5-(1,3-tiazol-2-il)-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1R)-7-etil-5-piridin-2-il-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1R)-7-etil-5-(3-metilpiridin-2-il)-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1R)-7-etil-5-(4-metilpiridin-2-il)-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;
N-[(1S,2R)-3-{[1-acetil-4-(3-isopropilfenil)piperidin-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[4-(3-isopropilfenil)-1-(metilsulfonil)piperidin-4-il]amino}propil)acetamida;
N-((1R,2S)-1-[4-(benciloxi)-3-fluorobencil]-3-{[(1S)-7-(2,2-dimetilpropil)-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;
N-[(1R,2S)-3-{[4-(3-terc-butilfenil)tetrahidro-2H-piran-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-[(1R,2S)-1-(3,5-difluorobencil)-2-hidroxi-3-({1-[3-(trifluorometil)fenil]ciclohexil}amino)propil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4R)-6-(2,2-dimetilpropil)-3,4-dihidro-2H-cromen-4-il]amino}-2-

630

629

hidroxipropil)-2-fluoroacetamida;
N-((1R,2S)-1-(3,5-difluorobencil)-2-hidroxi-3-{[4-(3-isopropoxifenil)tetrahidro-2H-piran-4-il]amino}propil)-N'-fenilurea;
{(1R,2S)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-isopropoxi-1,1-dimetil-3,4-dihidro-1H-isocromen-4-il)amino]propil}carbamato de fenilo;
N-((1R,2S)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(2-isobutil-1,3-tiazol-5-il)-1-metiletil]amino}propil)acetamida;
N-[(1S,2R)-3-({1-[3-(2-adamantil)fenil]ciclohexil}amino)-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-[(1S,2R)-3-{[1-(3-ciclopentilfenil)ciclopropil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-[(1S,2R)-3-{[1-(3-biciclo[2.2.1]hept-2-ilfenil)ciclopropil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
3-[3-(1-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}ciclohexil)fenil]propanoato de etilo;
N-[(1S,2R)-3-{[1-(3-sec-butilfenil)ciclopropil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3',5'-difluorobifenil-3-il)ciclopropil]amino}-2-hidroxipropil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[5-(2,2-dimetilpropil)-2-(2-propil-1H-imidazol-1-il)bencil]amino}-2-hidroxipropil)acetamida;
N-[(1S,2R)-3-{[1-(3-sec-butilfenil)ciclohexil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-({1-[3-(3-metilbutil)fenil]ciclohexil}amino)propil]acetamida;
N-[(1S,2R)-1-(3,5-difluorobencil)-3-({1-[3-(1-etilpropil)fenil]ciclohexil}amino)-2-hidroxipropil]acetamida;
N-[(1S,2R)-3-{[1-(3-ciclopentilfenil)ciclohexil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-pent-4-en-1-ilfenil)ciclohexil]amino}propil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-piridin-2-ilfenil)ciclohexil]amino}propil)acetamida;
N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-({1-[3-(3-metilpiridin-2-il)fenil]ciclohexil}amino)propil]acetamida;
N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-({1-[3-(1,3-tiazol-2-il)fenil]ciclohexil}amino)propil]acetamida;
N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-({1-[3-(3-metil-2-tienil)fenil]ciclohexil}amino)propil]acetamida;
N-[(1S,2R)-1-(3,5-difluorobencil)-3-({1-[3-(2-fluorobencil)fenil]ciclohexil}amino)-2-hidroxipropil]acetamida;
N-[(1S,2R)-1-(3,5-difluorobencil)-3-({1-[3-(4-fluorobencil)fenil]ciclohexil}amino)-2-hidroxipropil]acetamida;
N-[(1R,2S)-3-{[(1S)-7-(2,2-dimetilpropil)-1,2,3,4-tetrahidronaftalen-1-il]amino}-1-(3-fluoro-4-hidroxibencil)-2-hidroxipropil]acetamida; y
N-((1S,2S)-1-(3,5-difluorobencil)-2-hidroxi-3-{[3-(3-isopropilfenil)tetrahidro-2H-piran-3-il]amino}propil)acetamida.

Example 136
Se han preparado los siguientes compuestos de acuerdo esencialmente con los procedimientos establecidos en los ejemplos y esquemas anteriores.

630

(1S,2R)-N-[3-[1-(3-terc-butil-fenil)-4-oxo-ciclohexilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

(1S, 2R)-N-[3-[5-(3-terc-butil-fenil)-2-oxo-[1,3]oxazinan-5-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

(1S, 2R)-N-[3-[5-(3-terc-butil-fenil)-2-oxo-hexahidro-pirimidin-5-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

(1S,2R)-N-[3-[1-(3-Bromo-5-terc-butil-fenil)-ciclohexilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

(1S,2R)-N-[3-[1-(3-terc-butil-5-etil-fenil)-ciclohexilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

(1S,2R)-N-[3-[4-(3-terc-butil-5-etil-fenil)-tetrahidropiran-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxipropil]-acetamida;

(1S,2R)-N-[3-[4-(3-Bromo-5-terc-butil-fenil)-tetrahidropiran-4-ilamino]-1-(3,5-difluorobencil)-2-hidroxipropil]-acetamida;

(1S,2R)-N-[3-[1-(3-terc-butil-5-etilfenil)ciclopropilamino]-1-(3,5-difluorobencil)-2-hidroxipropil]-acetamida;

(1S,2R)-N-[3-{1-[3-Bromo-5-(2,2-dimetil-propil)-fenil]-ciclopropilamino}-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

(1S,2R)-N-(1-(3,5-Difluorobencil)-3-{1-[5-(2,2-dimetilpropil)-2-imidazol-1-il-fenil]-ciclopropilamino}-2-hidroxi-propil)-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetilpropil)-2-(5-etil-imidazol-1-il)-bencilamino]-2-hidroxipropil}-acetamida;

(1S,2R)-N-[3-[3-Cloro-5-(2,2-dimetil-propil)-2-imidazol-1-il-bencilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-tetrazol-1-il-bencilamino]-2-hidroxi-propil}-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-oxazol-5-il-bencilamino]-2-hidroxi-propil}-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-oxazol-2-il-bencilamino]-2-hidroxi-propil}-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[6-(2,2-dimetil-propil)-1-metil-1,2,3,4-tetrahidro-quinolin-4-ilamino]-2-hidroxi-propil}-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[6-(2,2-dimetil-propil)-tiocroman-4-ilamino]-2-hidroxi-propil}-acetamida;

631

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[6-(2,2-dimetil-propil)-8-etil-croman-4-ilamino]-2-hidroxi-propil}-acetamida;

(1S,2R)-N-[3-[8-Bromo-6-(2,2-dimetilpropil)-croman-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxipropil]-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[6-(2,2-dimetil-propil)-2-oxo-croman-4-ilamino]-2-hidroxi-propil}-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[7-(2,2-dimetil-propil)-4-oxo-1,2,3,4-tetrahidro-naftalen-1-ilamino]-2-hidroxi-propil}-acetamida;

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[6-(2,2-dimetil-propil)-1-oxo-1λ^4-tiocroman-4-ilamino]-2-hidroxipropil}-acetamida; y

(1S,2R)-N-{1-(3,5-Difluoro-bencil)-3-[6-(2,2-dimetil-propil)-1,1-dioxo-1λ^6-tiocroman-4-ilamino]-2-hidroxi-propil}-acetamida.

Example 137

Se han preparado los siguientes compuestos de acuerdo esencialmente con los procedimientos establecidos en los ejemplos y esquemas anteriores.

N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[1-(3-isopropil-fenil)-ciclobutilamino]-propil}-acetamida;

N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[1-(3-isopropil fenil)-ciclopentilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[3-(3-isopropil-fenil)-biciclo[3.1.0]hex-3-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[3-(3-isopropil-fenil)-6-aza-biciclo[3.1.0]hex-3-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[3-(3-isopropil-fenil)-6-metil-6-aza-biciclo[3.1.0]hex-3-ilamino]-propil}-acetamida;
N-[3-[6-Acetil-3-(3-isopropil-fenil)-6-aza-biciclo[3.1.0]hex-3-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[3-(3-isopropil-fenil)-6-metanosulfonil-6-aza-biciclo[3.1.0]hex-3-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[1-(3-isopropil-fenil)-2,2,4,4-tetrametil-3-oxo-ciclobutilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[3-hidroxi-1-(3-isopropil-fenil)-2,2,4,4-tetrametil-ciclobutilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-(3-isopropil-fenil)-octahidro-ciclopenta[c]pirrol-5-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-(3-isopropil-fenil)-2-metil-octahidro-ciclopenta[c]pirrol-5-ilamino]-propil}-acetamida;
N-[3-[2-Acetil-5-(3-isopropil-fenil)-octahidro-ciclopenta[c]pirrol-5-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-(3-isopropil-fenil)-2-metanosulfonil-octahidro-ciclopenta[c]pirrol-5-ilamino]-propil}-acetamida;

632

N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-5-oxo-octahidro-pentalen-2-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-hidroxi-2-(3-isopropil-fenil)-octahidro-pentalen-2-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-3a,6a-dimetil-5-oxo-octahidro-pentalen-2-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-hidroxi-2-(3-isopropil-fenil)-3a,6a-dimetil-octahidro-pentalen-2-ilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-5-oxo-ciclohexilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-hidroxi-2-(3-isopropil-fenil)-5-metil-ciclohexilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-5-metanosulfonilamino-ciclohexilamino]-propil}-acetamida;
N-[3-[5-Acetilamino-2-(3-isopropil-fenil)-ciclohexilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-4-oxo-ciclohexilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-hidroxi-2-(3-isopropil-fenil)-4-metil-ciclohexilamino]-propil}-acetamida;
N-[3-[4-Acetilamino-2-(3-isopropil-fenil)-ciclohexilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-4-metanosulfonilamino-ciclohexilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-4-oxo-ciclopentilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-hidroxi-2-(3-isopropil-fenil)-4-metil-ciclopentilamino]-propil}-acetamida;
N-[3-[4-Acetilamino-2-(3-isopropil-fenil)-ciclopentilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[2-(3-isopropil-fenil)-4-metanosulfonilamino-ciclopentilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-3-[4-(2,2-dimetil-propil)-piridin-3-ilamino]-2-hidroxi-propil}-acetamida;
N-(1-(3,5-Difluoro-bencil)-3-{[4-(2,2-dimetil-propil)-piridin-3-ilmetil]-amino}-2-hidroxi-propil)-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(5-isobutil-2-piperazin-1-il-bencilamino)-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-isobutil-2-(4-metil-piperazin-1-il)-bencilamino]-propil}-acetamida;
N-[3-[2-(4-Acetil-piperazin-1-il)-5-isobutil-bencilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-isobutil-2-(4-metanosulfonil-piperazin-1-il)-bencilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-3-[4-(2,2-dimetil-propil)-piperidin-3-ilamino]-2-hidroxi-propil}-acetamida;
N-(1-(3,5-Difluoro-bencil)-3-{[4-(2,2-dimetil-propil)-piperidin-3-ilmetil]-amino}-2-hidroxi-propil)-acetamida;
N-[3-[1-Acetil-4-(2,2-dimetil-propil)-piperidin-3-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

633

N-[3-{[1-Acetil-4-(2,2-dimetil-propil)-piperidin-3-ilmetil]-amino}-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-3-[4-(2,2-dimetil-propil)-1-metanosulfonil-piperidin-3-ilamino]-2-hidroxi-propil}-acetamida;
N-(1-(3,5-Difluoro-bencil)-3-{[4-(2,2-dimetil-propil)-1-metanosulfonil-piperidin-3-ilmetil]-amino}-2-hidroxi-propil)-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(6-isopropil-2-oxo-1,2,3,4-tetrahidro-quinolin-4-ilamino)-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(5-isopropil-2-oxo-2,3-dihidro-1H-indol-3-ilamino)-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(7-isopropil-3-oxo-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(3-hidroxi-7-isopropil-3-metil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida;
N-[3-(3-Acetilamino-7-isopropil-1,2,3,4-tetrahidro-naftalen-1-ilamino)-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(7-isopropil-3-metanosulfonilamino-1,2,3,4-tetrahidro-naftalen-1-ilamino)-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(6-isopropil-2-oxo-indan-1-ilamino)-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(2-hidroxi-6-isopropil-2-metil-indan-1-ilamino)-propil]-acetamida;
N-[3-(2-Acetilamino-6-isopropil-indan-1-ilamino)-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(6-isopropil-2-metanosulfonilamino-indan-1-ilamino)-propil]-acetamida;
N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(5-isobutil-2-piperidin-4-il-bencilamino)-propil]-acetamida;
N-[3-[2-(1-Acetil-piperidin-4-il)-5-isobutil-bencilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{1-(3,5-Difluoro-bencil)-2-hidroxi-3-[5-isobutil-2-(1-metanosulfonil-piperidin-4-il)-bencilamino]-propil}-acetamida;
N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-piperidin-4-il-bencilamino]-2-hidroxi-propil}-acetamida;
N-[3-[2-(1-Acetil-piperidin-4-il)-5-(2,2-dimetil-propil)-bencilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida
N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-(1-metanosulfonil-piperidin-4-il)-bencilamino]-2-hidroxi-propil}-acetamida;

N-[1-(3,5-Difluoro-bencil)-2-hidroxi-3-(6-isobutil-2,2-dioxo-1,2,3,4-tetrahidro-2λ^6-benzo[c][1,2]tiazin-4-ilamino)-propil]-acetamida;

N-{1-(3,5-Difluoro-bencil)-3-[6-(2,2-dimetil-propil)-1-metil-2,2-dioxo-1,2,3,4-tetrahidro-2λ^6-benzo[c][1,2]tiazin-4-ilamino]-2-hidroxi-propil}-acetamida;

N-{3-[6-(2,2-Dimetil-propil)-2,2-dioxo-1,2,3,4-tetrahidro-2λ^6-benzo[c][1,2]tiazin-4-ilamino]-1-(3-fluoro-4-hidroxi-bencil)-2-hidroxi-propil]-acetamida;

N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-metanosulfonilamino-bencilamino]-2-hidroxi-propil}-acetamida;

634

N-[3-[2-Bencenosulfonilamino-5-(2,2-dimetil-propil)-bencilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;

N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-fenilsulfamoil-bencilamino]-2-hidroxi-propil}-acetamida;

N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-metilsulfamoil-bencilamino]-2-hidroxi-propil}-acetamida;

N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-(2-oxo-piperidin-4-il)-bencilamino]-2-hidroxi-propil}-acetamida;

N-{1-(3,5-Difluoro-bencil)-3-[5-(2,2-dimetil-propil)-2-(1-metil-2-oxo-piperidin-4-il)-bencilamino]-2-hidroxi-propil}-acetamida;

N-[3-[6-(2,2-Dimetil-propil)-croman-4-ilamino]-1-(3-fluoro-4-hidroxi-bencil)-2-hidroxi-propil]-acetamida;

N-[3-[7-(2,2-Dimetil-propil)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-1-(3-fluoro-4-hidroxi-bencil)-2-hidroxi-propil]-acetamida;

N-[3-[7-(2,2-Dimetil-propil)-1,2,3,4-tetrahidro-naftalen-1-ilamino]-2-hidroxi-1-(5-hidroxi-piridin-2-ilmetil)-propil]-acetamida;

N-[3-[6-(2,2-Dimetil-propil)-croman-4-ilamino]-2-hidroxi-1-(5-hidroxi-piridin-2-ilmetil)-propil]-acetamida;

N-[3-[4-(3-terc-butil-fenil)-tetrahidro-piran-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-butil]-acetamida;

N-[3-[4-(3-terc-butil-fenil)-tetrahidro-piran-4-ilamino]-1-(3,5-difluoro-bencil)-2,4-dihidroxi-butil]-acetamida;

N-[3-(5-terc-butil-2-imidazol-1-il-bencilamino)-1-(3,5-difluoro-bencil)-2-hidroxi-butil]-acetamida;

N-[3-(5-terc-butil-2-imidazol-1-il-bencilamino)-1-(3,5-difluoro-bencil)-2,4-dihidroxi-butil]-acetamida;

N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-tetrahidro-tiopiran-4-ilamino]-propil}-acetamida;

N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-1,1-dioxo-tetrahidro-tiopiran -4-ilamino]-propil}-acetamida;

N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-1-oxo-tetrahidro-tiopiran -4-ilamino]-propil}-acetamida;

N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-1-metanosulfonil-piperidin-4-ilamino]-propil}-acetamida;

635

Acetic acid (2R,3S)-2-acetilamino-3-(3,5-difluoro-fenil)-1-{[4-(3-isopropil-fenil)-piperidin-4-ilamino]-metil}-propil ester;
Acetic acid (2R,3S)-2-acetilamino-1-{[1-acetil-4-(3-isopropil-fenil)-piperidin-4-ilamino]-metil}-3-(3,5-difluoro-fenil)-propil éster;
N-[(1S,2R)-3-[1-Acetil-4-(3-isopropil-fenil)-piperidin-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-piperidin-4-ilamino]-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-1-trifluoroacetil-piperidin-4-ilamino]-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-1,1-dimetil-piperidin-4-ilamino]-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-3-[1-formil-4-(3-isopropil-fenil)-piperidin-4-ilamino]-2-hidroxi-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-3-[1-etil-4-(3-isopropil-fenil)-piperidin-4-ilamino]-2-hidroxi-propil}-acetamida;
N-[3-[4-(3-terc-butil-fenil)-tetrahidro-piran-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-tetrahidro-piran-4-ilamino]-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-2-hidroxi-3-[4-(3-isopropil-fenil)-1-metil-piperidin-4-ilamino]-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-3-[1-etanosulfonil-4-(3-isopropil-fenil)-piperidin-4-ilamino]-2-hidroxi-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-3-[1-propanosulfonil-4-(3-isopropil-fenil)-piperidin-4-ilamino]-2-hidroxi-propil}-acetamida;
N-{(1S,2R)-1-(3,5-Difluoro-bencil)-3-[2-propanosulfonil-4-(3-isopropil-fenil)-piperidin-4-ilamino]-2-hidroxi-propil}-acetamida;
N-[(1S,2R)-3-[4-(3-terc-butil-fenil)-1-etanosulfonil-piperidin-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-[(1S,2R)-3-[4-(3-terc-butil-fenil)-1-metanosulfonil-piperidin-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
4-[(2R,3S)-3-Acetilamino-4-(3,5-difluoro-fenil)-2-hidroxi-butilamino]-4-(3-terc-butil-fenil)-piperidine-1-carboxílico ácido amida;

636

4-[(2R,3S)-3-Acetilamino-4-(3,5-difluoro-fenil)-2-hidroxi-butilamino]-4-(3-terc-butil-fenil)-piperidine-1-carboxílico ácido metilamida;
4-[(2R,3S)-3-Acetilamino-4-(3,5-difluoro-fenil)-2-hidroxi-butilamino]-4-(3-terc-butil-fenil)-piperidine-1- ácido carboxílico metil éster;N-[(1S,2R)-3-[(4S)-4-(3-terc-butil-fenil)-1-metanosulfonil-azepan-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-[(1S,2R)-3-[(4R)-4-(3-terc-butil-fenil)-1-metanosulfonil-azepan-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida;
N-[(1S,2R)-3-[(4R)-4-(3-terc-butil-fenil)-azepan-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida; y
N-[(1S,2R)-3-[(4S)-4-(3-terc-butil-fenil)-azepan-4-ilamino]-1-(3,5-difluoro-bencil)-2-hidroxi-propil]-acetamida.

Ejemplo 138

Los siguientes compuestos se preparan esencialmente según los procedimientos descritos en los ejemplos y esquemas indicados anteriormente.
N-[(1S,2R)-3-[(3-bromobencil)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4R)-6-isopropil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il]amino}propil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il]amino}propil)acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;
Hidrocloruro de N-[(1S,2R)-3-{[1-(3-bromofenil)ciclopropil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-bromofenil)propanoato de metilo;
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}acetamida;
3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoato de metilo;

637

Ácido 3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoico;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-3-hidroxipropil]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(1S)-1,2,3,4-tetrahidronaftalen-1-ilamino]propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-2-methilamino-acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-iodobenzil)amino]propil}acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-iodofenil)propanoato de metilo;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(3-hidroxiprop-1-inil)fenil]propanoato de metilo;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[3-hidroxi-1-(3-iodofenil)propil]amino}propil)acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(3-hidroxipropil)fenil]propanoato de metilo;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(7-methoxy-1,2,3,4-tetrahidronaftaleno-1-il)amino]propil}acetamida;

2-Amino-N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[6-etil-2-(metilsulfonil)-1,2,3,4-tetrahydroisoquinolin-4-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-7-etil-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1R)-7-etil-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-3-{[1-(3-bromofenil)ciclopropil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(5-formiltieno-2-il)fenil]propanoato de metilo;

638

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(2'-acetil-1,1'-bifenil-3-il)propanoato de metilo;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-3-metil-butiramida;

N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-({1-[3'-(hidroximetil)-1,1'-bifenil-3-il]ciclopropil}amino)propil]acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-3-({1-[3-(5-formiltieno-2-il)fenil]ciclopropil}amino)-2-hidroxipropil]acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-3-(9H-fluoreno-9-ilamino)-2-hidroxipropil]acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(trifluorometil)fenil]propanoato de metilo;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-cianofenil)propanoato metilo;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-3-hidroxi-2,2-dimetil-propionamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopropil]amino}-2-hidroxipropil)acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-bromofenil)propanoato de metilo;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etinilfenil)ciclopropil]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-3-[(2-bromo-9H-fluoreno-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-9H-fluoreno-9-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2,2-dióxido-3,4-dihidro-1,2-benzoxatiina-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-iodo-3,4-dihidro-2H-cromeno-4-il)amino]propil}acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-iodo-3,4-dihidro-2H-cromeno-4-il]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4R)-6-iodo-3,4-dihidro-2H-cromeno-4-il]amino}propil)acetamida;

N-[1-(3,5-difluor

670

Comentario [PC1]:

639

bencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-3-hidroxi-propionamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1,2-benzoxatiina-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1,2-benzoxatiina-4-il)amino]-2-hidroxipropil}acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[4-(3-etilfenil)tetrahidro-2H-piran-4-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)butil]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromeno-4-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4R)-6-etil-3,4-dihidro-2H-cromeno-4-il]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(7-etil-1,2,3,4-tetrahidronaftaleno-1-il)amino]-2-hidroxipropil}acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-3-hidroxi-butiramuro;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclohexil]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopentil]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-3,4-dihidro-1H-isotiocromano-4-ilo)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-5-fluoro-9H-fluoreno-9-il)amino]-2-hidroxipropil}acetamida;

(3S)-3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)butanoato de metilo;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isobutilisoxazol-5-il)ciclopropil]amino}propil)acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-2-fenil-acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-7-fluoro-9H-fluoreno-9-il)amino]-2-hidroxipropil}acetamida;

640

metil (3R)-3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)butanoato;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2,5-dipropilbencil)amino]-2-hidroxipropil}acetamida;

{[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propilcarbamil]-metil}-metil-carbamato de terc-butilo;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isobutil-9H-fluoreno-9-il)amino]propil}acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-6-etil-2,3-dihidro-1H-inden-1-il]amino}-2-hidroxipropil)acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-2-metil-2-metilamino-propionamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-etil-1-(3-etilfenil)propil]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1H-2,1-benzotiazina-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dioxido-3,4-dihidro-1H-2,1-benzotiazina-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-3-metil-2,2-dioxido-3,4-dihidro-1H-isotiocromeno-4-ilo)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-3-metil-2,2-dioxido-3,4-dihidro-1H-isotiocromeno-4-ilo)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolina-4-il)amino]-2-hidroxipropil}acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoato de metilo;

N-[1-(3,5-difluorobencilo)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-2-(1H-imidazol-4-il)-acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoato de metilo;

N-[(1S,2R)-3-[(2-bromo-9-metil-9H-fluoreno-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(1-etilpropil)-9H-fluoreno-9-il]amino}-2-hidroxipropil)acetamida;

641

N-[(1S,2R)-3-[(2-ciclopentil-9H-fluoreno-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocromano-4-ilamino)-2-hidroxi-propil]-propionamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-9-metil-9H-fluoreno-9-il)amino]-2-hidroxipropil}acetamida;

N-[(1S,2R)-3-[(2-ciclohexil-9H-fluoreno-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(4-etilpiridina-2-il)ciclopropil]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1H-pirrol-3-il)-3,4-dihidro-2H-cromeno-4-il]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(5R)-3-etil-6,7,8,9-tetrahidro-5H-benzo[7]anuleno-5-il]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-3-{[1-(3-bromofenil)-1-metiletil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(dimetilamino)-9H-fluoreno-9-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(1S)-7-propil-1,2,3,4-tetrahidronaftaleno-1-il]amino}propil)acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-3-({(1S)-7-[(dimethilamino)metil]-1,2,3,4-tetrahidronaftaleno-1-il}amino)-2-hidroxipropil]acetamida;

N-[(1S,2R)-3-{[(1S)-7-bromo-1,2,3,4-tetrahidronaftaleno-1-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-propilfenil)ciclopropil]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)cicloheptil]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-isopropil-3,4-dihidro-2H-cromeno-4-il)amino]propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2-hidroxi-2,3-dihidro-1H-inden-1-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-6-fluoro-9H-fluoreno-9-il)amino]-2-hidroxipropil}acetamida;

642

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(metoximetil)-9H-fluoreno-9-il]amino}propil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-2-(5-metil-1,3-oxazol-2-il)etil]amino}-2-hidroxipropil)acetamida hidrocloruro;
N-[(1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromeno-4-ilamino)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-etil-5-(trifluorometil)-9H-fluoreno-9-il]amino}-2-hidroxipropil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(3-metilbutil)-9H-fluoreno-9-il]amino}propil)acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isopropil-9H-fluoreno-9-il)amino]propil}acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-neopentil-9H-fluoreno-9-il)amino]propil}acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isopropenil-9H-fluoreno-9-il)amino]propil}acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil]amino}-2-hidroxipropil)acetamida hidrocloruro;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromeno-4-il]amino}propil)acetamida;
N-[(1S,2R)-3-{[(4S)-6-cyano-3,4-dihidro-2H-cromeno-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromeno-4-il]amino}propil)acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-2H-cromeno-4-il)amino]propil}acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(isopropilamino)-9H-fluoreno-9-il]amino}propil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isobutilfenil)ciclopropil]amino}propil)acetamida; y
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino}propil)acetamida.

Generalmente, la protección de los aminos se realiza, donde corresponde, por métodos conocidos por personal especializado. Los grupos protectores de aminos son conocidos por personal

643

especializado. Por ejemplo, ver "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Capítulo 7; "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973, Capítulo 2. Cuando los grupos protectores de aminos ya no son necesarios, se retiran con métodos conocidos para personal especializado. Por definición el grupo protector de aminos debe ser fácilmente retirable. Una variedad de metodologías apropiadas son conocidas por el personal especializado; ver también T.W. Green y P.G.M. Wuts en "Protective Groups in Organic Chemistry, John Wiley and Sons, 3rd edition, 1999. Grupos protectores de aminos apropiados incluyen a *t*-butoxicarbonilo, benciloxicarbonilo, formilo, tritilo, talimido, tricloro-acetilo, cloroacetilo, bromoacetilo, iodoacetilo, 4-fenilbenciloxicarbonilo, 2-metilbenciloxicarbonilo, 4-etoxibenciloxicarbonilo, 4-fluorobenciloxicarbonilo, 4-clorobenciloxicarbonilo, 3-clorobenciloxicarbonilo, 2-clorobenciloxicarbonilo, 2,4-diclorobenciloxicarbonilo, 4-bromobenciloxicarbonilo, 3-bromobenciloxicarbonilo, 4-nitrobenciloxicarbonilo, 4-cianobenciloxicarbonilo, 2-(4-xenil)isopropoxicarbonilo, 1,1-difenilet-1-iloxicarbonilo, 1,1-difenilprop-1-iloxicarbonilo, 2-fenilprop-2-iloxicarbonilo, 2-(*p*-toluil)prop-2-iloxi-carbonilo, ciclopentaniloxicarbonilo, 1-metilciclo-pentaniloxicarbonilo, ciclohexaniloxicarbonilo, 1-metil-ciclohexaniloxicabonilo, 2-metilciclohexaniloxicarbonilo, 2-(4-toluilsulfonilo)etoxicarbonilo, 2-(metilsulfonil)-etoxicarbonilo, 2-(trifenilfosfino)etoxicarbonilo, fluorenilmetoxicarbonilo, 2-(trimetilsilil)etoxi-carbonilo, alliloxicarbonilo, 1-(trimetilsililmetil)prop-1-eniloxicarbonilo, 5-benzisoxalilmetoxicarbonilo, 4-acetoxibenciloxicarbonilo, 2,2,2-tricloroetoxicarbonilo, 2-etinil-2-propoxicarbonilo, ciclopropilmetoxicarbonilo, 4-(deciloxil)benciloxicarbonilo, isoborniloxicarbonilo, 1-piperidiloxicarbonilo, 9-fluoroenilmetil carbonato, -CH-CH=CH_2 y fenil-C(=N-)-H.

Se prefiere que el grupo protector sea *t*-butoxicarbonilo (BOC) y/o benciloxicarbonilo (CBZ), se prefiere más que el grupo protector sea *t*-butoxicarbonilo. Personal especializado reconocerá métodos apropiados de introducir un grupo protector *t*-butoxicarbonilo o benciloxicarbonilo y como guía puede consultar además T.W. Green y P.G.M. Wuts en "Protective Groups in Organic Chemistry, John Wiley and Sons, 3rd edition, 1999.

Los compuestos de la invención pueden contener isómeros geométricos u ópticos como tautómeros. Así, la invención incluye todos los tautómeros e isómeros geométricos puros, tales como los isómeros geométricos *E* y *Z*, y sus correspondientes combinaciones. Aún más, la invención incluye enantiómeros puros, diastereómeros y/o sus combinaciones incluyendo mezclas racémicas. Los isómeros geométricos individuales, enantiómeros o diastereómeros se pueden preparar o aislar con métodos conocidos para personal especializado, incluyendo pero sin

limitarse a la cromatografía quiral; preparar diastereómeros, separar los diastereómeros y luego convertir los diastereómeros en enantiómeros.

Los compuestos de la invención con estereoquímica definida se pueden incluir en mezclas, incluyendo las racémicas, con otros enantiómeros, diastereómeros, isómeros geométricos o tautómeros. En un aspecto preferido, los compuestos de la invención están típicamente presentes en estas mezclas en excesos diastereoméricos y/o enantioméricos de al menos 50 por ciento. Preferentemente, los compuestos de la invención están presentes en estas mezclas en excesos diastereoméricos y/o enantioméricos de al menos 80 por ciento. Más preferentemente, los compuestos de la invención con la esteroquímica deseada están presentes en excesos diastereoméricos y/o enantioméricos de al menos 90 por ciento. Incluso aún más preferentemente, los compuestos de la invención con la esteroquímica deseada están presentes en excesos diastereoméricos y/o enantioméricos de al menos 99 por ciento. De preferencia los componentes de la invención tienen la configuración "S" en la posición 1. También se prefieren compuestos que tengan la configuración "R" en la posición 2. Más preferidos son los compuestos que tengan la configuración "1S,2R".

Todos los nombres de los compuestos fueron generados usando ACD Namepro versión 5.09, Chemdraw v. 6.02, o fueron derivados a partir de ellos.

Varios de los componentes de la fórmula (I) son aminas y como tales forman sales cuando reaccionan con ácidos. Se prefieren las sales aceptables farmacéuticamente a las correspondientes aminas debido a que las sales producen compuestos que son más solubles en agua, estables y/o más cristalinos. Las sales aceptables farmacéuticamente son cualquier sal que retenga la actividad del compuesto matriz y que no imparta ningún efecto nocivo o indeseado en el sujeto al cual se le administre y en el contexto bajo el cual fue administrada. Las sales aceptables farmacéuticamente incluyen sales tanto de ácidos inorgánicos como orgánicos. Las sales aceptables farmacéuticamente preferidas incluyen sales de los siguientes ácidos: acético, aspártico, bencenosulfónico, benzoico, bicarbónico, bisulfúrico, bitartárico, butírico, edetato cálcico, canfílico, carbónico, clorobenzoico, cítrico, edético, edisílico, estólico, esilo, esílico, fórmico, fumárico, glucéptico, glucónico, glutámico, glicolilarsanílico, hexámico, hexilresorcinoico, hidrabámico, hidrobrómico, hidroclórico, hidroiódico, hidroxinaftoico, isetiónico, láctico, lactobiónico, maleico, málico, malónico, mandélico, metanosulfónico, metilnítrico, metilsulfúrico, múcico, mucónico, napsílico, nítrico, oxálico, p-nitrometanosulfónico, pamoico, pantoténico, fosfórico, monohidrógeno fosfórico, dihidrógeno fosfórico, ftálico, poligalactourónico, propiónico, salicílico, esteárico, sucínico, sulfámico, sulfanílico, sulfónico,

6X6

605

sulfúrico, tánico, tartárico, teóclico y toluenosulfónico. Para conocer otras sales aceptables, ver *Int. J. Pharm.*, 33, 201-217 (1986) y *J. Pharm. Sci.*, 66(1), 1, (1977).

La invención proporciona compuestos, composiciones, partes y métodos para inhibir la actividad de la enzima beta-secretasa y la producción del péptido de A beta. La inhibición de la actividad de la enzima beta-secretasa detiene o reduce la producción de A beta desde APP y reduce o elimina la formación de depósitos beta-amiloides en el cerebro.

Métodos de la invención

Los compuestos de la invención y las sales aceptables farmacéuticamente descritas aquí, son útiles para tratar a seres humanos o animales que sufran de una condición caracterizada por una forma patológica de péptido beta-amiloide, tal como placas beta-amiloide, y para ayudar a prevenir o demorar el inicio de tal condición. Por ejemplo, los compuestos son útiles para tratar la enfermedad de Alzheimer, para ayudar a prevenir o demorar el inicio de la enfermedad de Alzheimer, para tratar a pacientes con trastornos cognitivos leves (en inglés, MCI - mild cognitive impairment) y prevenir o demorar el inicio de la enfermedad de Alzheimer en aquellas personas que podrían evolucionar desde MCI a AD, para tratar el síndrome de Down, para tratar a personas que padezcan de Hemorragia cerebral hereditaria con amiloidosis del tipo holandés (en inglés, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type), para tratar la angiopatía amiloide cerebral y evitar sus potenciales consecuencias, i.e. hemorragias lobulares únicas y recurrentes, para el tratamiento de otras demencias degenerativas, incluyendo demencias de origen vascular y degenerativo mixto, demencia asociada con la enfermedad de Parkinson, demencia asociada con parálisis supranuclear progresiva, demencia asociada con degeneración basal cortical y enfermedad de Alzheimer del tipo corporal difuso de Lewy. Los compuestos y composiciones de la invención son especialmente útiles para tratar y prevenir la enfermedad de Alzheimer. Al tratar o prevenir estas enfermedades, los compuestos de la invención pueden usarse individual o combinadamente, según lo que sea mejor para el paciente.

Tal como se usa en este documento, el término "tratamiento" significa que los compuestos de la invención se pueden usar en personas con al menos un diagnóstico tentativo de la enfermedad. Los compuestos de la invención retardarán o disminuirán el avance de la enfermedad brindándole de esa manera una expectativa de vida más útil para la persona.

El término "prevenir" significa que los compuestos de la invención son útiles cuando se administran a un paciente a quien no se le ha diagnosticado al momento de la administración la posibilidad de padecer la enfermedad, pero de quien normalmente se esperaría que desarrolle la enfermedad o que tenga un riesgo mayor a la enfermedad. Los componentes de la invención

606

retrasarán el desarrollo de los síntomas de la enfermedad, demorarán el inicio de la enfermedad o prevendrán que la persona desarrolle la enfermedad. La prevención también incluye la administración de los compuestos de la invención a aquellos individuos que se piensa que tienen predisposición a la enfermedad debido a la edad, antecedentes familiares, anormalidades genéticas o cromosómicas y/o debido a la presencia de uno o más marcadores biológicos para la enfermedad, tales como una mutación conocida de APP o productos de división de APP en tejidos o fluidos cerebrales.

Al tratar o prevenir las enfermedades indicadas anteriormente, los compuestos de la invención son administrados en una cantidad terapéuticamente efectiva. La cantidad terapéuticamente efectiva variará dependiendo del compuesto específico que se use así como de la vía de administración, tal como es conocido por personal especializado.

Al tratar a un paciente que presente cualquiera de las condiciones diagnosticadas anteriormente un médico puede administrar inmediatamente un compuesto de la invención y continuar administrándolo indefinidamente según sea necesario. Al tratar pacientes a quienes no se les haya diagnosticado la enfermedad de Alzheimer, pero de quienes se piensa que tienen un riesgo importante de desarrollar la enfermedad de Alzheimer, el médico perferentemente debería iniciar el tratamiento cuando el paciente experimente síntomas tempranos previos a Alzheimer tales como, problemas de memoria o cognitivos asociados con el envejecimiento. Además, existen algunos pacientes que puedan considerarse estar en riesgo de desarrollo de la enfermedad Alzheimer a través de la detección de un marcador genético tal como APOE4 u otros indicadores biológicos que son predictivos de la enfermedad de Alzheimer. En estas situaciones, incluso a pesar de que el paciente no tenga síntomas de la enfermedad, la administración de los compuestos de la invención se puede iniciar antes de que aparezcan los síntomas y el tratamiento se puede continuar indefinidamente para prevenir o retrasar el inicio de la enfermedad.

<u>Formas y cantidades de dosis</u>

Los compuestos de la invención se pueden administrar oral, parenteral, (IV, IM, depo-IM, SQ y depo SQ), sublingual, intranasal (inhalación), intratecal, tópica o rectalmente. Formas de dosis conocidas para el personal especializado son apropiadas para la entrega de los compuestos de la invención.

Se proporcionan composiciones que contienen cantidades terapéuticamente efectivas de los compuestos de la invención. Los compuestos se formulan preferentemente en preparaciones farmacéuticas apropiadas tales como tabletas, cápsulas o elixires para administración oral o en soluciones o suspensiones estériles para administración parenteral. Generalmente los compuestos

697

descritos anteriormente se formulan en composiciones farmacéuticas usando técnicas y procedimientos especializados reconocidos.

Cerca de 1 a 500 mg de un compuesto o mezcla de compuestos de la invención o una sal fisiológicamente aceptable se combinan con un vehículo, portador, excipiente, aglutinante, preservante, estabilizante, saborizante, etc. fisiológicamente aceptable en una forma de dosis unitaria según lo indiquen las prácticas farmacéuticas aceptadas. La cantidad de principio activo en aquellas composiciones o preparaciones es tal que se obtiene una dosis apropiada en el rango indicado. Las composiciones se formulan preferentemente en una forma de dosis unitaria, cada dosis contiene entre cerca de 2 y cerca de 100 mg, más preferentemente alrededor de 10 a cerca de 30 mg del principio activo. El término "forma de dosis unitaria" se refiere a unidades físicamente discretas apropiadas como dosis unitarias para personas y otros mamíferos, donde cada unidad contiene una cantidad predeterminada de principio activo calculado para producir el efecto terapéutico deseado conjuntamente con un excipiente farmacéuticamente apropiado.

Para preparar composiciones, se mezclan uno o más compuestos de la invención con un portador apropiado aceptable farmacéuticamente. Después de la mezcla o adición del(de los) compuesto(s), la mezcla resultante puede ser una solución, suspensión, emulsión o similar. Las suspensiones liposomáticas también pueden ser apropiadas como portadores aceptables farmacéuticamente. Estas se pueden preparar de acuerdo a métodos conocidos para personal especializado. La forma de la mezcla resultante depende de una cantidad de factores, incluyendo el modo deseado de administración y la solubilidad del compuesto en el portador o vehículo seleccionado. La concentración efectiva es suficiente para reducir o aminorar al menos un síntoma de la enfermedad, trastorno o condición tratada y se puede determinar empíricamente.

Los portadores o vehículos farmacéuticos apropiados para la administración de los compuestos provistos por este medio incluyen portadores conocidos por personal especializado como apropiados para esa forma particular de administración. Además, los materiales activos también se pueden mezclar con otros materiales activos que no interfieren con la acción deseada, o con materiales que suplementen la acción deseada o que tengan otra acción. Los componentes se pueden formular como el ingrediente farmacéuticamente activo único en el compuesto o se pueden combinar con otros ingredientes activos.

Cuando los compuestos exhiben insuficiente solubilidad, se pueden usar métodos para solubilizarlos. Tales métodos son conocidos e incluyen, pero no se limitan sólo a, uso de cosolventes tales como dimetilsulfóxido (DMSO), usando surfactantes tales como Tween® y

648

solución acuosa de bicarbonato de sodio. Los derivados de los componentes, tales como sales o prodrogas también se pueden usar para formular composiciones farmacéuticas efectivas.

La concentración del compuesto es efectiva para entregar una cantidad que al ser administrada reduce o aminora al menos un síntoma del trastorno para el cual se administra el compuesto. Típicamente los compuestos se formulan para administración de dosis únicas.

Los compuestos de la invención se pueden preparar con portadores que les protegen de la eliminación rápida del organismo, tales como formulaciones o revestimientos de liberación prolongada. Tales portadores incluyen formulaciones de liberación controlada, tales como, pero sin limitarse sólo a, sistemas de entrega microencapsulados. El principio activo se incluye en un portador farmacéuticamente aceptable en una cantidad suficiente para ejercer un efecto terapéutico útil sin presentar efectos secundarios indeseados en el paciente tratado. La concentración terapéuticamente efectiva se puede determinar empíricamente probando los compuestos en sistemas modelo *in vitro* e *in vivo* conocidos para el trastorno tratado.

Los compuestos y las composiciones de la invención se pueden colocar en contenedores de dosis múltiples o únicas. Por ejemplo, los compuestos y composiciones incluidas se pueden proporcionar en partes incluyendo componentes que se pueden ensamblar para su uso. Por ejemplo, se puede entregar como componentes separados un compuesto inhibidor liofilizado junto con un disolvente apropiado para su combinación antes de usarlos. Un conjunto puede incluir un compuesto inhibidor y un segundo agente terapéutico para su co-administración. El inhibidor y el segundo agente terapéutico se pueden entregar como partes componentes separadas. Un conjunto puede incluir una variedad de contenedores, donde cada contenedor alberga una o más unidades de dosis del compuesto de la invención. Los contenedores se adaptan preferentemente para el modo deseado de administración, incluyendo, sin limitarse sólo a tabletas, cápsulas de gelatina, cápsulas de liberación prolongada y similares para la administración oral; productos de almacén, jeringas preparadas, ampolletas, botellitas y similares para administración parenteral; así como parches, medipads, cremas y similares para administración tópica.

La concentración del principio activo en la composición de la droga dependerá de las tasas de absorción, inacción y eliminación del principio activo, el programa de dosis y la cantidad administrada junto con otros factores conocidos para personal especializado.

El ingrediente activo se puede administrar de una sola vez o se puede dividir en una cantidad de dosis más pequeñas administradas en intervalos de tiempo. Se entiende que la dosis precisa y la

duración del tratamiento dependen de la enfermedad tratada y se pueden determinar empíricamente usando protocolos de prueba conocidos o extrapolando datos de pruebas *in vivo* o *in vitro*. Se debe notar que los valores de las concentraciones y dosis también pueden variar según la gravedad de la condición que se pretende aliviar. También se debe comprender que para cualquier sujeto en particular, los regímenes de dosis específicos se deberían ajustar con el correr del tiempo de acuerdo con la necesidad individual y el criterio profesional de la persona que esté administrando o supervisando la administración de los compuestos y que los rangos de concentración indicados son sólo ejemplos y que no están diseñados para limitar la práctica o el alcance de los compuestos reivindicados.

Si se desea administración oral, el compuesto debería proporcionarse en una composición que le proteja del ambiente ácido del estómago. Por ejemplo, la composición se puede formular en un revestimiento entérico que mantenga su integridad en el estómago y que libere el principio activo en el intestino. La composición también se puede formular en combinación con un antiácido u otro ingrediente similar.

Las composiciones orales generalmente incluirán un disolvente inerte o un portador comestible y se puede comprimir en tabletas o incluir en cápsulas de gelatina. Con el fin de administración oral terapéutica, el principio activo o principios activos se pueden incorporar con excipientes y usarse en forma de tabletas, cápsulas, o grageas. Como parte de la composición se pueden incluir agentes y materiales aglutinantes compatibles farmacéuticamente.

Las tabletas, píldoras, cápsulas, grageas y similares pueden contener cualquiera de los siguientes ingredientes o compuestos de naturaleza similar: un aglutinantes tal como, pero sin limitarse sólo a, goma adragante, acacia, almidón de maíz o gelatina; un excipiente tal como celulosa microcristalina, almidón o lactosa; un agente disolvente tal como, pero sin limitarse sólo a, ácido algínico y almidón de maíz; un lubricante tal como, pero sin limitarse sólo a, estearato de magnesio; un dorador, tal como, pero sin limitarse sólo a, dióxido de silicona coloidal; un agente endulzante tal como sucrosa o sacarina; y un agente saborizante como menta, metil salicilato o sabor de frutas.

Cuando la forma de dosis unitaria es una cápsula, ella puede contener, además del material del tipo indicado arriba, un portador líquido tal como un aceite graso. Además, las formas de dosis unitaria pueden contener otros diversos materiales, los cuales modifican la forma física de la unidad de dosis, por ejemplo, revestimientos de azúcar y otros agentes entéricos. Los compuestos también se pueden administrar como un componente de un elixir, suspensión, jarabe, oblea, goma

650

de mascar o similares. Un jarabe puede contener, aparte de los principios activos, sucrosa como agente endulzante y ciertos preservantes, tintas y colorantes, y sabores.

Los principios activos también se pueden mezclar con otros principios activos que no interfieren con la acción deseada o con materiales que suplementan la acción deseada.

Las soluciones o suspensiones usadas para aplicaciones parenteral, intradermal, intratecal o tópicas pueden incluir cualquiera de los siguiente componentes: un disolvente estéril como agua para las inyecciones, solución salina, aceite fijo, un aceite vegetal de presencia natural como el aceite de ajonjolí, aceite de coco, aceite de cacahuate, aceite de semilla de algodón y similares, o bien, un vehículo graso sintético tal como etil oleato y similares, glicol polietileno, glicerina, glicol propileno u otro solvente sintético; agentes antimicrobianos tales como alcohol bencílico y parabencenos metílicos; antioxidantes tales como ácido ascórbico y bisulfito de sodio; agentes quelatantes tales como ácido etilenodiaminotetraacético (en inglés, ethylenediaminetetraacetic acid - EDTA); amortiguadores tales como acetatos, citratos y fosfatos; y agentes para el ajuste de la tonicidad tales como cloruro de sodio y dextrosa. Las preparaciones parenterales se pueden incluir en ampolletas, jeringas desechables o botellitas para dosis múltiple fabricadas de vidrio, plástico u otro material apropiado. Los amortiguadores, preservantes, antioxidantes y similares se pueden incorporar en la medida que se requieran.

Cuando se administra intravenosamente, los portadores apropiados incluyen soluciones salinas fisiológicas, de fosfato amortiguado (en inglés, phosphate buffered saline - PBS) así como soluciones que contienen agentes espesantes o solubilizadores tales como glucosa, glicol polietileno, glicol polipropileno y mezclas de los mismos. Las suspensiones liposomáticas que incluyen liposomas dirigidos a los tejidos también pueden ser apropiados como portadores farmacéuticamente aceptados. Estos se pueden preparar de acuerdo a los métodos conocidos; por ejemplo como se describe en la patente U.S. Patent No. 4,522,811.

Los principios activos se pueden preparar con portadores que protejan al compuesto contra la rápida eliminación del organismo, tal como formulaciones o revestimientos de liberación prolongada. Tales portadores incluyen formulaciones de liberación controlada tales como, pero sin limitarse sólo a, implantes y sistemas de entrega microencapsulados, y polímeros biodegradables y biocompatibles tales como colágeno, etileno acetato de vinilo, polianhídridos, ácido poliglicólico, poliortoésteres, ácido poliláctico y similares. Los métodos para la preparación de tales formulaciones especializadas son reconocidos.

651

Los compuestos de la invención se pueden administrar oral, parenteral (IV, IM, depo-IM, SQ y depo-SQ), sublingual, intranasal (inhalación), intratecal, tópica o rectalmente. Las formas de dosis conocidas por el personal especializado son apropiadas para la entrega de los compuestos de la invención.

Los compuestos de la invención se pueden administrar enteral o parenteralmente. Cuando se administran oralmente, los compuestos de la invención se pueden administrar en formas de dosis usuales para la administración oral que son muy conocidas por el personal especializado. Estas formas de dosis incluyen las formas de dosis usuales de tabletas y cápsulas así como formas de dosis líquidas tales como soluciones, suspensiones y elixires. Cuando se usan las formas de dosis sólidas, es preferible que ellas sean del tipo de liberación prolongada de manera que los compuestos de la invención requieran ser administrados sólo una o dos veces al día.

Las formas de dosis orales se administran al paciente 1, 2, 3 ó 4 veces al día. Es preferible que los compuestos de la invención se administren tres o menos veces, siendo aún más preferible una o dos veces al día. Por lo tanto, se prefiere que los compuestos de la invención se administren en forma de dosis oral. Se prefiere que sin importar la forma de dosis oral usada, esta sea diseñada para proteger los compuestos de la invención del ambiente ácido del estómago. Las tabletas entéricas revestidas son muy conocidas por el personal especializado. Además, las cápsulas rellenas con pequeñas esferas cada una revestida para proteger del estómago acídico también son muy conocidas por el personal especializado.

Cuando se administra oralmente, una cantidada administrada terapéuticamente efectiva para inhibir la actividad de beta-secretasa, para inhibir la producción de A beta, para inhibir la deposición de A beta, o para tratar o prevenir AD es desde cerca de 0.1 mg/día hasta aproximadamente 1,000 mg/día. Es preferible que la dosis oral sea de entre cerca de 1 mg/día a cerca de 100 mg/día. Es aún más preferible que la dosis oral sea de entre cerca de 5 mg/día a unos 50 mg/día. Se entiende que aunque se inicie a un paciente con una dosis, esa dosis puede alterarse a medida que cambie la condición del paciente.

Los compuestos de la invención también se pueden entregar ventajosamente en una formulación de dispersión de nanocristales. Por ejemplo, la preparación de tales formulaciones se describe en la patente U.S. Patent 5,145,684. Las dispersiones nanocristalinas de inhibidores de la proteasa del VIH y su método de uso se describen en la patente U.S. Patent No. 6,045,829. Las formulaciones nanocristalinas a menudo permiten una mayor biodisponibilidad de componentes de drogas.

Por ejemplo, los compuestos de la invención se pueden administrar parenteralmente mediante IV, IM, depo-IM, SC o depo-SC. Cuando se administran parenteralmente, se debería entregar una

652

cantidad terapéuticamente efectiva de cerca de 0.5 hasta alrededor de 100 mg/día, preferentemente desde cerca de 5 hasta cerca de 50 mg diariamente. Cuando se usa una formulación de almacén para inyección mensual o quincenal, la dosis debería ser de cerca de 0.5 mg/día hasta 50 mg/día, o una dosis mensual de unos 15 mg hasta 1,500 mg. Debido parcialmente a lo olvidadizos que son los pacientes con la enfermedad de Alzheimer, es preferible que la forma de dosis parenteral sea una formulación de almacén.

Los compuestos de la invención se pueden administrar sublingualmente. Cuando se entreguen sublingualmente, los compuestos de la invención deberían entregarse de una a cuatro veces al día en las cantidades descritas anteriormente para la administración IM.

Los compuestos de la invención se pueden administrar intranasalmente. Cuando se entreguen por esta vía, las formas de dosis apropiadas son atomizador nasal o en polvo, como es conocido para personal especializado. La dosis de los compuestos de la invención para la administración intranasal es la cantidad descrita anteriormente para la administración IM.

Los compuestos de la invención se pueden administrar intratecalmente. Cuando se entreguen por esta vía, la forma de dosis apropiada puede ser una dosis parenteral como es conocida para personal especializado. La dosis de los compuestos de la invención para la administración intratecal es la cantidad descrita anteriormente para la administración IM.

Los compuestos de la invención se pueden administrar tópicamente. Cuando se entreguen por esta vía, la forma de dosis apropiada es una crema, ungüento o parche. Debido a la cantidad de los compuestos de la invención a administrarse se prefiere el parche. Cuando se administra tópicamente, la dosis varía entre cerca de 0.5 mg/día a alrededor de 200 mg/día. Debido a que la cantidad que se puede entregar con un parche es limitada, se pueden usar dos o más parches. La cantidad de parches y su tamaño no son importantes, lo que sí es importante es que una cantidad terapéuticamente efectiva de los compuestos de la invención se entreguen como es conocido por personal especializado. Los compuestos de la invención se pueden administrar rectalmente con supositorios como es conocido por personal especializado. Cuando se administra vía supositorio, la cantidad terapéuticamente efectiva va desde cerca de 0.5 mg hasta alrededor de 500 mg.

Los compuestos de la invención se pueden administrar mediante implantes como es conocido por personal especializado. Al administrar un compuesto de la invención vía implante, la cantidad terapéuticamente efectiva es la cantidad descrita anteriormente para una administración de almacén.

Dado un compuesto particular de la invención y una forma de dosis deseada, el personal especializado podría saber cómo preparar y administrar la forma de dosis apropiada.

653

Los compuestos de la invención se usan de la misma manera, por las mismas vías de administración, usando las mismas formas de dosis farmacéuticas y el mismo programa de dosis como se describió anteriormente, para prevenir la enfermedad o para tratar pacientes con trastornos cognitivos leves (en inglés, MCI - mild cognitive impairment) así como prevenir o retrasar el inicio de la enfermedad de Alzheimer en aquellas personas que podrían avanzar desde MCI a AD, para el tratamiento o prevención del síndrome de Down, para el tratamiento de personas que padezcan de Hemorragia cerebral hereditaria con amiloidosis del tipo holandés, para tratar la angiopatía amiloide cerebral y evitar sus potenciales consecuencias, i.e. hemorragias lobulares únicas y recurrentes, para el tratamiento de otras demencias degenerativas, incluyendo demencias de origen vascular y degenerativo mixto, demencia asociada con la enfermedad de Parkinson, demencia asociada con parálisis supranuclear progresiva, demencia asociada con degeneración basal cortical y enfermedad de Alzheimer del tipo corporal difuso de Lewy.
Los compuestos de la invención se pueden usar en combinación, entre ellos o con otros agentes o enfoques terapéuticos usados para tratar o prevenir las condiciones indicadas anteriormente. Tales agentes o enfoques incluyen: inhibidores de acetilcolina esterasa tales como tacrina (tetrahidroaminoacridina, comercializada como COGNEX®), hidrocloruro de donepezil, (comercializado como Aricept® y rivastigmina (comercializada como Exelon®); inhibidores de gamma-secretasa; agentes antiinflamatorios tales como inhibidores de ciclooxigenasa II; antioxidantes tales como la vitamina E y ginkólidos; enfoques inmunológicos, tales como por ejemplo, inmunización con péptido A beta o administración de anticuerpos antipéptido A beta; estatinas; y agentes neurotrópicos directos o indirectes tales como Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454), y otros agentes neurotrópicos del futuro.

Además, los compuestos de la fórmula (I) también se pueden usar con inhibidores de P-glicoproteína (P-gp). Los inhibidores de P-gp y el uso de tales compuestos son conocidos por el personal especializado . Ver, por ejemplo, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), y las publicaciones internacionales WO99/64001 y WO01/10387. Lo importante es que el nivel sanguíneo del inhibidor de P-gp sea tal que ejerza su efecto inhibiendo que la P-gp reduzca los niveles de los compuestos de la fórmula (A) en las células sanguíneas del cerebro. Con ese fin el inhibidor de P-gp y los compuestos de la fórmula (A) se pueden administrar al mismo tiempo, por la misma o distinta vía de administración, o en distintas horas. Lo importante no es la hora de la administración sino que se tenga un nivel efectivo de inhibidor de P-gp en la sangre.
Inhibidores de P-gp apropiados incluyen ciclosporina A, verapamil, tamoxifeno, quinidina, Vitamin E-TGPS, ritonavir, acetato de megestrol, progesterona, rapamicina, 10,11-

659

metanodibenzosuberano, fenotiacinas, derivados de acridina tales como GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 y otros esteroides. Se debe comprender que se encontrarán agentes adicionales que tienen la misma función y por lo tanto logran el mismo resultado; tales compuestos también se consideran útiles.

Los inhibidores de P-gp se pueden administrar oral, parenteral, (IV, IM, IM-depo, SQ, SQ-depo), tópica, sublingual, rectal, intranasal, intratecalmente y por implante.

La cantidad terapéuticamente efectiva de inhibidores de P-gp varía entre cerca de 0.1 hasta cerca de 300 mg/kg/día, preferentemente cerca de 0.1 a alrededor de 150 mg/kg diariamente. Se comprende que aunque a un paciente se le inicie con una dosis, esa dosis puede ser alterada con el tiempo de acuerdo a los cambios en la condición del paciente.

Cuando se administran oralmente, los inhibidores de P-gp se pueden administrar en formas de dosis usuales para la administración oral que son conocidas por el personal especializado. Estas formas de dosis incluyen las formas de dosis usuales para unidades sólidas de tabletas y cápsulas así como para formas de dosis líquidas tales como soluciones, suspensiones y elixires. Cuando se usen las formas de dosis sólida, se prefiere que éstas sean del tipo de liberación prolongada de manera que los inhibidores de P-gp se administren solamente una o dos veces al día. Las formas de dosis orales se administran al paciente entre una y cuatro veces al día. Se prefiere que los inhibidores de P-gp se administren tres veces o menos al día, preferiblemente una o dos veces al día. Por lo tanto, se prefiere que los inhibidores de P-gp se administren en forma de dosis sólida y, aún más, se prefiere que la forma de dosis sólida sea de liberación prolongada que permite dosis diarias únicas o dobles. Se prefiere que sin importar la forma de dosis elegida, que esta sea diseñada para proteger a los inhibidores de P-gp del ambiente acídico del estómago. Las tabletas entéricas revestidas son reconocidas por personal especializado. Además, las cápsulas rellenas con pequeñas esferas cada una revestida para protegerlas del estómago acídico, también son bien conocidas por el personal especializado.

Por otra parte, los inhibidores de P-gp se pueden administrar parenteralmente. Con esta técnica, se pueden administrar vía IV, IM, depo-IM, SQ o depo-SQ.

Los inhibidores de P-gp se pueden entregar sublingualmente. Cuando se administran sublingualmente, los inhibidores de P-gp deberían proporcionarse entre una y cuatro veces al día en la misma cantidad que para la administración vía IM.

Los inhibidores de P-gp se pueden entregar intranasalmente. Cuando se proporcionan por esta vía de administración, las formas de dosis apropiadas son atomizador nasal y en polvo como es conocido para personal especializado. La dosis de los inhibidores de P-gp para administración intranasal es la misma que para administracín vía IM.

655

Los inhibidores de P-gp se pueden entregar intratecalmente. Cuando se entregan por esta vía de administración la forma de dosis apropiada puede ser una forma de dosis parenteral conocida para personal especializado.

Los inhibidores de P-gp se pueden entregar tópicamente. Cuando se entregan por esta vía de administración la forma de dosis apropiada es una crema, ungüento o parche. Debido a que la cantidad de los inhibidores de P-gp a administrarse se prefiere el parche. Sin embargo, la cantidad que se puede entregar con un parche es limitada. Por lo tanto, se pueden necesitar dos o más parches. La cantidad de parches y su tamaño no son importantes, lo que sí es importante es que una cantidad terapéuticamente efectiva de los inhibidores de P-gp se entreguen como es conocido por personal especializado.

Los inhibidores de P-gp se pueden administrar rectalmente con supositorios o por implantes, ambas técnicas son conocidas por personal especializado.

No existe nada nuevo acerca de la vía de administración o de las formas de dosis para administrar los inhibidores de P-gp. Dado un inhibidor de P-gp particular y una forma de dosis deseada, el personal especializado podrá saber cómo preparar y administrar la forma de dosis apropiada para el inhibidor de P-gp.

Para el personal especializado debería ser aparente que la dosis exacta y la frecuencia de administración dependerán de los compuestos de la invención particulares administrados, la condición particular bajo tratamiento, la gravedad de la condición tratada, la edad, el peso y condición física general del paciente en particular así como otros medicamentos que la persona pueda estar tomando que sean conocidos por los médicos tratantes especializados.

Inhibición de la escisión de la APP

Los compuestos de la invención inhiben la escisión de la APP entre las posiciones Met595 y Asp596, de acuerdo a la numeración usada para la isoforma APP695, o una mutación de la misma, o en un sitio correspondiente de una isoforma diferente, tal como la APP751 o la APP770, o una mutación de las mismas (a veces este sitio se conoce como el "sitio de la beta secretasa"). Aunque no se desee permanecer limitado a ninguna teoría en particular, se piensa que la inhibición de la actividad de la beta secretasa inhibe la producción del péptido amiloide beta (A beta). La actividad inhibitoria se demuestra por uno de varios ensayos de inhibición, en dónde la escisión de un sustrato de APP en la presencia de una enzima beta secretasa se analiza en la presencia del compuesto inhibitorio, bajo condiciones que normalmente son suficientes para dar como resultado la escisión en el sitio de escisión de la beta secretasa. La reducción en la escisión de la APP en el sitio de escisión de la beta secretasa en comparación con un control no tratado o

656

inactivo se correlaciona con la actividad inhibitoria. Los sistemas de ensayo que pueden ser usados para demostrar la eficacia de los compuestos inhibidores son conocidos. Se describen, por ejemplo, sistemas de ensayo representativos en las patentes de los Estados Unidos Nos. 5.942.400, 5.744.346, así como en los Ejemplos que se dan más abajo.

La actividad enzimática de la beta secretasa y la producción de A beta pueden ser analizadas *in vitro* o *in vivo*, usando sustratos de APP naturales, mutados, y/o sintéticos, una enzima natural, mutada, y/o sintética, y el compuesto a ser analizado. El análisis puede involucrar células primarias o secundarias que expresen APP y enzima nativas, mutantes, y/o sintéticas, modelos animales que expresen la APP y la enzima nativas, o puede utilizar modelos animales transgénicos que expresen el sustrato y la enzima. Se puede detectar la actividad enzimática mediante el análisis de uno o más de los productos de escisión por medio de, por ejemplo, inmunoensayos, ensayos cromogénicos o fluorimétricos, cromatografía líquida de alto rendimiento (HPLC, siglas en inglés) y otros medios de detección. Se determinan como compuestos inhibitorios aquellos compuestos que tengan la capacidad de disminuir la cantidad de productos de escisión de la beta secretasa producidos en comparación con un control, donde la escisión por la beta secretasa en el sistema reaccionante se observa y mide en la ausencia de compuestos inhibitorios.

Beta secretasa

Se conocen varias formas de la enzima beta secretasa que están disponibles y son útiles para ensayos de la actividad enzimática y de la inhibición de dicha actividad. Las mismas incluyen formas nativas, recombinantes y sintéticas de la enzima. La beta secretasa humana se conoce como la enzima de escisión de la APP en el sitio beta (BACE, siglas en inglés), Asp2, y Memapsin 2, y ha sido caracterizada, por ejemplo, en la patente de los Estados Unidos No. 5.744.346 y en las publicaciones de las solicitudes de patentes presentadas bajo el Tratado de Cooperación en Patentes (PCT, por sus siglas en inglés) WO98/22597, WO00/03819, WO01/23533, y WO00/17369, así como en publicaciones en la literatura científica (Hussain et al., 1999, *Mol. Cell. Neurosci.* 14:419-427; Vassar et al., 1999, *Science* 286:735-741; Yan et al., 1999, *Nature* 402:533-537; Sinha et al., 1999, *Nature* 40:537-540; y Lin et al., 2000, *PNAS USA* 97:1456-1460). También se han descrito formas sintéticas de la enzima (WO98/22597 y WO00/17369). La beta secretasa puede ser extraída y purificada a partir de tejido cerebral humano y puede ser producida en células, por ejemplo células de mamíferos que expresen la enzima recombinante.

657

Los compuestos preferidos son eficaces para reducir en un 50% la actividad enzimática de la beta secretasa a una concentración menor que 50 micromolar, preferentemente a una concentración de 10 micromolar o menor, más preferentemente 1 micromolar o menor, y aún más preferentemente 10 nanomolar o menor.

Sustrato de APP

Los ensayos que demuestran la inhibición de la escisión de la APP por la beta secretasa pueden utilizar cualquiera de las formas conocidas de la APP, incluyendo el isotipo "normal" de 695 aminoácidos descrito por Kang et al., 1987, *Nature* 325:733-6, el isotipo de 770 aminoácidos descrito por Kitaguchi et. al., 1981, *Nature* 331:530-532, y variantes tales como la mutación sueca (KM670-1NL) (APP-SW), la mutación de Londres(V7176F), y otras. Véase por ejemplo, la patente de los Estados Unidos No. 5.766.846 y también Hardy, 1992, *Nature Genet.* 1:233-234, para tener una reseña de las variantes mutacionales conocidas. Otros sustratos útiles incluyen la modificación aminoácida dibásica, APP-KK, divulgada, por ejemplo, en WO 00/17369, fragmentos de APP, y péptidos sintéticos que contengan el sitio de escisión de la beta secretasa, tipos salvajes (WT, siglas en inglés) o formas mutadas, por ejemplo, SW, como se describe, por ejemplo, en la patente de los Estados Unidos No. 5.942.400 y en WO00-03819.
El sustrato de APP contiene el sitio de escisión de la APP por la beta secretasa (KM-DA o NL-DA) por ejemplo, un péptido completo de APP o variante, un fragmento de APP, una APP recombinante o sintética, o un péptido de fusión. Preferentemente, el péptido de fusión incluye el sitio de escisión de la beta secretasa unido a un péptido que contiene una porción útil para el ensayo enzimático, por ejemplo, una porción que tenga propiedades de aislamiento y/o detección. Una porción útil puede ser un epítopo antigénico para ligar anticuerpos, un marcador u otra porción de detección, un sustrato ligante, y similares.

Anticuerpos

Se pueden medir los productos característicos de la escisión de la APP mediante inmunoensayos que utilizan diversos anticuerpos, como se describe, por ejemplo, en Pirttila et al., 1999, *Neuro. Lett.* 249:21-4, y en la patente de los Estados Unidos No. 5.612.486. Los anticuerpos de utilidad para detectar A beta incluyen, por ejemplo, el anticuerpo monoclonal 6E10 (Senetek, St. Louis, MO) que específicamente reconoce un epítopo en los aminoácidos 1-16 del péptido A beta; los anticuerpos 162 y 164 (New York State Institute for Basic Research, Staten Island, NY) que son específicos para los péptidos A beta humanos 1-40 y 1-42, respectivamente; y los anticuerpos que reconocen la región de unión del péptido amiloide beta, el sitio entre los residuos 16 y 17, como

658

se describe en la patente de los Estados Unidos No. 5.593.846. Los anticuerpos generados en contra de un péptido sintético de los residuos 591 a 596 de la APP y el anticuerpo SW192 generado en contra de los residuos 590-596 de la mutación sueca son también útiles en inmunoensayos de la APP y sus productos de escisión, como se describe en las patentes de los Estados Unidos Nos. 5.604.102 y 5.721.130.

Sistemas de ensayo

Los ensayos para determinar la escisión de la APP en el sitio de escisión de la beta secretasa son bien conocidos en la técnica. Ejemplos de estos ensayos se describen, por ejemplo, en las patentes de los Estados Unidos Nos. 5.744.346 y 5.942.400, y en los Ejemplos de más abajo.

Ensayos libres de células

Los ejemplos de ensayos que pueden usarse para demostrar la actividad inhibitoria de los compuestos de la invención se describen, por ejemplo, en las publicaciones WO00/17369, WO 00/03819, y las patentes de los Estados Unidos Nos. 5.942.400 y 5.744.346. Tales ensayos pueden realizarse en incubaciones libres de células o en incubaciones celulares que usen células que expresen una beta secretasa y un sustrato de APP que tenga un sitio de escisión de la beta secretasa.

Se incuba un sustrato de la APP conteniendo el sitio de escisión de la beta secretasa, por ejemplo, una APP completa o variante, un fragmento de la APP, o un sustrato de APP recombinante o sintético conteniendo las secuencias de aminoácidos KM-DA o NL-DA, en la presencia de la enzima beta secretasa, un fragmento de la misma, o una variante polipéptida recombinante o sintética que tenga actividad de beta secretasa y que sea efectiva en escindir la APP en el sitio de escisión de la beta secretasa, bajo condiciones de incubación apropiadas para la actividad escindente de la enzima. Los sustratos apropiados opcionalmente incluyen derivados que pueden ser proteínas o péptidos de fusión que contengan el sustrato del péptido y una modificación útil para facilitar la purificación o la detección del péptido o de sus productos de escisión por la beta secretasa. Las modificaciones útiles incluyen la inserción de un epítopo antigénico para ligar anticuerpos; ligar un marcador o una porción detectable; ligar un sustrato ligante; y similares. Las condiciones de incubación apropiadas para un ensayo *in vitro* libre de células incluyen, por ejemplo: una solución acuosa, aproximadamente 200 nanomolar a 10 micromolar en el sustrato, aproximadamente 10 a 200 picomolar en la enzima, y aproximadamente 0.1 nanomolar a 10 micromolar en el compuesto inhibitorio, a un pH de aproximadamente 4-7, a aproximadamente 37 grados C, por un período de aproximadamente 10 minutos a 3 horas. Estas condiciones de

660
659

incubación son a modo de ejemplo únicamente, y pueden ser variadas como lo requieran los compuestos particulares a ser ensayados y/o el sistema de medición deseado. La optimización de las condiciones de incubación para los componentes particulares a ser ensayados debe tomar en cuenta la enzima beta secretasa específica a ser usada y su pH óptimo, enzimas y/o marcadores adicionales que puedan ser usados en el ensayo, y similares. Tal optimización es de rutina y no requiere ninguna experimentación indebida.

Un ensayo de utilidad emplea un péptido de fusión que contiene una proteína ligante de maltosa (MBP, siglas en inglés) unida a la terminal C de los 125 aminoácidos de la APP-SW. La porción MBP es capturada en un sustrato de ensayo por el anticuerpo de captura anti-MBP. La incubación de la proteína de fusión capturada en la presencia de la beta secretasa da como resultado la escisión del sustrato en el sitio de escisión de la beta secretasa. Se puede analizar la actividad escindente mediante, por ejemplo, inmunoensayos de los productos de escisión. Uno de tales inmunoensayos detecta un epítopo único expuesto en la terminal carboxi de la proteína de fusión escindida utilizando, por ejemplo, el anticuerpo SW192. Este ensayo se describe, por ejemplo, en la patente de los Estados Unidos No 5.942.400.

Ensayo celular

Se pueden usar numerosos ensayos basados en células para analizar la actividad de la beta secretasa y/o el procesamiento de la APP para liberar A beta. Se puede usar el contacto dentro de la célula de un sustrato de APP con la enzima beta secretasa en la presencia o ausencia de un compuesto inhibitorio de la invención para demostrar la capacidad inhibitoria de la beta secretasa del compuesto. Preferentemente, el ensayo en la presencia de un compuesto inhibitorio útil provee una inhibición de la actividad enzimática de al menos alrededor de un 30%, más preferentemente de al menos alrededor de un 50%, en comparación con un control no inhibido.

En una materialización, se usan células que naturalmente expresan la beta secretasa. Alternativamente, se modifican las células para que expresen una beta secretasa recombinante o una variante sintética de la enzima como se discute más arriba. El sustrato de APP puede ser agregado al medio de cultivo y se prefiere que sea expresado en las células. Se pueden usar células que expresen naturalmente la APP, formas variantes o mutantes de la APP, o células transformadas para expresar una isoforma de la APP, formas variantes o mutantes de la APP, APP sintética o recombinante, fragmentos de APP, o un péptido o proteína de fusión de APP sintéticos que contengan el sitio de escisión de la APP por la beta secretasa, siempre que se le permita a la APP expresada entrar en contacto con la enzima y que la actividad de escisión enzimática pueda ser analizada.

660

Las líneas de células humanas que normalmente procesan A beta a partir de la APP suministran un medio útil para ensayar las actividades inhibitorias de los compuestos de la invención. Se puede medir la producción y la liberación de A beta y/o otros productos de escisión en el medio de cultivo mediante, por ejemplo, inmunoensayos tales como el Western Blot e enzimo-inmunoensayos (EIA, siglas en inglés) tales como el ensayo ELISA.

Las células que expresan un sustrato de APP y una beta secretasa activa pueden ser incubadas en la presencia de un compuesto inhibitorio para demostrar la inhibición de la actividad enzimática por comparación con un control. Se puede medir la actividad de la beta secretasa mediante el análisis de uno o más de los productos de escisión del sustrato de APP. Por ejemplo, sería de esperar que la inhibición de la actividad de la beta secretasa sobre el sustrato de APP disminuya la liberación de productos específicos de la escisión de la APP inducida por la beta secretasa tales como el péptido A beta.

Aunque tanto las células neurales como las no neurales procesan y liberan A beta, los niveles de actividad de la beta secretasa endógena son bajos y a menudo difíciles de detectar mediante EIA. Entonces, se prefiere el uso de tipos de células conocidos por incrementar la actividad de la beta secretasa, el procesamiento de la APP a A beta, y/o la producción de A beta. Por ejemplo, la transfección de células con la forma mutante sueca de la APP (APP-SW); con APP-KK; o con APP-SW-KK proporciona células que tienen la actividad de la beta secretasa incrementada y producen cantidades de A beta que pueden ser fácilmente medidas.

En tales ensayos, por ejemplo, las células que expresan la APP y la beta secretasa son incubadas en un medio de cultivo bajo condiciones adecuadas para la actividad enzimática de la beta secretasa sobre el sitio de escisión del sustrato de APP. Al exponer las células al compuesto inhibitorio, la cantidad de A beta liberada en el medio y/o la cantidad de fragmentos CTF99 de la APP en el lisado celular se reduce en comparación con el control. Los productos de escisión de la APP pueden ser analizados, por ejemplo, mediante reacciones inmunes con anticuerpos específicos, como se ha descrito con anterioridad.

Las células preferidas para el análisis de la actividad de la beta secretasa incluyen células neuronales humanas primarias, células neuronales primarias de animales transgénicos donde el transgene es APP, y otras células tales como líneas de células 293 estables que expresen APP, por ejemplo, APP-SW.

Ensayos *in vivo*: Modelos animales

Se pueden utilizar diversos modelos animales para analizar la actividad de la beta secretasa y/o el procesamiento de la APP para liberar A beta, como se ha descrito con anterioridad. Por ejemplo,

66

se pueden usar animales transgénicos que expresen el sustrato de APP y la enzima beta secretasa para demostrar la actividad inhibitoria de los compuestos de la invención. Ciertos modelos de animales transgénicos han sido descritos, por ejemplo, en las patentes de los Estados Unidos Nos. 5.877.399; 5.612.486; 5.387.742; 5.720.936; 5.850.003; 5.877.015, y 5.811.633, y en Ganes et al., 1995, *Nature* 373:523. Se prefieren animales que exhiban características relacionadas a la patofisiología de la EA. La administración de los compuestos inhibitorios de la invención a los ratones transgénicos descritos aquí provee un método alternativo para demostrar la actividad inhibitoria de los compuestos. Se prefiere que la administración de los compuestos sea en un vehículo farmacéuticamente eficaz y mediante una vía de administración que permita que se alcance al tejido objetivo en una cantidad terapéuticamente apropiada.

En estos animales, se puede analizar la inhibición de la escisión de la APP por medio de la enzima sobre el sitio de escisión de la beta secretasa y la liberación de A beta midiendo los fragmentos de escisión en los líquidos corporales, tales como los tejidos o los líquidos cerebrales de estos animales. Se prefiere el análisis de los depósitos o placas de A beta en los tejidos cerebrales.

Al contactar un sustrato de APP con una enzima beta secretasa en la presencia de un compuesto inhibitorio de la invención bajo condiciones tales que permitan la escisión enzimática de la APP y/o la liberación de A beta del sustrato, los compuestos de la invención son eficaces para reducir la escisión de APP por la acción de la enzima sobre el sitio de escisión de la beta secretasa y/o eficaces para reducir la cantidad liberada de A beta. Cuando tal contacto consiste en la administración de los compuestos inhibitorios de la invención a un modelo animal, por ejemplo, como se describe arriba, los compuestos son eficaces para reducir el depósito de A beta en los tejidos cerebrales del animal, y para reducir el número y/o el tamaño de las placas amiloides beta. Cuando se los administra a un sujeto humano, los compuestos son eficaces para inhibir o retardar la progresión de la enfermedad que se caracteriza por el aumento de la cantidad de A beta, retardar la progresión de la EA, y/o prevenir el inicio o la evolución de la EA en los pacientes a riesgo de sufrir la enfermedad.

A menos que se definan de otra manera, todos los términos científicos y técnicos usados aquí tienen el mismo significado que les asignaría una persona capacitada en las técnicas a las cuales pertenece esta invención. Todas las patentes y publicaciones referidas aquí son incorporadas por referencia a este documento para todo propósito.

Definiciones

662

Las definiciones y explicaciones dadas abajo se aplican a los términos usados en todo este documento incluyendo tanto la memoria técnica como las reivindicaciones.

Se debe notar que, como se usa en la memoria técnica y en las reivindicaciones adjuntas, las formas singulares "un," "una," "el," y "la" incluyen referencias plurales a menos que el contexto claramente indique lo contrario. Así, por ejemplo, una referencia a una composición conteniendo "un compuesto" incluye una mezcla de dos o más compuestos. Se debe notar también que el término "o" se emplea generalmente con el sentido de incluir "y/o" a menos que el contexto claramente indique lo contrario.

Cuando se indica que sustituyentes múltiples se encuentran unidos a una estructura, se debe entender que los sustituyentes pueden ser los mismos o diferentes. Así por ejemplo, la expresión "R_m opcionalmente sustituido con 1, 2 o 3 grupos R_q" indica que R_m esta sustituido con 1, 2, o 3 grupos R_q donde los grupos R_q pueden ser los mismos o diferentes.

Se define APP (siglas en inglés), proteína precursora del amiloide, como cualquier polipéptido APP, incluyendo variantes, mutaciones, e isoformas de la APP como se divulga, por ejemplo, en la patente de los Estados Unidos No. 5.766.846.

Se define como A beta, péptido amiloide beta, cualquier péptido que resulte de la escisión de la APP por medio de la beta secretasa, incluyendo péptidos de 39, 40, 41, 42, y 43 aminoácidos, y que se extienden desde el sitio de escisión de la beta secretasa a los aminoácidos 39, 40, 41, 42, o 43.

La beta secretasa (BACE1, Asp2, Memapsin 2) es una proteasa aspartilo mediante la cual se escinde la APP en el borde de la terminal amino de A beta. La beta secretasa humana se describe, por ejemplo, en WO00/17369.

La expresión "farmacéuticamente aceptable" se refiere a aquellas propiedades y/o sustancias que son aceptables para el paciente desde un punto de vista farmacológico/toxicológico y para el químico farmacéutico fabricante desde un punto de vista físico/químico en lo que respecta a la composición, formulación, estabilidad, aceptación por el paciente y biodisponibilidad.

Una cantidad "terapéuticamente eficaz" se define como una cantidad eficaz para reducir o disminuir al menos uno de los síntomas de la enfermedad bajo tratamiento o que reduce o retrasa la aparición de uno o más de los marcadores clínicos o síntomas de la enfermedad.

Por "alquilo" y "C_1-C_6 alquilo" en la presente invención se entiende grupos alquilo de cadena lineal o ramificada que tengan de 1 a 6 átomos de carbono, tales como, metilo, etilo, propilo, isopropilo, n-butilo, sec-butilo, terc-butilo, pentilo, 2-pentilo, isopentilo, neopentilo, hexilo, 2-hexilo, 3-hexilo, y 3-metilpentilo. Se entiende que en los casos donde una cadena alquilo de un sustituyente (por ejemplo, de un grupo alquilo, alcoxi o alquenilo) sea más corta o

más larga que 6 carbonos, esto se indicará en el segundo "C." Así, por ejemplo, "C_1-C_{10}" indica un máximo de 10 carbonos.

Por "alcoxi" y "C_1-C_6 alcoxi" en la presente invención se entiende grupos alquilo de cadena lineal o ramificada que tengan de 1 a 6 átomos de carbono, unidos a través de al menos un átomo de oxígeno bivalente, como por ejemplo, metoxi, etoxi, propoxi, isopropoxi, n-butoxi, sec-butoxi, terc-butoxi, pentoxi, isopentoxi, neopentoxi, hexoxi, y 3-metilpentoxi.

Por el término "halógeno" en la presente invención se entiende fluor, bromo, cloro, y yodo.

Por "alquenilo" y "C_2-C_6 alquenilo" se entiende radicales de hidrocarbonos lineales y ramificados que tengan de 2 a 6 átomos de carbono y de 1 a 3 enlaces dobles e incluye, por ejemplo, etenilo, propenilo, 1-but-3-enilo, 1-pent-3-enilo, 1-hex-5-enilo y similares.

Por "alquinilo" y "C_2-C_6 alquinilo" se entiende radicales de hidrocarbonos lineales y ramificados que tengan de 2 a 6 átomos de carbono y uno o dos enlaces triples e incluye etinilo, propinilo, butinilo, pentin-2-ilo y similares.

Como se usa aquí, el término "cicloalquilo" se refiere a radicales carbocíclicos saturados que tengan de tres a doce átomos de carbono. El cicloalquilo puede ser be monocíclico, un sistema policíclico fusionado, o un sistema de puente bi o policíclico, tal como adamantilo o biciclo [2.2.1] heptilo. Ejemplos de tales radicales incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Los grupos cicloalquilo preferidos son ciclopentilo, ciclohexilo, y cicloheptilo. Aquí, los grupos cicloalquilo no están sustituidos o, si se especifica, están sustituidos con diversos grupos en una o más posiciones sustituibles. Por ejemplo, tales grupos cicloalquilo pueden ser opcionalmente sustituidos con, por ejemplo, C_1-C_6 alquilo, C_1-C_6 alcoxi, halógeno, hidroxi, ciano, nitro, amino, mono(C_1-C_6)alquilamino, di(C_1-C_6)alquilamino, C_2-C_6alquenilo, C_2-C_6alquinilo, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, amino(C_1-C_6)alquilo, mono(C_1-C_6)alquilamino(C_1-C_6)alquilo o di(C_1-C_6)alquilamino(C_1-C_6)alquilo.

Por "arilo" se entiende un grupo carbocíclico aromático que contenga un anillo simple (por ejemplo, fenilo) o múltiples anillos condensados en los que al menos uno es aromático, (por ejemplo, 1,2,3,4-tetrahidronaftilo, naftilo), el que es opcionalmente mono-, bi-, o trisustituido. Los grupos arilo preferidos de la presente invención son fenilo, 1-naftilo, 2-naftilo, indanilo, indenilo, dihidronaftilo, fluorenilo, tetralinilo o 6,7,8,9-tetrahidro-5H-benzo[a]cicloheptenilo. Aquí, los grupos arilo no están sustituidos o, si se especifica, están sustituidos con diversos grupos en una o más posiciones sustituibles. Por ejemplo, tales grupos arilo pueden ser opcionalmente sustituidos con, por ejemplo, C_1-C_6 alquilo, C_1-C_6 alcoxi, halógeno, hidroxi, ciano, nitro, amino, mono(C_1-C_6)alquilamino, di(C_1-C_6)alquilamino, C_2-C_6alquenilo, C_2-C_6alquinilo, C_1-

665

664

C_6 haloalquilo, C_1-C_6 haloalcoxi, amino(C_1-C_6)alquilo, mono(C_1-C_6)alquilamino(C_1-C_6)alquilo o di(C_1-C_6)alquilamino(C_1-C_6)alquilo.

Por "heteroarilo" se entiende uno o más sistemas de anillos aromáticos de anillos de 5, 6, o 7 miembros, incluyendo sistemas de anillos fusionados de 9-11 átomos conteniendo al menos uno y hasta cuatro heteroátomos seleccionados de nitrógeno, oxígeno, o azufre. Los grupos heteroarilo preferidos de la presente invención incluyen piridinilo, pirimidinilo, quinolinilo, benzotienilo, indolilo, indolinilo, piridazinilo, pirazinilo, isoindolilo, isoquinolilo, quinazolinilo, quinoxalinilo, ftalazinilo, imidazolilo, isoxazolilo, pirazolilo, oxazolilo, tiazolilo, indolizinilo, indazolilo, benzotiazolilo, bencimidazolilo, benzofuranilo, furanilo, tienilo, pirrolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, oxazolopiridinilo, imidazopiridinilo, isotiazolilo, naftiridinilo, cinolinilo, carbazolilo, beta-carbolinilo, isocromanilo, cromanilo, tetrahidroisoquinolinilo, isoindolinilo, isobenzotetrahidrofuranilo, isobenzotetrahidrotienilo, isobenzotienilo, benzoxazolilo, piridopiridinilo, benzotetrahidrofuranilo, benzotetrahidrotienilo, purinilo, benzodioxolilo, triazinilo, fenoxazinilo, fenotiazinilo, pteridinilo, benzotiazolilo, imidazopiridinilo, imidazotiazolilo, dihidrobencisoxazinilo, bencisoxazinilo, benzoxazinilo, dihidrobencisotiazinilo, benzopiranilo, benzotiopiranilo, cumarinilo, isocumarinilo, cromonilo, cromanonilo, N-óxido de piridinilo, tetrahidroquinolinilo, dihidroquinolinilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidrocumarinilo, dihidroisocumarinilo, isoindolinonilo, benzodioxanilo, benzoxazolinonilo, N-óxido de pirrolilo, N-óxido de pirimidinilo, N-óxido de piridazinilo, N-óxido de pirazinilo, N-óxido de quinolinilo, N-óxido de indolilo, N-óxido de indolinilo, N-óxido de isoquinolilo, N-óxido de quinazolinilo, N-óxido de quinoxalinilo, N-óxido de ftalazinilo, N-óxido de imidazolilo, N-óxido de isoxazolilo, N-óxido de oxazolilo, N-óxido de tiazolilo, N-óxido de indolizinilo, N-óxido de indazolilo, N-óxido de benzotiazolilo, N-óxido de bencimidazolilo, N-óxido de pirrolilo, N-óxido de oxadiazolilo, N-óxido de tiadiazolilo, N-óxido de triazolilo, N-óxido de tetrazolilo, S-óxido de benzotiopiranilo, S,S-dióxido de benzotiopiranilo, tetrahidrocarbazol, tetrahidrobetacarbolino. Aquí, los grupos heteroarilo no están substituidos o, como se especifique, están sustituidos con diversos grupos en una o más de las posiciones sustituibles. Por ejemplo, tales grupos heteroarilo pueden ser opcionlmente sustituidos con, por ejemplo, C_1-C_6 alquilo, C_1-C_6 alcoxi, halógeno, hidroxi, ciano, nitro, amino, mono(C_1-C_6)alquilamino, di(C_1-C_6)alquilamino, C_2-C_6alquenilo, C_2-C_6alquinilo, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, amino(C_1-C_6)alquilo, mono(C_1-C_6)alquilamino(C_1-C_6)alquilo o di(C_1-C_6)alquilamino(C_1-C_6)alquilo.

Por "heterociclo", "heterocicloalquilo" o "heterociclilo" se entiende uno o más sistemas de anillos carbocíclicos de anillos de 4, 5, 6, o 7 miembros incluyendo sistemas de anillos fusionados de 9-11 átomos conteniendo al menos uno y hasta cuatro heteroátomos seleccionados de nitrógeno, oxígeno, o azufre. Los heterociclos preferidos de la presente invención incluyen

665

morfolinilo, tiomorfolinilo, S-óxido de tiomorfolinilo, S,S-dióxido de tiomorfolinilo, piperazinilo, homopiperazinilo, pirrolidinilo, pirrolinilo, tetrahidropiranilo, piperidinilo, tetrahidrofuranilo, tetrahidrotienilo, homopiperidinilo, homomorfolinilo, homotiomorfolinilo, S,S-dióxido de homotiomorfolinilo, oxazolidinonilo, dihidropirazolilo, dihidropirrolilo, dihidropirazinilo, dihidropiridinilo, dihidropirimidinilo, dihidrofurilo, dihidropiranilo, S-óxido de tetrahidrotienilo, S,S-dióxido de tetrahidrotienilo y S-óxido de homotiomorfolinilo. Aquí, los grupos heterociclos no están substituidos o, como se especifique, están sustituidos con diversos grupos en una o más de las posiciones sustituibles. Por ejemplo, tales grupos heterocíclicos pueden ser opcionalmente sustituidos con, por ejemplo, C_1-C_6 alquilo, C_1-C_6 alcoxi, halógeno, hidroxi, ciano, nitro, amino, mono(C_1-C_6)alquilamino, di(C_1-C_6)alquilamino, C_2-C_6alquenilo, C_2-C_6alquinilo, C_1-C_6 haloalquilo, C_1-C_6 haloalcoxi, amino(C_1-C_6)alquilo, mono(C_1-C_6)alquilamino(C_1-C_6)alquilo, di(C_1-C_6)alquilamino(C_1-C_6)alquilo ú =O.

Todas las patentes y publicaciones aquí referidas son incorporadas por referencia para todo propósito.

Las estructuras han sido nombradas (en inglés) usando el Name Pro IUPAC Naming Software, versión 5.09, disponible en Advanced Chemical Development, Inc., 90 Adelaide Street West, Toronto, Ontario, M5H 3V9, Canadá.

Se puede entender mejor la presente invención en referencia a los siguientes ejemplos. Estos ejemplos intentan ser representativos de materializaciones específicas de la invención pero no intentan limitar la extensión de la misma.

Las siguientes abreviaturas pueden ser usadas en los Ejemplos:

EDC representa 1-(3-dimetilaminopropil)-3-etilocarbodiimida o la sal de clorhidrato;

DIEA representa diisopropiletilamina;

PyBOP representa hexafluorofosfato de benzotriazol-1-iloxi)tripirrolidinofosfonio;

HATU representa hexafluorofosfato de O-(7-azabenzotriazol-1-ilo)-1,1,3,3-tetrametiluronio;

THF representa tetrahidrofurano;

EtBz representa etilbenzeno;

DCM representa diclorometano.

EJEMPLOS BIOLÓGICOS

Ejemplo A

Ensayo de inhibición de la enzima

Se analiza la actividad inhibitoria de los compuestos de la invención mediante el ensayo MBP-C125. Este ensayo determina la inhibición relativa de la escisión por la beta secretasa de un sustrato APP de modelo, MBP-C125SW, por los compuestos ensayados en comparación con un control no tratado. Se puede encontrar una descripción detallada de los parámetros del ensayo, por ejemplo, en la patente de los Estados Unidos No. 5.942.400. Brevemente, el sustrato es un péptido de fusión formado por una proteína ligante de maltosa (MBP, siglas en inglés) y los 125 aminoácidos de terminal carboxi de la APP-SW, la mutación sueca. La enzima beta secretasa se deriva de tejido cerebral humano como se describe en Sinha et al, 1999, *Nature* 40:537-540) o se produce en forma recombinante como la enzima de longitud completa (aminoácidos 1-501), y

666

puede prepararse, por ejemplo, a partir de las células 293 que expresan el cADN recombinante, como se describe en WO00/47618.

La inhibición de la enzima se analiza, por ejemplo, mediante inmunoensayos de los productos de escisión de la enzima. Un ejemplo del ensayo ELISA utiliza un anticuerpo de captura anti-MBP que se deposita sobre placas de alta unión con 96 pocillos las que han sido prerrecubiertas y bloqueadas, a lo que se sigue con una incubación con una dilución del sobrenadante de la reacción enzimática, una incubación con un anticuerpo de detección específico, por ejemplo, el anticuerpo de detección anti-SW192 biotinilado, y una incubación posterior con estreptavidina/fosfatasa alcalina. En el ensayo, la escisión de la proteína de fusión MBP-C125SW intacta da como resultado la generación de un fragmento amino-terminal truncado lo que expone un nuevo epítopo positivo al anticuerpo SW-192 en la terminal carboxi. La detección se efectúa mediante una señal del sustrato fluorescente al ser escindido por la fosfatasa. El ensayo ELISA sólo detecta escisiones posteriores a la posición Leu 596 en el sitio de mutación APP-SW 751 del sustrato.

Procedimiento de ensayo específico:

Los compuestos se diluyen en una serie de diluciones 1:1 sobre una curva de concentración de seis puntos (dos pocillos por concentración) en una fila de 96 placas por compuesto analizado. Cada uno de los compuestos a analizar se prepara en sulfóxido de dimetilo (DMSO, siglas en inglés) dando como resultado una solución stock 10 milimolar. La solución stock se diluye en serie en DMSO para obtener una concentración final de 200 micromolar en el compuesto en el punto superior de una curva de dilución de 6 puntos. Se agregan diez (10) microlitros de cada dilución a cada uno de los dos pocillos en la fila C de la correspondiente placa de fondo en V, a la cuál se le había agregado 190 microlitros de una solución 52 milimolar de NaOAc, 7,9% DMSO, y de pH 4,5. La placa del compuesto diluido con NaOAc se hace girar para precipitar las partículas y se transfieren 20 microlitros por pocillo a una placa de fondo plano a la que se le agrega 30 microlitros de una mezcla de enzima y sustrato helada (2,5 microlitros de sustrato MBP-C125SW, 0,03 microlitros de enzima y 24,5 microlitros de 0,09% TX100 helado por cada 30 microlitros). La mezcla de reacción final de concentración 200 micromolar en el compuesto en el punto más alto de curva es 5% en DMSO, 20 milimolar en NaOAc, 0,06% TX100, y su pH es 4,5.

Se inicia la reacción enzimática mediante el calentamiento de las placas a 37 grados C. Luego de 90 minutos a 37 grados C, se agregan 200 microlitros por pocillo del diluyente del espécimen frío para parar la reacción y se transfieren 20 microlitros por pocillo a la correspondiente placa ELISA

667

recubierta con el anticuerpo anti-MBP para la captura, placa que contiene 80 microlitros del diluyente del espécimen por pocillo. Se deja incubar la reacción durante toda la noche a 4 grados C, y al día siguiente se desarrolla el ensayo ELISA después de 2 horas de incubación con el anticuerpo anti-192SW, seguido por Estreptavidina-AP conjugada y el sustrato fluorescente. La señal se lee sobre una placa lectora fluorescente.

La potencia inhibitoria relativa del compuesto se determina calculando la concentración del compuesto que presente una reducción del cincuenta por ciento en la señal detectada (IC_{50}) cuando se la compara con la señal de la reacción enzimática en los pocillos de control a los que no se les ha agregado ningún compuesto. En este ensayo, los compuestos preferidos de la invención presentan una IC_{50} menor que 50 micromolar.

Ejemplo B

Ensayo de inhibición libre de células utilizando un sustrato de APP sintético

Se puede determinar la actividad de la beta secretasa en la presencia o ausencia de los compuestos inhibitorios de la invención mediante un sustrato de APP sintético que pueda ser escindido por la beta secretasa, que tenga una biotina N-terminal, y que se haya hecho fluorescente por medio de la unión covalente de verde de Oregón en el residuo Cys. Los sustratos útiles incluyen los siguientes:

Biotina-SEVNL-DAEFRC[verde de Oregón]KK [SEQ ID NO: 1]
Biotina-SEVKM-DAEFRC[verde de Oregón]KK [SEQ ID NO: 2]
Biotina-GLNIKTEEISEISY-EVEFRC[verde de Oregón]KK [SEQ ID NO: 3]
Biotina-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEFRC
[verde de Oregón]KK [SEQ ID NO: 4]
Biotina-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC
[verde de Oregón]KK [SEQ ID NO: 5]

La enzima (0,1 nanomolar) y los compuestos a analizar (0,001-100 micromolar) se incuban en placas negras (de 384 pocillos) de baja afinidad y prebloqueadas, a 37 grados durante 30 minutos. La reacción se inicia mediante la adición de un sustrato 150 milimolar a un volumen final de 30 microlitros por pocillo. Las condiciones de ensayo finales son: 0,001-100 micromolar de compuesto inhibitorio; 0,1 molar de acetato de sodio (pH 4,5); 150 nanomolar de sustrato; 0,1 nanomolar de beta secretasa soluble; 0,001% Tween 20; y 2% de DMSO. La mezcla de ensayo se incuba durante 3 horas a 37 grados C, y la reacción se termina mediante la adición de una

668

concentración saturante de estreptavidina inmunopura. Después de incubar con estreptavidina a temperatura ambiente durante 15 minutos, se mide la polarización fluorescente, por ejemplo, usando un equipo LJL Acquest (Ex485 nm/ Em530 nm). La actividad de la enzima beta secretasa se determina mediante los cambios en la polarización fluorescente que ocurren cuando el sustrato es escindido por la enzima. La incubación en la presencia o ausencia del compuesto inhibitorio demuestra la inhibición específica de la escisión enzimática por la beta secretasa de su sustrato de APP sintético. En este ensayo, los compuestos preferidos de la invención presentan una IC_{50} menor que 50 micromolar. Los compuestos más preferidos presentan una IC_{50} menor que 10 micromolar. Aún más preferidos son los compuestos de la invención que presentan una IC_{50} menor que 5 micromolar.

Ejemplo C

Inhibición de la beta secretasa: Ensayo P26-P4'SW

Los sustratos sintéticos que contienen el sitio de escisión de la APP por la beta secretasa se usan para ensayar la actividad de la beta secretasa mediante los métodos descritos, por ejemplo, la solicitud de patente WO00/47618, presentada y publicada bajo los términos del Tratado de Cooperación en Patentes (PCT). El sustrato P26-P4'SW es un péptido de secuencia:
(biotina)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF [SEQ ID NO: 6]
El estándar P26-P1 tiene la secuencia:
(biotina)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7].
Brevemente, en este ensayo, los sustratos sintéticos acoplados a la biotina se incuban a una concentración de alrededor de 0 hasta alrededor de 200 micromolar. Cuando se analizan los compuestos inhibitorios, se prefiere un sustrato de concentración de alrededor de 1,0 micromolar. Los compuestos a analizar diluidos en DMSO se agregan a la mezcla reaccionante, con una concentración final de DMSO del 5%. Los controles también tienen una concentración final de DMSO del 5%. La concentración de la enzima beta secretasa es variada, para dar concentraciones del producto dentro del rango lineal del ensayo ELISA, alrededor de 125 a 2000 picomolar, después de la dilución.
La mezcla reaccionante también incluye acetato de sodio 20 milimolar, pH 4,5, y 0,06% de Triton X100, y es incubada a 37 grados C por un período de 1 a 3 horas. Las muestras se diluyen entonces en una solución amortiguadora de ensayo (por ejemplo, cloruro de sodio 145,4 nanomolar, fosfato de sodio 9,51 milimolar, azida sódica 7,7 milimolar, 0,05% Triton X405, albúmina de suero bovino 6g/litro, pH 7,4) para extinguir la reacción, y se diluyen aún más para los inmunoensayos de los productos de escisión.

670

669

Los productos de escisión pueden analizarse mediante el ensayo ELISA. Se incuban las muestras diluidas y los estándares en placas de ensayo recubiertas con un anticuerpo de captura, por ejemplo, SW192, durante alrededor de 24 horas a 4 grados C. Después de un lavado con el amortiguador TTBS (cloruro de sodio 150 milimolar, Tris 25 milimolar, 0,05% Tween 20, pH 7,5), las muestras se incuban con estreptavidina-AP conforme a las instrucciones del fabricante. Después de una hora de incubación a temperatura ambiente, las muestras se lavan en TTBS, y se incuban con una solución de sustrato A fluorescente (31,2 g/litro de 2-amino-2-metil-1-propanol, 30 mg/litro, pH 9,5). La reacción con estreptavidina-fosfato alcalino permite la detección por fluorescencia. Los compuestos que son inhibidores efectivos de la actividad de la beta secretasa presentan una reducción en la escisión del sustrato cuando se comparan con un control.

Ejemplo D

Ensayos usando sustratos de oligopéptidos sintéticos

Los oligopéptidos sintéticos son preparados para que incorporen el conocido sitio de escisión de la beta secretasa, y opcionalmente marcadores detectables, tales como porciones fluorescentes o cromogénicas. Ejemplos de tales péptidos, así como sus métodos de producción y detección, son descritos en la patente de los Estados Unidos No. 5.942.400, incorporada aquí como referencia. Los productos de escisión pueden ser detectados mediante cromatografía líquida de alto rendimiento, o métodos de detección fluorescentes o cromogénicos apropiados para el péptido a ser detectado, conforme a métodos muy conocidos en la técnica.

A modo de ejemplo, uno de tales péptidos tiene la secuencia SEVNL-DAEF [SEQ ID NO: 8], y el sitio de escisión se encuentra entre los residuos 5 y 6. Otro sustrato preferido tiene la secuencia ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], y el sitio de escisión se encuentra entre los residuos 26 y 27.

Se incuban estos sustratos de APP sintéticos en presencia de la beta secretasa bajo condiciones tales que den como resultado la escisión del sustrato por la beta secretasa. La comparación de los resultados de la escisión en la presencia del compuesto inhibitorio con los resultados del control proporciona una medida de la actividad inhibitoria del compuesto.

Ejemplo E

Inhibición de la actividad de la beta secretasa: Ensayo celular

Un ejemplo de un ensayo para el análisis de la inhibición de la actividad de la beta secretasa utiliza la línea de células embriónicas de riñón humano HEKp293 (ATCC No. de Acceso CRL-1573) transfectadas con APP751 que contiene la doble mutación Lys651Met52 a Asn651Leu652

670

(de acuerdo a la numeración para APP751) que ocurre naturalmente, la comúnmente llamada mutación sueca que se ha demostrado que produce un exceso de A beta (Citron et al., 1992, *Nature* 360:672-674), como se describe en la patente de los Estados Unidos No. 5.604.102. Las células se incuban en la presencia/ausencia del compuesto inhibitorio (diluido en DMSO) a la concentración deseada, generalmente hasta 10 microgramos/ml. Al final del período de tratamiento, se analiza el medio así condicionado por la actividad de la beta secretasa, por ejemplo, analizando los fragmentos escindidos. Se puede analizar el A beta por medio de inmunoensayos, usando anticuerpos de detección específicos. La actividad enzimática se mide en la presencia y la ausencia de los compuestos inhibitorios para demostrar la inhibición específica de la escisión del sustrato de APP por la beta secretasa.

Ejemplo F

Inhibición de la beta secretasa en modelos animales de la EA

Se pueden usar diversos modelos animales para investigar la inhibición de la actividad de la beta secretasa. Ejemplos de modelos animales útiles en esta invención incluyen, sin estar limitados a ratones, conejillos de India, perros, y similares. Los animales pueden ser de tipo salvaje, transgénicos, o modelos copia. Además, los modelos mamíferos pueden expresar mutaciones de APP, tales como la APP695-SW y similares que se describen aquí. Ejemplos de modelos mamíferos transgénicos no humanos se describen en las patentes de los Estados Unidos Nos. 5.604.102, 5.912.410 y 5.811.633.

Los ratones PDAPP, preparados como se describe en Games et al., 1995, *Nature* 373:523-527, son útiles para analizar *in vivo* la supresión de la liberación de A beta en presencia de compuestos inhibitorios putativos. Como se describe en la patente de los Estados Unidos No. 6.191.166, se administra a ratones PDAPP de 4 meses de edad un compuesto formulado en un vehículo tal como aceite de maíz. Los ratones reciben dosis del compuesto (1-30 mg/ml; preferentemente 1-10 mg/ml). Después de un tiempo, por ejemplo, 3-10 horas, se sacrifica a los animales y se les extrae el cerebro para ser analizado.

Se administra a los animales transgénicos una cantidad del compuesto inhibitorio formulada en un vehículo apropiado para el modo de administración elegido. Los animales de control se dejan sin tratar, o son tratados sólo con el vehículo o con un compuesto inactivo. La administración puede ser aguda, es decir, una dosis única o dosis múltiples en un sólo día, o puede ser crónica, esto es, una dosis que se repite diariamente durante un período de días. Comenzando al tiempo 0, se obtienen muestras del tejido o líquido cerebral de los animales seleccionados y se analiza para detectar la presencia de péptidos de escisión de la APP, incluyendo el A beta, por ejemplo,

671

mediante inmunoensayos usando anticuerpos específicos para la detección del A beta. Al final del período de prueba, los animales son sacrificados y se analiza el tejido o líquido cerebral para detectar la presencia de A beta y/o placas amiloides beta. El tejido también se analiza por necrosis.

Se espera que los animales a los que se les administraron los compuestos inhibitorios de la invención presenten una reducción de A beta en los tejidos o líquidos cerebrales y una reducción de las placas amiloides beta en el tejido cerebral, en comparación con los controles no tratados.

Ejemplo G

Inhibición de la producción de A beta en pacientes humanos

Los pacientes que sufren de la enfermedad de Alzheimer (EA) presentan un aumento en la cantidad de A beta en el cerebro. Se administra a los pacientes con EA una cantidad del compuesto inhibitorio formulada en un vehículo apropiado para el modo elegido de administración. La administración se repite diariamente durante el período de prueba. Comenzando el día 0, se realizan pruebas de memoria y cognitivas, por ejemplo, una vez por mes. Se espera que los pacientes que recibieron los compuestos inhibitorios presenten un retardo o una estabilización en la progresión de la enfermedad, lo que se analiza estudiando los cambios en uno o más de los siguientes parámetros de la enfermedad: presencia de A beta en el LCR o en el plasma, volumen del hipocampo o del cerebro, depósitos de A beta en el cerebro, presencia de placas amiloides en el cerebro, y los resultados de los exámenes de la función de memoria y cognitiva, en comparación con un grupo de control formado por pacientes que no fueron tratados.

Ejemplo H

Prevención de la producción de A Beta en pacientes a riesgo de EA

Los pacientes que están predispuestos o a riesgo de desarrollar EA pueden ser identificados ya sea por el reconocimiento de características familiares hereditarias, por ejemplo, la presencia de la mutación sueca, y/o por el seguimiento de los parámetros de diagnóstico. A los pacientes identificados como predispuestos o a riesgo de desarrollar EA se les administra una cantidad del compuesto inhibitorio formulada en un vehículo apropiado para el modo de administración elegido. La administración se repite diariamente durante el período de prueba. Comenzando el día 0, se realizan exámenes cognitivos y de memoria, por ejemplo, una vez por mes.

Se espera que los pacientes a los que se les administraron los compuestos inhibitorios presenten un retardo o una estabilización en el progreso de la enfermedad, lo que se analiza estudiando los cambios en uno o más de los siguientes parámetros de la enfermedad: presencia de A beta en el

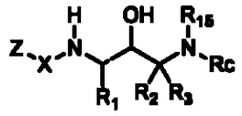
672

LCR o en el plasma, volumen del hipocampo o del cerebro, depósitos de A beta en el cerebro, y los resultados de los exámenes de la función de memoria y cognitiva, en comparación con el grupo de control formado por pacientes no tratados.

La invención ha sido descrita en referencia a varias materializaciones y técnicas preferidas específicas. Sin embargo, se debe entender que se pueden hacer muchas variaciones y modificaciones y aún así permanecer dentro del espíritu y el alcance de la invención.

Lo que se reivindica es:

1. Un compuesto de la fórmula I:



(I)

o sales farmacéuticamente aceptables del mismo, en dónde

Z es hidrógeno, $(C_3-C_7$ cicloalquil$)_{0-1}(C_1-C_6$ alquilo$)$-, $(C_3-C_7$ cicloalquil$)_{0-1}(C_2-C_6$ alquenilo$)$-, alcoxialcoxialquilo, $(C_3-C_7$ cicloalquil$)_{0-1}(C_2-C_6$ alquinilo$)$- o $(C_3-C_7$ cicloalquilo$)$-, en dónde cada uno de dichos grupos se encuentra opcionalmente sustituido con 1, 2, o 3 grupos R_Z, en dónde 1 o 2 grupos metileno en dichos grupos $(C_3-C_7$ cicloalquil$)_{0-1}(C_1-C_6$ alquilo$)$-, $(C_3-C_7$ cicloalquil$)_{0-1}(C_2-C_6$ alquenilo$)$-, $(C_3-C_7$ cicloalquil$)_{0-1}(C_2-C_6$ alquinilo$)$- o $(C_3-C_7$ cicloalquilo$)$- son opcionalmente remplazados con -(C=O)-;

en dónde en cada ocurrencia R_Z es independientemente halógeno, -OH, -SH, -CN, $-CF_3$, $-OCF_3$, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o $-NR_{100}R_{101}$;

dónde R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, $CO(C_1-C_6$ alquilo$)$ o $SO_2C_1-C_6$ alquilo;

X es -(C=O)-, -(C=S)- $-(SO_2)$-;

R_1 es C_1-C_{10} alquilo opcionalmente sustituido con 1, 2, o 3 grupos independientemente seleccionados de halógeno, -OH, =O, -SH, -CN, $-CF_3$, $-OCF_3$, $-C_{3-7}$ cicloalquilo, $-C_1-C_4$ alcoxi, amino, mono- dialquilamino, arilo, heteroarilo, y heterocicloalquilo, en dónde cada grupo arilo es opcionalmente sustituido con 1, 2 o 3 grupos R_{30};

R_{30} es seleccionado de halógeno, OH, SH, CN, $-CO-(C_1-C_4$ alquilo$)$, $-NR_7R_8$, $-S(O)_{0-2}-(C_1-C_4$ alquilo$)$, C_1-C_6 alquilo, C_2-C_4 alquenilo, C_2-C_6 alquinilo, C_1-C_8 alcoxi, -O-bencilo, alqueniloxi, alcoxialcoxialcoxi, y C_3-C_8 cicloalquilo;

en dónde los grupos alquilo, alquenilo, alquinilo, alcoxi y cicloalquilo son opcionalmente sustituido con 1 o 2 sustituyentes independientemente

623

seleccionados de C_1-C_4 alquilo, halógeno, OH, -NR_5R_6, CN, C_1-C_4 haloalcoxi, NR_7R_8, y C_1-C_4 alcoxi;

R_5 y R_6 son independientemente H o C_1-C_6 alquilo; ó

R_5 y R_6 y el nitrógeno al cuál se encuentran unidos forman un anillo heterocicloalquilo de 5 o 6 miembros; y

R_7 y R_8 son independientemente seleccionados de H; -C_1-C_4 alquilo opcionalmente sustituido con 1, 2, o 3 grupos independientemente seleccionados de -OH, -NH_2, y halógeno; -C_3-C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; y -C_2-C_4 alquinilo;

en dónde cada heteroarilo es opcionalmente sustituido con 1 o 2 grupos R_{50};

en dónde cada grupo heterocicloalquilo es opcionalmente sustituido con 1 o 2 grupos que son independientemente R_{50} o =O;

R_2 y R_3 son independientemente seleccionados de

-H;

-F;

-C_1-C_6 ALQUILO OPCIONALMENTE SUSTITUIDO CON UN SUSTITUYENTE SELECCIONADO DE -F, -OH, -C≡N, -CF_3, C_1-C_3 ALCOXI, Y -NR_5R_6;

-$(CH_2)_{0-2}$-R_{17};

-$(CH_2)_{0-2}$-R_{18};

-C_2-C_6 ALQUENILO O C_2-C_6 ALQUINILO, EN DÓNDE CADA UNO ES OPCIONALMENTE SUSTITUIDO CON UN SUSTITUYENTE INDEPENDIENTE SELECCIONADO DE -F, -OH, -C≡N, -CF_3 Y C_1-C_3 ALCOXI;

-$(CH_2)_{0-2}$-C_3-C_7 CICLOALQUILO, OPCIONALMENTE SUBSTITUIDO CON UN SUSTITUYENTE INDEPENDIENTE SELECCIONADO DE -F, -OH, -C≡N, -CF_3, C_1-C_3 ALCOXI Y -NR_5R_6; Ó

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en dónde R_2, R_3 y el carbono al cuál están unidos forman un carbociclo de tres a siete átomos de carbono, en dónde un átomo de carbono es opcionalmente remplazado por un grupo seleccionado de –O-, -S-, -SO_2-, o -NR_7-;

dónde en cada ocurrencia R_{17} es un grupo arilo seleccionado de fenilo, 1-naftilo, 2-naftilo, indanilo, indenilo, dihidronaftilo y tetralinilo, en dónde dichos grupos

679

arilo son opcionalmente sustituidos con uno o dos grupos que son independientemente

-C_1-C_3 alquilo; -C_1-C_4 alcoxi; CF_3; ó

-C_2-C_6 alquenilo o -C_2-C_6 alquinilo cada uno de los cuales es opcionalmente sustituido con un sustituyente seleccionado de F, OH, C_1-C_3 alcoxi; ó

-halógeno;

-OH;

-C≡N;

-C_3-C_7 cicloalquilo;

-CO-(C_1-C_4 alquilo);

-SO_2-(C_1-C_4 alquilo);

dónde R_{18} es un grupo heteroarilo seleccionado de piridinilo, pirimidinilo, quinolinilo, indolilo, piridazinilo, pirazinilo, isoquinolilo, quinazolinilo, quinoxalinilo, ftalazinilo, imidazolilo, isoxazolilo, oxazolilo, tiazolilo, furanilo, tienilo, pirrolilo, oxadiazolilo o tiadiazolilo, en dónde cada uno de dichos grupos heteroarilo es opcionalmente sustituido con uno o dos grupos que son independientemente

-C_1-C_6 alquilo opcionalmente sustituido con un sustituyente seleccionado de OH, C≡N, CF_3, C_1-C_3 alcoxi, y -NR_5R_6;

en dónde R_{15} es seleccionado de hidrógeno, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 alcoxi C_1-C_6 alquilo, hidroxi C_1-C_6 alquilo, halo C_1-C_6 alquilo, bencilo, -$C(O)_2$-bencilo, y alcoxicarbonilo, en dónde la porción alquilo y fenilo de cada uno no está sustituida o está sustituida con 1, 2, 3, o 4 grupos independientemente seleccionados de halógeno, C_1-C_6 alquilo, hidroxi, C_1-C_6 alcoxi, NH_2, y -R_{26}-R_{27};

en dónde R_{26} es seleccionado de –C(O)-, -SO_2-, -CO_2-, -C(O)NR_5-, y -NR_5C(O)-, en dónde R_{27} es seleccionado de C_1-C_6 alquilo, C_1-C_6 alcoxi, aril C_1-C_6 alquilo, heterocicloalquilo, y heteroarilo, en dónde cada uno de los precedentes es no sustituido o sustituido con 1, 2, 3, 4, o 5 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno, haloalquilo, hidroxialquilo, -NR_5R_6, -C(O)NR_5R_6;

en dónde R_C es seleccionado de

-$(CH_2)_{0-3}$-(C_3-C_8) cicloalquilo en dónde el cicloalquilo es opcionalmente sustituido con 1, 2, o 3 grupos independientemente seleccionados de -R_{205}, y -CO_2-(C_1-C_4 alquilo);

-$(CR_{245}R_{250})_{0-4}$-arilo;

675

-$(CR_{245}R_{250})_{0-4}$-heteroarilo;

-$(CR_{245}R_{250})_{0-4}$-heterocicloalquilo;

-$(CR_{245}R_{250})_{0-4}$-aril-heteroarilo;

-$(CR_{245}R_{250})_{0-4}$-aril-heterocicloalquilo;

-$(CR_{245}R_{250})_{0-4}$-aril-arilo;

-$(CR_{245}R_{250})_{0-4}$-heteroaril-arilo;

-$(CR_{245}R_{250})_{0-4}$-heteroaril-heterocicloalquilo;

-$(CR_{245}R_{250})_{0-4}$-heteroaril-heteroarilo;

-$(CR_{245}R_{250})_{0-4}$-heterocicloalquil-heteroarilo;

-$(CR_{245}R_{250})_{0-4}$-heterocicloalquil-heterocicloalquilo;

-$(CR_{245}R_{250})_{0-4}$-heterocicloalquil-arilo;

- un anillo monocíclico o bicíclico de 5, 6, 7 8, 9, o 10 carbonos unidos a 1 o 2 grupos arilo, heteroarilo, o heterocicloalquilo en dónde 1, 2 o 3 carbonos del anillo monocíclico o bicíclico es opcionalmente remplazado con

-NH,

-$N(CO)_{0-1}R_{215}$,

-$N(CO)_{0-1}R_{220}$,

-O, or

-$S(=O)_{0-2}$,

y en dónde el anillo monocíclico o bicíclico es opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente -R_{205}, -R_{245}, -R_{250} o =O;

-C_2-C_6 alquenilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-C_2-C_6 alquinilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

en dónde cada grupo arilo unido directa o indirectamente al grupo -$(CR_{245}R_{250})_{0-4}$ es opcionalmente sustituido con 1, 2, 3 o 4 grupos R_{200};

en dónde cada grupo heteroarilo unido directa o indirectamente al grupo -$(CR_{245}R_{250})_{0-4}$ es opcionalmente sustituido con 1, 2, 3, o 4 R_{200};

en dónde cada heterocicloalquilo unido directa o indirectamente al grupo -$(CR_{245}R_{250})_{0-4}$ es opcionalmente sustituido con 1, 2, 3, o 4 R_{210};

en dónde en cada ocurrencia R_{200} es independientemente seleccionado de

-C_1-C_6 alquilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-OH;

-NO_2;

-halógeno;

676

-C≡N;

-CHO;

-$(CH_2)_{0-4}$-CO-$NR_{220}R_{225}$;

-$(CH_2)_{0-4}$-CO-(C_1-C_8 alquilo);

-$(CH_2)_{0-4}$-CO-(C_2-C_8 alquenilo);

-$(CH_2)_{0-4}$-CO-(C_2-C_8 alquinilo);

-$(CH_2)_{0-4}$-CO-(C_3-C_7 cicloalquilo);

-$(CH_2)_{0-4}$-$(CO)_{0-1}$-arilo;

-$(CH_2)_{0-4}$-$(CO)_{0-1}$-heteroarilo;

-$(CH_2)_{0-4}$-$(CO)_{0-1}$-heterocicloalquilo;

-$(CH_2)_{0-4}$-CO_2R_{215};

-$(CH_2)_{0-4}$-SO_2-$NR_{220}R_{225}$;

-$(CH_2)_{0-4}$-$S(O)_{0-2}$-(C_1-C_8 alquilo);

-$(CH_2)_{0-4}$-$S(O)_{0-2}$-(C_3-C_7 cicloalquilo);

-$(CH_2)_{0-4}$-N(H or R_{215})-CO_2R_{215};

-$(CH_2)_{0-4}$-N(H or R_{215})-SO_2-R_{220};

-$(CH_2)_{0-4}$-N(H or R_{215})-CO-$N(R_{215})_2$;

-$(CH_2)_{0-4}$-N(-H or R_{215})-CO-R_{220};

-$(CH_2)_{0-4}$-$NR_{220}R_{225}$;

-$(CH_2)_{0-4}$-O-CO-(C_1-C_6 alquilo);

-$(CH_2)_{0-4}$-O-(R_{215});

-$(CH_2)_{0-4}$-S-(R_{215});

-$(CH_2)_{0-4}$-O-(C_1-C_6 alquilo opcionalmente sustituido con 1, 2, 3, o 5 -F);

-C_2-C_6 alquenilo opcionalmente sustituido con 1 o 2 grupos R_{205};

-C_2-C_6 alquinilo opcionalmente sustituido con 1 o 2 grupos R_{205};

y

-$(CH_2)_{0-4}$- C_3-C_7 cicloalquilo;

en dónde cada grupo arilo incluido en R_{200} es opcionalmente sustituido con 1, 2, o 3 grupos que son independientemente

-R_{205},

-R_{210} ó

-C_1-C_6 alquilo sustituidos con 1, 2, o 3 grupos que son independientemente R_{205} o R_{210};

677

en dónde cada grupo heterocicloalquilc incluido en R_{200} es opcionalmente sustituido con 1, 2, o 3 grupos que son independientemente R_{210};

en dónde cada grupo heteroarilo incluido en R_{200} es opcionalmente sustituido con 1, 2, o 3 grupos que son independientemente

-R_{205},

-R_{210}, ó

-C_1-C_6 alquilo sustituidos con 1, 2, o 3 grupos que son independientemente

-R_{205} ó

-R_{210};

en dónde en cada ocurrencia R_{205} es independientemente seleccionado de

-C_1-C_6 alquilo,

-C_2-C_6 alquenilo,

-C_2-C_6 alquinilo,

-C_1-C_6 haloalcoxi

-$(CH_2)_{0-3}$(C_3-C_7 cicloalquilo)

-halógeno,

-$(CH_2)_{0-6}$-OH,

-O-fenilo,

-alquenil-fenilo,

-SH,

-$(CH_2)_{0-6}$-C≡N,

-$(CH_2)_{0-6}$-C(=O)$NR_{235}R_{240}$

-CF_3,

-$C(O)_2$-bencilo,

-C_1-C_6 alcoxi, y

-$NR_{235}R_{240}$,

en dónde en cada ocurrencia R_{210} es independientemente seleccionado de

-C_1-C_6 alquilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-C_2-C_6 alquenilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-C_2-C_6 alquinilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-halógeno;

-C_1-C_6 alcoxi;

678

-C_1-C_6 haloalcoxi;

-$NR_{220}R_{225}$;

-OH;

-C≡N;

-C_3-C_7 cicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-CO-(C_1-C_4 alquilo);

-$SO_2NR_{215}R_{240}$;

-$CO-NR_{215}R_{240}$;

-SO_2-(C_1-C_4 alquilo); y

=O;

en dónde en cada ocurrencia R_{215} es independientemente seleccionado de

-C_1-C_6 alquilo,

-$(CH_2)_{0-2}$-(arilo),

-C_2-C_6 alquenilo,

-C_2-C_6 alquinilo,

-C_3-C_7 cicloalquilo,

-$(CH_2)_{0-2}$-(heteroarilo), y

-$(CH_2)_{0-2}$-(heterocicloalquilo);

en dónde el grupo arilo incluido en R_{215} es opcionalmente sustituido con 1, 2, o 3 grupos que son independientemente

-R_{205} o

-R_{210};

en dónde el grupo heterocicloalquilo incluido en R_{215} es opcionalmente sustituido con 1, 2, o 3 R_{210};

en dónde cada grupo heteroarilo incluido en R_{215} es opcionalmente sustituido con 1, 2, o 3 R_{210};

en dónde en cada ocurrencia R_{220} y R_{225} son independientemente seleccionados de

-H,

-C_1-C_6 alquilo,

-hidroxi C_1-C_6 alquilo,

-amino C_1-C_6 alquilo,

-halo C_1-C_6 alquilo,

-$(CH_2)_{0-2}$-(C_3-C_7 cicloalquilo),

-(C_1-C_6 alquilo)-O-(C_1-C_3 alquilo),

-C_2-C_6 alquenilo,

-C_2-C_6 alquinilo,

-arilo,

-heteroarilo, y

-heterocicloalquilo;

en dónde los grupos arilo, heteroarilo o heterocicloalquilo incluidos en R_{220} y R_{225} son opcionalmente sustituido con 1, 2, o 3 grupos R_{270},

en dónde en cada ocurrencia R_{270} es independientemente

-R_{205},

-C_1-C_6 alquilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-C_2-C_6 alquenilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-C_2-C_6 alquinilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-halógeno;

-C_1-C_6 alcoxi;

-C_1-C_6 haloalcoxi;

-$NR_{235}R_{240}$;

-OH;

-C≡N;

-C_3-C_7 cicloalquilo opcionalmente sustituido con 1, 2, o 3 grupos R_{205};

-CO-(C_1-C_4 alquilo);

-SO_2-$NR_{235}R_{240}$;

-CO-$NR_{235}R_{240}$;

-SO_2-(C_1-C_4 alquilo); y

=O;

en dónde en cada ocurrencia R_{235} y R_{240} son independientemente

-H, ó

-C_1-C_6 alquilo;

-fenilo

en dónde en cada ocurrencia R_{245} y R_{250} son independientemente seleccionados de

-H,

-$(CH_2)_{0-4}CO_2C_1$-C_4 alquilo

-$(CH_2)_{0-4}C(=O)C_1$-C_4 alquilo

-C_1-C_4 alquilo,

-C_1-C_4 hidroxialquilo,

680

-C_1-C_4 alcoxi,

-C_1-C_4 haloalcoxi,

-$(CH_2)_{0-4}$-C_3-C_7 cicloalquilo,

-C_2-C_6 alquenilo,

-C_2-C_6 alquinilo,

-$(CH_2)_{0-4}$ arilo,

-$(CH_2)_{0-4}$ heteroarilo, y

-$(CH_2)_{0-4}$ heterocicloalquilo, ó

en dónde R_{245} y R_{250} son tomados en conjunto con el carbono al cuál están unidos para formar un monociclo o biciclo de 3, 4, 5, 6, 7, 8, 9, o 10 átomos de carbono, opcionalmente dónde 1 o 2 átomos de carbono son remplazados por un heteroátomo seleccionado de

-O-,

-S-,

-SO_2-, y

-NR_{220}-; o en dónde un grupo -CH_2- es remplazado con un grupo -C(O)-;

en dónde los grupos arilo, heteroarilo o heterocicloalquilo incluidos en R_{245} y R_{250} son opcionalmente sustituidos con 1, 2, o 3 grupos que son independientemente halógeno, C_{1-6} alquilo, CN o OH.

2. Un compuesto de acuerdo a la reivindicación 1, en dónde Z es (C_3-C_7 cicloalquil)$_{0-1}$(C_1-C_6 alquilo)-, (C_3-C_7 cicloalquil)$_{0-1}$(C_2-C_6 alquenilo)-, (C_3-C_7 cicloalquil)$_{0-1}$(C_2-C_6 alquinilo)- o (C_3-C_7 cicloalquilo)-, dónde cada uno de dichos grupos es opcionalmente sustituido con 1, 2, o 3 grupos R_Z;

en dónde, en cada ocurrencia R_Z es independientemente halógeno, -OH, -CN, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi, -$NR_{100}R_{101}$;

dónde R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, CO(C_1-C_6 alquilo) o SO_2C_1-C_6 alquilo.

3. Un compuesto de acuerdo a la reivindicación 1, en dónde X es –(C=O)-.

4. Un compuesto de acuerdo a la reivindicación 3, en dónde Z es H.

681

5. Un compuesto de acuerdo a la reivindicación 1, en dónde R_1 es C_1-C_{10} alquilo opcionalmente sustituido con 1 o 2 grupos independientemente seleccionados de halógeno, -OH, =O, $-CF_3$, $-OCF_3$, $-C_{3-7}$ cicloalquilo, $-C_1$-C_4 alcoxi, amino o arilo, en dónde el grupo arilo es opcionalmente sustituido con 1 o 2 grupos R_{50};

en dónde R_{50} es seleccionado de halógeno, OH, $-CO-(C_1$-C_4 alquilo), $-NR_7R_8$, C_1-C_6 alquilo, C_1-C_6 alcoxi y C_3-C_8 cicloalquilo;

en dónde los grupos alquilo, alcoxi y cicloalquilo son opcionalmente sustituido con 1 o 2 sustituyentes independientemente seleccionados de C_1-C_4 alquilo, halógeno, OH, $-NR_5R_6$, NR_7R_8, y C_1-C_4 alcoxi;

en dónde R_5 y R_6 son independientemente H o C_1-C_6 alquilo; ó en dónde R_5 y R_6 y el nitrógeno al cuál están unidos forman un anillo heterocicloalquilo de 5 o 6 miembros; y

en dónde R_7 y R_8 son independientemente seleccionados de -H; $-C_1$-C_4 alquilo opcionalmente sustituido con 1, 2, o 3 grupos independientemente seleccionados de -OH, $-NH_2$, y halógeno; $-C_3$-C_6 cicloalquilo; $-(C_1$-C_4 alquilo)-O-(C_1-C_4 alquilo).

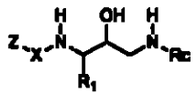
6. Un compuesto de acuerdo a la reivindicación 5, en dónde R_1 es $-CH_2$-fenilo dónde el anillo fenilo es opcionalmente sustituido con 1 o 2 grupos independientemente seleccionados de halógeno, C_1-C_2 alquilo, C_1-C_2 alcoxi e hidroxi.

7. Un compuesto de acuerdo a la reivindicación 6, en dónde R_1 es bencilo, 3-fluorobencilo o 3,5-difluorobencilo.

8. Un compuesto de acuerdo a la reivindicación 1, en dónde R_{15} es H.

9. Un compuesto de acuerdo a la reivindicación 7, en dónde R_{15} es H.

10. Un compuesto de acuerdo a la reivindicación 1 de la fórmula II:



(II)

682

en dónde Z es hidrógeno, -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo, dónde cada uno de dichos grupos es opcionalmente sustituido con 1 o 2 grupos R_Z, en dónde 1 o 2 grupos metileno en dichos grupos -C_1-C_6 alquilo, -C_2-C_6 alquenilo, -C_2-C_6 alquinilo o -C_3-C_7 cicloalquilo son opcionalmente remplazados con -(C=O)-;

en dónde en cada ocurrencia R_Z es independientemente halógeno, -OH, -CN, -CF_3, C_1-C_6 alcoxi, C_3-C_7 cicloalquilo, C_3-C_7 cicloalcoxi o -$NR_{100}R_{101}$;

dónde R_{100} y R_{101} son independientemente H, C_1-C_6 alquilo, fenilo, CO(C_1-C_6 alquilo) o SO_2C_1-C_6 alquilo;

en dónde X es -C(=O)-;

en dónde R_1 es C_1-C_{10} alquilo opcionalmente sustituido con 1 o 2 grupos independientemente seleccionados de halógeno, -OH, =O, -CN, -CF_3, -OCF_3, -C_3-C_7 cicloalquilo, -C_1-C_4 alcoxi, amino, mono- dialquilamino, arilo, heteroarilo o heterocicloalquilo, en dónde el grupo arilo es opcionalmente sustituido con 1 o 2 grupos R_{50};

dónde R_{50} es halógeno, OH, CN, -CO-(C_1-C_4 alquilo), -NR_7R_8, C_1-C_6 alquilo, C_2-C_6 alquenilo, C_2-C_6 alquinilo, C_1-C_6 alcoxi y C_3-C_8 cicloalquilo;

dónde R_7 y R_8 son seleccionados de H; -C_1-C_4 alquilo opcionalmente sustituido con 1, 2, o 3 grupos seleccionados de -OH, -NH_2 y halógeno; -C_3-C_6 cicloalquilo; -(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo); -C_2-C_4 alquenilo; y -C_2-C_4 alquinilo;

en dónde R_C es seleccionado de

-$(CR_{245}R_{250})_{0-4}$-arilo;

-$(CR_{245}R_{250})_{0-4}$-heteroarilo;

-$(CR_{245}R_{250})_{0-4}$-heterocicloalquilo;

dónde el grupo arilo unido al grupo -$(CR_{245}R_{250})_{0-4}$- es opcionalmente sustituido con 1, 2, 3 o 4 grupos R_{200};

dónde el grupo heteroarilo unido al grupo -$(CR_{245}R_{250})_{0-4}$- es opcionalmente sustituido con 1, 2, 3, o 4 grupos R_{200};

dónde el grupo heterocicloalquilo unido al grupo -$(CR_{245}R_{250})_{0-4}$- es opcionalmente sustituido con 1, 2, 3, o 4 grupos R_{210}.

11. Un compuesto de acuerdo a la reivindicación 10, en dónde Z es -C_1-C_6 alquilo; R_1 es C_1-C_{10} alquilo sustituido con 1 grupo fenilo, dónde el grupo fenilo unido al alquilo es opcionalmente sustituido con 1 o 2 grupos R_{50}, dónde cada R_{50} es independientemente halógeno, OH, CN, o C_1-C_6 alquilo; y

683

R_C es $-(CR_{245}R_{250})_{0-4}$-arilo o $-(CR_{245}R_{250})_{0-4}$-heteroarilo, dónde los grupos arilo y heteroarilo son opcionalmente sustituido con 1 o 2 grupos R_{200}.

12. Un compuesto de acuerdo a la reivindicación 1, el cuál es
N-[(1S,2R)-3-[(3-bromobencil)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4R)-6-isopropil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il]amino}propil)acetamida;
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isopropil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il]amino}propil)acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;
hidrocloruro de N-[(1S,2R)-3-{[1-(3-bromofenil)ciclopropil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;
3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-bromofenil)propanoato de metilo;
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}acetamida;
3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoato de metilo;
ácido 3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoico;
N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-3-hidroxipropil]amino}-2-hidroxipropil)acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(1S)-1,2,3,4-tetrahidronaftalen-1-ilamino]propil}acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;
N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-2-metilamino-acetamida;
N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(3-yodobencil)amino]propil}acetamida;
3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-yodofenil)propanoato de metilo;

684

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(3-hidroxiprop-1-inil)fenil]propanoato de metilo;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[3-hidroxi-1-(3-yodofenil)propil]amino}propil)acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(3-hidroxipropil)fenil]propanoato de metilo;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(7-metoxi-1,2,3,4-tetrahidronaftalen-1-il)amino]propil}acetamida;

2-Amino-N-[1-(3,5-difluoro-bencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[6-etil-2-(metilsulfonil)-1,2,3,4-tetrahidroisoquinolin-4-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-7-etil-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1R)-7-etil-1,2,3,4-tetrahidronaftalen-1-il]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-3-{[1-(3-bromofenil)ciclopropil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(5-formiltien-2-il)fenil]propanoato de metilo;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(2'-acetil-1,1'-bifenil-3-il)propanoato de metilo;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-3-metil-butiramida;

N-[(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-({1-[3'-(hidroximetil)-1,1'-bifenil-3-il]ciclopropil}amino)propil]acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-3-({1-[3-(5-formiltien-2-il)fenil]ciclopropil}amino)-2-hidroxipropil]acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-3-(9H-fluoren-9-ilamino)-2-hidroxipropil]acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-[3-(trifluorometil)fenil]propanoato de metilo;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-cianofenil)propanoato de metilo;

685

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-3-hidroxi-2,2-dimetil-propionamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopropil]amino}-2-hidroxipropil)acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-bromofenil)propanoato de metilo;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etinilfenil)ciclopropil]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-3-[(2-bromo-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-9H-fluoren-9-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2,2-dióxido-3,4-dihidro-1,2-benzoxatiin-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-yodo-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-yodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4R)-6-yodo-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-3-hidroxi-propionamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1,2-benzoxatiin-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1,2-benzoxatiin-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-{[4-(3-etilfenil)tetrahidro-2H-piran-4-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)butil]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4S)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(4R)-6-etil-3,4-dihidro-2H-cromen-4-il]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(7-etil-1,2,3,4-tetrahidronaftalen-1-il)amino]-2-hidroxipropil}acetamida;

686

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-3-hidroxi-butiramida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclohexil]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)ciclopentil]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-5-fluoro-9H-fluoren-9-il)amino]-2-hidroxipropil}acetamida;

(3S)-3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)butanoato de metilo;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isobutilisoxazol-5-il)ciclopropil]amino}propil)acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-2-fenil-acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-7-fluoro-9H-fluoren-9-il)amino]-2-hidroxipropil}acetamida;

(3R)-3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)butanoato de metilo;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2,5-dipropilbencil)amino]-2-hidroxipropil}acetamida;

{[1-(3,5-Difluoro-bencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propilcarbamil]-metil}-metil-carbamato terc-butilo;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isobutil-9H-fluoren-9-il)amino]propil}acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(1S)-6-etil-2,3-dihidro-1H-inden-1-il]amino}-2-hidroxipropil)acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-2-metil-2-metilamino-propionamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-etil-1-(3-etilfenil)propil]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1H-2,1-benzotiazin-4-il)amino]-2-hidroxipropil}acetamida;

687

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2,2-dióxido-3,4-dihidro-1H-2,1-benzotiazin-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-3-metil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-3-metil-2,2-dióxido-3,4-dihidro-1H-isotiocromen-4-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-1-metil-1,2,3,4-tetrahidroquinolin-4-il)amino]-2-hidroxipropil}acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoato de metilo;

N-[1-(3,5-Difluoro-bencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-2-(1H-imidazol-4-il)-acetamida;

3-{[(2R,3S)-3-(acetilamino)-4-(3,5-difluorofenil)-2-hidroxibutil]amino}-3-(3-etilfenil)propanoato de metilo;

N-[(1S,2R)-3-[(2-bromo-9-metil-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(1-etilpropil)-9H-fluoren-9-il]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-3-[(2-ciclopentil-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-[1-(3,5-difluorobencil)-3-(6-etil-2,2-dioxo-2l^6-isotiocroman-4-ilamino)-2-hidroxi-propil]-propionamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-9-metil-9H-fluoren-9-il)amino]-2-hidroxipropil}acetamida;

N-[(1S,2R)-3-[(2-ciclohexil-9H-fluoren-9-il)amino]-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(4-etilpiridin-2-il)ciclopropil]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-(1H-pirrol-3-il)-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[(5R)-3-etil-6,7,8,9-tetrahidro-5H-benzo[7]anulen-5-il]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-3-{[1-(3-bromofenil)-1-metiletil]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

688

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-(dimetilamino)-9H-fluoren-9-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(1S)-7-propil-1,2,3,4-tetrahidronaftalen-1-il]amino}propil)acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-3-({(1S)-7-[(dimetilamino)metil]-1,2,3,4-tetrahidronaftalen-1-il}amino)-2-hidroxipropil]acetamida;

N-[(1S,2R)-3-{[(1S)-7-bromo-1,2,3,4-tetrahidronaftalen-1-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-propilfenil)ciclopropil]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)cicloheptil]amino}-2-hidroxipropil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-isopropil-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(6-etil-2-hidroxi-2,3-dihidro-1H-inden-1-il)amino]-2-hidroxipropil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(2-etil-6-fluoro-9H-fluoren-9-il)amino]-2-hidroxipropil}acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(metoximetil)-9H-fluoren-9-il]amino}propil)acetamida;

Hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-2-(5-metil-1,3-oxazol-2-il)etil]amino}-2-hidroxipropil)acetamida;

N-[(1S,2R)-1-(3,5-difluorobencil)-3-(3,4-dihidro-2H-cromen-4-ilamino)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-3-{[2-etil-5-(trifluorometil)-9H-fluoren-9-il]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(3-metilbutil)-9H-fluoren-9-il]amino}propil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isopropil-9H-fluoren-9-il)amino]propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-neopentil-9H-fluoren-9-il)amino]propil}acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(2-isopropenil-9H-fluoren-9-il)amino]propil}acetamida;

690

689

Hidrocloruro de N-((1S,2R)-1-(3,5-difluorobencil)-3-{[1-(3-etilfenil)-1-metiletil]amino}-2-hidroxipropil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-isobutil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida;

N-[(1S,2R)-3-{[(4S)-6-ciano-3,4-dihidro-2H-cromen-4-il]amino}-1-(3,5-difluorobencil)-2-hidroxipropil]acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4S)-6-neopentil-3,4-dihidro-2H-cromen-4-il]amino}propil)acetamida;

N-{(1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-[(6-neopentil-3,4-dihidro-2H-cromen-4-il)amino]propil}acetamida;

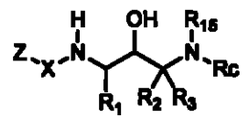
N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[2-(isopropilamino)-9H-fluoren-9-il]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[1-(3-isobutilfenil)ciclopropil]amino}propil)acetamida;

N-((1S,2R)-1-(3,5-difluorobencil)-2-hidroxi-3-{[(4-isobutil-1,1'-bifenil-2-il)metil]amino}propil)acetamida; ó

una sal farmacéuticamente aceptable de los mismos.

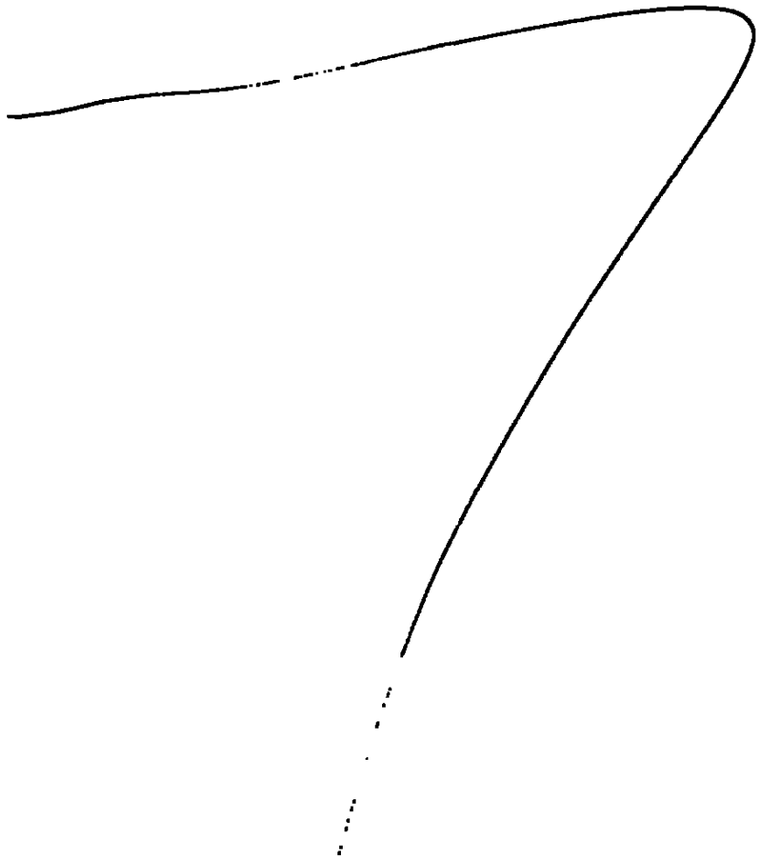
13. Un método para preparar un compuesto de la fórmula



o una sal farmacéuticamente aceptable del mismo, en dónde Z, X, R_1, R_2, R_3, R_{15} y R_c son definidos en la reivindicación 1.

14. El uso de un compuesto de acuerdo a la reivindicación 1 o una sal de dicho compuesto en la fabricación de un medicamento para ser usado en: el tratamiento de un sujeto que tiene, o la prevención de que el sujeto desarrolle, la enfermedad de Alzheimer (EA); la prevención o el retardo de la aparición de la enfermedad de Alzheimer; el tratamiento de sujetos con discapacidad cognitiva leve (MCI, siglas en inglés); la prevención o el retardo de la aparición de la enfermedad de Alzheimer en sujetos que progresan de MCI a EA; el tratamiento del síndrome de Down; el tratamiento de sujetos con hemorragia cerebral hereditaria con amiloidosis del tipo holandés; el tratamiento de la angiopatía amiloide cerebral y la prevención de sus consecuencias potenciales; el tratamiento de otras demencias degenerativas; el tratamiento de la demencia asociada con la

enfermedad de Parkinson, la parálisis supranuclear progresiva, o la degeneración córticobasal; el tratamiento de EA del tipo de cuerpos de Lewy difusos; y el tratamiento de demencias frontotemporales con parkinsonismo (FTDP, siglas en inglés).

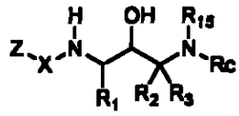


692

691

RESUMEN

Se divulgan compuestos de la fórmula:



dónde las variables Z, X, R_{15}, R_2, R_3, y R_c son definidas aquí. Los compuestos divulgados aquí son inhibidores de la enzima beta secretasa y, por lo tanto, son útiles para el tratamiento de la enfermedad de Alzheimer y otras enfermedades caracterizadas por la deposición del péptido A beta en un mamífero.

COLO 14692-841-002-7
PRP/WPC14692/ID-000006

692

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

Item	Expediente No	050 32254 No de Unidades	No de Folio
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	1	5
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

contiene art final

693 69X

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 19,199
FECHA : MARZO 14 DE 2005

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	41376756	14/03/2005	30,080,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Rdo 14692-841-0027

695

694

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN **MODELO DE UTILIDAD**	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	( )	( )
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
- Representación gráfica del esquema de trazado	( )	( )
- Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación: [illegible]

Fecha: [illegible]

Traslado: [illegible]

Prioridad: [illegible]

Observaciones: [illegible]

Industria y Comercio
SUPERINTENDENCIA

Folio 695

2020
Bogotá, D.C.,

Doctor(a)
EMILIO FERRERO
Apoderado(a)
ELAN PHARMACEUTICALS, INC.
PHARMACIA & UPJOHN LLC.

Oficio Nº 13140

ASUNTO:		
	Radicación Nº	05-32254
	Solicitud Internacional	PCT/US2003/028503
	Fecha límite inicio fase nacional	10/04/2005
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente de los inventores a los solicitantes o a sus causantes. (Art. 26-k) Decisión 486.

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

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

ALIX CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha, 01 JUL. 2005

202027

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1 lutolos